their degree of satisfaction with the pen on a scale from 0 (worst) to 5 (best). Overall, 9% of patients rated the pen as 5, 38.4% as 4, 26.4% as 3, 11.7% as 2, 8.8% as 1, and 2.9% as 0. A significant amount (61.7%) of subjects exchanged their OptiPen Pro-1 for an insulin syringe or insulin detemir.

In the U.K., the MHRA has issued an alert about possible problems with the OptiPen Pro-1. Possible damage to an internal component of the pen during assembly could mean that the dosage button fails to engage at the end of an injection. This could lead people to believe that an injection has not been successful and, therefore, subsequently duplicate the dose. The MHRA asked all National Health Service boards (confidential health advice and information service for Scotland) and pharmacists to ensure that patients using the system were aware of the potential for dose button failure (1). The leakage and dosage button problems observed with OptiPen Pro-1 raise uncertainty as to whether diabetic patients should continue to use this product.

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Improvement of Type 2 Diabetes in a Lung Cancer Patient Treated With Erlotinib

A 72-year-old woman, with BMI 30 kg/m^2, had established type 2 diabetes for 2 years before her diagnosis of non–small cell lung cancer (NSCLC). Initially, her HbA_{1c} (A1C) was 10.3%. After treatment with pioglitazone and glyburide for 1 year, she attained an A1C of 8.2%, with average fasting glucose levels of 130–160 mg/dl. She presented to our care with metastatic NSCLC. After two cycles of chemotherapy with carboplatin and paclitaxel, her tumor progressed, and subsequently her treatment was changed to 150 mg erlotinib once a day. Within the first 4 weeks of erlotinib use, the patient noted frequent episodes of hypoglycemia, and her premeal glucose levels decreased to <90 mg/dl. Notably, her appetite and nutritional intake were not changed, her weight remained stable, and no other medications known to affect glucose metabolism had been introduced. A morning cortisol level and renal and hepatic functions were also found to be normal. Glyburide at 10 mg twice a day was eventually discontinued. Her fasting glucose levels stabilized at ~90–110 mg/dl. The patient achieved a small reduction in the size of her tumor burden with erlotinib. After 8 months of erlotinib therapy, and while continuing 30 mg pioglitazone once a day, her A1C was measured at 6.5%. Unfortunately, 1 month later, symptomatic leptomeningeal central nervous system lesions progressed and the patient was transferred to a hospice program.

Erlotinib (Tarceva; OSI Pharmaceuticals) is an analinoquinazolone inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase and has been approved as second-line treatment in NSCLC (1). Hypoglycemia or glucose derangements were not reported as side effects in the phase III randomized trial (1) or in the available literature of these specific tyrosine kinase inhibitors (2). However, of interest to this case, the crystal structure of the kinase activation loop of EGFR adopts a conformation similar to that of the phosphorylated active form of the kinase domain of the insulin receptor (3). Downstream targets of EGFR, such as Akt (protein kinase B) and extracellular signal–regulated kinase, are also involved in the complex pathway of insulin signaling (4). Of note, regression of type 2 diabetes has been described with the use of another tyrosine kinase inhibitor, imatinib mesylate (Gleevec; Novartis) (5). Further investigation of the possible connection of EGFR-mediated pathways active in cancer and in the pathogenesis of diabetes as well as the possible use of analinoquinazolone EGFR inhibitor compounds in hyperglycemic states may be warranted.

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Insulin Allergy and Immunologic Insulin Resistance Caused by Interleukin-6 in a Patient With Lung Cancer

Simultaneous occurrence of insulin allergy and immunologic insulin resistance has been reported in a few cases (1). A 62-year-old man with type 2 diabetes, who had been treated with insulin (premixed insulin of 30% aspart and 70% protaminated insulin aspart) for 3 months, noticed urticariform erythema and induration of the skin at the insulin-injection site. Erythema appeared imme-

diately after the injection of insulin and disappeared after ~20 min, while induration persisted for 3–4 days. HbA_{1c} rose from 8.0 to 10.4% in the next 3 months. The plain chest X-ray film and chest computed tomography revealed a mass with a diameter of 3 cm in the right upper lobe, which was diagnosed as adenocarcinoma of the lung.

His serum insulin level was elevated (912 pmol/l while fasting) due to a high level of IgG anti-insulin antibodies (99.7% bound, reference range <10%). Human insulin–specific IgE, as determined by a radioallergosorbent test (RAST), was also elevated (12.20 UA/ml, RAST class 3, reference range <0.34 UA/ml). Despite injection of insulin aspart before each meal, the blood glucose level increased to 23.1 mmol/l postprandially and declined to 4.9 mmol/l during the night. This daily blood glucose pattern was not improved by the administration of mitiglinide and voglibose instead of insulin. Plasma interleukin (IL)-6 was elevated to 96.4 pg/ml (reference range <4.0 pg/ml). Chemotherapy was performed with carboplatin and docetaxel. As a result, the lung tumor was remarkably reduced in size. Three weeks later, the patient's blood glucose level ranged from 5.1 to 11.9 mmol/l on therapy with mitiglinide and voglibose. Insulin IgG antibodies (percent bound), fasting serum insulin level, and human insulin-specific IgE antibodies declined to 82%, 305 pmol/l, and 4.67 UA/ml (RAST class 3), respectively. Plasma IL-6 level also fell to 8.0 pg/ml.

Increased serum levels of IL-6 have been reported in patients with lung cancer (2). IL-6 stimulates activated B-cells to induce the production of IgM, IgG, and IgA, as well as potentiates the IL-4–dependent response of IgE (3). IL-6 is also involved in the activation, growth, and differentiation of T-cells (3). In this case, multiple immune responses to insulin, including immediate allergy, delayed cutaneous hypersensitivity, and immunologic insulin resistance, were thought to have occurred as a paraneoplastic syndrome based on IL-6 secretion by lung cancer because chemotherapy resulted in a decrease of tumor size, a decline of plasma IL-6, and a reduction of insulin antibodies.

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Relapse of Diabetes After Interruption of Chronic Administration of Anti–Tumor Necrosis Factor-α Antibody Infliximab

A case observation

Tumor necrosis factor-α (TNF-α), a proinflammatory cytokine, plays a prominent role in obesity-associated insulin resistance and β-cell dysfunction (1) and, therefore, in the development of diabetes. An association between obesity and elevated TNF-α levels and, furthermore, the substantial decline of TNF-α levels with the simultaneous restoration of insulin sensitivity during weight loss was reported by Dandona et al. (2). Recently, we found evidence that prolonged administration of anti–TNF-α antibody is able to improve insulin sensitivity in insulin-resistant subjects (3); this finding has been confirmed by Kiortsis et al. (4).

Here, we report a case demonstrating the relapse of diabetes in a former type 2 diabetic patient after an interruption of prolonged treatment for psoriatic arthritis with infliximab, an anti–TNF-α antibody. The improvement in insulin sensitivity of this patient has been reported along with post hoc evidence that chronic administration of infliximab improves insulin resistance in a small sample of patients with inflammatory joint diseases (3).

The patient, a 33-year-old male with a BMI of 22.4 kg/m^2, had been treated with infliximab continuously until April 2003. From April 2003 to October 2003, infliximab was stopped due to remission of psoriatic arthritis. Readministration of infliximab was started again in October 2003 because of increased disease activity. In the interval without infliximab treatment, we observed a significant increase of fasting capillary blood glucose (monitored by self measurement) from a mean of 4.93 ± 0.18 mmol/l in the pre-interruption period to 6.77 ± 0.26 mmol/l in the infliximab-free period (Fig.

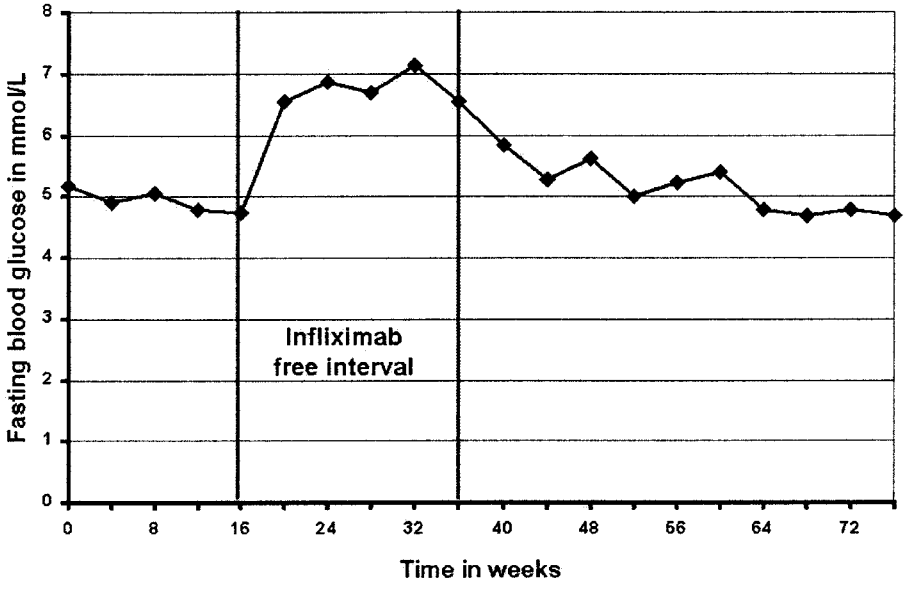

Figure 1— *Self-monitored fasting blood glucose in mmol/l. ◆, mean of a 4-week interval.*