## Diabetes Short Courses and the Internet

There has been a considerable proliferation of short courses in the area of diabetes. Typically, short courses are announced in professional journals or mailed at hospitals and universities and then applied to by mail. The difficulty of these traditional approaches is that often the brief short-course circulars reach only a small audience, and publishing and bulk mailing costs can be significant. Recently, two members (A.S. and R.L.) of the World Health Organization (WHO) DiaMond group argued that the Internet can be an important contributor to diabetes care and research (1). Perhaps, it could also be of advantage to diabetes short courses.

We have evaluated this by developing a World Wide Web homepage for the WHO international short course in diabetes epidemiology and public health concerns held every 3 years in Cambridge, U.K. The sixth such course was advertised using the traditional approaches. During the short course, however, eight students took it upon themselves to establish a homepage for the course. None had any training in developing homepages. However, by the end of the 10-day course, a homepage had been constructed that could form the basis for bringing diabetes educational courses onto the Internet.

The site can be visited at http://www.pitt.edu/~akira/CAMB/home.htm.

It contains the meeting agenda and a hypertext yearbook of individual photographs (taken by digital camera), addresses, and research interests of all 46 participants and the resident faculty. Each participant can be contacted by clicking on the e-mail feature. It is very important for future applicants to learn what previous participants have gained from the short course. Before the next course in 1999, an application form will be included on the homepage.

This effort demonstrated the utility of the homepage for short courses in diabetes. In addition to promoting a wider interest in upcoming seminars, the ability for participants (students and faculty) to communicate quickly and easily with each other electronically in the future was highly appreciated. Moreover, it demonstrated that a multinational group of clinicians with no training in construction of WWW homepages could develop a state-of-the-art page if given initial guidance.

WORLD HEALTH ORGANIZATION
DIAMOND GROUP ON THE INTERNET

The WHO DiaMond Group consists of U. Schneider, Austria; S. Taback, Canada; F. Collado, Cuba; A. Neu, Germany; P. Stella, Hungary; A. Sekikawa, Japan; P. Jarosz-Chobot, Poland; S. Hasseb-Elrasoul, Sudan; R. LaPorte, USA; N. Wareham, United Kingdom; R. Mtonga, Zambia.

Address correspondence to Ronald LaPorte, PhD, Diabetes Research Center, Rangos Research Center, 3460 Fifth Ave., 5th Floor, Pittsburgh, PA 15213.

**Reference**

1. LaPorte RE, Akazawa S, Drash A, Camboa C, Lee HK, Libman I, Marler E, Orschiedt S, Songer T, Tajima N: Diabetes and the Internet. *Diabetes Care* 18:890–895, 1995

## Lactic Acidosis Associated With Glucophage Use in a Man With Normal Renal and Hepatic Function

The incidence of lactic acidosis with metformin (Glucophage, Bristol-Myers Squibb) therapy for type II diabetes has been reported to be ten- to twentyfold lower than with another biguanide, phenformin, in the range of 0.0–0.084 cases/1,000 patient-years (1). Major contraindications to metformin administration are abnormal renal or hepatic function and intercurrent conditions causing hypoxia or ischemia (2). We recently treated a man for lactic acidosis associated with metformin use who had none of these risk factors. The 58-year-old patient, who had been diabetic for 7 years, was first seen in the office in January of 1995 with a postprandial blood sugar of 327 mg/dl (18.1 mmol/l) on 10 mg glyburide daily. His only other medication was nifedipine and he denied alcohol use. Physical exam was notable for obesity (BMI, 31.6 kg/m$^2$) and background diabetic retinopathy. The patient was started on mixed human NPH and regular insulin, and the sulfonylurea was discontinued. One year later, he returned, requesting treatment with metformin. Postprandial blood glucose was 572 mg/dl (31.7 mmol/l) off insulin. Liver function profile was normal, and creatinine was 1.0 mg/dl (88.4 μmol/l). He was started on 500 mg Glucophage twice daily and instructed to continue insulin administration. Six weeks later the patient arrived in the emergency department, complaining of shortness of breath and weakness. Physical exam revealed him to be agitated but afebrile, with Kussmaul respirations at 26 per minute, a blood pressure of 207/116 mmHg, and a pulse of 121 per minute. There was no evidence of trauma or intercurrent illness. Arterial pH was 7.1; $P_{CO_2}$, 11 mmHg; serum bicarbonate, 10 mmol/l; serum glucose, 516 mg/dl (28.6 mmol/l); serum acetone, trace positive; serum lactic acid, 17.3 mg/dl (1.94 mmol/l), which peaked at 22 mg/dl (2.46 mmol/l) (normal, 3.0–12.0 mg/dl); and anion gap, 21 (normal, <12). Creatinine level had increased to 1.8 mg/dl (159.1 mmol/l), and urea nitrogen was 18 mg/dl (6.43 mmol/l). A diagnosis of lactic acidosis due to metformin use was made, and the patient began receiving a high-volume intravenous normal saline infusion, plus bicarbonate and insulin drips. Within 8 h, serum acetone was negative and creatinine was 1.1 mg/dl (97.2 mmol/l), while the anion gap increased and pH declined. He gradually improved, requiring 9 days of treatment before serum lactic acid levels returned to normal.

Elevated serum lactate levels (albeit to a moderate degree) and acidosis developed in this patient while on metformin therapy in the absence of standard risk factors. The metabolic picture presented in this case is consistent with previous descriptions of lactic acidosis with metformin use (3). It is plausible that, as a result of osmotic diuresis, diabetic patients in poor control can eventually experience a decrease in renal perfusion, thus allowing the accumulation of metformin to dangerous levels (4). We recommend that great caution be exercised when initiating metformin therapy in the face of marked hyperglycemia.

GARY M. PEPPER, MD
MARLENE SCHWARTZ, MD

From the Diabetes Treatment Center (G.M.P.) and the Intensive Care Unit (M.S.), Brooklyn Hospital Center, Brooklyn, New York.

Address correspondence to Gary M. Pepper, MD, Palm Beach Diabetes and Endocrine Specialists, 1411 N. Flagler Dr., Suite 4600, W. Palm Beach, FL 33409.

References

1. Bailey CJ: Biguanides and NIDDM. *Diabetes Care* 15:755–772, 1992
2. Bailey CJ, Turner RC: Metformin. *N Engl J Med* 334:574–579, 1996
3. Lu RD, Schmulling RM, Eggstein M: Lactic acidosis in biguanide-treated diabetics. *Diabetologia* 14:75–87, 1978
4. Gan SCG, Barr J, Arieff AI, Pearl RG: Biguanide-associated lactic acidosis. *Arch Int Med* 152:2333–2336, 1992

## Response to Pepper and Schwartz

The patient described by Pepper and Schwartz did not have lactic acidosis. The emergency admission appears to have been attributable to inadequate insulin therapy for decompensated insulin-requiring diabetes, which led to incipient ketoacidosis, rather than to an effect of metformin therapy. Metformin-induced lactic acidosis is rare, and it is unfortunate to see metformin being blamed inappropriately for this illness.

At the emergency admission, the patient presented with acidosis with Kussmaul respiration, pH 7.1, with a low bicarbonate and a large anion gap. However, the serum lactate level, ~2 mmol/l, was only just above the quoted normal range and was a minor contributor to the anion gap of 21 mmol/l (normal, <12 mmol/l). The circulating metformin concentration was not measured. When a diabetic patient presents with acidosis and a blood glucose of 28.6 mmol/l, ketoacidosis is the most likely cause, and it is surprising that the serum acetone was only trace positive. This may have been a bedside test of uncertain accuracy, or the predominant ketone body may have been 3-hydroxybutyrate. The patient was appropriately treated with intravenous normal saline, insulin, and bicarbonate and recovered. It is doubtful whether bicarbonate therapy is needed, unless the pH is <7.1. Raised blood lactate is often encountered in patients with ketoacidosis (1), possibly due to the dehydration and reduced perfusion of muscles. While ketoacidosis is the most likely diagnosis, other unlikely possibilities include raised formic acid levels from unsuspected methyl alcohol ingestion or the self-administration of aspirin.

It was reasonable to change from a sulphonylurea to an insulin regimen, but it appears that the patient's blood glucose control and response to therapy was not adequately monitored, possibly because the patient was lost to follow-up. When he returned, having discontinued therapy with a postprandial blood glucose of 31.7 mmol/l, it was correct to restart insulin administration. However, appropriate monitoring to evaluate the response to therapy was not done, because of either an inadequate appreciation of the severity of the hyperglycemia or poor patient compliance. When postprandial blood glucose is >20 or 25 mmol/l after 'sulphonylurea failure', patients have a marked β-cell deficiency. If good blood glucose control is to be achieved, these patients need "full" insulin therapy with blood glucose monitoring in a similar fashion to patients with IDDM (2). Whether the addition of sulphonylurea or metformin to insulin therapy provides clinical benefit at that stage is uncertain.

ROBERT C. TURNER, MD, FRCP
CLIFF J. BAILEY, PHD, FRCPATH

From the Diabetes Research Laboratories (R.C.T.), Radcliffe Infirmary, Woodstock Road, Oxford; and the Pharmaceutical Science Department (C.J.B.), Aston University, Aston Triangle, Birmingham, U.K.

Address correspondence to Robert C. Turner, MD, FRCP, University of Oxford, Nuffield Department of Clinical Medicine, Diabetes Research Laboratories, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, U.K. E-mail: ivy@drl.ox.ac.uk.

References

1. Nattrass M, Alberti KGMM: Lactate metabolism in diabetes. In *Lactate in Acute Conditions*. Bossart H, Perret C, Eds. Basel, Karger, 1979, p. 83–101
2. Holman RR, Turner RC: A practical guide to basal and prandial insulin therapy. *Diabet Med* 2:45–53, 1985

## Type I Diabetes and the "Milk Hypothesis"

### Is there a role for the insulin in mother's milk?

The hypothesis that early exposure to cow's milk may be associated with an increased risk for the development of type I diabetes has stimulated a considerable amount of research in this field, reviewed recently by Scott et al. (1). The cornerstone of the "milk hypothesis" is the assumption that an immune response against bovine albumin may trigger an autoimmune process directed against β-cells.

I would like to extend the "milk hypothesis" further by drawing attention to the frequently ignored fact that human mother's milk contains a considerable amount of insulin. The insulin concentration in human milk is highest immediately postpartum and thereafter parallels maternal plasma insulin concentrations (2) with a lag time of 60–80 min. The physiological role of insulin in human milk is not known.

One may speculate that the presence of insulin in mother's milk could contribute to the development of oral tolerance. Accumulated evidence suggests that oral tolerance can be mediated by orally activated humoral and cellular factors. In animal models, the development of several T-cell–mediated diseases, such as rheumatoid arthritis, uveitis, and type I diabetes, can be inhibited. In particular, oral immunization with insulin delayed the onset and reduced the incidence of type I diabetes in NOD mice (3). Extending this line of argument further, feeding with cow's milk may contribute to an altered development of oral tolerance by preventing the exposure to human insulin and eventually predispose to the development of type I diabetes. I wonder if the occurrence of insulin autoantibodies seen in subjects with preclinical type I diabetes may be related to a lack of oral tolerance. Current evidence suggests that the appearance of insulin autoantibodies is associated with an increased risk of type I diabetes (4). In addition, it is worth noting that the incidence of positive thyroid antibodies was reported to be two and a half times higher in children fed soy-containing formula than in breast-fed diabetic children (5). To appreciate the relevance of insulin in mother's milk fully, more information on its physiological role has to be gathered.

PETER KOTANKO, MD

From the Department of Internal Medicine, Krankenhaus Barmherzige Brüder, Graz, Austria.

Address correspondence to Peter Kotanko, MD, Department of Internal Medicine, Krankenhaus Barmherzige Brüder, Marschallgasse 12, A-8020 Graz, Austria.