Table 1. Baseline characteristics of Japanese IDDM patients

Age at onset (years)	0–5	6–12	13–19	20–
n	72	171	163	162
Male/female	32/40	63/108	55/108	53/109
Sensory hearing disturbance	0	1	0	0
Mental retardation	0	1[a]	0	0
MELAS	0	0	0	0
Short stature	2	0	0	0
History of obesity	0	0	0	0
History of diabetes in first-degree relatives	6 (8%)	15 (9%)	16 (10%)	15 (9%)
Coma or ketoacidosis at diagnosis	65 (90%)	151 (88%)	114 (70%)	111 (69%)
3243 bp mutation	0	0	0	0

[a] with Down's syndrome.
MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

strates that the 3243 bp mutation was undetectable in Japanese patients with well-defined IDDM.

Yours sincerely,
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Molecular mimicry and the T-cell repertoire

Dear Sir,
We are grateful to Drs. Pujol-Borrell and Pérez de Guzman for their constructively critical comments [1] on our suggestion that molecular mimicry between peptides of, respectively, α_2 macroglobulin and glutamic acid decarboxylase (GAD) might be implicated in the autoimmune pathogenesis of insulin-dependent diabetes mellitus (IDDM) [2].

These comments require us to be more specific about the current status of our hypothesis on the role of mimicry between ubiquitous internal proteins [3] and tissue-specific autoantigens, which has since become more refined and gained greater credence [4]. We propose that the T-cell repertoire generated in the thymus must be based upon what is available to be presented. The commonest self-peptides eluted from class II-MHC molecules actually derive from class I or II molecules, hence our major interest in "MHC molecular mimicry" [4]. Thus, we believe that the CD4 + T-cell repertoire becomes biased by interaction with class II MHC molecules presenting class-I- or II-derived peptides. This may seem paradoxical in the light of current views on the development of self-tolerance, but it is a pragmatic view of the process of thymic positive and negative selection, and is supported by the fact that it is now recognised that whilst tight binding between T-cell receptor and MHC-ligand complex leads to T-cell anergy or apoptosis, weaker binding leads to selection [5].

In the light of these considerations, we return to our original observation of striking similarities between, on the one hand, T-cell epitopes of bacterial and viral immunogens and, on the other, self MHC-derived peptides [3]. Such examples underpin the concept that T cells selected centrally for modest affinity to such latter epitopes might in the periphery have higher affinity, or a qualitatively different reactivity [6] for mimicking epitopes. This establishes a scenario for preferential immunological responsiveness and, under appropriate circumstances, for autoimmune disease.

MHC-derived peptides are not the only peptides presented by antigen-presenting cells (APCs) in association with class II MHC molecules, and a major plasma protein such as a α_2 macroglobulin is highly likely to be represented in the repertoire of peptides presented by thymic APCs during T-cell ontogeny. So our speculation is that T cells, binding with moderate-low affinity to the GAD-mimicking peptide that we have identified, could be positively selected; the availability of this selected T-cell receptor defines the immunodominant epitope in any subsequent response, for example to infection with coxsackie virus. In that case, the T cells selected by recognition of the PEVKSK peptide of α_2 macroglobulin [2] are stimulated by an APC presenting the PEVKEK sequence of the P2-C replicative complex of coxsackie B4. That response then sets the scene for a mimicry-driven reactivity against the corresponding peptide in GAD.

We are aware that much of this is conjecture, although now based on a growing body of circumstantial evidence. However, we believe that the underlying concept is a fruitful one, ac-

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counting as it does for the selection of a limited number of T-cell epitopes from complex immunogens (e.g. the PEVKEK sequence in the case of coxsackie B4) and for MHC association with autoimmune disease under circumstances where there does not seem to be restricted presentation of relevant T-cell epitopes [7].

Yours sincerely,
H. Baum, M. Peakman, M. N. Norazmi, D. Vergani

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Diabetes mellitus and Alzheimer's disease: glycation as a biochemical link

Dear Sir,
Advanced glycation end products (AGE) are a family of complex, evolved post-translational modifications initiated by the condensation of reducing sugars with protein amino groups via the Maillard reaction [1]. Considerable evidence suggests that glycation of proteins and AGE play a role in the pathological processes of diabetes. Recently, several independent investigations have revealed that AGE-relate modifications are also found in Alzheimer's disease, the leading cause of senile dementia [2]. In Alzheimer's disease, the protein components of the pathological lesions (i.e., neurofibrillary tangles and senile plaques) contain AGE modifications and these post-translational events are thought to be involved in the formation of the lesions [3–6]. Additionally, together with evidence of free radical damage in Alzheimer's disease [2, 7, 8], these findings suggest that, as with diabetes, glycoxidation (i.e., glycation-related oxidative processes) is likely to play a role in the pathogenesis of Alzheimer's disease [2].

The occurrence of AGE modifications in both diabetes and Alzheimer's disease might lead one to predict a higher-than-expected incidence of concurrent diabetes and Alzheimer's disease. However, predictions of diabetes and concurrent Alzheimer's disease unfortunately must await epidemiological analyses that consider the lowered life expectancy of uncontrolled diabetic patients, in whom glycation is greatest. Conversely, life-long glycation may result in compensations, leading instead to discordance of Alzheimer's disease and diabetes. Obviously, further investigation is essential to bear out either association.

Whether glycation in Alzheimer's disease is a primary or secondary event is controversial [9]. However, the presence of AGE modifications in the earliest pathological changes in Alzheimer's disease indicates that AGE-modification, in synergy with oxidative modifications, are likely early *in vivo* events [2, 10]. Indeed, other factors may initiate Alzheimer's disease, predisposing them toward glycoxidative damage, and such an interpretation is attractive when one considers the sporadic onset of most cases and the individual variation that includes mentally normal individuals with abundant senile plaques. Demonstration of links between Alzheimer's disease and metabolic disturbances of glucose metabolism or imbalances in free radical or reactive oxygen species detoxification may clarify these issues. In any event, the commonality of AGE modifications and free radical damage in diabetes and Alzheimer's disease suggests that common therapeutic rationales might be considered.

Yours sincerely,
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