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RESUMENES DE CONFERENCIAS PRESENTADAS

PREDICTION AND PREVENTION OF TYPE 1 DIABETES MELLITUS

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Diabetes Mellitus Type 1 is a burdensome disease that requires constant vigilance to monitor blood glucose, adjust insulin doses by injection or by programmable devices such as insulin pumps and to integrate nutrition and exercise with the given doses of insulin so as to avoid both hypoglycemia and hyperglycemia. The ability to predict this disease before all of the insulin secretory cells have been destroyed by the autoimmune process that is the cause of type 1 diabetes would be of clinical benefit. Hence, the rationale is that prediction before the appearance of clinical features and symptoms may allow intervention to preserve beta cell function. This ideal is supported by a host of intervention studies in animal models, especially the non-obese diabetic (NOD) mouse. In this species, a variety of interventions have been successful. However, in human beings, no interventions to date have been proven to demonstrate long term success.

In this presentation, I review the current understanding of type 1 diabetes mellitus as an autoimmune disease in which certain genes, especially those of the HLA complex confer susceptibility to diabetes which is then trigger by an, as yet, unidentified environmental insult. The existent of auto-immunity is evident from the appearance and persistence of various antibodies to the components of the pancreatic beta cell including insulin, GAD, IA-2, and non-specific islet cell antibodies (ICA). The combination of various HLA genotypes confers greater susceptibility to the development of type 1 diabetes. In addition, the antibodies are also markers of prediction and the higher the titer and greater the number of positive antibodies, greater is the likelihood of developing diabetes. Combing both the HLA genotype and the presence of islet antibodies with the ability to secrete insulin in response to a pulse of intravenous glucose, the so-called first phase insulin response (FPIR) allows fairly accurate prediction of

those likely to develop diabetes mellitus type 1 within five years.

This body of evidence has evolved over the past twenty years and is supported by a strong scientific base which indicates that type 1 diabetes mellitus is primarily an auto-immune disease. Therefore, strategies to prevent the disease have focused largely on means to modulate the immune response.

Different immune modulators have been used but none with success. These include the immunosuppressive cyclosporin which does induce a brief remission that does not last more than one year or so. Steroids and other immunosuppressants also have not been effective in the long term. Recently, two multi-center international studies have attempted to predict and prevent diabetes in first degree relatives of patients with the disease. The Diabetes Prevention Trial for Type-1 in the United States was a massive undertaking that screened over 80,000 people in order to eventually permit randomization into treatment and non-treatment groups with subcutaneous insulin. The results of this study in the New England Journal of Medicine demonstrated that the disease could be predicted with a high degree of accuracy but intervention with insulin injections did not prevention. Likewise, the European Nicotinamide Diabetes Intervention Trial (ENDIT) treated patients with the drug Nicotinamide which is thought to modulate DNA Repair. Again, the results demonstrated the feasibility of conducting large multi-site clinical trials that were accurate in predicting those most likely to develop diabetes within 5 years. However, again Nicotinamide was not successful.

A number of other agents are currently being attempted. These include anti-CD3 antibodies injected intravenously or possibly orally, oral rather than intravenous insulin, the monoclonal antibody CD-20

known as Rituximab, and newer immunosuppressants. Avoidance of cow's milk at birth by promoting breast feeding and then switching to a homogenized (Nurtramigan) formula rather than cow's milk is being investigated.

It must be emphasized that all of these preventive strategies are still in the domain of research and are not yet ready for wide spread routine clinical application.

Finally, if time permits, we will briefly review the current status of islet cell transplantation for the reversal or cure of type 1 diabetes.

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