3. Keefe FE, Surwit RS, Pilon RN: Biofeedback, autogenic training and progressive relaxation in the treatment of Raynaud's disease. *J Appl Behav Anal* 13:3–11, 1980
4. Blanchard EB, Theobald D, Williamson D, Silver B, Brown B: Temperature feedback in the treatment of migraine headaches. *Arch Gen Psychiatry* 35:581–88, 1978
5. Feinglos MN, Hastedt P, Surwit RS: Effects of relaxation therapy on patients with type I diabetes mellitus. *Diabetes Care* 10:72–75, 1987
6. Stabler B, Morris MA, Litton J, Feinglos MN, Surwit RS: Differential glycemic response to stress in type A and type B individuals with IDDM (Letter). *Diabetes Care* 9:550–52, 1986
7. Stabler B, Surwit RS, Lane JD, Morris MA, Litton J, Feinglos MN: Type A behavior pattern and blood glucose control in diabetic children. *Psychosom Med* 49:313–16, 1987

Miscibility of Human Isophane Insulin With Human Soluble Insulin

We recently studied the effects of mixing regular porcine (Actrapid MC, Novo, Copenhagen) and lente porcine (Monotard MC, Novo) insulin on absorption course and biologic effect of regular insulin (1). In this study, we investigated the miscibility of a new human isophane preparation (Protaphane HM U-40, Novo) with human regular insulin (Actrapid HM U-40, Novo).

We studied six insulin-dependent diabetic patients aged 18–53 yr. They were all within 10% of their ideal body weight, duration of insulin treatment was 4–34 yr (median 12 yr), and insulin requirement was 26–50 U/day (median 30 U/day). Circulating anti-insulin antibodies, expressed as percentage of binding of ^{125}I-labeled insulin on charcoal-extracted sera ranged from 10 to 32% (median 21%, normal values <12%).

Our experimental design and the methods employed are reported in a previous paper (1). On two different days, each patient received 0.16 U/kg s.c. regular insulin and 0.24 U/kg of human isophane insulin alternatively with separate injections or in combination in the same syringe. A 4-h glucose clamp was then performed, and amount of glucose infused to sustain glycemia was taken as an expression of the biologic activity of the hormone. Venous plasma samples were drawn during the study for the determination of free-insulin (2) and C-peptide levels. We compared free-insulin curves and action profiles of the hormone after separate or combination injections. Statistical analysis was performed by Student's *t* test for paired samples.

Mean basal glucose levels (±SE) were 149 ± 5 mg/dl before separate injections and 138 ± 12 mg/dl before the combination injection. The variation of basal blood glucose for each subject between the two tests ranged from 7 to 20%. During the steady state maximal variations of blood glucose levels in individual studies were always within 14%. Free-insulin curves and C-peptide and blood glucose levels during glucose infusion to sustain glycemia are reported in Fig. 1.

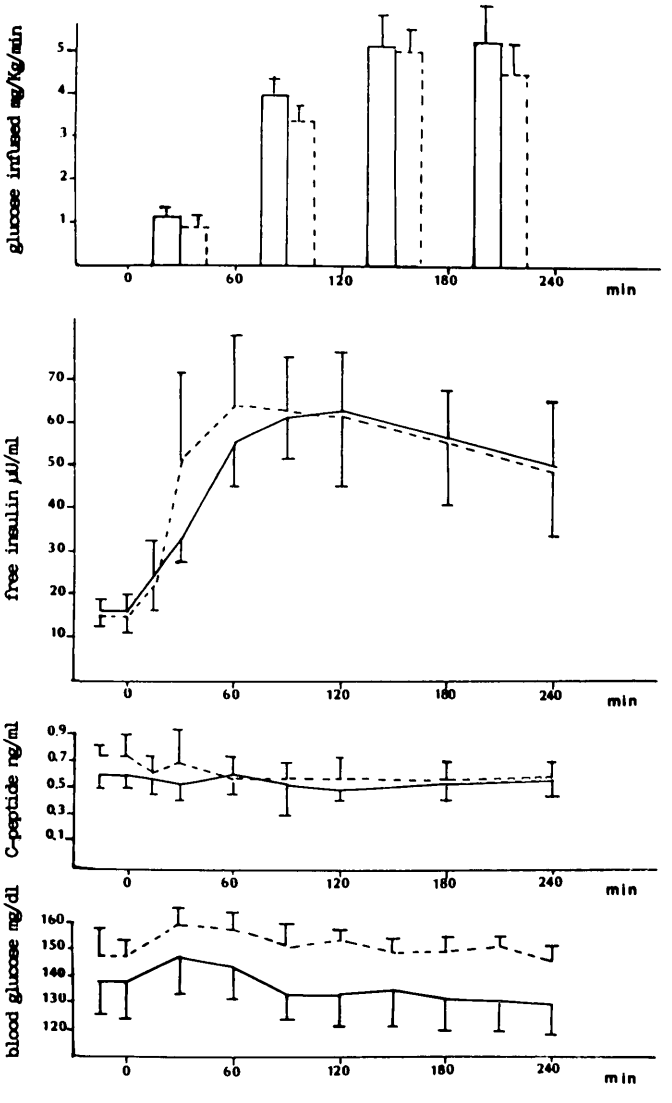

FIG. 1. Glucose infused to sustain glycemia, free-insulin profiles, and C-peptide levels and blood glucose after administration of Actrapid HM (0.16 IU/kg) and Protaphane HM (0.24 IU/kg) in separate injections (*dashed lines*) and in combination in same syringe (*solid lines*).

The amount of infused glucose did not show any significant differences. Plasma free-insulin levels were slightly higher up to 60 min after separate injections, but the difference did not reach statistical significance (incremental areas of free insulin on basal levels were 28 ± 10 $\mu U \cdot ml^{-1} \cdot min^{-1}$ with separate injections and 18 ± 4 $\mu U \cdot ml^{-1} \cdot min^{-1}$ with combination injection). Plasma C-peptide levels remained at the basal concentrations during the experiment.

Absorption rate and action profile of regular insulin are not influenced by mixing with isophane insulin in a 2:3 proportion. Our data confirm the results obtained with different methods and isophane insulin preparations by other authors studying the effects of mixing regular and interme-

diate-acting insulin (NPH and lente) in normal (3–5) and diabetic (6–8) subjects. Other reports on the miscibility of regular with long-acting insulin are available (9,10).

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REFERENCES

1. Forlani G, Santacroce G, Ciavarella A, Capelli M, Mattioli L, Vannini P: Effects of mixing short- and intermediate-acting insulins on absorption course and biologic effect of short-acting preparation. *Diabetes Care* 9:587–90, 1986
2. Collins AC, Pickup JC: Sample preparation and radioimmunoassay for circulating free and antibody-bound insulin concentrations in insulin-treated diabetics: a re-evaluation of methods. *Diabetic Med* 2:456–60, 1985
3. Berger M, Cüppers HJ, Hegner H, Jörgens V, Berchtold P: Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. *Diabetes Care* 5:77–90, 1982
4. Galloway JA, Spradlin CT, Nelson RL, Wentworth SM, Davidson JA, Swarner JL: Factors influencing the absorption, serum insulin concentration, and blood glucose responses after injections of regular insulin and various insulin mixtures. *Diabetes Care* 4:366–76, 1981
5. Heine RJ, Bilo HJG, Fonk T, van der Veen EA, van der Meer J: Absorption kinetics and action profiles of mixtures of short and intermediate-acting insulins. *Diabetologia* 27:558–62, 1984
6. Heine RJ, Bilo HJG, Sikkenk AC: Mixing short and intermediate acting insulins in the syringe: effect on post prandial blood glucose concentrations in type 1 diabetics. *Br Med J* 290:204–205, 1985
7. Colagiuri S, Villalobos S: Assessing effect of mixing insulins by glucose-clamp technique in subjects with diabetes mellitus. *Diabetes Care* 9:579–86, 1986
8. Kolendorf K, Aaby P, Westergaard S, Deckert T: Absorption, effectiveness and side effects of highly purified porcine NPH-insulin preparations (Leo). *Eur J Pharmacol* 14:117–24, 1978
9. Francis AJ, Hanning I, Alberti KGMM: The effect of mixing human soluble and human crystalline zinc-suspension insulin: plasma insulin and blood glucose profiles after subcutaneous injection. *Diabetic Med* 2:177–80, 1985
10. Muhlhauser I, Tsotsalas M, Broermann C, Berger M: Miscibility of human and bovine ultralente insulin with soluble insulin. *Br Med J* 289:1656–57, 1984

Ice-Water Addiction Complicating Painful Diabetic Neuropathy in Childhood

Acute painful diabetic neuropathy, a rare syndrome in childhood (1), can have incapacitating symptoms. Adequate pain management is difficult to achieve in these patients, and depression and anorexia frequently accompany the clinical picture (2). No medications, including narcotics, consistently relieve the pain, but some patients have found immersion of the painful extremity in cold water to be effective analgesia (2). Prolonged exposure to this wet and cold environment, however, may result in the insidious development of cold injury that is ignored because of the accompanying anesthesia (3). We report the occurrence of acute painful neuropathy in a pediatric diabetic patient whose dependence on ice-water immersion for pain relief resulted in deep-seated cold injury (immersion foot).

CASE HISTORY

A 14 yr-old boy with insulin-dependent diabetes mellitus was referred for evaluation of severe bilateral foot pain of 2 wk duration. The patient complained of a continuous burning sensation punctuated by brief stabbing pains, exacerbated by walking and worse at night. Aspirin had been ineffective, but immersion of his feet in cold water gave significant relief. The patient, who lived on a farm, denied exposure to lead, pesticides, or other toxins. He always wore shoes and felt that a localized cutaneous exposure to an allergen or toxin could not have occurred.

After the initial diagnosis of diabetes 5 yr earlier, the patient received NPH insulin twice a day at a maximum dose of 13 U each morning and 3 U each evening (~0.4 U/kg). Glycosylated hemoglobin had not been measured. Three months before referral, after hospitalization for diabetic ketoacidosis, his dose of insulin was increased to 46 U NPH and 10 U regular each morning and 17 U NPH and 15 U regular each evening (~1.9 U/kg) over 4–6 wk. On this regimen, he had experienced several mild hypoglycemic episodes.

Physical examination revealed a thin adolescent in extreme pain: height 158 cm, weight 46 kg, blood pressure 102/80 mmHg, pulse 90 beats/min. Funduscopic exam was normal. The feet were red and swollen, and sparse petechiae and small vesicles were noted on several toes. Arterial pulsations were easily palpable. Strength, proprioception, and sensation to light touch and pinprick were normal. Deep tendon reflexes were present and symmetric. The patient walked with a shuffling gait, refusing to bear weight on either forefoot.

Diagnostic studies included an erythrocyte sedimentation rate of 35 mm/h (normal range 0–15 mm/h), glycosylated hemoglobin 7.7% (normal range 5–8%), normal levels of erythrocyte lead, and undetectable levels of mercury and arsenic. Cultures of vesicular fluid were negative. Nerve-conduction studies revealed absent sural nerve responses bilaterally and slowing of conduction velocity in both peroneal nerves, indicative of a sensorimotor polyneuropathy. Ophthalmologic examination revealed no evidence of diabetic retinopathy. A nerve biopsy was not performed.

Various medications including naproxen, amitriptyline hydrochloride, meperidine hydrochloride, and morphine sulfate failed to relieve his discomfort. He insisted on nearly constant immersion of his feet in ice water; withdrawal of this therapy