FAMILY STUDIES OF INSULIN-DEPENDENT DIABETES: THE UK EXPERIENCE

E.A.M. Gale, P.J. Bingley, and A.C. Tarn

Department of Diabetes and Immunogenetics
St. Bartholomew's Hospital, London

The presentation of insulin-dependent diabetes (IDDM) in children and young adults usually appears to be sudden (1), suggesting an acute pathology, but we now know that this is only the final step in a process of cumulative beta-cell damage extending over months or even many years. By the time of diagnosis some 80–90% of beta cells have been destroyed. Clinical trials have shown that immunosuppression of newly diagnosed patients may prolong the survival of the remaining beta cells, but it would be logical to intervene at an earlier stage, when the majority of these cells are still viable. This approach could only be considered if it were possible to predict accurately the onset of diabetes in a given individual.

POPULATION STUDY

The Family Study Approach

Prospective analysis of individuals at increased risk offers the best chance of developing and testing a predictive index. The highest risk of all is present in twins discordant for diabetes. Some 30–50% of unaffected twins will develop IDDM, usually within the first ten years from diagnosis of their cotwin (2). Children of two parents with IDDM have an almost equally high risk - around 33% - but they and discordant twins are of course extremely rare. First degree relatives of a child with diabetes offer a more convenient cohort for prospective study. This approach, now widely employed, allows continuing analysis of genetic, immunological and metabolic markers of risk, as well as permitting investigation of possible environmental factors. A large population base is needed before susceptible individuals can be identified in sufficient numbers; intensive study of this group may, in time, allow simpler and more precise markers to be developed.

The Bart's Windsor Family Study

This was started by the late Professor Andrew Cudworth in 1978. The rationale for prospective follow-up was provided by the recognition of HLA associations (3), the observation that siblings HLA identical with the proband were at increased risk (4), the discovery of islet cell antibodies in newly diagnosed diabetic patients (5) and the possibility of prospective screening for viral infections suspected of being implicated in the pathogenesis of Type I diabetes (6).
The original study was based on a clinic register developed by Dr. John Lister, with a number of other families being recruited from other local clinics, making a total of 204 families. All the families were caucasian, contained a diabetic proband diagnosed before the age of 20 and at least one unaffected sibling under that age. The families have been visited regularly at home by field workers over the past 10 years and, following initial tissue typing, blood has been taken at 4-6 monthly intervals for organ-specific antibodies, viral studies and a variety of other investigations. Of the original total, some 185 families remain in contact with the study, though many are now only under postal follow-up.

In 1984 the Bart's Windsor cohort was frozen at 204 families but maintained under long-term surveillance. Since then a new family study known as the Bart's Oxford Study has been established. This is based on a defined population of 2.4 million people in the Oxford Region. Newly diagnosed diabetic patients under the age of 21 (approximately 120 cases per year to date) will be ascertained over a 5 year period, and their families recruited for the study. Surveillance is maintained by 4 locally based nurses who have taken over the role of field workers, and regular blood samples are taken from all the family members. For reasons of cost screening is based upon measurement of ICA and HLA typing is restricted to families with an ICA positive non-diabetic member and an equal number of control families. The central aim of the new extended study is recruitment of high risk individuals in sufficient numbers for prospective study.

METHODOLOGY

Genetic Markers

Diabetes develops on a basis of genetic susceptibility, but is not simply a disease of genetic predestination. The classic demonstration of this comes from the study of identical twins. If one twin develops IDDM diabetes, the other has a 50-70% change of avoiding the disease completely. In contrast only 10% of twins are discordant for non-insulin-dependent diabetes (NIDDM) indicating a much stronger genetic component in this variety of diabetes. Further evidence that the genetic contribution to NIDDM is of greater importance than that to IDDM comes from analysis of the frequency of diabetes within first degree relatives. The life-time risk of developing IDDM has been calculated as 2.9% for parents, 6.6% for siblings and 4.9% for children of an individual with IDDM (7).

Despite many efforts, the mode of inheritance of IDDM remains unclear. The HLA associations of Type I diabetes have been studied extensively, and powerful links with HLA-DR3 and DR4 have been established. A study of 123 subjects diagnosed before the age of 20 (8) found that 98% possessed either DR3 (relative risk = 5.0), DR4 (relative risk = 6.8) or both (relative risk = 14.3) The relative risk conferred by DR3 is more than merely additive with that conferred by DR4, suggesting that each makes a separate contribution in predisposing to diabetes, but that they also have an unexplained complementary effect in combination.

HLA analysis has a more specific role in predicting risk within first degree relatives. Siblings who are HLA identical with the proband are most at risk. This risk has been put as high as 30% (9,10), but our current estimate is rather lower, giving a cumulative risk by Life Table analysis of 15.7% of developing diabetes by the age of 25 for HLA identical siblings and 8.6% for haploidentical siblings, while none of the non-identical siblings were in our sample projected to be diabetic by that age. The Pitts-