Workshop Reports

Immunological Aspects of Type 1 (Insulin-Dependent) Diabetes: Pathogenesis and Therapy

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A meeting on Immunology and Diabetes was held in Luxembourg from 14 to 15 April 1982. The aims of the meeting were to try and define the 'State of the Art' and reach conclusions for future work. The present article is intended to summarize and give a subjective view on the major topics discussed.

Aetiology and Genetics of the Disease

For years the prevailing concept of the aetiology of Type 1 (insulin-dependent) diabetes aetiology has been the assumption that a combination of viral damage and autoimmune reactions is responsible for the destruction of B islet cells (leading to hypoinsulinaemia and hyperglycaemia). Depending on genetic and environmental factors one of the two pathogenic processes would be dominant. This would explain the observed heterogeneity of the disease.

Several observations indicate that Type 1 diabetes in general is not a straightforward viral disease. Many viruses have been implicated in the aetiology of the disease (e.g. mumps, coxsackie B), but there is no consistent association with epidemics of any viral disease and no epidemics of Type 1 diabetes have occurred. Animal studies have shown that virus-induced diabetes (M variant of EMC virus, reovirus Type 1) can be prevented by immunosuppression, hinting at the important role of virus-induced pancreatic autoimmunity. However, J.-W. Yoon (Bethesda) described one highly diabetogenic variant of EMC virus, which induces diabetes in susceptible mouse strains without the involvement of autoimmune reactions.

It is not known which are the diabetogenic viruses in man. There is no persistent correlation between high titres of virus antibodies and the manifestation of the disease. K. Helmke (Giessen) reported that the appearance of islet cell antibodies after mumps infection was not seen again in later studies. Recently, two cases of virus infection with subsequent Type 1 diabetes have been thoroughly studied. In one case the virus was identified as coxsackie B5 (R. Assan, Paris), in the other the human isolate was weakly related to the coxsackie B4 serotype (J.-W. Yoon).

The genetic association of Type 1 diabetes with HLA-DR3 and DR4 (in >90% of patients) is well known. At first sight DR3 or DR4 antigens appear to be of low importance in the aetiology of the disease since these antigens have a high prevalence (40%–50%) in normal Caucasoid populations, whereas Type 1 diabetes afflicts <0.5% of persons. J. Nerup (Gentofte) pointed out that a different picture emerges when one considers that 55%–60% of Type 1 diabetic patients are heterozygous for DR3/DR4 in contrast to 1%–3% of the total population. This qualifies HLA-DR3/DR4 as a useful marker of Type 1 diabetes. J. Nerup suggested that the DR3/DR4 antigens might form an unusual hybrid molecule on lymphocytes or on B islet cells and thus somehow trigger specific autoimmune reactions. It would be most interesting to study healthy persons of HLA-type DR3/DR4.

J. Bertrams (Essen) and J. I. Rotter (Torrance, California) reported on other markers beside HLA which have been found to be associated with Type 1 diabetes. From his extensive family studies, A. G. Cudworth (London) concluded that HLA genes probably contribute to about 80% of genetic effects seen in Type 1 diabetes limiting the impact of non-HLA genes. Furthermore, an association of the disease with immunoglobulin allotype (Gm) markers was not observed.

There is much circumstantial evidence but no final proof that autoimmune reactions seen in Type 1 diabetes significantly contribute to the pathogenesis of the disease. W. Gepts (Brussels) reported that at least two types of islet cell surface antibodies (ICSA) exist (one of them is specific for B islet cells, another binds to B as well as non-B cells). Although most islet cell cytoplasmic antibodies (ICA) react with all endocrine cells within an islet, G. F. Bottazzo (London) has identified one sub-type that only binds to B islet cells and another that reacts with the majority of but not with all islet cells. In the laboratory of A. Lernmark (Gentofte) two different islet cell antigens have so far been isolated (proteins of molecular weight 64 K and 38 K) of which the cellular localization is not yet known.

Several groups reported that islet cell antibodies (probably ICSA) block the physiological response of B islet cells to glucose and mediate lysis of these cells in the presence of complement. W. J. Irvine (Edinburgh) pointed out that the cytotoxic activity of ICSA appears to be rather weak. Furthermore, experiments to induce diabetes (hyperglycaemia) in mice by passive antibody transfer have only led to transient glucose intolerance (R. Assan). The determination of islet cell antibodies is of clinical importance since they appear to be a useful prognostic marker (see below).

The analysis of cellular immunity to B islet cells has not made much progress in recent years except for animal studies. In a summary of these studies, given by W. Gepts, it became evident that cellular immunity, i.e. lymphocytic infiltrations in islets (insulitis), can occur as a consequence of virus infections or of chemical islet cell destruction, during states of immune dysregulation or spontaneously in certain mouse and rat strains. In general, cellular immune reactions affect only B islet cells. The association of autoimmune reactions to B islet cells with immune disorders in animals parallels in a way findings of K. Buschard (Copenhagen) and P. Pozzilli (Rome) describing a decrease of T suppressor cells in the peripheral blood of Type 1 diabetic patients.

Further progress in the analysis of cellular immunity probably will depend on the development of appropriate *in vitro* assays.

Pre-diabetes and Prognosis of Type 1 Diabetes

An important step forward in understanding Type 1 diabetes was the recognition of a pre-diabetes period which may last from a few weeks to several years. This conclusion primarily stems from studies of first

degree relatives of Type 1 diabetic patients reported by G. F. Bottazzo and A. G. Cudworth and from studies of patients with organ-specific autoimmune diseases by C. Betterle (Padua). These groups carry a higher diabetes risk and therefore were chosen for prospective studies. In each case a prediabetic phase characterized by persistent islet cell antibody production was found. The most predictive sub-type of antibodies appeared to be complement-fixing ICA (CF-ICA). Some 50% of people with CF-ICA in their serum developed Type 1 diabetes within 3–30 months. The presence of ICA thus seems to reflect the process of islet cell destruction (ICA may be cause or consequence). Earlier reports had indicated that the occurrence of ICA in the serum will predict insulin deficiency also in other high risk groups: in patients with gestational diabetes and in Type 2 (non-insulin-dependent) diabetes (secondary failures). In gestational diabetes it has been observed that between 60 and 70% of ICA-positive patients developed Type 1 diabetes in the following years. A similarly high probability was found by W. J. Irvine (Edinburgh) for ICA-positive patients with Type 2 diabetes (treated by oral hypoglycaemic agents) to develop insulin-deficiency in the next years. It may be expected that ICA determinations will be routinely used to predict insulin deficiency in high risk persons.

Immunotherapy of Type 1 Diabetes

A review on present immune intervention studies was given by G. F. Cahill (Boston). The first clinical trials to cure Type 1 diabetes by immune intervention started a few years ago. For this purpose, patients with recently diagnosed Type 1 diabetes (usually not children) have been treated with corticosteroids, azathioprine, antilymphocyte serum, levamisole, dapson, interferon and plasmapheresis. Except for two cases, no convincing effect of immune intervention was noted. D. Pyke (London) used a combination of prednisolone, antilymphocyte globulin, azathioprine and in one case nine sessions of plasmapheresis. In one of four patients (male, age: 18 years or older) complete remission for 15 months occurred, after which he relapsed into insulin dependency. A. G. Cudworth described a 41-old female patient with polyendocrine autoimmune disease who was treated with a combination of plasmapheresis (nine sessions), prednisolone, azathioprine and antilymphocyte globulin. Three months later remission was seen. Normoglycaemia persisted for more than 2 years, after which she again became diabetic and needed insulin.

P. Grob (Zürich) pointed out that immunotherapy in general still is in the phase of trial and error since little is known about regulatory circuits of the human immune system. At present clinical trials are planned or underway in various countries testing the effect of corticosteroids, azathioprine, antilymphocyte serum, plasmapheresis, inosiplex, cyclosporin A and total lymphoid irradiation. Immune intervention studies have to cope with several problems. At the time of diagnosis of Type 1 diabetes, the destruction of islet tissue (including stem cells) may have proceeded too far to allow substantial regeneration after blocking further viral or autoimmune damage. Immunosuppression might favour further viral damage (also to other organs) and in addition, especially in children, might have serious side effects. It has been suggested therefore by H. Kolb and F. A. Gries (Düsseldorf) to try, at least at the present state, substances which have been shown to be effective in animal models of Type 1 diabetes (i. e., the low-dose streptozotocin-induced diabetes or the BB-rat) and which do not lead to severe depression of the immune system.

It may turn out that immune intervention therapy is too late in overt diabetes. To stop the process of the disease at an earlier stage it will be necessary to recognize the prediabetic period. For this purpose markers (including the presence of CF-ICA) are urgently needed.

Finally, little effort has been made so far to determine what the physiological protective mechanisms of an organism are to compensate for an increasing loss of B islet cells during prediabetes (e. g. increased insulin secretion by remaining B islet cells, B islet cell regeneration). Islet cell regeneration can be induced by several means and one would hope that the application of 'islet cell growth factors' might help compensate viral or immune damage to the organ.

It can be expected that we will know in a few years whether classical ways of immune intervention are beneficial in recently diagnosed Type 1 diabetes. In addition, islet cell antibody tests then will be standardized and probably of much help in the recognition of prediabetic periods thus allowing for earlier immune intervention and eventually prevention of diabetes manifestation.

The proceedings of the meeting will be published in book form by Hans Huber Publishers, Berne, Switzerland.

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