Table 1—*SI and insulin secretion in prediabetic subjects*

Patient	Age (yr)	Body mass index (kg/m^2)	SI (10^{-4} min · MU^{-1} · ml^{-1})	FPIR (pM)	JDF titer
1	15	23.0	1.30	1536	80
2	26	26.0	1.41	552	320
3	18	29.3	1.45	918	80
4	16	26.1	3.66	678	320
5	12	16.9	5.49	1086	160
6	39	23.4	5.80	528	160
7	6	18.6	10.9	396	40

Diabetes camp provides an ideal setting for sampling of first-degree relatives of children with IDDM. We encourage the entire family to have serum obtained yearly for the measurement of ICA. We have identified 15 ICA^+ individuals among the 475 first-degree relatives sampled. Seven have been tested further to determine their ability to secrete insulin and their sensitivity to insulin.

Seven ICA^+ individuals were studied with the modified minimal-model FSIGT (1,2). This method involves the administration of 0.3 g/kg glucose at time zero and then 0.03 U/kg regular insulin at 20 min. With insulin and glucose concentration from FSIGT, we can calculate SI (2) and FPIR (1-min insulin plus 3-min insulin minus baseline insulin; 3). Results are shown in Table 1.

The subjects' JDF titers range from 40 to 320 and their SI values from 1.41 to 10.9 (a higher SI indicates increased sensitivity). Normal SI values in children are from 3 to 11 and in adults from 2 to 8. No correlations between FPIR and SI or JDF titer were apparent. All FPIR values except one were >402 pM, a level below which is considered predictive of clinical diabetes (3). In subject no. 7, a normal-sized 6-yr-old boy, low FPIR may be caused by increased SI (SI = 10.9), which diminished insulin need. Subject no. 2 had a low SI, high JDF titer, and normal FPIR. Both subjects will be monitored closely, and should the FPIR decline, they will be referred for immunotherapy.

The FSIGT provides a reliable, fairly easy method of determining SI and insulin secretory capacity. In individuals who are ICA^+, insulin resistance may be an additional risk factor for further β-cell damage and progression to clinical diabetes. Our ICA^+ subjects demonstrated a wide range of values for SI, and none were clearly prediabetic. Longitudinal follow-up in these subjects will be important to determine the possible role of SI in the pathogenesis of IDDM.

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IDDM, insulin-dependent diabetes mellitus; ICA, islet cell antibody; FSIGT, frequent-sampling intravenous glucose tolerance test; FPIR, first-phase insulin release; SI, insulin sensitivity; JDF, Juvinile Diabetes Foundation.

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Discussing the Role of Glucagonlike Peptide-I

We would like to comment on an article that appeared in the February issue of *Diabetes Care* by Nathan, Schreiber, Fogel, Mojsov, and Habener. The article deals with the insulinotropic action of glucagonlike peptide-I-(7–37) in diabetic and nondiabetic subjects.

However, because of a significant lack of reference to published work from European groups, some of the conclusions presented appear inaccurate and misleading:

1. In humans, glucagonlike peptide-I-(7–37) does not seem to be a naturally occurring intestinal peptide as postulated. The naturally occurring intestinal peptide is glucagonlike peptide-1 (7–36 amide) (or proglucagon 78–107 amide) as has been shown by Ørskov et al. (*J Biol Chem*, 264:12826, 1989) and Kreymann et al. (Lancet 2:1300, 1987).

2. The first to report on the insulinotropic action of glucagonlike peptide-I (7–36 amide) were Ørskov and Holst in 1986 (*Diabetologia* 29: A549). Neither this communication nor the subsequent full paper (Holst et al., FEBS Lett 211:169, 1987) (which appeared earlier than the quoted paper on "insuli-

notropin" [Mojsov et al. *J Clin Invest*, 79:616]) are cited.

3. GLP-1 7–37 is suggested as a potential therapeutic agent for the treatment of type II diabetes. The true natural peptide GLP-1 (7–36 amide) stimulates insulin secretion with at least equal potency and, in addition, inhibits glucagon secretion, as reported by Kreymann et al. (*Lancet* 2:1300, 1987), Ørskov et al. (*Endocrinology* 123:2009, 1988), and Komatsu et al. (*Diabetes* 38:902, 1989), whereas GLP-1 7–37, at least in rats, has no effect on glucagon secretion (Weir et al. *Diabetes* 38:338, 1989). Thus, GLP-1 7–36 amide, the naturally occurring peptide, is a better candidate as a therapeutic agent for the treatment of type II diabetes.

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Reply

The comments by Holst and Ørskov on our report of the insulinotropic actions of glucagonlike peptide-I (7–37) in diabetic and nondiabetic subjects raise some interesting and important points (1). Because of the preliminary stage of our studies, the editors requested that our report be condensed. This necessitated an abbreviation of the reference list, which is quite extensive considering the many publications from United States, European, and Japanese investigators (reviewed in Fehmann and Habener 2). In our view, whether or not one or the other of the isoforms of glucagonlike peptide-I (7–37) or (7–36) amide is the predominant form of the peptide, or whether either one has unique biological actions, remains to be proven. In the rat intestine, both isoforms are expressed, and all-or-none expression of one or the other of the isoforms in the human intestine is not yet established (3). Regardless of the levels of expression of the two isopeptides, both appear to have equivalent potencies of insulinotropic actions.

The issue of whether or not glucagonlike peptide-I suppresses glucagon secretion by a direct action on α-cells or indirectly by stimulating insulin release, which in turn exerts a paracrine suppression of glucagon is unsettled (4). There is no a priori reason to believe that the two isoforms of glucagonlike peptide-I would differ in their actions, either direct or indirect, on glucagon-producing α-cells.

We are in complete agreement with Drs. Holst and Ørskov that glucagonlike peptide-I appears to be a potentially novel therapeutic agent for the treatment of NIDDM, a devastating disease for which minimal progress in treatment has been made over the last decade. Our studies, and those reported later in the year by Gutniak et al. (5), provide an impetus to pursue further the potential of glucagonlike peptide-I in the treatment of NIDDM.

Finally, in our report we had no intention of laying claim to priority of the discovery of the insulinotropic actions of glucagon-like peptide-1. Our goals are to extend understanding of the actions of the peptide and its role in the causation and treatment of NIDDM.

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Lp(a) Serum Concentrations and Metabolic Control

Epidemiological studies have identified Lp(a) as a major risk factor for coronary heart disease (1). Elevated concentrations in diabetic patients could contribute to their increased risk. Despite this possibly important link, little information is available concerning the dependence of Lp(a) on metabolic control.

Eighteen patients (9 with NIDDM, 9 with IDDM; 9 women, 9 men; mean age 45 yr, range 16–76 yr) were studied prospectively for 21 days after hospitalization for improvement of diabetic control. All of these patients suffered from long-term poor metabolic control without recent deterioration (e.g., because of infection). Lp(a) deter-