is different from that for insulin.[2] The potential pharmacologic effects of this hormone have not previously been studied in diabetes mellitus.

Mendenhall's syndrome is a rare congenital disorder characterized by short stature, somatic abnormalities, and severe insulin-resistant diabetes mellitus.[3] Most patients with the syndrome have died from ketoacidotic coma in childhood. We studied the short-term effects of intravenously administered IGF-I in a 13-year-old boy with Mendenhall's syndrome.[4] His diabetes was first treated by dietary restriction of carbohydrates, which was unsuccessful. Subsequent therapeutic trials of tolbutamide and metformin were equally ineffective. Subcutaneous or intravenous injections of insulin (up to 3 units per kilogram of body weight) had no effect on mean daily levels of blood glucose (>20 mmol per liter) or glycosylated hemoglobin (14.2 percent; laboratory normal, <8 percent). In addition to severe chronic hyperglycemia he had, as expected, massive hyperinsulinemia (fasting plasma insulin level, 2442 pmol per liter), intermittent ketonuria, and elevated growth hormone secretion (fasting serum growth hormone level, 11 μg per liter; normal, <5).

Therapy with IGF-I was then considered, on the basis of the known properties of the hormone and knowledge that the child's endogenous plasma levels of IGF-I were subnormal (5.2 nmol per liter; normal range for age, approximately 13 to 50). Informed consent was obtained from the patient's parents before the administration of IGF-I. The hormone, donated by Fujisawa Pharmaceutical Company, was biosynthesized by recombinant technology and had an amino acid sequence identical to that of native IGF-I.[5] Lyophilized IGF-I was dissolved in normal saline and injected as a single bolus dose of 3 mg (100 μg per kilogram) after breakfast. Venous blood was drawn for analysis 0, 2, 5, 15, 30, 60, 120, and 150 minutes after injection. For comparison purposes, an identical experiment was performed after the injection of normal saline. Blood glucose declined within 5 minutes after the injection of IGF-I and reached a nadir of 11.2 mmol per liter after 150 minutes. Plasma insulin declined rapidly from 7650 to 1890 pmol per liter, C peptide from 1.92 to 0.88 nmol per liter, and growth hormone from 11.2 to <0.5 mU per liter (Fig. 1). The marked decline in serum growth hormone is in contrast to the effects of IGF-I on serum growth hormone in Laron-type dwarfism[6]; the disparity probably reflects the fact that in our patient frank hypoglycemia never developed as a stimulus for the release of growth hormone. These results lend weight to the concept of a direct negative-feedback effect of IGF-I on the release of growth hormone, as suggested by previous in vitro and animal studies.[7,8]

Severe insulin resistance due to decreasd insulin binding is the chief abnormality of Mendenhall's syndrome.[9] After the intravenous administration of IGF-I, we have demonstrated a prompt decline in concentrations of blood glucose and plasma insulin and C peptide. The short-term use of IGF-I may thus have therapeutic benefits in patients with severe insulin-resistant states.

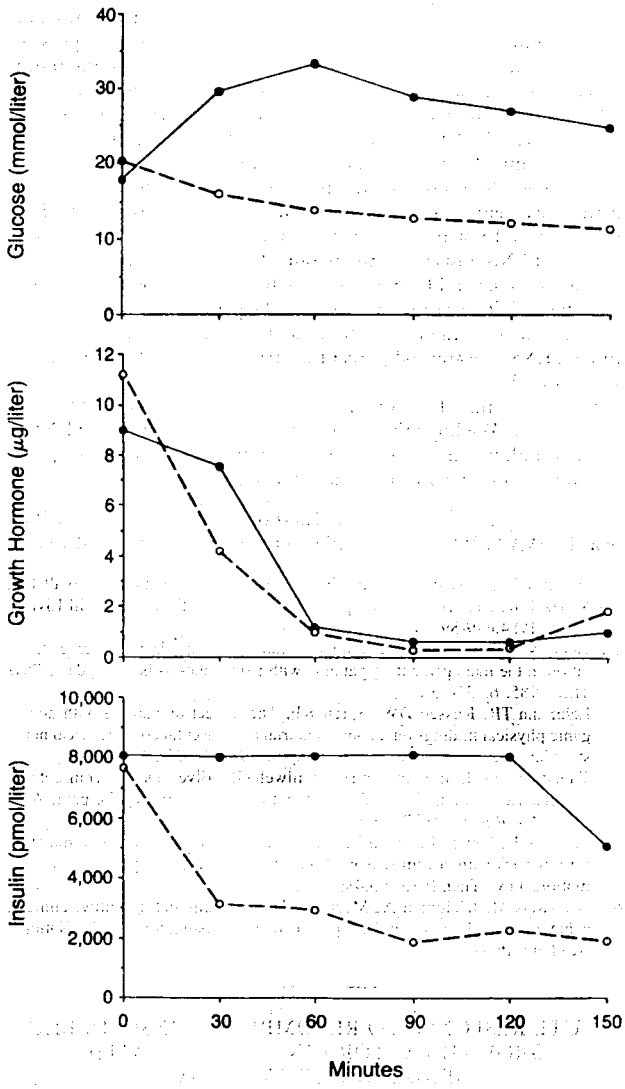

Figure 1. Plasma Glucose, Serum Growth Hormone, and Plasma Insulin Levels after Intravenous Injection of Isotonic Saline (●) or IGF-I (3 mg) (○) Immediately after a Standard Breakfast (Carbohydrate Content, 50 g) in a Patient with Mendenhall's Syndrome.

JOHN D. QUIN, M.R.C.P.
B. MILES FISHER, M.D.
KENNETH R. PATERSON, F.R.C.P.
Glasgow G4 0SF, Scotland — Glasgow Royal Infirmary

AKIRA INOUE, PH.D.
Osaka, Japan — Fujisawa Pharmaceutical Co.

GRAHAM H. BEASTALL, PH.D.
ANGUS C. MACCUISH, M.D.
Glasgow G4 0SF, Scotland — Glasgow Royal Infirmary

1. Guler H-P, Zapf J, Froesch ER. Short-term metabolic effects of recombinant human insulin-like growth factor I in healthy adults. N Engl J Med 1987; 317:137-40.
2. Fujita-Yamaguchi Y, LeBon TR, Tsubokawa M, et al. Comparison of insulin-like growth factor I receptor and insulin receptor purified from human placental membranes. J Biol Chem 1986; 261:16727-31.
3. Mendenhall EN. Tumor of the pineal body with high insulin resistance. J Indiana State Med Assoc 1950; 43:32-6.
4. Rittey CD, Evans TJ, Gray CE, Paton RD, Bojkowski C. Melatonin state in Mendenhall's syndrome. Arch Dis Child 1988; 63:852-4.
5. Niwa M, Sato S, Saito Y, et al. Chemical synthesis, cloning, and expression of genes for human somatomedin C (insulin-like growth factor I) and 59Val-somatomedin C. Ann N Y Acad Sci 1986; 469:31-52.
6. Laron Z, Klinger B, Erster B, Anin S. Effect of acute administration of insulin-like growth factor-I in patients with Laron-type dwarfism. Lancet 1988; 2:1170-2.
7. Ceda GP, Davis RG, Rosenfeld RG, Hoffman AR. The growth hormone (GH)-releasing hormone (GHRH)-GH-somatomedin axis: evidence for rapid inhibition of GHRH-elicited GH release by insulin-like growth factors I and II. Endocrinology 1987; 120:1658-62.
8. Yamashita S, Melmed S. Insulinlike growth factor I regulation of growth hormone gene transcription in primary rat pituitary cells. J Clin Invest 1987; 79:449-52.
9. Taylor SI, Underhill LH, Hedo JA, Roth J, Rios MS, Blizzard RM. Decreased insulin binding to cultured cells from a patient with the Rabson-Mendenhall syndrome: dichotomy between studies with cultured lymphocytes and cultured fibroblasts. J Clin Endocrinol Metab 1983; 56:856-61.

LEFT-HANDEDNESS AND MATERNAL AGE

To the Editor: In a recent letter to the *Journal* (June 7 issue),[1] Coren presented data from a study of 2228 university freshmen suggesting that higher maternal age is associated with a greater incidence of left-handedness. Coren concluded that "these results are consistent

Table 1. Maternal and Paternal Age at Parturition, According to Sex and Handedness of Offspring.

Variable	Right-Handed Offspring	Left-Handed Offspring	P Value*
Mothers of boys			
Mean age ±SD (yr)	27.47±5.70	27.16±5.34	0.146
No.	5661	832	—
Mothers of girls			
Mean age ±SD (yr)	27.50±5.67	27.41±6.01	0.705
No.	5587	583	—
Fathers of boys			
Mean age ±SD (yr)	30.53±6.49	30.14±6.21	0.110
No.	5484	811	—
Fathers of girls			
Mean age ±SD (yr)	30.63±6.32	30.75±6.78	0.665
No.	5381	555	—

*By t-test.

with the supposition that older mothers have more stressful deliveries and gestational periods and that prenatal and perinatal stress contributes to the appearance of left-handedness." That conclusion is somewhat at odds with the meta-analysis[2] that he coauthored (and that he cited in his letter), in which it was concluded that "meta-analyses revealed that all of the relationships [between left-handedness and birth stress], including the significant ones, were very weak, were close to zero, and accounted for less than 1% of the variance."[2] The specific relation between parental age and handedness of offspring has been examined before[3] in a larger, prospective study cited in that same meta-analysis, and no evidence was found for an association.

Previously I have reported a reanalysis of data collected by the National Child Development Study, a cohort study of all children born in the United Kingdom during one week in March 1958[3] (and unpublished data). Obstetrical information was collected at the time of birth by obstetricians and midwives, and children were followed up at the ages of 7, 11, 16, and 23. For the present purposes, handedness was assessed at the age of 11, on the basis of both stated preference and performance. No association was found between any obstetrical factor and left-handedness. Table 1 shows the mean maternal and paternal ages at the time of the children's birth, according to the sex and handedness of the offspring.[3,4] There is no suggestion that left-handed persons have older mothers; in fact, they have somewhat younger mothers, although the effect does not reach statistical significance. Since the sample is more than five times as large as that described by Coren,[1] we may be confident that there is little likelihood that left-handedness is associated with parental age.

London W2 1NY, United Kingdom
I.C. McManus, M.D., Ph.D.
St. Mary's Hospital Medical School

1. Coren S. Left-handedness in offspring as a function of maternal age at parturition. N Engl J Med 1990; 322:1673.
2. Searleman A, Porac C, Coren S. Relationship between birth order, birth stress, and lateral preferences: a critical review. Psychol Bull 1989; 105:397-408.
3. McManus IC. Handedness and birth stress. Psychol Med 1981; 11:485-96.
4. *Idem*. Determinants of laterality in man. (Ph.D. thesis. Cambridge, England: University of Cambridge, 1979.)

To the Editor: In regard to the letter by Coren, I wonder whether the handedness of the mother was recorded and whether the seeming increase in left-handedness in relation to maternal age was modified according to maternal handedness.

San Diego, CA 92093
Harold J. Simon, M.D., Ph.D.
University of California

To the Editor: If birth stress causes left-handedness, it is likely to be the result of damage to the left side of the brain, so that the right side of the body becomes subordinate. Those with a corresponding injury on the right side of the brain will not be distinguishable against the background of normal right-handed persons. They might, however, be marked by a greater-than-normal difference in hand size, most easily detected by measurement of how far down a ring will go on a middle phalanx. It would be interesting to know whether hand size is also related to the mother's age when giving birth, as Dr. Coren has found left-handedness to be.

Fordingbridge, Hampshire SP6 2EJ, United Kingdom
T.H. Hughes-Davies, F.R.C.P.
Breamore Marsh

The above letters were referred to Dr. Coren, who offers the following reply:

To the Editor: Dr. McManus is correct in his observation that our recent literature review and meta-analysis found a small relation between birth stress and left-handedness.[1] What he fails to point out is that although small, the relation was statistically significant and extremely consistent, appearing in 30 of 33 experimental comparisons.

To test further the relation between sinistrality and the risk of birth complications as reflected by maternal age, let me present some data from an ongoing study in our laboratory. The handedness of 2318 university students was determined by a behaviorally validated inventory,[2] and the mother's age at the time of the subject's birth was determined by a questionnaire.

In a first analysis, I used the statistical method described by McManus, dichotomizing persons into left-handed and right-handed groups and looking at the mean maternal age at parturition for each group. To my surprise, my results were quite similar to those that McManus presents, with maternal ages of 27.9 and 27.4 years for left-handers and right-handers, respectively, which is not a statistically significant difference ($t_{2316} = 1.02$, P not significant). Since the results of my previous study were statistically significant[3] but were based on measures of frequency, I reanalyzed the present data. I dichotomized the handedness of the offspring into left and right, and the age of the mothers at parturition into younger and older. The cutoff point that I used for maternal age was 29 years, since Lesinski's review of 22 studies on birth risk concluded that mothers 30 years old or older were at more than the median risk for birth complications.[4] In this analysis I found that 11.8 percent of the offspring of older mothers were left-handed, as opposed to 9.2 percent for younger mothers. This result is statistically significant (chi-square with 1 degree of freedom, 4.14; $P<0.05$) and corresponds to a relative risk of left-handed offspring in older mothers of 1.28.

It is difficult to know why the two forms of statistical analysis produce different results. I can only speculate that perhaps, in the very oldest mothers, birth complications that would produce left-handed children result in spontaneous abortion or stillbirth, rather than the expected live left-handed offspring. There is ample evidence that the incidence of such problems is elevated in older mothers.[4] Only a few much older mothers would be needed to affect the statistical significance of comparisons based on mean maternal age. It is certainly the case that if we consider birth complications in the current sample, we find a pattern similar to that observed for maternal age. In the sample of persons without reported birth complications (defined here as prematurity, low birth weight, breathing difficulty, prolonged labor, Rh incompatibility, multiple birth, breech delivery, instrument delivery, or cesarean section), 9.1 percent were left-handed, as compared with 11.6 percent in the group with stress at birth. This is a statistically significant difference (chi-square = 4.61), corresponding to a relative risk of sinistrality of 1.27. This finding provides additional support for the hypothesis that there is a causal relation between birth stress and left-handedness.

In response to Dr. Simon, in our published study[3] I did not have information on maternal handedness, although we are collecting such data. I also do not have the data on hand size suggested by Dr. Hughes-Davies, which might be interesting to look at.

Vancouver, BC V6T 1Y7, Canada
Stanley Coren, Ph.D.
University of British Columbia