Diabetes mellitus (DM) was described 3500 years ago (the Egyptian papyrus discovered by Georg Ebers) (21). Though it has been recognized as a pathologic condition since antiquity, the knowledge regarding its pathogenesis and therapy remained poor for a long time.

Year 1922 represented a milestone in the therapy of type 1 DM patients. Insulin was then administered for the first time to a boy with diabetes ketoacidosis, his life being saved. The contribution of the Romanian physiologist Nicolae Paulescu to the discovery of insulin has to be noted (21).

The last 25 years of the 20th century witnessed numerous important discoveries regarding the pathogenesis and therapy of type 1 DM. During this period, the theory of autoimmune destruction of the pancreas was imagined, the insulin analogs were synthesized, modern devices for insulin therapy (insulin pens and pumps) were discovered and self blood glucose monitoring became a routine in many countries (16).

Despite all these progresses, the therapeutic results of type 1 DM are often discouraging. The patients continue to develop severe chronic complications, even at young ages, are prone to hypoglycemia, have neuro-psychological problems during childhood and social difficulties during the whole life and have to bear the discomfort of multiple daily injections. Furthermore, the therapy is expensive and sometimes not available.

All these issues support the need for an efficient prevention. This research field represented a priority of the last 3 decades. However, a safe and efficacious preventive method is not known so far (6).

A mandatory condition for developing a preventive method is the possibility of an accurate prediction (20). Data regarding type 1 DM prediction are numerous and often discordant. However, the markers commonly used are:

- genetic: predisposing HLA haplotypes (1);
- immunologic: pancreatic autoantibodies (PAAs): islet cell autoantibodies (ICAs), insulin autoantibodies (IAAs), glutamic acid decarboxylase...
autoantibodies (GADAs) and autoantibodies directed against insulinoma-associated pancreatic antigen (IA-2As) (10, 13, 15);
- metabolic: decrease of first phase of insulin response (FPIR) during intravenous glucose tolerance test (19).

The prognostic significance of the same marker varies according to the study. This is due to the discrepancies between the groups regarding prevalence of diabetes, genetic factors, age and sex ratio, and to the differences concerning lab techniques, duration of follow-up and methodology. It is worth mentioning that the diagnosis of type 1 DM is sometimes difficult on clinical basis (18) and that type 2 DM in children and teenagers is more often recognized. Furthermore, type 1 DM is not a unitary disease; nowadays, the existence of 2 subtypes with no sign of humoral autoimmunity is recognized (14).

There are 3 possible strategies for prediction:

1. If the subject is a first-degree relative of a patient with type 1 DM, the risk of developing the disease is 15-20 fold higher as compared to the general population. These individuals represent the target screening group for prevention studies. The aim is to discover cases with high or very high probability of becoming diabetics. This attitude empowers the study and avoids exposure of a person with a low probability of disease occurrence to a substance with only hypothetic prevention effect and possible side effects (6).

The strategy applied has a high specificity and a low sensitivity (3). According to the Guidelines of the Immunology of Diabetes Society (5), strategies for full evaluation of risk should include determination of at least 3 of the 4 best-established markers (ICAs, IAAs, GADAs and IA-2As). Individuals with elevated levels of 2 or more PAAs should be considered as being at high risk. The measurement from the very beginning of the 3 biochemical PAAs (IAAs, GADAs and IA-2As) instead of ICAs seems to be more facile and to have the same sensitivity and a better specificity (8). Metabolic testing with evaluation of the FPIR can be used to identify the subgroup of individuals with elevated levels of multiple PAAs who are at the greatest risk of progression to diabetes in short term (3) (figure 1).

2. If the subject is not a relative of a diabetic patient, the probability of progressing to disease is low. In order to identify high risk persons from the general population, the first step recommended is the search for genetic markers. Only in case of the presence of predisposing HLA haplotypes (4), the measurement of immunologic markers, as described in the first section, is recommended (figure 1).

This protocol is very expensive due to the need of a very large population to be screened for the positivity of genetic markers. It is suitable for newborns (umbilical cord HLA typing), being widely accepted by the parents, and it is able to provide

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**Figure 1. Risk assessment in type 1 diabetes mellitus**
participants for clinical trials regarding natural evolution and prevention of type 1 DM (2, 12, 22).

3. It is hoped that an effective and nontoxic preventive method will soon be available. In order to reduce the incidence of type 1 DM, the aim of the prediction is to identify subjects having at least intermediate risk. Consequently, the strategy applied has a high sensitivity, despite a low specificity (3). The data from literature are scarce regarding this problem.

Individuals with intermediate risk are representatives of the general population having ICA titer > 4 JDFu (Juvenile Diabetes Foundation units) and first-degree relatives positive for at least 1 autoantibody (3, 5) (figure 1).

Data regarding the pathogenesis of type 1 DM continue to show up and the research is directed towards the discovery of a marker of prediction close to the ideal one. Much hope relies on the new ELISPOT test for T cells (11, 17). It is supposed that this assay could identify an incipient autoimmune process, the preventive measures being more effective in this situation (7, 9).

The next years will certainly clarify the value and practical applicability of all the screening methods for type 1 DM.

References: