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Coxsackie virus and diabetes revisited

To the editor — The recent *News & Views* article that considered the role of Coxsackievirus in insulin-dependent diabetes mellitus (IDDM) outlined a mechanism known as molecular mimicry, in which an immune response directed against an environmental agent stimulates a cross-reactive response against a homologous peptide from an autoantigen. In the case of IDDM, an epitope of glutamic acid decarboxylase (GAD65) shares strong sequence similarity with the PC2 protein of Coxsackie B viruses, including an exact six-amino acid match, PEVKEK. The *News & Views* described data from two articles[2,3], demonstrating a potential for T-cell cross-reactivity between GAD65 and Coxsackie PC2 PEVKEK peptides. Reference was also made to our recent work in this field and we wish to clarify the interpretation of our results.

We have undertaken a comparison of the GAD65 amino acid sequence against the OWL protein database[4], identified 17 regions of similarity to virus proteins, and investigated T-cell proliferative responses to 13 of these viruses in subjects with IDDM. Our data (manuscript in preparation) suggest that significant differences in the frequency of positive response and magnitude of response occur only for Coxsackie B viruses and adenovirus. Of the 13 viruses studied, only the Coxsackie B viruses exhibited sequence homology in the PEVKEK region.

Current evidence suggests that there are two dominant T-cell epitopes for GAD65 in IDDM. The first occurs at amino acids 509–543 in the NOD mouse[4], and in a region between 473 and 555 in humans[5]. We did not find any virus protein homology in this region, but have previously noted homology to the cellular stress protein hsp60, which may also be an antigen in IDDM[6]. The second epitope contains the PEVKEK sequence and has now been confirmed as an epitope in both NOD mouse[2] and human IDDM[3]. Our data using T-cell proliferation assays strengthen the support for a Coxsackie infection as a triggering event in human IDDM. Although serological studies have failed to find significant titres of Coxsackie B virus-specific immunoglobulin, this could be a consequence of the long prodromal period before clinical symptoms are observed.

Our evidence indicates that proliferative responses to Coxsackie B viruses are found in the majority of subjects with IDDM. The case for Coxsackie B virus involvement in IDDM is in our view stronger than that implied in the recent *News & Views* article by Solimena and De Camilli.

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