

tion without a clear cause, especially if they are suffering from hypertension. We usually do this routinely in our work.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; BMI, BODY MASS INDEX.

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Carbon Monoxide Poisoning Presenting as Apparent Ketoacidosis

Ketoacidosis is regarded as a hallmark of type 1 diabetes. We report three cases that presented with the biochemical features of ketoacidosis and were found to have carbon monoxide poisoning.

Four members of one Asian family were admitted to the accident and emergency department. Two were unconscious and one was dead on arrival. The other (girl, 17 yr of age) was drowsy but orientated. She reported that she had eaten dinner with her family at 2000, went to bed at 2200, and was subsequently woken by her father who then collapsed. On admission, her blood glucose was 14.2 mM, arterial pH 7.24, and bicarbonate 14.2 mM. Her father (45 yr of age) was unconscious. His blood glucose was 19.3 mM and serum potassium 2.9 mM; the arterial pH was 7.24 and bicarbonate 13.8 mM. The third patient (woman, 72 yr of age) was also unconscious. Her blood glucose was 20.0 mM, serum potassium 2.9 mM, arterial pH

7.27, and bicarbonate 14.0 mM. All three had glycosuria and ketonuria. They were treated with intravenous insulin and normal saline. Repeat arterial blood gas estimations fortuitously revealed all three had severe carboxy-hemoglobinemia (31-56%). They were given 100% oxygen by face mask and rapidly regained consciousness. All three made a complete recovery. Subsequently a 75-g glucose tolerance test was normal in all cases. A faulty gas boiler was found in their house.

Hyperglycemia and lactic acidosis have been reported previously as a feature of carbon monoxide poisoning in animal models and human subjects (1,2) but have not been mentioned in recent reviews of the subject (3,4). The cause of hyperglycemia in carbon monoxide poisoning is not clear, but in experimental animals is not caused by impairment of insulin secretion (5). It can be prevented in rats by adrenalectomy, which would suggest it may be part of a stress response (6). Acidosis and elevation of lactate and pyruvate in carbon monoxide poisoning are probably secondary to widespread tissue hypoxia caused by carbon monoxide binding to hemoglobin, myoglobin, and cytochrome oxidase (1,3).

The degree of acidosis and lactate elevation, unlike the carboxy-hemoglobin level, appear to correlate well with the severity of carbon monoxide poisoning in humans and may therefore be useful prognostic markers (2). To our knowledge, ketonuria has not previously been reported, and the cause is not clear. Whether treating these biochemical abnormalities would have any effect on the outcome of carbon monoxide poisoning is unknown. High concentration oxygen therapy remains the mainstay of treatment (1).

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TYPE 1 DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS.

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Prolonged Desensitization Required for Treatment of Generalized Allergy to Human Insulin

Generalized insulin allergy is a rare complication of therapy with human insulin (1). Most cases can be rapidly desensitized within several hours (2). Patients who do not respond to desensitization may require long-term therapy with systemic glucocorticoids and antihistamines (3). We report a patient

who required an extremely long period to become desensitized.

A 30-yr-old female had developed type 1 diabetes 7 yr earlier and had always been treated with human insulin (Lilly, Indianapolis, IN). At the time of presentation she was on twice-daily NPH and had an HbA_{1c} of 0.085 (0.038-0.060). She had no past history of any type of allergy and no significant past medical history. One month prior to admission, the patient developed urticaria at her insulin injection sites. This progressed to generalized edema and erythema following injection but no shortness of breath, tachycardia, or hypotension. She was changed to lente insulin which was tolerated for 2 days but then produced a similar reaction to NPH. Oral antihistamines and glucocorticoids decreased but did not eliminate the symptoms.

She was admitted to hospital for desensitization. Test doses of different types and species of insulins all produced immediate wheal and flare reactions. Total IgE was normal and insulin-specific IgE was not measured. Desensitization was started using a kit and protocol from Lilly (2). In brief, serial dilutions of regular insulin are prepared and administered. The dose range begins at 1 U of 0.005 U/ml and ends at 8 U of 50 U/ml, with a total of 15 steps. The injections are given intradermally at 30-min intervals. Whenever a reaction is noted at the injection site, the protocol is restarted two steps lower than that which caused the reaction. During the desensitization protocol, glucose control was maintained with a single injection of 30 U of lente each day.

The protocol was started each morning and continued without interruption until late evening over a 9-day period. A total of 237 desensitizing injections were given without success. We were unable to progress beyond 4 U of 0.5 U/ml. The 30 U of lente produced only a local reaction when administered. The protocol was stopped because of patient fatigue, and she was discharged on lente. She again began developing gener-

alized urticaria and was readmitted 18 days later for repeat desensitization. The same protocol was repeated. After a further 117 injections given over 5 days, desensitization was finally achieved. Nine months later she was taking NPH insulin twice daily with no evidence of any local or generalized reaction.

Generalized insulin allergy is mediated by IgE directed against the insulin molecule (4). Although the mechanism by which desensitization works is uncertain, it probably involves the depletion of mediators and the induction of blocking IgG antibody (2). The protocol described above has been reported effective in 94% of patients with pork insulin. No published figures are available for human insulin, presumably because generalized insulin allergy is rare. Galloway states that most patients are desensitized within 10 h although some may require several days (2). Very little other literature is available on the success and duration of this desensitization protocol.

The treatments available for patients who fail insulin allergy have significant side effects. Systemic antihistamines can be sedating, and the use of antihistamines in the insulin syringe, which has been suggested (5), may not be advisable (6). The long-term use of systemic steroids has many complications. For these reasons, we chose to try a prolonged desensitization protocol in our patient with eventual success. It is not clear from the literature if this extended procedure has been attempted in other patients who have failed desensitization. We suggest that it should be tried in other patients before concluding that desensitization has been unsuccessful.

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TYPE 1 DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS; IGE, IMMUNOGLOBULIN E.

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Hypoglycemia and Cognitive Function

The review by Dr. Brouhard in *Diabetes Care* (15:583-84, 1992) of a study by Reichard et al. (1), uncritically accepted that this study provided reasonable evidence that cognitive function is not impaired as a result of repeated episodes of severe hypoglycemia.

However, we would draw your commentator's attention to the subsequent correspondence (2) suggesting that this study may have incorporated a type 2 statistical error.

The study by Reichard et al. (1) was designed to address the effects of intensive conventional insulin treatment on cognitive function, and not the effect of frequent episodes of severe hypoglycemia on cognitive function. Although the mean number of episodes was 1.1 in their intensely treated group of diabetic patients, 56% of the standard treatment group also reported one or more episodes of severe hypoglycemia. Reanalysis of the data with respect to the incidence of severe hypoglycemia and irrespective of the treatment mode may have produced a different result.

The duration of the study was only 5 yr, and this may be too short a period to identify any emerging cognitive deficit. The battery of neuropsychological tests included finger tapping and digit span, which are unlikely to be sufficiently sensitive to demonstrate subtle changes in cognitive function resulting from recurrent severe hypoglycemia, and interpretation of the Necker cube test is uncertain. The statistical power of the study was not high. The power of detecting a difference of 0.5 SDs between the two groups was 0.67, and the power of detecting a difference of 0.3 SDs was only 0.3.

Although the review article discusses one of the important earlier studies identifying cognitive deficits in adolescents with diabetes (3), some other relevant studies in diabetic adults have not been cited. In 1973, Bale et al. (4) identified an association between the frequency of severe hypoglycemia and cognitive dysfunction. Wredling et al. (5) in Sweden demonstrated impaired motor ability, problem solving, visuospatial skills, and frontal lobe dysfunction in a group of IDDM patients who had a history of recurrent episodes of severe hypoglycemia. More recently, Langan et al. (6), with the NART and WAIS-R,

identified a reduction in IQ in a subgroup of 100 IDDM patients exposed to recurrent severe hypoglycemia. NART is an assessment of the best global cognitive function ever attained irrespective of time; and when this premorbid assessment of IQ is compared with present IQ (measured by WAIS-R), any deterioration in IQ that has occurred can be identified. The diabetic patients exposed to five or more episodes of severe hypoglycemia were found to have a definite deterioration in IQ (6).

It is premature to state that cognitive functioning remains normal in well-controlled diabetic patients who are exposed to multiple episodes of severe hypoglycemia. This important issue remains unresolved, and it is possible that repeated episodes of severe hypoglycemia do have a cumulative detrimental effect on cognitive function.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NART, NATIONAL ADULT READING TEST; WAIS-R, WECHSLER ADULT INTELLIGENCE SCALE-REVISED.

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The Lost Symposium

Diabetes and Exercise 1990

The term lost has been applied by historians to a generation of people and by Hollywood to describe a missing weekend. Likewise, musicologists have their lost chord and the Bible its lost tribes. This letter deals with what may be the first instance of a lost symposium. The symposium in question is entitled "Diabetes and Exercise 1990," and it occupies pages 1675-1813 of the November 1992 issue of *Diabetes Care*. Unfortunately, the table of contents in this issue did not list the 19 individual articles and, as a result, many readers were not aware of their presence. This lack of identification has been rectified, and thanks to the efforts of Allan Drash and the editorial staff of *Diabetes Care*, a full table of contents appeared in the January 1993 issue.

Over the past 20 years, the view of physicians and scientists concerning the role of exercise in diabetes therapy has been on a roller coaster. In the 1970s, enthusiasm was high, as studies in humans and experimental animals and the development of new methods to study muscle, in vitro, led to a vast increase in our understanding of both the

metabolism of exercise and how it is altered in patients with types I and II diabetes. Much of this work was summarized at a milestone Kroc Foundation Conference on Diabetes and Exercise held in Santa Ynez, California in 1979 (1). Also presented at this meeting were the first reports suggesting that physical activity might be useful in improving glucose homeostasis and in diminishing coronary risk factors in patients with type II diabetes.

The next half-dozen years were characterized by a flurry of activity in the study of diabetes and exercise. The combined effect of exogenous insulin and physical activity on glucose homeostasis in patients with type I diabetes was clarified (2). In addition, the basic elements of the exercise prescription (3) and its potential benefits in patients with type II diabetes (3,4) were defined more conclusively. Thus, clear-cut improvement in HbA_{1c} levels, glucose tolerance, plasma triglycerides, and in some instances, blood pressure, were noted by numerous investigators in patients performing endurance-type exercise at least three times/wk. Likewise, because of the increase in insulin sensitivity that it caused, the notion that physical training might be useful in treating other disorders characterized by hyperinsulinemia and insulin resistance was proposed (5). Singled out in this regard were hypertriglyceridemia, essential hypertension, and coronary heart disease. Contemporary epidemiological studies that demonstrated that heart attacks are less frequent in physically active individuals (3) and that hyperinsulinemia may be an independent risk factor for coronary heart disease added greatly to the momentum of this idea (3).

Soon after the initial burst of interest in its use, it became apparent that exercise could be used only to improve glycemic control in a small percentage of patients with type I diabetes. Also, the results of long-term exercise programs in patients with type II diabetes, especially the elderly, were often disappointing because of a high drop-out rate (6) and

because of the relatively modest improvement achieved in many patients. Furthermore, in many type II diabetic patients, the ability to exercise was limited as a result of clinically significant vascular disease and/or neuropathy. Largely for these reasons, an NIH consensus panel issued in 1988 a "somewhat controversial, rather sobering statement . . . that downplayed the role of exercise in the management of type II diabetes (7,8)." "Why then did a rather large group of clinical diabetologists, epidemiologists, physiologists, biochemists, and exercise physiologists feel it appropriate to meet for a symposium on diabetes and exercise in May 1990 (8)?" In part, the symposium was undoubtedly a response to the NIH statement. In addition, several concurrent developments made the timing of the meeting particularly appropriate. One of these was the tremendous increase in the interest of patients with diabetes in sports and physical activity.

As pointed out in the original introduction to the symposium (8), a "drastic increase in the number of publications directed to sports activities in journals edited for diabetic patients all over the world" has occurred. Also, "much of the momentum motivating clinical diabetologists to reinvestigate a number of aspects of acute exercise in insulin-dependent (type I) diabetes has been prompted by the activities following the 1988 founding of the IDAA in Arizona." In keeping with the increasingly greater participation of diabetic patients in exercise, the history and purpose of the IDAA were described at the symposium by Harper and Thurm, and a written version of their presentation appears in the proceedings.

The symposium also occurred at a time when important new insights were being made into the molecular biology and physiology of glucose transport. The GLUT4 glucose transporter had been discovered and its gene cloned in the preceding two years. At the symposium, this work as well as newer studies of the