

Is the Etiology of Insulin-Dependent Diabetes Mellitus Related to Superantigen Involvement?

The etiology of insulin-dependent diabetes mellitus (IDDM) remains obscure, although most accept that this is usually a T cell-mediated autoimmune disease, the onset and/or progression of which is very possibly triggered by unknown environmental factors (possibly viruses) acting on a predisposing genetic background. Conrad et al studied the islet-infiltrating T (IIT) cells from 2 IDDM patients who were dying at the onset of disease. Their results can be interpreted as providing evidence for the involvement of a pancreatic islet cell membrane-bound superantigen (SAG) as an etiologic factor.

Conrad et al report a correlation between the presence of insulinitis and the presence of an abundance of CD4⁺ (helper cells). CD8⁺ (killer cells) were also present in the areas of insulinitis. In another article in the same issue of *Nature*,

MacDonald and Acha-Orbea comment upon the definition and function of SAGs. The foundation for their speculation is based primarily upon a unique property of SAGs—ie, their ability to activate a large population of T cells in a given person by interacting specifically with amino acid sequences on the “variable” domain (V) of the β chain (β) of the T-cell receptors (TCRs), and, therefore, the TCR V β and, specifically in the instance of insulin producing cells, the TCR V β 7 receptor. Conrad et al demonstrated a strong overexpression of the V β 7 family of cells in the IIT cells from the 2 patients studied, suggesting the presence of a SAG that triggers preferentially V β 7 and T cells, rather than conventional Ags, in the etiology of IDDM.

SAGs are unique products of ubiquitous bacteria and viruses. They postulated that if the first exposure to the SAG is at a very

early age, potentially autoreactive T-cell clones are inactivated. The silencing of such "dangerous" T-cell clones may then protect against the development of IDDM. If instead the first exposure is several years after birth, many different T-cell clones expressing the same TCR V β will become simultaneously activated; and in a genetically predisposed individual, some of these T cells are able to initiate the process that eventually results in the destruction of the β cells of the pancreas.

MacDonald and Acha-Orbea discuss 2 possible theses for how the polyclonal T cell-activating property of SAg could be responsible for the onset of a specific autoimmune disease such as IDDM. Readers who are interested in these alternatives are referred to the excellent presentation by MacDonald and Acha-Orbea, who point out that all SAGs identified to date are the products of either bacteria or viruses. This raises the obvious possibility that the IDDM-associated SAG, if it exists, is of infectious origin. These commentators further state that although the arguments advanced by Conrad et al in favor of SAg involvement in IDDM are thought provoking, they should be hedged with caveats. First, the authors have data on only 2 rather unusual IDDM patients who died rapidly after the onset of disease; and second, neither the SAG nor its putative causative agent has been identified.

Conrad B, et al. Evidence for superantigen involvement in insulin-dependent diabetes mellitus aetiology. *Nature* 1994; 371:351-355.

MacDonald HR, Acha-Orbea H. Superantigen as suspect. *Nature* 1994;371:283-284.

Editor's comment: *The concepts presented above are exciting to consider. Thirty-four years ago in 1961, my collaborators and I postulated that IDDM was an autoimmune disease in many instances. This theory, although slow in being accepted, has now been accepted for approximately 20 years. However, the causative factors in the autoimmune process remain unclear. Pursuit of the SAG hypothesis is essential. Recently, some of us received a letter from Dr. Dorothy Becker, in which she requested your potential collaboration in helping elucidate further the possible role of SAGs in the etiology of IDDM. Because your assistance in this elucidation is important, I have invited Dr. Becker to add her own comment below.*

Robert M. Blizzard, MD

Dorothy Becker, MD

2nd Editor's comment: *It is now clear that the development of IDDM in animal models and the majority of humans with the disorder is an autoimmune process that develops in genetically susceptible individuals. Our group has sought an environmental trigger for the induction of this process for the past 15 years. Work from Pittsburgh, as well as that from many groups around the world, has shown epidemiologic associations with a variety of viruses and food components. However, rigorous examination has continually failed to elicit a clear association of IDDM with any one environmental agent. The relatively recent explosion in the application of immunologic techniques to IDDM research and the availability of pancreatic tissue from new-onset IDDM children have allowed the proposal of the SAG theory in the etiology of IDDM described above. As SAGs have been invoked as causative agents in other autoimmune diseases, this theory has some precedent. If a SAG could be proved to be an initial trigger or a subsequent "hit" that either induces or allows the continued progression of the autoimmune process, IDDM theoretically could be prevented by antibiotic treatment of the agent (such as streptococcal disease) or vaccination against the agent. We therefore feel that this avenue of research has to be pursued as we continue our efforts to ultimately prevent the onset of IDDM in children. Fortunately, any given center in the United States does not experience frequent mortality in children with IDDM, which, unfortunately, leads to a major lack of availability of material with which to work. Therefore, Dr. Massimo Trucco and I have requested the assistance of pediatric endocrinologists and pediatricians around the country in obtaining fresh pancreatic material from any individual who might die at the onset of IDDM. In addition, it is important to investigate individuals from different regions of the country to ensure that Dr. Trucco's findings in 2 children who came from the same area are applicable over a wider geographic region. We feel that Dr. Trucco's work in the immunogenetics division of the Children's Hospital and University of Pittsburgh is extremely exciting, and we hope we can get the assistance and support of pediatricians around the country, which would allow its rapid continuation and progress. Dr. Trucco can be reached at (412)692-6570, or one of our colleagues can be reached at any time through the operator at Children's Hospital of Pittsburgh, (412)692-5325.*

Cognitive Abilities Associated With the Silver-Russell Syndrome

The developmental status of 25 children between 6.0 and 11.8 years of age (20 males, 5 females) with the Silver-Russell syndrome was evaluated. Based on assessment of the father's occupation, more than half of the children were from middle class and upper socioeconomic groups and the ascertainment bias of sample would, if anything, be expected to have identified children with above average abilities. Of the 25 children, only 3 (12%) had full-scale IQ scores above average (IQ >116 to 130); 9 (36%) scored within average range of abilities (IQ 85 to 115); 5 (20%) had scores in the range of borderline mental retardation (IQ 70 to 84); and 8 (32%) had scores in the range associated with mild to moderate learning disability (IQ <70). There was little variation between the mean full-scale IQ

of 85.9 ± 23.7 (using the Wechsler Intelligence Scale for Children [WISC]), the mean verbal IQ of 89.3 ± 22.6 , and the mean performance IQ of 84.3 ± 23.5 . The authors reported that mean performance IQ scores were lower in girls than in boys; however, the number of females (n=5) studied was small.

The IQ scores correlated best with head circumference measured at the time of the test. The 3 children with superior IQ scores all had normal head circumferences for chronologic age. Utilizing the Neale analysis of reading ability, the mean reading comprehension was delayed relative to chronologic age by 15.4 months, accuracy by 14.4 months, and rate of reading by 13.8 months. Twelve of the 25 children required special education or remedial assistance.