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Pancreatic Polypeptide Response to Food and Autonomic Neuropathy in Diabetics

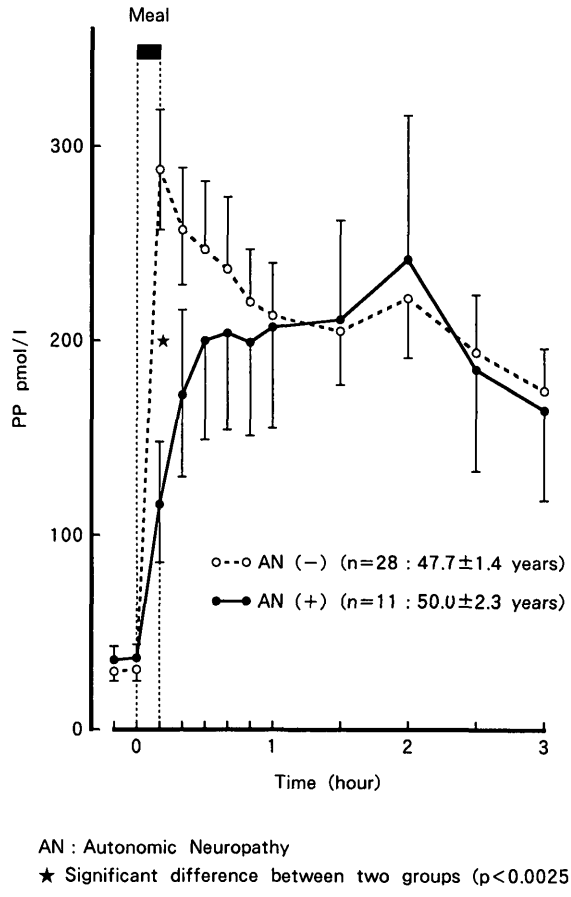

Figure 1—*Impaired PP response to meal in diabetics with autonomic neuropathy.*

Pancreatic polypeptide (PP) is a hormone under vagal control and is assumed to be a sensitive marker for vagal neuropathy (1). Previous studies have demonstrated that impaired secretion of PP serves as a marker for autonomic neuropathy in both diabetic (2,3) and nondiabetic patients. The cephalic phase of PP secretion was studied by insulin-induced hypoglycemia (2) and by sham feeding (3). However, insulin hypoglycemia may induce serious complications such as myocardial infarction in elderly people, and sham feeding is a less consistent stimulus for PP secretion. Since food is a potent stimulus for PP secretion and since autonomic neuropathy may (4) or may not affect the postprandial PP secretion, we examined the PP response to a mixed meal in diabetic patients with or without autonomic neuropathy. Autonomic neuropathy was confirmed by the presence of orthostatic hypotension and/or decreased beat-to-beat variation in heart rate by deep breathing (5). Plasma PP was measured by radioimmunoassay (6).

After loading a mixed meal (640 kcal; 36% carbohydrate, 36% fat, 28% protein), biphasic PP response was observed with the cephalic phase followed by the prolonged gastrointestinal phase, the former of which is totally under vagal control (5). As shown in Fig. 1, impaired PP secretion was observed in its cephalic, but not gastrointestinal, phase in diabetics with autonomic neuropathy. When we examined the ratio of cephalic phase PP secretion to total PP secretion ($IPPR_{40}$/$IPPR_{120}$; IPPR, integrated PP response), the ratio was consistent irrespective of ages from 20 to 50 in normal control subjects (0.37 ± 0.01, $n = 34$). The diabetic subjects without signs of autonomic neuropathy showed the same ratio (0.39 ± 0.07, $n = 56$), whereas diabetic subjects with autonomic neuropathy had a significantly decreased value (0.24 ± 0.02, $n = 13$, $P < 0.0005$).

Our observations demonstrate that meal loading is a safe and sensitive stimulus for detecting vagal neuropathy as far as the cephalic phase of PP secretion is concerned. The early detection of autonomic neuropathy appears to be important for retarding the advancement of the disease and for protecting patients from sudden death assumed to be caused by this complication of diabetes.

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Decrease in Mortality from Diabetic Nephropathy in Pima Indians

Silvers et al. (1) report a decrease in death rate in Pima Indians from diabetic nephropathy when comparing the years 1975–1982 with 1983–1989. They attribute this decline to improvements in renal replacement therapy.

Even with adequate dialysis, the prognosis remains abysmal for end-stage diabetic nephropathy even in younger people (2), and unless a significant number of transplants were performed, it would seem unlikely that improvement in renal replacement therapy would explain a 44.4% decline in the death rate from diabetic nephropathy.

A more likely reason for this improvement would be the use of ACE inhibitors, which were not used for diabetic nephropathy during the first period but became standard of care during the second period. By postponing the development of end-stage renal disease, the increased frequency of ischemic heart disease associated with early diabetic nephropathy (3) and the increasing age of the diabetic subjects would account for the swing toward ischemic heart disease as a cause of death.

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Precocious and Exaggerated Seric IgA Production in Children Affected by IDDM

The role of autoimmunity in the pathogenesis of IDDM is well known (1). Among the initially recognized markers for autoimmune disease is an immunoglobulin deficiency or excess attributed to dysregulated "T-dependent" B-cell activation (2). Conflicting data have been reported on the abnormalities of immunoglobulin secretion in IDDM. Some studies show lower levels of IgG, IgA, and IgM at the onset of disease, followed by a gradual normalization (3). Meanwhile, abnormal serum immunoglobulin concentrations in patients with IDDM have been described by others, mainly as influenced by the degree of glycemic control (4,5). Furthermore, because few data are available in young patients affected by IDDM, we investigated the serum levels of IgA, IgG, and IgM in 92 IDDM patients (57 male, 35 female) who had a duration of the disease that ranged from 0.1 to 6.0 years and in which any concomitant infection was ruled out by physical and biochemical examination. HbA_{1c} levels ranged from 7.8 to 11% (normal value 3.5–6.5%) and fructosamine levels ranged from 245 to 450 μmol/l (normal value <285 μmol/l). The patients were divided into two age-groups based on the pattern of distribution of immunoglobulins in the Italian pediatric population (ages 1–5 years and 5–12 years old, respectively) (6): group A (20 patients, 3.4 ± 0.9 years old) and group B (72 patients, 8.8 ± 2.0 years old). The results (expressed as means ± SD) were compared with a local population of 62 sex- and age-matched healthy control subjects. Comparisons between groups were made with the Mann-Whitney nonparametric test for the abnormally distributed variables.

IgG and IgM levels in patients did not statistically differ from those in control subjects, whereas IgA levels showed a peculiar pattern. Both group A (IgA, 113 ± 61 mg/dl) and group B (178 ± 75 mg/dl) showed higher levels of IgA when compared with their matched control groups (IgA, 73 ± 30, $P < 0.02$; IgA, 121 ± 54, $P < 0.001$, respectively). Moreover, when the IgA values from the diabetic children or the control subjects were expressed as percentages of mean adult values (6), it resulted an exaggerated and precocious pattern of IgA maturation in most IDDM patients (group A 83 ± 45% vs. control subjects 54 ± 22%, $P < 0.02$; group B 131 ± 55% vs. control subjects 95 ± 40%, $P < 0.001$). On the contrary, three patients had a total deficit (<5 mg/dl) and two a partial deficit (<30 mg/dl) of IgA. No correlation was found between IgA levels and the duration of the disease or the parameters of metabolic control.

In our investigation, we found that IgA production may be influenced in one direction or another in IDDM patients. The incidence of selective IgA deficiency is in agreement with that reported by Smith et al. (7). The age of the three patients affected by IgA deficit (12 years) excludes a transient immaturity of production and suggests an HLA-associated defect, as previously described (7). The presence of abnormal serum IgA concen-