Olanzapine was discontinued, and 15 days later, the insulin requirement decreased and then stopped because of the low blood glucose level. Basal C-peptide was 1.69 nmol/l and rose to 2.6 nmol/l after glucagon. The patient was discharged with diet information and with his usual antipsychotic treatment without any olanzapine. He remained metabolically stable, and 8 months later he is still free of diabetic symptoms, his blood glucose tolerance is quite normal, and his HbA_{1c} is normal.

Severe hyperglycemia and diabetic ketoacidosis have already been reported with clozapine, but no such adverse effects have been noted with olanzapine. Our patient has no family or personal history of diabetes. Obesity was the only predisposing factor to diabetes, but his initial presentation with ketoacidosis and weight loss is not a common means of initial type 2 diabetes diagnosis. Moreover Colli's recent report (1) suggests an increase in insulin resistance phenomena as the underlying mechanism of glucose metabolism perturbation with clozapine. The C-peptide level and its evolution after olanzapine removal in our observation is not in accord with Colli's observations, and studies are needed to investigate the mechanism by which olanzapine and clozapine interfere with glucose metabolism. Clinicians should now be on alert when blood glucose deteriorates in psychotic patients, and glucose level should perhaps be monitored when these drugs are used.

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Revised Concept for the Estimation of Insulin Sensitivity From a Single Sample

Insulin resistance is common in the general population and is related to glucose intolerance, dyslipidemia, and high blood pressure. Accurate and reproducible methods for measuring insulin sensitivity in vivo, such as the euglycemic clamp or the minimal model procedure, require trained personnel and are rather expensive (1). There is undoubtedly a need for simpler tests, especially in the field of large epidemiological studies. The circulating level of insulin has been widely used as a surrogate for insulin sensitivity, since a high plasma insulin concentration is supposed to reflect a state of insulin resistance, when the insulin-glucose feedback is considered. Different indexes have been proposed from baseline values of plasma insulin and glucose. Actually, there is a paradox concerning this approach, since both the product of fasting insulin and fasting glucose and their ratio are found to be correlated with insulin sensitivity. Recently, Kahn et al. (2) supported the concept that a hyperbolic relationship existed between fasting insulin and insulin sensitivity. Such a relationship could be described by a formula on the model of insulin sensitivity (S_I) = *a*/insulin (I), where the coefficient *a* would be a constant. Therefore, the general ratio *a*/I could be proposed as a new index of insulin sensitivity.

First, we tried to determine a value for coefficient *a*. A sample of 70 subjects (22 normal subjects who had participated as control subjects in previous metabolic studies, and 48 overweight patients; age 11–73 years, BMI 17–43 kg/m^2, female/male ratio 1:1) was randomly selected from a file of patients who performed an intravenous glucose tolerance test for calculation of S_I by the minimal model, as previously described (3,4). They represented the whole range of S_I values (0.01–25 10^{-4} min^{-1} · [μU/ml]$^{-1}$). All subjects were nondiabetic, control subjects had normal glucose tolerance, and 21 overweight patients were glucose intolerant, according to World Health Organization criteria. Plasma insulin was assayed by the Bi-Insulin immunoradiometric assay kit (ERIA-Diagnostics Pasteur, Marnes la Coquette, France), which shows excellent performance characteristics in terms of sensitivity (0.2 μU/ml) and reproducibility and does not cross-react with proinsulin. Plasma glucose was measured by the glucose oxidase method (Beckman, Palo Alto, CA).

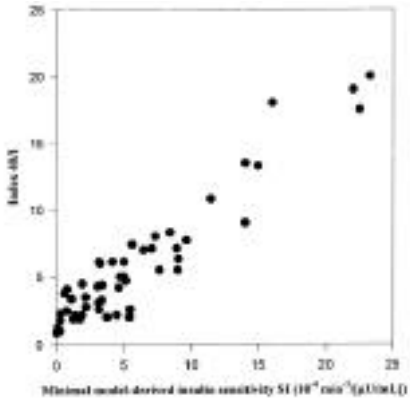

Figure 1—*Correlation between S_I and the index 40/I.* n = *49,* r = *0.882,* P < *0.0001.*

The best-fit relationship was described by S_I (10^{-4} min^{-1} · (μU/ml)$^{-1}$ × I (μU/ml) = 39.65 (r = 0.880, P < 0.0001), i.e., $S_I \times I = \sim 40$.

Second, a separate sample of 49 subjects (14 normal subjects and 35 overweight patients; age 19–62 years, BMI 19–41.5 kg/m^2) was built on the same criteria to compare the accuracy of four indexes in the assessment of insulin sensitivity: the well-known HOMA-R (homeostatis model assessment, defined as the product of fasting insulin and fasting glucose divided by 22.5) (5), fasting insulin, the ratio of fasting insulin to fasting glucose (I/G), and the above-defined ratio 40/I. The statistical analysis was performed using the SigmaStat package (Jandel Scientific, Erkrath, Germany). The index 40/I gave a better prediction of minimal model–derived S_I (r = 0.882, P < 0.0001, Fig. 1) than did HOMA-R (r = 0.546, P < 0.01), fasting insulin (r = 0.589, P < 0.01), and I/G (r = 0.597, P < 0.01). Fasting glucose was not correlated to S_I (r = 0.09, NS).

In conclusion, the ratio 40/I, with methods and units used in this study, proved to be a more precise marker of insulin sensitivity than the fasting value of insulin recommended by epidemiologists. Nevertheless, further studies are needed to validate this measure in other populations.

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Acute Hyperinsulinemia Reduces Plasma Concentrations of Homocysteine in Healthy Men

Recent studies suggested that hyperhomocysteinemia is an important risk factor for the development of premature cardiovascular disease in type 2 diabetes (1,2). Insulin resistance and/or hyperinsulinemia is also a risk factor for cardiovascular disease (3). However, there is only one report on the relationship between plasma homocysteine levels and acute hyperinsulinemia. Fonseca et al. (4) reported that acute hyperinsulinemia using a hyperinsulinemic-euglycemic clamp decreases plasma homocysteine levels in nondiabetic, but not type 2 diabetic, subjects. Unfortunately, however, they did not describe the serum insulin levels during the hyperinsulinemic-euglycemic clamp, and they did not observe any dose-dependent effect of insulin on plasma homocysteine levels. Therefore, we investigated whether plasma homocysteine levels are decreased by insulin in a dose-dependent manner.

We measured serum insulin and plasma homocysteine levels during fasting and during a hyperinsulinemic-euglycemic clamp (at 90 and 180 min) in nine healthy men (age 26.7 ± 3.1 [mean ± SD] years, BMI 22.4 ± 2.2 kg/m^2) without hypertension, glucose intolerance, or hyperlipidemia. The glucose clamp study was performed as follows: each subject was connected to the artificial pancreas (Nikkiso STG-22; Nikkiso, Tokyo) and received a constant infusion of insulin (Novolin R; Novo Nordisk, Copenhagen, Denmark) for two successive 90-min periods at rates of 0.5 and 3.0 mU · kg^{-1} · min^{-1}, respectively, using a modified version of the method of Rizza et al. (5). Serum insulin levels were measured by immunoradiometric assay, and plasma homocysteine by high-performance liquid chromatography.

During the glucose clamp study, serum insulin levels increased from 38.4 ± 24.0 pmol/l at baseline to 234.6 ± 75.6 and 1,464.0 ± 214.2 pmol/l at 90 and 180 min, respectively. Plasma homocysteine levels decreased from 11.9 ± 1.5 nmol/ml to 10.3 ± 1.4 ($P < 0.05$) and 9.5 ± 1.4 nmol/ml ($P < 0.0l$), respectively. These results confirm the reduction of plasma homocysteine levels by acute hyperinsulinemia in healthy subjects and concord well with the results of Fonseca et al. (4). However, our results on the dose-dependency of the suppressive effect of insulin are in conflict with the data of Fonseca et al. (4), which showed no dose-dependent effect of insulin on plasma homocysteine levels. The reason for this discrepancy remains unclear, but it may be partly due to the difference in BMI between the two studies (22.4 ± 2.2 vs. 30.7 ± 5.3 kg/m^2). The mechanism of the suppressive effect of insulin on plasma homocysteine levels also remains unclear. Although we did not evaluate type 2 diabetic subjects, Fonseca et al. (4) reported that acute hyperinsulinemia did not influence plasma homocysteine levels, suggesting that a resistance to insulin's effect on homocysteine may contribute to the increased cardiovascular disease associated with insulin resistance syndrome and type 2 diabetes. We can be sure, at least, that acute hyperinsulinemia cannot induce the elevation of plasma homocysteine levels. Further investigation of the effect of chronic hyperinsulinemia on plasma homocysteine levels using long-term glucose clamp study will be needed.

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Switching Insulin-Sensitizing Agents in Patients With Type 2 Diabetes Who Require Insulin

Because insulin resistance is a major metabolic defect in people with type 2 diabetes, the development of drugs that increase the sensitivity of hepatic and peripheral tissues to the action of insulin