In reply

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In reply: Non-insulin-dependent diabetes mellitus (NIDDM) and Alzheimer's disease (AD) are both devastating diseases of older adults. In response to suggestions that they may actually be dissociated, we investigated NIDDM and Apolipoprotein-E (Apo-E) genotype in our demented patients. We found a strong dissociation, such that NIDDM occurred in patients meeting criteria for vascular and mixed dementia, but not in those with "pure" AD.¹

The Apo-E data also suggested a dissociation between these disease processes. The E4 allele occurred frequently in AD (71%) as expected, but it occurred with only average frequency in NIDDM (39%). Importantly, in mixed dementia cases, E4 occurred frequently overall (55.6%) and in those with NIDDM (60%). Based on these results and the association of NIDDM with vascular dementia,² we hypothesized that those with NIDDM develop mixed dementia and, thus, are not diagnosed for AD.¹

Responses to our paper have stimulated other explanations as well.³,⁴ Halter³ suggests that the weight loss associated with AD may reduce insulin resistance and prevent
hyperglycemia. However, weight change is more common in 
the advanced stages of AD and in our experience, it is 
associated with increased appetite, lack of satiety, and a 
preference for "sweets." These symptoms may reflect hypo-
thalamic dysfunction occurring with progressive neurode-
generation. Halter also suggests the converse; perhaps hyper-
glycemia enhances accessibility to "brain fuel" and reduces 
the rate of degenerative lesion deposition. The latter is in 
intriguing possibility that needs further investigation, but 
the suggestion that chronic hyperglycemia may be beneficial is 
refuted by many reports of negative cognitive consequences 
in NIDDM.6,7

We suggest that chronic hyperglycemia is a risk factor for 
developing vascular dementia with AD. This could arise by 
accelerated deposition of advanced glycation end-products 
(AGEPs) and oxidative damage.8,9 AGEPs accumulate in 
long-lived proteins through nonenzymatic reactions of glu-
cose and other reducing sugars with free amino groups, 
particularly the ε-amino group lysine. These products are 
found in plaques, tangles, and vessels, and as they form, can 
cross-link adjacent peptides and proteins and thereby initiate 
the neural and vascular cell degeneration.10 Positive feedback 
mechanisms can drive these processes, including β-amyloid, 
which binds to the RAGE receptor, stimulating oxidative 
damage and inflammatory responses.11 Thus, it is possible 
that common pathways exist for both vascular and neuronal 
damage, making those with NIDDM at high risk for mixed 
dementia.

Landler et al4 suggest that oral hypoglycemic agents (sul-
fonylureas) used for treating NIDDM can inhibit ATP-
sensitive K⁺ channels, much like tacrine does, thereby pro-
tecting NIDDM patients against AD. While this clearly 
merits further study, there is no evidence that tacrine slows 
degeneration in AD. Perhaps it is more important that oral 
hypoglycemic agents may mask or slow the onset of the 
clinical symptoms of AD, potentially leading to late or ero-
nious diagnosis.

Mixed dementias are relatively common (approximately 
22% of our clinical population) and are often overlooked. 
The factors that drive this condition represent a critical area 
for further research, and the diabetes condition is one of the 
first leads into the problem.

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