Erythrocyte and Plasma Antioxidant Activity and Subclinical Complications in Young Diabetic Patients

The review article entitled "Oxidative Stress and Diabetic Vascular Complications" accumulates evidence indicating that oxidative stress may play an important role in the etiology of diabetic complications (1). However, there are nearly no studies of diabetic children and adolescents developing subclinical complications. To our knowledge, only Jos et al. (2) have suggested that there is a relationship between retinopathy and decreased glutathione peroxidase activity in young diabetic patients. Very recently, we published a study to verify Jos's data in a larger group of patients and to extend the antioxidant parameters and subclinical complications searched for (3).

Some biological parameters involved in cell defense against oxygen radicals (plasma vitamins C and E, erythrocyte glutathione peroxidase, glutathione reductase, and superoxide dismutase) were measured in single blood samples from 119 diabetic infants, adolescents, and young adults.

Data were studied in relation to residual insulin secretion determined by C-peptide, the level of metabolic control appreciated by glycosylated hemoglobin, lipid abnormalities, and subclinical complications (retinopathy by fluorescein angiography, neuropathy by peroneal motor nerve conduction velocity, and nephropathy by 24-hour microalbuminuria).

There was no change in antioxidant parameters with residual insulin secretion. Patients with poor glycemic control and high plasma lipids had higher levels of plasma vitamin E. Patients with nephropathy had lower plasma vitamin C levels, and those with neuropathy showed lower erythrocyte glutathione peroxidase activity. Plasma vitamin C concentrations and erythrocyte glutathione reductase activities were negatively correlated with the age of the patients and the duration of the disease.

In conclusion, higher transport capacity of vitamin E probably explains the elevated levels of vitamin E that were observed in patients with high lipid levels and long-lasting illness. The lower levels of vitamin C in the presence of nephropathy may be caused by an increased renal excretion of this vitamin. The reduction of glutathione peroxidase, glutathione reductase activities, and vitamin C levels confirms the existence of an oxidative stress in young type I diabetic patients.

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Response to Logwin et al.

In the recent paper by Logwin et al. (1), two publications of ours were misquoted and distorted: their reference 4 refers to our paper published that was in *Diabetic Medicine* (2), not in *Diabetes Care* as printed, and reference 6 never claimed that the release of silicone oil may occur "from insulin-pen injectors." On the contrary, we have shown that silicone oil is indeed released from disposable insulin syringes (3); Logwin et al. seem not to have read our original paper. We hope that Logwin's data have been elaborated more carefully than their report.

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Are Research and Policy Advocacy Two Separate Worlds?

I recently participated in two back-to-back meetings of the American Diabetes Association (ADA), the ADA Research Policy Committee meeting and the Public Policy and Leadership meeting, in March 1996 in Washington, DC. Although these two meetings were sponsored by the same organization and were held in the same location, it struck me how vastly dissimilar they were. In the Research Policy Committee meeting, discussion was restricted predominantly to "basic research" and the internal environment of patients with diabetes, e.g., the GENNID project, the diabetes prevention trials, etc. In contrast, the Public Policy meeting focused almost exclusively on health care policy issues, self-management education and resources, political advocacy, and the legislative environment.

It is to the ADA's credit to realize that research and advocacy activities are essential to the mission of our organization and complementary. I wonder, however, if faster progress would not be made if these two factions of the organization had more interaction. I was struck by the fact that almost all of the scientists left after the committee meetings. The Public Policy meeting was attended almost exclusively by volunteers and staff from the ADA state delegations.

Is this division because research and policy activities are inherently two totally different and incompatible worlds? Or is it

a historical accident of the way American medicine and legislative activity have evolved that makes the two seem strange bedfellows? The current environment of health care reform presents both a challenge and an opportunity to change this fractionated 'separate but equal' approach to research and policy/advocacy activities in the diabetes field.

A lesson can be learned from research on tobacco use, which started by focusing almost exclusively on individual factors. It then moved to consider the combined impact of biological and behavioral factors, such as how to best combine nicotine gum and coping-skills training. This is similar to the current stage of diabetes research. We realize what needs to be done, and that combined bio-behavioral approaches and multidisciplinary collaboration are needed to accomplish our goals. However, tobacco researchers later learned that in order to have a lasting population-wide public-health impact, it was necessary to *a*) become politically active and *b*) conduct research on policy and contextual factors that influence cigarette smoking behavior (1). Recently, tobacco researchers and advocates have achieved important policy changes and documented the effects of smoke-free work and public areas, restrictions on access to tobacco products by youth, and tobacco advertising and tax incentives on smoking behavior.

Is not the diabetes field in a similar position? Can we not achieve greater progress by researching and lobbying for policy and health care reform initiatives such as team-based diabetes care, integrated systems approaches, coverage for diabetes self-management education, etc.? Conversely, advocacy efforts could be stronger if supported by more scientific data (and more scientists) on the efficacy and cost-effectiveness of such proposed changes. Such an integration of policy and research activities would strengthen the ADA, and help it better achieve its stated mission of making a difference in the everyday lives of people who have diabetes.

Policy research can be quite methodologically sophisticated and has been conducted in other health-related areas (although it may require alternatives to the traditional double-blind placebo-controlled randomized trial). There are obvious obstacles to such integration of research and policy, not the least of which is the academic training of physicians and scientists which taught many of us that "research was pure" and should be kept distinct from "dirty" politics and advocacy activities. I suggest, however, that ADA could achieve its strategic objectives more quickly if there was more cross-fertilization and if we were to focus more on the interface between research and policy.

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Mitochondrial Gene Abnormalities and α- and β-Cell Dysfunction

Abnormal secretion of insulin and proinsulin has been reported by Walker et al. (1) in subjects with the 3243bp mutation of mitochondrial DNA (mtDNA). Insulin secretory defects have been implicated in the responsibility for the development of diabetes in patients carrying this mutation (2). However, preserved glucagon secretion has also been implicated as a contributing factor for the development of diabetes (3).

The reported patient had Kearns-Sayre syndrome, a subtype of chronic progressive external ophthalmoplegia (CPEO), which is one of the three principal mitochondrial myopathies. He had had diabetes since he was 8 years old, and insulin treatment resulted in generally stable glycemic control. He died at the age of 21. His pancreatic islets contained predominantly glucagon-containing cells with no evidence of β-cells, and his islet structure was relatively conserved. Preserved pancreatic α-cells suggest that both deficient insulin secretion and preserved glucagon secretion may contribute to the pathogenesis of diabetes in patients with mtDNA abnormalities. However, in another report, all of the five diabetic patients carrying the 3243bp mutation showed >2 SD decreases in glucagon concentration in response to L-arginine infusion, indicating the presence of α- and β-cell dysfunction in these patients (4).

These two observations seem conflicting, but glucagon secretion may be preserved in CPEO but not in patients with the 3243bp mutation. To investigate whether glucagon secretion is preserved in patients with CPEO, we performed an L-arginine infusion test on a patient carrying multiple deletions of mtDNA. We analyzed insulin and glucagon secretion. The 58-year-old male was diagnosed as CPEO at the age of 44. He was 172 cm in height and 56.6 kg in weight (BMI, 19.1 kg/m^2) and was not obese to develop marked insulin resistance. He had normal glucose tolerance, and therefore hyperglycemia or extreme insulin deficiency were unlikely to influence his glucagon secretion. Over a 30-min period, 10% of L-arginine (30 g) was infused, and plasma immunoreactive insulin (IRI) and immunoreactive glucagon (IRG) were measured. Hypersecretion of insulin was observed in the absence of hyperglycemia, though fasting IRI was not elevated. The peak IRI was 750 pmol/l. In contrast to insulin hypersecretion, the subject showed 4.8–8.8 SE decreases in glucagon peak concentration (137 ng/l at 30 min after infusion) below the average values of normal control subjects (Table 1).

Our observations, together with the previous report (4), suggest that, in some patients with mtDNA abnormalities, glucagon secretion is also impaired in the presence or absence of impaired insulin secretion and with the 3243bp mutation or deletions. These findings may be attributable to different proportions of mutant mtDNA in α- or β-cells of the patients' pancreases (heteroplasmy). Another possibility is that these differences are caused by different clinical stages of diabetes in the observed patients. Some time after the destruction of β-cells, α-cell destruction may ensue. But this seems unlikely because α-cells are well preserved in Poulton's subject (3) who had a 13-year duration of IDDM and in our patient with normal glucose tolerance who had impaired glucagon responses.

In conclusion, these findings suggest that heterogeneous destruction of islet cells occurs in different individuals,