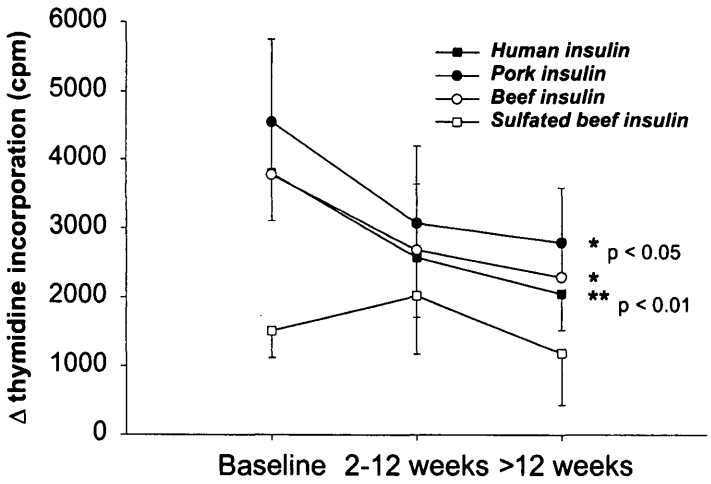

Figure 1—*T-cell proliferative response to different insulins (500 μg/ml) at baseline and after switch to HI.*

with respect to reducing IIR. However, we caution the reader against overinterpretation of these data, based on the small and clinically insignificant increase in insulin dose and the small number of cases in which data were available for analysis. No patient had any local or systemic allergic reaction to or untoward effect from the introduction of HI. The patients' weight did not significantly change during the study (85.3 ± 25.2 kg at baseline vs. 87.4 ± 25.2 kg at >12 weeks, P = NS).

The levels of IgG anti-insulin antibodies observed at baseline in patients treated with SI were similar to those of diabetic patients treated with HI (data not shown). There was a trend toward a decline of anti-insulin IgG levels after the switch from SI to HI (0.200 ± 0.034 OD at baseline vs. 0.166 ± 0.039 OD at 2–12 weeks vs. 0.114 ± 0.031 OD at >12 weeks, P = 0.07). The profile of anti-insulin antibodies detected was not altered after switching to HI. There was a statistically significant decline ($P < 0.05$) in the specific T-cell proliferation response to pork, beef, and HI over time (Fig. 1).

Our results are consistent with the study by Davidson et al. (5) showing a decrease of ^{125}I-labeled insulin binding after the switch to HI in patients taking sulfated beef insulin for IIR. In that study, the only insulin associated with a recurrence of IIR was beef insulin, and the use of SI for >1 year before the switch provided protection against recurrence. Of note, none of our patients used SI for <3 years before changing to HI.

Several of the patients in our study had never used HI before. In accordance with the view that HI is less immunogenic than animal insulin, particularly beef insulin, it is possible that the majority of the patients would never have had clinically significant IIR if HI had been available for use earlier (5). However, even the highly purified HI preparations available today can still lead to immune complications (6). Recently, the insulin analog lispro (Lys [B28], Pro [B29]) has been used successfully to treat severe IIR, although the precise mechanism of its decreased immunogenicity remains uncertain (2). It is our conviction that the universal use of HI as well as the advent of synthetic insulin analogs renders treatment with SI outdated and that patients using SI can be safely switched to these newer forms of insulin treatment.

Since the completion of our study, Novo Nordisk has discontinued the production of SI, the last lot having expired in September 1997. With the discontinuation of SI production, another page in the history of diabetes treatment has been turned.

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Is Diabetic Ketoacidosis a Cause of Meningeal Syndrome?

Case report

Infectious agents have to be ruled out when a patient presents with meningeal syndrome. However, several entities can cause aseptic meningitis (1), and fever per se can produce meningeal irritation (2). We report a patient presenting with diabetic ketoacidosis (DKA) and meningeal syndrome, which resolved with metabolic abnormalities.

A 32-year-old woman admitted in the emergency room presented with severe headache for 5 days and vomiting in the last 48 h. In addition to diabetes diagnosed when she was 18 years old, she had type II dyslipemia, idiopathic hirsutism, and hypertension, which was treated with enalapril and spironolactone. She had no diabetic complications and had received insulin since diagnosis of her diabetes. In March 1996, C-peptide was 1,009 pmol/l when measured 6 min after administration of 1 mg glucagon. β-cell function was considered to be acceptable, insulin therapy was withdrawn, and a follow-up visit was scheduled in 3 weeks. The patient did not perform regular blood glucose monitoring, did not show up at the scheduled visit, and presented with DKA 4 months later. On arrival, she was dehydrated and had nuchal rigidity and no fever. Biochemical workup revealed a blood glucose level of 15.5 mmol/l, strong ketonuria, pH 7.17, plasma bicarbonate level of 12.5 mmol/l, osmolality of 340 mOsm/kg, cholesterol level of 53.77 mmol/l, and triglyceride level of 38.1 mmol/l. Normal results were found on urine culture and thorax X-ray examination. Lumbar puncture was performed, and colorless fluid was obtained (2 cells per milliliter, 12.1 mmol/l glucose, 800 mg/l protein, 0.4 U/l adenosine deaminase). The DKA was treated with intravenous fluids and regular insulin infusion, and metabolic improvement ensued. Blood glucose was <12 mmol/l from 24 h onward, venous plasma had pH 7.31 and normal osmolality at 48 h; cholesterol level was 32.64 mmol/l, and triglyceride level was 13.98 mmol/l by the 6th day. Nuchal rigidity was absent by the 3rd day, and headache had resolved by the 7th day. Results of cerebrospinal fluid (CSF) Gram staining, bacterial and viral cultures, and polymerase chain reaction for herpesvirus were negative.

This patient's diabetes was NIDDM in origin (hyperlipidemia, hypertension, significant β-cell function, DKA development 4 months after stopping insulin). She presented with DKA and meningeal syndrome, which resolved after improvement of glycemia, acidosis, and lipid profile. Headache, neck stiffness, and high CSF protein indicate meningeal irritation, although diabetes with (and occasionally without) polyneuropathy can be associated with high CSF protein (3). No cause of meningeal syndrome could be found, and the temporal association with DKA suggests that the DKA was responsible. Improvement of several parameters (pH, plasma bicarbonate, plasma glucose, osmolality, lipids) antedated or coincided with the resolution of meningeal syndrome. We have not found a similar case in a MEDLINE search (DM + meningeal syndrome/ acidosis/ CSF/ aseptic meningitis and meningeal syndrome + acidosis/ chylomicronemia). Acidosis, dehydration, and chylomicronemia syndrome can produce neurologic disturbances, but none of these conditions has been associated with meningeal syndrome (4–6). Pericarditis and pleuritis have been reported in patients with hyperglycemic decompensations, and they have been associated with dehydration, acidosis, and biochemical disturbances (7–9), but no single abnormality was common to all cases.

We suggest that DKA and meningeal syndrome were causally related in this patient, although we cannot specify the metabolic abnormality that was responsible.

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Organospecific Lymph Node Enlargement in Autoimmune Polyglandular Syndrome

We describe here the enlargement of lymph nodes around the pancreas and thyroid gland in two sisters who were followed for 8 years during childhood and who had developed overt type 1 diabetes, vitiligo, hypothyroidism (polyendocrine syndrome type III [1]), and multiple autoantibodies against endocrine organs. Two daughters of a mother with type 1 diabetes were tested for autoantibodies to islet cells in the context of a German family screening program for prediction of type 1 diabetes in relatives (2). Offspring C1 developed antibodies to insulin (IAA) at 9 months of age, followed by antibodies to GAD65 (GADA) at 22 months and antibodies to the protein tyrosine phosphatase IA-2 (IA2A) and islet cells (ICA) by 3 years of age (Table 1). At the age of 7 years, she developed clinical type 1 diabetes, and 4 months later, being positive for peroxidase (TPO) and thyroglobulin (TG) antibodies, she required thyroxin substitution. Adrenal antibodies (AA) were negative. Her older sister (C2) presented with IAA, GADA, and ICA at 2 years of age, and overt type 1 diabetes was diagnosed at the age of 4 years. Shortly after diabetes manifestation, she developed vitiligo and was found to have TPO, TG, and anti-parietal cell antibodies (PCA). Overt hypothyroidism was diagnosed at the age of 8 years. The HLA type of offspring C1 was uncommon for polyendocrine diseases, whereas offspring C2 exhibited the characteristic susceptibility haplotype (C1: A2/26, B39/60, DR11/2, DQA1*0501/0102, DQB1*0301/0502; C2: A1/1, B8/14, DR3/3, DQA1*0501/0501, DQB1*0201/ 0201) (3). Figure 1 shows an ultrasound examination of the pancreas of offspring C1 at 7 years of age, when type 1 diabetes and hypothyroidism were diag-