Is Insulin the Only Treatment for Obese NIDDM Patients Poorly Controlled By Oral Hypoglycemic Agents?[b]

To the editor:

In their paper on 1-yr insulin treatment of obese and nonobese NIDDM patients poorly controlled by oral hypoglycemic agents, Yki-Jarvinen *et al.* (1) have shown that nonobese patients display a constant improvement of metabolic control, while obese patients, after an initial improvement have a deterioration of glucose metabolism and a greater gain in body weight than nonobese patients, suggesting that this deterioration is linked to a disproportionate increase in insulin requirement, due to a greater insulin resistance; they conclude that weight gain in obese patients is harmful, as it is associated with increases in blood pressure and low density lipoprotein cholesterol. Previous studies had indicated that insulin treatment improves glucose metabolism for a limited period of time and that insulin induces a higher increase in body weight and in blood pressure in obese than in nonobese patients (2).

The issue raised by Yki-Jarvinen *et al.* is of great importance; in fact, the frequency of insulin-treated NIDDM patients is exceptionally high, as half of all insulin-treated patients (IDDM plus NIDDM) were originally diagnosed as NIDDM (3). This has led to the general assumption that the majority of NIDDM patients are eventually treated with insulin. However, the few available studies on the role of body weight in NIDDM do not support this assumption; the pathogenesis of NIDDM is different in obese and in nonobese NIDDM, being mainly caused in the former by increased insulin resistance, and in the latter by decreased insulin release (4, 5). Insulin requirement is more frequent in nonobese than in obese patients, and is due, in nonobese patients, to a further reduction of insulin release, but this does not seem to apply to obese patients (2, 6). In addition, insulin treatment is irreversible in nonobese patients (2). In contrast, progression to insulin is avoidable in obese patients by education (7), and insulin-treated obese patients can be transferred back to oral agents when body weight is reduced (2). Hyperglycemia is a risk factor for micro- and macroangiopathy in NIDDM (8); however, one should consider the value of insulin treatment in the prevention of diabetic complications; similar to that reported for IDDM in the DCCT study (9), intensive insulin regimens delayed the appearance and progression of microangiopathy in lean NIDDM patients (10); in contrast, cardiovascular mortality was increased, not decreased, in obese patients treated with intensive insulin regimens (11). This raises the issue of improving glucose metabolism while avoiding insulin resistance, especially in obese patients. Insulin together with triglycerides induces insulin resistance and releases endothelin-1, a potent vasoconstrictor peptide (12), and this is only one of the possible reasons why hyperinsulinemia and insulin resistance *per se* represent a major risk factor for ischemic heart disease in diabetic (13) and in nondiabetic individuals (14). Therefore, while combined treatment (oral agents plus insulin) or insulin alone appear adequate for nonobese NIDDM patients poorly controlled with oral agents, it does not seem justified to treat obese NIDDM patients with high doses of insulin simply to compensate hyperglycemia; reduction of body weight should be obtained whenever possible. Alternatively, the use of acarbose (15), metformin (16), and benfluorex (17) has been shown to improve the effect of insulin and to allow reduction of insulin doses. For the massively obese patients, gastric by-pass has been shown to be a long-standing solution to NIDDM and to hypertension (18).

Antonio E. Pontiroli
Istituto Scientifico San Raffaele and Università degli Studi
Milano, Italy 20132

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Further Evidence for a Dominant Form of Familial Persistent Hyperinsulinemic Hypoglycemia of Infancy: A Family with Documented Hyperinsulinemia in Two Generations[c]

To the editor:

Until recently, the familial form of persistent hyperinsulinemic hypoglycemia of infancy (PHHI) was considered to be inherited as an autosomal recessive trait (1). Linkage analysis of this familial form has resulted in the detection of two mutated genes located on chromosome 11p14-15.1. Both of them, SUR1, the gene for a sulfonylurea receptor (2) and Kir6.2 (3) encode subunits of a potassium channel. In the JCEM, Kukuvitis *et al.* (4) recently reported a French-Canadian kindred, in which PHHI is inherited in an autosomal dominant manner and is linked neither to the SUR1 nor to the Kir6.2 locus. Over three generations, hypoglycemia with severe sequelae or early death was documented. In two of five affected first cousins in generation III, documented hypoglycemia could be associated with hyperinsulinemia. As consanguinity between the parents was ruled out, this pedigree provides evidence for the existence of an autosomal dominant form of PHHI.

Because the authors were not able to demonstrate hyperinsulinism in the generations II and I, we describe a German family with documented hyperinsulinism in two generations. Our index patient is the second child of nonconsanguineous German parents. The girl was born at term with a birth weight of 2800 g. During the newborn period tetralogy of Fallot was diagnosed. At that time no hypoglycemia was noted. At the

[b] Received February 24, 1998. Address correspondence to: Antonio E. Pontiroli, M.D., Istituto Scientifico San Raffaele and Università degli Studi, Via Olgettina 60, 20132 Milano, Italy.

[c] Received March 16, 1998. Address correspondence to: Markus Hufnagel, M.D., Department of Pediatrics, University Children's Hospital Kiel, Schwanenweg 20, 24105 Kiel, Germany.

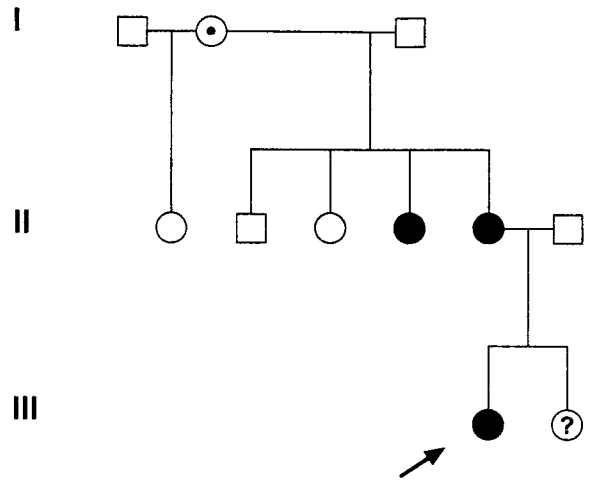

FIG. 1. Pedigree of the family with dominant form of PHHI. The index patient is indicated by the *arrow*. *Squares* denote male family members, *circles* female family members, *solid symbols* subjects with documented hyperinsulinism, and *dot symbols* subjects with documented hypoglycemia.

age of 15 months, the patient had a first hypoglycemic seizure (plasma glucose 36 mg/dL). Since the age of 19 months hypoketotic hypoglycemia was repeatedly documented in the fasted and in the fed state. During hypoglycemic episodes, plasma insulin concentration was repeatedly found to be elevated up to a value of 16.9 μU/mL. Consecutively, the insulin (μU/mL)/glucose (mg/dL) ratio was elevated (0.54, normal <0.4). An oral provocation test with leucine (150 mg/kg) resulted in severe hypoglycemia from inappropriately high insulin secretion (insulin/glucose ratio up to 0.9). Other causes of hypoglycemia were excluded (normal values for plasma cortisol, growth hormone, lactate, ammonia, amino acids, and urine organic acids). On ultrasound no focal lesion in the pancreas was detected.

The child's mentally retarded mother and her sister are also suffering from PHHI (see pedigree in Fig. 1). The mother had her first symptoms when she was 11 months old, the mother's sister at the age of 6 months. In both cases hyperinsulinemia could be documented. During hypoglycemia plasma insulin concentrations were increased to values of 71 μU/mL and 43 μU/mL, respectively, resulting in insulin/glucose ratios of 6.5 and 3.9 respectively. Three other siblings of the mother are not affected. The mother's mother also had documented hypoglycemia. Further examinations, however, were not performed on her. We have no information on our patient's younger sister, who was adopted by another family soon after birth.

Our case report for the first time describes hyperinsulinemic hypoglycemia in two consecutive generations. It thus provides further evidence for the existence of a dominant form of persistent hyperinsulinemic hypoglycemia and underlines the clinical heterogeneity of this condition. Further genes are most likely involved in the regulation of insulin secretion and, only recently, a heterocygous (activating) mutation within the glucokinase gene has been reported to result in familial hyperinsulinism (5). Molecular genetic investigations in our family are under way.

Markus Hufnagel, Dirk Eichmann, Jürgen Stieh, and René Santer
University Children's Hospital Kiel
Schwanenweg 20, 24105 Kiel, Germany

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Comment on Human Fetal Pituitary Expresses Functional GHRP Receptors[d]

To the editor:

In the January issue of *The Journal of Clinical Endocrinology and Metabolism*, a paper was published by Shimon *et al.* (1) on the direct effects of GHRP on human pituitary GH secretion, in which it was stated ". . .whereas **all** *in vitro* studies have employed rodent, bovine, or ovine pituitary cells" (last paragraph of *Introduction*) and "we have used a unique model of human pituitary cells in primary culture to show, **for the first time**, direct effects of GHRP on human pituitary GH secretion" (*Discussion*, 3rd paragraph). Whilst we agree that this is the first study to examine the direct effects of GHRP on normal human fetal pituitary cells, there have certainly been a number of previously published studies on human pituitary somatotroph responsiveness to GHRP *in vitro*, including two in Endocrine Society journals (2, 3). Credit should also be given to Bressin-Bepoldin *et al.* (4) and Lei *et al.* (5), who both reported on the intracellular mechanism of action of GHRP on human somatotrophs in culture.

We appreciate how difficult it is for journals and authors to be aware of all previous publications in a particular area but feel, in this case, that the statements by Shimon *et al.* unfairly dilute the significant contribution made by other groups in the very important area of synthetic growth hormone secretagogues.

Eric Adams and Michael Buchfelder
Neurochirurgische Klinik der Universität Erlangen-Nürnberg
Erlangen, Germany 91054

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Human Fetal Pituitary Expresses Functional GHRP Receptors—Authors' Response[e]

To the editor:

We appreciate the comments of Drs. Adams and Buchfelder in the letter above. As we wrote, the aim of our study was to study GHRP receptor expression in normal pituitary cells. Despite previous reports

[d] Received March 18, 1998. Address correspondence to: Eric Adams, Ph.D., Neuroendokrinologisches Labor, Neurochirurgische Klinik der Universität Erlangen-Nürnberg, Schwabachanlage 6, Erlangen, Germany 91054.

[e] Received March 26, 1998. Address correspondence to: Shlomo Melmed, Division of Endocrinology and Metabolism, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Suite B-131, Los Angeles, California 90048.