

The plasma concentration of cifenline succinate, which was measured by high-performance liquid chromatography, was higher (2,482 ng/ml) than the standard therapeutic plasma concentrations of 300–600 ng/ml.

Cifenline succinate can induce hypoglycemia even at a low dose, as in the present case. Dementia-like symptoms caused by chronic hypoglycemia, such as insulinoma, are often undiagnosed. Recently, the underlying mechanism of pathogenesis on cifenline succinate-induced hypoglycemia became clear. Cifenline succinate blocks pancreatic ATP-sensitive K⁺ channels via a binding site distinct from the sulphonylurea receptor (5) and stimulates insulin secretion in rats (6). Furthermore, an additive effect of increased insulin sensitivity caused by enalapril (7) may have played a role in the present case.

Therefore, careful attention should be paid to the possible increased risk of dementia caused by chronic hypoglycemia when cifenline succinate, even at a low dose, is given in elderly NIDDM patients with nephropathy.

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Hyperglycemia and Coronary Heart Disease

In her otherwise insightful discussion of hyperglycemia and coronary heart disease (CHD), Dr. Barrett-Connor (1) largely ignores the data from type 1 diabetes studies, limiting her comments to the suggestive, but inconclusive, Diabetes Control and Complications Trial data (2). Because type 1 diabetes is, in its etiology, independent of enhanced cardiovascular risk (being autoimmune in nature), it perhaps provides a clearer source of data to examine such relationships than type 2 diabetes, whose etiology involves a major cardiovascular disease (CVD) risk factor, i.e., insulin resistance (3). Indeed, insulin resistance, and its associated risk factor changes, could explain much of the inconsistent blood sugar relationship with CHD in the nondiabetic state (4).

Two type 1 studies have recently reported relevant data. While the 4-year incidence of each microvascular complication in the Pittsburgh (Epidemiology of Diabetes Complications) study was clearly and strongly related to baseline HbA_{1c}, CHD showed no such relationship (5). A more in-depth analysis of risk factors showed identical baseline HbA_{1c} levels in women with and without subsequent coronary artery disease (CAD), while in men, those with later CAD had a nonsignificantly lower HbA_{1c} (6). Cox proportional hazard modeling confirmed the lack of any association between HbA_{1c} and CAD incidence (6). Interestingly, waist-to-hip ratio, Beck Depression Inventory Score, and physical activity (all possibly related to insulin resis-

tance) were predictors in women.

A large European Study (EURODIAB) also recently reported on the cross-sectional correlates of cardiovascular disease in 3,250 type 1 patients from 16 countries (7). Although 10% of the population had CVD, there was no relationship demonstrable between HbA_{1c} and CVD status in either sex.

Although the pathogenesis of CVD in type 1 diabetes is likely to be complicated and partially linked to renal disease (8), especially in men (6), the type 1 diabetes data further support Barrett-Connor's conclusion that any direct glycemia-CHD association is likely to be weaker than that seen for other major CHD risk factors.

The question that remains, as Barrett-Connor raises, is what are the clinical implications of these observations? In type 1 diabetes, it seems that the mean glycemic exposure experienced at the time of the onset of major complications (proliferative retinopathy, overt nephropathy, and neuropathy) is around 1,000 A_{1c} months (equivalent to having a mean HbA_{1c} of 2% units above normal for 42 years), a level above which the risk of complications increases steeply (9). The American Diabetes Association HbA_{1c} goal (7%) and action levels (8%) (assuming an upper limit normal of 6%) would, therefore, seem very appropriate for type 1 (and probably younger type 2) subjects. If strictly adhered to, these goals should help the majority of such patients avoid advanced microvascular complications at least until their elderly years. If, however, these glycemic exposure calculations from type 1 can be applied to type 2 diabetes (which may be problematic because of the older age of type 2 subjects), tight glycemic control, i.e., <8% HbA_{1c} would appear to be of less importance in type 2 diabetes from both a microvascular (overall life expectancy may not exceed the lifetime risk of complications) and macrovascular (tight glycemic control is of unproven benefit for CHD) viewpoints. The preventive priority should, therefore, be vigorous treatment of other CVD risk factors, notably hypercholesterolemia, which is proven to be of benefit in diabetes (10), as Barrett-Connor recommends.

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Diabetic Mastopathy

A frequent source of confusion with lobular breast carcinoma

The association between mastopathy and type 1 diabetes of long duration has been previously reported (1,2), but this clinical condition is poorly recog-

nized, since breast examination is not routinely performed in young diabetic patients.

We recently observed eight diabetic patients (mean age 41 years [28-64]) after 24.4 ± 8 years of type 1 diabetes who presented clinical palpable breast masses. All these patients suffered from microvascular complications, i.e., retinopathy and/or nephropathy or polyneuropathy. No clear distinction of diabetic mastopathy from malignancy was possible, as indicated by others, using clinical examination and mammography (3). Interestingly, during ultrasonographic examination, characteristic patterns were observed that included the presence of an important acoustic attenuation behind the palpable nodules and sometimes in additional areas of the breast. The presence of breast nodules led to histological analysis in seven of the eight patients, revealing the presence of lymphocytic lobulitis in five patients and dense keloid-like stromal fibrosis in all patients. In one patient, bilateral mastectomy was performed because of the suspicion of an invasive lobular carcinoma. This hypothesis was not confirmed by histological analysis. Lymphocytic infiltrates were composed predominantly of B-cells and were associated with a fibrous stromal reaction containing anti-keratin-negative, but anti-vimentin-positive, epithelioid cells. No recurrence was observed in this patient during follow-up. The presence of lymphocytic infiltrates has been described as the hallmark of this disease (4). This may correspond to an autoimmune reaction against advanced glycosylation end products of the extracellular matrix.

Our clinical observations reinforce the need to examine the breasts of diabetic patients of long duration. However, histological analysis of biopsy specimens and/or lumpectomy appear to be sufficient to make the diagnosis in these young patients, moving them away from mutilating surgery.

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Methylenetetrahydrofolate Reductase Gene, Dietary Folate, NIDDM, and Atherosclerosis in Canadian Oji-Cree

Oji-Cree from Northern Ontario have a high prevalence of NIDDM (1). Like other Canadian aboriginal people, the Oji-Cree historically have had a standardized mortality for cardiovascular disease of ~ 0.60 compared with the general population of Canada (2). While this might have been due to the influence of protective environmental factors, these people could also harbor some genetic resistance to cardiovascular disease. It would thus be of interest to characterize the possible molecular basis of such apparent genetic resistance. The methylenetetrahydrofolate reductase gene (*MTHFR*) encodes the key enzyme in the methylation of homocysteine (3-5). The *MTHFR* C677T mutation causes a temperature-related loss of function (3-5), one consequence of which is the accumulation of plasma homocysteine. Homozygosity for *MTHFR* C677T appears to be a genetic risk factor for cardiovascular disease (3-6), especially when the diet is low in folate. At least one other Canadian aboriginal group, the Inuit of the Northwest Territories, have a markedly reduced prevalence of the *MTHFR* C677T variant compared with the rest of Canada (7).

We hypothesized that the low prevalence of cardiovascular disease in Canadian Oji-Cree would be associated with a low frequency of *MTHFR* C677T. We studied 728 Oji-Cree subjects, representing 72% of