Type I diabetes mellitus is known to be associated with many organ-specific autoimmune diseases, including celiac disease, alopecia, and vitiligo. Type I diabetic patients are commonly found to have PICAs at the time of diagnosis (4). In 1976, Bottazo and Doniach (4) subdivided type I diabetic patients into two groups—those with temporary PICA positivity (possibly thought to be due to viral insulitis), called IA, and those with PICA activity of a longer duration and associated autoimmune conditions, called type IB. It is known that PICAs are IgG antibodies that react with cells other than β-cells in the islets of Langerhans and hence the possible basis for the associated autoimmune phenomena in type IB diabetes mellitus (5). Under this classification, our patient had type IB diabetes mellitus, which followed his initial presentation with acquired factor VIII deficiency.

In previously reported cases, acquired factor VIII inhibitors in the serum have preceded the development of other autoimmune disorders, e.g., rheumatoid arthritis (6). We believe this is the first case of acquired hemophilia preceding the onset of type IB diabetes mellitus.

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Assay for Islet Cell Antibodies With Rat Pancreas and Peroxidase Protein A

Measurement of cytoplasmic islet cell antibodies (ICAs) has been used to detect individuals at high risk of developing type I (insulin-dependent) diabetes mellitus (1,2). A major drawback of the ICA assay is the difficulty obtaining human pancreas and the marked interlaboratory variation in measurement of standard sera partly due to the differing sensitivity of human pancreas substrates (3). We have recently shown that Wistar-Furth rat pancreas expresses autoantigens with similar immunocytochemical properties to human pancreas and that this rat tissue can substitute for human pancreas in the ICA assay employing fluorescein isothiocyanate–conjugated protein A (FITC-pA) (4).

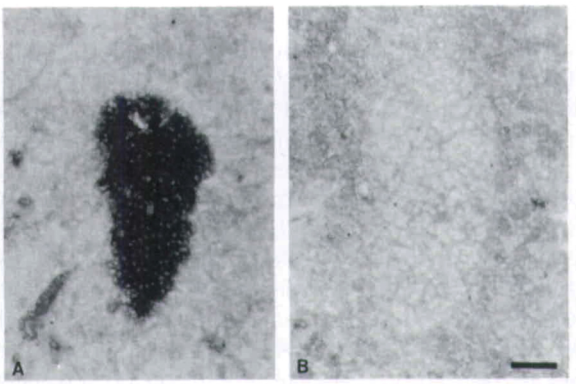

FIG. 1. Islet cell–antibody (ICA) assay with Wistar-Furth rat pancreas and peroxidase-conjugated protein A. Incubation was with ICA-positive (*A*) or control (*B*) serum (*bar* = 50 μm).

To further simplify the ICA assay, we substituted peroxidase-conjugated protein A (perox-pA) for FITC-pA, thus eliminating the need for a fluorescence microscope and enabling slides to be stored indefinitely for future review (Fig. 1). Before assay, sera were absorbed for 12 h with rat liver powder. Sections were incubated with absorbed sera for 60 min, washed, and then incubated with perox-pA (1:100; Boehringer Mannheim, Indianapolis, IN) for 60 min. The chromogenic reaction

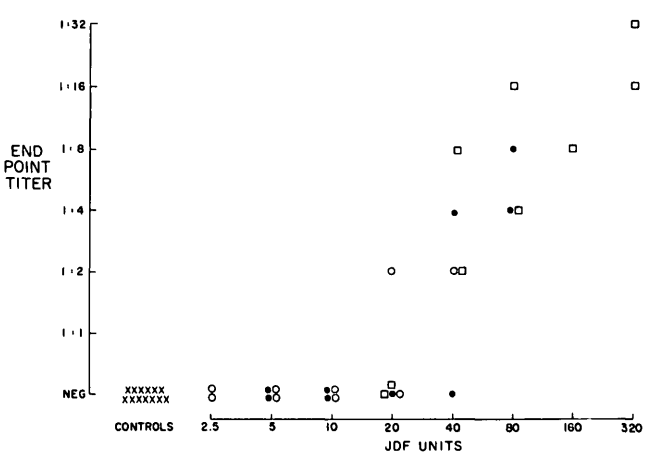

FIG. 2. Results of dilutions of 3 islet cell–antibody (ICA)-positive serum pools and normal control sera converted to Juvenile Diabetes Foundation (JDF) units. ●, JDF standard pool (80 JDF U); ○, insulin-dependent diabetic children pool (40 JDF U); □, high-titer ICA pool (320 JDF U); X, control sera.

was initiated by addition of diaminobenzidine tetrachloride (0.5 mg/ml) in 0.05 M Tris buffer containing 0.001% hydrogen peroxide, and after washing, the slides were mounted with AFT systems mounting medium (Behring Diagnostic, La Jolla, CA). Sera from 17 of 18 high-risk subjects, previously identified to be ICA positive by use of human pancreas and FITC-pA, were also positive by use of Wistar-Furth rat pancreas and perox-pA. Sera from 2 subjects who developed type I diabetes without ICA demonstrable with human pancreas and FITC-pA were also negative with rat pancreas and perox-pA. Sera from 34 control subjects were negative by both assays. We are now using Wistar-Furth rat pancreas and perox-pA for our screening studies to detect subjects at high risk of developing type I diabetes. Such an assay is easier and quicker to evaluate than the standard ICA assay and should be much easier to standardize.

Note added in proof. The rat perox-pA assay was used for blinded duplicate samples provided from the Immunology of Diabetes Workshop Stage III ICA standardization. Results of dilutions of three ICA-positive serum pools and normal control sera converted to Juvenile Diabetes Foundation (JDF) units are shown in Fig. 2. No control sera were positive; all three pools were detected with a minimum detection limit for the assay at 40–80 JDF U.

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Diabetic Ketoalkalosis

We report a case that presented with diabetes mellitus, metabolic alkalosis, and ketonuria. Few such cases have previously been reported (1–5). A 36-yr-old man without preexisting diabetes mellitus was admitted to the hospital in January 1985 with a 4-wk history of weight loss, polyuria, and polydipsia. Abdominal pain and vomiting had been present for 3 days. For several months he had been treated, possibly for vertigo, with a diuretic (chlorthalidone) and betahistine. On admission he was lethargic and very dehydrated, with Kussmaul respiration, and suffered from intense abdominal pain. Temperature was normal, blood pressure was 120/90 mmHg, and pulse was 92 beats/min.

Initial laboratory evaluation included blood glucose 25.8 mM, serum sodium 143 mM (normal value), potassium 3.0 mM (3.5–5.0), and creatinine 143 μM (60–125). Serum chloride was not measured. Blood gas analysis gave standard bicarbonate 21.2 mM (21.3–25.8) and pH 7.54 (7.35–7.42). P_{O_2} was 14.6 kPa (10.0–14.5) and P_{CO_2} 2.4 kPa (4.5–6.0). Urinalysis showed 3+ ketones and 3+ glucose.

Treatment with intravenous saline and potassium was started immediately, and insulin was given in hourly doses of 8 IU. After 24 h, his general condition had improved, blood glucose was normal, the ketones had disappeared, and there was no vomiting or abdominal pain. Standard bicarbonate was 27.2 mM, serum potassium 3.3 mM, and pH 7.46.

After recovery, he was taken off all medication and discharged. His blood glucose remained normal for 5 mo, but it then began to rise. He has since been maintained on a low dose of insulin (12 IU).

We have no definite explanation for the development of alkalosis in this patient. However, betahistine, like histamine, stimulates the secretion of gastric acid, and it is therefore possible that the severe vomiting caused excessive loss of acid, thus counteracting the tendency for a metabolic acidosis to develop. Although the role of thiazides in precipiting diabetes is controversial, another idiosyncrasy might have been present. Chlorthalidone and thiazides have identical side effects, and an impaired glucose tolerance might have developed during treatment, thus precipiting the diabetes. In favor of this theory is the low concentration of plasma potassium on admission, although the severe vomiting would also have contributed to this.

Patients with diabetic ketoalkalosis are severely dehydrated, and they should receive the standard treatment for ketoacidosis, i.e., intravenous saline, supplements of potassium, and hourly insulin. If not carefully investigated for ketonuria with routine blood gas analysis, the condition is easily misdiagnosed.

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