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

References

1. Pujol-Borrell R, Jaraquemada Perez de Guzman D (1995) Reply to Norazmi et al. *Diabetologia* 38: 875
2. Norazmi MN, Peakman M, Vergani D, Baum H (1995) Shared amino acid sequences between glutamic acid decar-

- boxylase 65 and 67 and alpha-2-macroglobulin. A focus for cross-reactive autoantibodies? *Diabetologia* 38: 874–875
3. Baum H, Butler P, Davies H, Sternberg M, Burroughs A (1993) Autoimmune disease and molecular mimicry: an hypothesis. *Trends Biochem Sci* 18: 140–144
4. Baum H, Brusci V, Choudhuri K, Cunningham P, Vergani D, Peakman M (1995) MHC molecular mimicry in diabetes. *Nature Med* 1: 388
5. Von Boehmer H (1994) Positive selection of lymphocytes. *Cell* 76: 219–228
6. Sloan-Lancaster J, Allen PM (1995) Significance of T-cell stimulation by altered peptide ligands in T-cell biology. *Curr Opin Immunol* 7: 103–109
7. Albani S, Keystone EC, Nelson JL et al. (1995) Positive selection in autoimmunity: abnormal immune responses to a bacterial dnaT antigenic determinant in patients with early rheumatoid arthritis. *Nature Med* 1: 448–452

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-related 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 spo-

radic 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,

M. A. Smith, L. M. Sayre, G. Perry

References

1. Monnier VM, Cerami A (1981) Nonenzymatic browning in vivo: possible process for aging of long-lived proteins. *Science* 211: 491–493
2. Smith MA, Sayre LM, Monnier VM, Perry G (1995) Radical AGEing in Alzheimer disease. *Trends Neurosci* 18: 172–176
3. Smith MA, Taneda S, Richey PL et al. (1994) Advanced Maillard reaction products are associated with Alzheimer disease pathology. *Proc Natl Acad Sci USA* 91: 5710–5714
4. Ledesma MD, Bonay P, Colaco C, Avila J (1994) Analysis of microtubule-associated protein tau glycation in paired helical filaments. *J Biol Chem* 269: 21614–21619
5. Yan S-D, Chen X, Schmidt A-M et al. (1994) Glycated tau protein in Alzheimer disease: a mechanism for induction of oxidant stress. *Proc Natl Acad Sci USA* 91: 7787–7791
6. Vitek MP, Bhattacharya K, Glendening JM et al. (1994) Advanced glycation end products contribute to amyloidosis in Alzheimer disease. *Proc Natl Acad Sci USA*, 91: 4766–4770
7. Smith MA, Kutty RK, Richey PL et al. (1994) Heme oxygenase-1 is associated with the neurofibrillary pathology of Alzheimer disease. *Am J Pathol* 145: 42–47
8. Pappolla MA, Omar RA, Kim KS, Robakis NK (1992) Immunohistochemical evidence of oxidative stress in Alzheimer's disease. *Am J Pathol* 140: 621–628
9. Mattson MP, Carney JW, Butterfield DA (1995) A tombstone in Alzheimer's? *Nature* 373: 481
10. Smith MA, Sayre LM, Vitek MP, Monnier VM, Perry G (1995) Early AGEing and Alzheimer's. *Nature* 374: 316

Corresponding author: Dr. M. A. Smith, Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106-2622, USA