Commentary: Population mixing and childhood diabetes

Anthony Staines

There has been a suspicion that Type 1 (insulin-dependent) diabetes (IDDM) is due to an infection since the early years of the last century. This arose from the typical acute clinical presentation of the disease. The specific hypothesis was that IDDM was due to direct virally mediated immune destruction of the pancreatic islets. A number of case reports of IDDM as a consequence of overwhelming enteroviral infection, and the high risk of IDDM amongst children with congenital rubella syndrome supported this view. However, recent studies using epidemiological, serological and molecular techniques have failed to identify any specific infectious agent in the vast majority of cases.1,2

A more interesting role for infectious disease, the ‘hygiene hypothesis’ has been proposed. This is that early protection from antigenic challenge, specifically that due to infection, increases the risk of developing IDDM. There is evidence from several lines of animal and epidemiological data that early life circumstances may affect later immune response, but the details and mechanisms involved remain frustratingly obscure. A shift in the balance between Th1 and Th2 responses, as has been suggested for asthma, is probably too simple an explanation for the complex changes seen in IDDM, and perhaps in atopy also.3–5

This study adds to a series of reports on small-area variation in diabetes incidence from the UK. There is an overall consistency in this body of work, with higher rates of IDDM in affluent areas than deprived areas, and in rural areas than in urban areas. This is consistent with the ‘hygiene hypothesis’, as there is good evidence that living in such areas reduces the risk of early exposure to infection.
The major limitations of this work are those of any ecological study, namely an untestable assumption about personal exposure correlating with area-level measurements. However, several of the measures used in this group of studies have no obvious person-level counterpart. It is difficult to see how population density, and population mixing could be measured meaningfully at an individual level. It is now critically important that further attempts are made to replicate these results outside the UK. This would then address the concern that these studies have merely identified some quirk of British life, which itself leads to an increased risk of IDDM.

The results of several recent case-control studies are also broadly consistent with this hypothesis, but suggest that the full picture may be quite complicated. Pundziute-Lycka et al.\(^6\) found that infection in the first six months of life reduced the risk of developing IDDM after the age of 5 years. The EURODIAB Substudy 2 study group\(^2\) found that while perinatal infections increased the risk of IDDM, attendance at pre-school facilities, known as a major source for exposure to infections, decreased the risk. If, as these results suggest, the precise timing of childhood infection is of the essence, very sophisticated studies will be needed to resolve these questions.

Another crucial area for research is an understanding of the biology of immune system development. Recent work has shown that relatives of people with IDDM, who are at high risk of developing IDDM themselves, as defined by raised islet-cell antibody titres, have Th1-like responses, but these are not found in children newly diagnosed with IDDM.\(^7\) At present while it is possible to talk about immune system maturation, it does not seem to be possible to measure it in ways which are biologically relevant for understanding the aetiology of IDDM. It is also unclear precisely what should be measured to define ‘exposure to infection’ in childhood.

The picture emerging from this body of work is still unclear. Evidence from ecological studies and case-control studies suggest that infection is important in the aetiology of Type 1 diabetes. Evidence from immunological studies in rats and humans suggest that the immune response in Type 1 diabetes is influenced in important ways by infection, and that certain patterns of abnormal immune response may predispose to Type 1 diabetes.\(^4,7,8\) The respective roles of breastfeeding, dietary exposure, and other perinatal events remain to be explained. The interplay between genetic susceptibility and patterns of immune response, as influenced by immunological experience is a promising area for further study.

References