During the next 10 mo on this regimen, her blood glucose improved (approximately half above and half below 11 mM). She regained 15 lb. Because her antibody values remained elevated (13 mU/ml), she was started on an insulin pump with sulfated beef regular insulin. The overnight hypoglycemic reactions became even less frequent, and the insulin-binding capacity of her antibodies decreased to values seen in most patients who form antibodies to beef or pork insulin (5 mU/ml). The patient's hypoglycemic reactions were much less frequent, occurring only once or twice a week and almost always overnight. Her response to sulfated beef regular insulin was much more rapid than to human regular insulin with a more normal peak response to sulfated beef insulin given either subcutaneously (2 h) or intravenously (50 min). This clinical response to sulfated beef insulin was consistent with in vitro studies evaluating the relative avidity of her antibodies for beef, pork, human, and sulfated beef insulin (4). The relative avidities were: beef, 1.00; pork, 0.49; human, 0.42; and sulfated beef, 0.09.

Although the patient was receiving only sulfated beef insulin via an insuln infusion pump, her antibody levels again rose to levels consistent with immune-mediated insulin resistance (16 mU/ml). This may have been due to the fact that the epitope for the stimulation of antibody formation is not altered by sulfation. However, the patient's favorable clinical course did not change. She discontinued the pump several months later and is currently taking sulfated beef regular insulin before each meal and at ~0400 each morning. Her hypoglycemic episodes have decreased markedly, occurring approximately once per week.

At least four other similar patients have been reported (5–8). All had frequent and profound hypoglycemia and markedly increased insulin-binding antibodies. Our patient fulfilled the criteria for brittle diabetes (1). Although she did not have clinical insulin resistance (>200 U/day), her insulin-antibody levels were consistent with values associated with immune-mediated insulin resistance. Although one patient cannot constitute proof, it seems likely that the increased binding capacity of her circulating antibody caused her brittle diabetes by interfering with a predictable pattern of insulin action after injection. Instead, insulin was probably bound by her antibodies and released at unpredictable times, accounting for her rapid shifts between hyperglycemia and hypoglycemia. To circumvent this problem, the patient was given sulfated regular beef insulin. Sulfation of insulin masks the site recognized by the antibody but does not eliminate the biological activity of insulin. Therefore, as we had expected, sulfated beef insulin was less avidly bound to her antibodies, and her brittle diabetes rapidly improved despite the fact that the antibody values, although initially decreased, eventually remained elevated. In conclusion, recurring, unanticipated, and clinically unexplainable hypoglycemia can occasionally be due to very high levels of insulin antibodies occurring in patients who do not require very large doses of insulin. If this is the case, successful treatment is possible with sulfated beef insulin.

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Postpartum Progression of Diabetic Retinopathy

We would like to highlight the difficulties in the management of diabetic retinopathy through report of a patient whose rapidly progressing retinopathy was not well controlled during pregnancy and progressed postpartum despite laser treatment.

The patient was a 26-yr-old white woman who had had insulin-dependent diabetes for 16 yr. For 7 yr she had had intermittent proteinuria, which had persisted for 5 yr. She smoked 15–20 cigarettes/day. Her diabetes was managed with Actrapid 70/30 Penfill (Novo, Copenhagen) three times daily and Ultratard (Novo) at night.

At 7 wk gestation, she had bilateral spoke opacities in her lenses and two hemorrhages on her right fundus. Blood pressure was 140/80 mmHg, urinary protein excretion was 2.3 g/24 h and creatinine clearance 51 ml/min.

At 17 wk gestation, the patient complained of blurred vision and was found to have severe preproliferative

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retinopathy with cystoid macular edema, cotton-wool spots, and hemorrhages. Visual acuity was 20/30 (right eye) and 20/60 (left eye). She was treated initially with furosemide for the retinal edema, but visual acuity continued to deteriorate and was 20/60 (right eye) and 20/80 (left eye) at 19 wk gestation. Panretinal photocoagulation was performed with 2000 laser burns to each eye, and there was some improvement in visual acuity to 20/30 in both eyes by 27 wk gestation.

At 28 wk gestation, the patient developed a marked increase in peripheral edema associated with hypertension (160/110 mmHg) and progression of nephropathy. Blood pressure was controlled aggressively with antihypertensive agents, but there was a deterioration in her retinopathy with the development of extensive proliferative lesions, for which she received further laser treatment in the left eye at 30 wk gestation.

The patient gave birth to a healthy child at 33 wk gestation by lower-segment cesarean section, at which point visual acuity was 20/80 (right eye) and 20/60 (left eye). Urinary protein secretion was now 5.6 g/24 h, creatinine clearance 41 ml/min, plasma creatinine 152 M, and albumin 24 g/L.

Postpartum, her retinopathy progressed in both eyes with further neovascularization, fibrosis, and preretinal hemorrhages on the right eye despite additional photocoagulation. She received a total of 4000 laser burns to the left eye and 3800 laser burns to the right eye.

Eight months postpartum, the patient detached her right macula, necessitating vitreoretinal surgery. Her subsequent visual acuity was 20/80 (right eye) and 20/30 (left eye), and retinopathy was now quiescent. Metabolic control during and after pregnancy was excellent, with HbA_{1c} values all within the normal range.

This case history illustrates a type of severe retinopathy shown to regress postpartum in several studies (2–4). However, in this case, the retinopathy was only just contained by laser treatment during pregnancy, and in contrast to the expected course, it continued to deteriorate after delivery. Some researchers suggest a more judicious use of laser treatment in the pregnant woman with retinopathy and demonstrate a high rate of regression of the type of lesions seen in our patient toward the end of pregnancy and postpartum (3,4).

In 1982, Moloney and Drury (2) reported progressive changes in background retinopathy in pregnant diabetic women that completely regressed to control levels 6 mo after delivery. New lesions occurring in a group of women with proliferative retinopathy also regressed, although not back to control values. Particular mention was made of a marked increase of streak and blob hemorrhages and soft exudates that completely resolved in the postpartum period.

Ohrt (3) noted increased soft exudates, hemorrhages, and retinal edema in 23 of 100 pregnancies, all of which regressed postpartum. In contrast, although regression occurred in the cases of new proliferations, this was not nearly as complete.

The preliminary report from a prospective study in Denmark supports these findings (4). Retinopathy in women at the onset of pregnancy deteriorated in 50% of the cases, but postpartum regression was common. Also, the development of proliferations was uncommon and also regressed by 6 mo postpartum. It was suggested that treatment with photocoagulation during pregnancy be restricted and close ophthalmological supervision be undertaken by a person familiar with the spontaneous course of retinopathy during diabetic pregnancy.

Our case showed a poor response to photocoagulation during the pregnancy with further deterioration postpartum. Although evidence suggests that a more limited use of laser treatment in such cases might be a reasonable option, there are not yet any methods of predicting which patients will do well or means of selecting those who warrant more aggressive treatment. Until then, withholding laser treatment must be attendant with anxiety.

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Hypoglycemia After Successful Pancreas Transplantation in Type I Diabetic Patients

One purported advantage of successful pancreas allograft transplantation over intensive insulin therapy in insulin-dependent (type I) diabetic patients is the achievement of physiological normoglycemia with consequent improvement in quality of life and potential stabilization of diabetic complications. Hypoglycemia, a very frequent occurrence in patients receiving an intensive insulin regimen, has not been reported after successful pancreas transplantation in type I diabetic recipients. We were therefore surprised to observe recurrent fasting and postprandial hypoglycemia (serum glucose <2.8 mM) in a subset of our pancreas transplant recipients. To examine this unexpected finding, we compared serum glucose, insulin, and C-peptide levels

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