(n = 21) and subjects with NIDDM (n = 135) were 6.81 ± 1.65 and 3.79 ± 2.20 mg · kg^{-1} · min^{-1} (mean ± SD), respectively (T.W. et al., unpublished observations). The GIR values obtained for subjects 1, 3, 4, and 5 were in the normal range, indicating normal insulin sensitivity. However, the GIR value in subject 2 was in the range found in subjects with the common late-onset form of NIDDM, indicating moderate insulin resistance. Subject 2 was tested on two occasions separated by 8 months with similar results, 2.90 and 2.99 mg · kg^{-1} · min^{-1}, respectively, although at the time of retesting she showed improvement in muscle strength and HbA_{1c} levels (Table 1).

These data, which demonstrate insulin resistance in only one of five subjects with the A-to-G mutation in the mitochondrial $tRNA^{Leu(UUR)}$ gene, are consistent with the conclusion that insulin resistance is a minor component in the pathophysiology of the diabetic syndrome in these subjects. The cause of the insulin resistance is not known. It does not appear to be secondary to the presence of hyperglycemia since the degree of insulin resistance in subject 2 was constant despite a fall in the HbA_{1c} levels from 9.9 to 8.3%. Furthermore, subject 3 showed normal insulin sensitivity with HbA_{1c} value of 8.2%, which is very similar to that seen in subject 2 at the time of the second study. It is also unlikely to be related to mitochondrial myopathy, since subject 5 had MELAS and normal insulin sensitivity, or serum lactate/pyruvate levels, since subject 4 had higher levels of both these metabolites and no impairment of insulin-stimulated glucose uptake. The moderate insulin resistance noted in subject 2 could reflect normal population variation with this subject having decreased insulin sensitivity for reasons other than the presence of a mitochondrial mutation. Prospective studies of these and other subjects with mitochondrial mutations are necessary to address this important issue. In contrast, all five subjects tested demonstrated inappropriately low insulin secretory responses to glucose in the face of hyperglycemia consistent with the primacy of the β-cell lesion in the pathophysiology of the hyperglycemia present in this condition.

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Five Cases of Hyperthyroidism in Type I Diabetic Patients Treated With Intraperitoneal Insulin Infusion

Intraperitoneal insulin infusion (IPII) using programmable implantable devices has been shown to be feasible and safe since it decreases patients' HbA_{1c} levels while reducing their risk of severe hypoglycemia (1).

From 1989 to early 1994, 62 C-peptide–negative type I diabetic patients were implanted with a pump in our center; the pumps use the Genapol-stabilized Hoescht 21PH insulin (Hoechst. AG). Ultrasensitive thyrotropin (TSH) serum concentrations (0.15–4.5 μU/ml) were performed every 6 months using an immunochemiluminometric assay (Beri-Lux). Anti-insulin antibodies (AIAs) were assessed every 3 months (n < 1.5%) by radioimmunoassay. Antimicrosomal antibodies (n < 100 U/ml), TSH-receptor antibodies (n < 10 U/ml) and free T_4 levels (n = 9–20 pg/ml) were assessed when needed.

Table 1—*Biological parameters of four patients*

	Patients			
	1	2	3	4
TSH (μU/ml)	0.01	0.001	0.012	0.05
free T_4 (pg/ml)	37	26.3	43	25
Antimicrosomal AB (U/ml)	210	2,115	2,880	2,480
Anti-TSH AB (U/ml)	9.7	54	10	5

AB, antibodies.

A dramatic increase in AIA titers was described (2) during IPII therapy in ~50% of the patients whose AIA titers increase to >15%.

During this period of time (229 patient-years), there were five cases of clinical hyperthyroidism. Four patients, two men ages 63 and 52 and two women ages 39 and 28 with no history of thyroid disease presented typical symptoms of hyperthyroidism after 4–30 months of IPII. Biological parameters are summarized in Table 1.

Technetium thyroid scans performed in three patients showed no nodule. The four echograms showed homogeneous or slightly heterogeneous glands. The fourth patient, now spontaneously euthyroid, presented a transient hypothyroidism episode (TSH: 10 μU/ml) 18 months after thyrotoxicosis.

The fifth patient, a 35-year-old man, presented hyperthyroidism in 1989 during IPII therapy with porcine insulin using a catheter attached to an external pump. TSH level was 0.05 μU/ml, free T_4 level was 25 pg/ml, and antimicrosomal antibody titer was 11,136 U/ml; the technetium scan showed an homogeneous uptake. He had stable low TSH levels (0.05 μU/ml) with normal free T_4 and free T_3 levels since 1986. After medical treatment, he was implanted with normal TSH and free T_4 levels. Three months after implantation, free T_4 rose to 23 pg/ml. Technetium scan and echogram results were the same as for the four other patients. His antimicrosomal antibody level was 4,560 U/ml, and antibody count against TSH was 6.3 U/ml. The patient recovered after 1 year of carbimazole therapy. After 2 years, the same type of hyperthyroidism was diagnosed again.

Compared with the data from Betterle et al. (3), the frequency of hyperthyroidism is very high in our population (8%). The five cases reported here are in favor of autoimmune hyperthyroidism because of the high levels of antimicrosomal antibodies and the homogeneous uptake at the technetium scan. No patient had an allele DR5 or B28DR3 in the major histocompatibility complex system. Three of these five patients had AIA levels >15%.

TSH in the 57 other patients remains in the normal range since implantation. IPII activates the immune system as shown by the increase in AIA levels and thus may favor the apparition of a thyroid autoimmune disease in type I diabetic patients whose genetic background is more susceptible to autoimmunity.

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