Recent advances in human genetics mean that it is now possible to identify new susceptibility genes for diseases with complex inheritance. To be successful, this approach requires a co-ordinated collection of multiple-case pedigrees in whom the phenotype under study has been carefully characterized. Given such a resource, analysis of the inheritance of genetic markers and disease in affected sibling pairs (linkage analysis) will identify novel markers of disease susceptibility. In this issue, the details of pedigrees from the first 100 confirmed RA families with affected sibling pairs are published; these have been collected by the Arthritis and Rheumatism Council’s Epidemiology Research Unit at the University of Manchester. It is hoped that this information will stimulate scientists to exploit this important resource. This initiative is in part modelled upon the Warren Repository of Multiplex Families familial resource is sufficiently large.

Type 1 (insulin-dependent) diabetes mellitus has a peak age-at-onset of 12 years and a lifetime risk of approximately 1-in-1500 in Caucasians. In the UK its incidence is increasing and it is now the second most common chronic disease of childhood [1]. Affected individuals require life-long insulin treatment and are prone to the disabling complications of retinopathy, nephropathy and neuropathy.

Disease aetiology is complex, involving both genetic and (unknown) environmental influences [2]. Significant progress has been made in identifying genetic susceptibility determinants. Genes within the human leukocyte antigen (HLA) region on chromosome 6 predispose to type 1 diabetes, alleles of the HLA-DQA1, -DOB1 and DRB1 loci correlating directly with disease susceptibility. Precise mechanisms have yet to be determined, but probably involve presentation of self-antigen by class II HLA molecules to T-lymphocytes. Alleles within the insulin gene region (INS) on chromosome 11 are also associated with disease in Caucasians and two family studies have shown evidence for linkage [3, 4].

This histological hallmark of type 1 diabetes is 'insulitis'. This is an autoimmune infiltration of the pancreatic islets of Langerhans by mononuclear cells including T-lymphocytes and macrophages. Insulitis leads to progressive destruction of insulin-producing pancreatic β-cells over a prolonged period (months to years). Only when 80–90% of β-cells have been destroyed do the typical symptoms of hyperglycaemia develop. The long prodrome of type 1 diabetes suggests that intervention aimed at preserving β-cell function is feasible. Identification of high-risk individuals is necessary to facilitate such a strategy and, in the general population, this is best achieved by genetic screening in the first instance. Known susceptibility markers at HLA and INS assign an absolute risk of approximately 1-in-15 [5]. The identification of additional non-HLA genes is therefore essential to raise the predictive power of genetic markers to levels where primary screening is viable.

A co-ordinated approach to mapping new susceptibility loci in complex diseases such as type 1 diabetes is now possible. Techniques in molecular biology have advanced sufficiently to enable rapid testing of candidate gene loci and, more importantly, exclusion mapping of the entire human genome. Analysis of cosegregation of genetic markers and disease in affected pedigrees (linkage analysis) has the potential to identify new susceptibility genes, so long as the familial resource is sufficiently large.

In 1989 the British Diabetic Association (BDA)
funded a major initiative to establish a genetic resource of type 1 diabetic pedigrees. This was made possible by a bequest by the Warren family and is known as the BDA-Warren Repository [6]. The primary objective of the project was to collect DNA from families with two or more diabetic offspring and living parents ('multiplex families'). Statistical comparison of the sharing of genetic markers by affected siblings with that expected by chance (sibling-pair analysis) can then be used to search for genetic linkage of markers and disease. Although type 1 diabetes is common in the British Isles, over 85% of cases are sporadic with no first degree family history. The number of multiplex families in any one area is therefore small, necessitating a nation-wide collection. This has been achieved by the collective efforts of physicians, paediatricians, nurse specialists and patient groups throughout the UK and Ireland.

The second aim of the project was to make the resource widely available to research groups throughout the world. This has been achieved by Epstein–Barr virus transformation of peripheral blood lymphocytes. These 'immortalized' cell lines retain their reproductive capacity and can be stored indefinitely at low temperature; theoretically, limitless amounts of DNA are therefore available for study. This process obviates the need for repeated blood sampling and facilitates widespread distribution of samples.

The BDA-Warren Repository is now the largest single collection of type 1 diabetes multiplex families. Additional funding from the Wellcome Trust (as part of the Wellcome Human Genetics Centre initiative in Oxford) has allowed the recruitment of pedigrees to continue and samples from 100 families are currently being studied by 11 groups worldwide; a further 100 pedigrees will shortly become available (via the BDA Research Director). Given that 50 fully informative families are needed to prove linkage to HLA, the minimum requirement for quantitatively less important loci may be 400–500 pedigrees.

The genetic analysis of type 1 diabetes will be a model for the study of complex diseases. Disease heterogeneity can be reduced by the use of strict clinical criteria in a way that is probably not possible in many other conditions (e.g. psychiatric disorders). Further, two linked susceptibility gene regions have already been identified. These features are in addition to the considerable amount of knowledge concerning the immunology of type 1 diabetes and the availability of animal models. Finally, a large ethnically homogenous genetic resource is now available to facilitate the necessary experimentation and, if the scientific will exists, a worldwide collaborative effort.

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