of the controls. This difference however, was not statistically significant. After oral glucose administration the mean growth hormone response of the diabetic children at $\frac{1}{2}$, 1, 2, 3, and 4 hours was lower than that of the control children; however, these differences were not statistically significant.

Only 7 out of the 12 children investigated with juvenile diabetes gave a normal growth hormone response of 7 ng/ml or more during the oral glucose tolerance test.

Discussion

The role of growth hormone (GH) in the pathogenesis of diabetes mellitus has been argued since Young (1937) first demonstrated the diabetogenic effect of anterior pituitary extracts. Our fasting GH results are in agreement with those of Parker *et al.* (1968) and Drash *et al.* (1968), but in disagreement with the results of Johansen and Hansen (1969).

The results presented here suggest that plasma GH concentrations in juvenile diabetes are not always normal, as suggested by Parker *et al.* (1968), or persistently raised, as suggested by Johansen and Hansen (1969). Only 7 out of 12 children investigated here gave a normal growth hormone response of 7 ng/ml or more during oral glucose tolerance test. 50% showed their maximum GH response during the fasting stage of the test, while in the normals this occurred 3 or 4 hours after the glucose load. It is possible that metabolic derangements and stress in the untreated diabetic children might have contributed to this phenomenon. The raised levels reported by Drash *et al.* (1968) after arginine infusion and the raised levels found during 24 hours by Johansen and Hansen (1969) may reflect increased GH secretion in the more severely ill untreated diabetic patient. We have previously reported normal GH levels in patients with mild diabetes, and raised levels in the more severely ill patients (Theodoridis *et al.*, 1970). It appears that an increase of GH levels in untreated diabetic children is not an invariable finding, and that low levels can be found in some cases. This makes it unlikely that growth hormone is a causative factor in the pathogenesis of juvenile diabetes.

Summary

Blood glucose and plasma growth hormone levels were measured during peroral glucose tolerance test in twelve untreated diabetic children. Normal growth hormone responses were found in 7 out of 12 children investigated; in the remaining 5 the responses were subnormal.

We thank Professor C. M. Anderson for her support and the consultant staff of the Birmingham Children's Hospital for permission to study their patients.

REFERENCES

- Discombe, G. (1963). An inexpensive method for the estimation of true glucose in blood and other fluids by the Auto-Analyser. *Journal of Clinical Pathology*, **16**, 170.
- Drash, A., Field, J. B., Garces, L. Y., Kenny, F. M., Mintz, D., and Vazquez, A. M. (1968). Endogenous insulin and growth hormone response in children with newly diagnosed diabetes mellitus. *Pediatric Research*, **2**, 94.
- Hartog, M., Gaafar, M. A., Meisser, B., and Fraser, R. (1964). Immunoassay of serum growth hormone in acromegalic patients. *British Medical Journal*, **2**, 1229.
- Johansen, K., and Hansen, A. P. (1969). High 24-hour level of serum growth hormone in juvenile diabetes. *British Medical Journal*, **2**, 356.
- Parker, M. L., Dildes, R. S., Chao, K. L., Cornblath, M., and Kipnis, D. M. (1968). Juvenile diabetes mellitus, a deficiency in insulin. *Diabetes*, **17**, 27.
- Theodoridis, C. G., Brown, G. A., Chance, G. W., and Rayner, P. H. W. (1969). Growth-hormone response to oral glucose in children with simple obesity. *Lancet*, **1**, 1068.
- Theodoridis, C. G., Chance, G. W., Brown, G. A., and Williams, J. (1970). Plasma insulin and growth hormone levels in untreated diabetic children. *Archives of Disease in Childhood*, **45**, 70.
- Young, F. G. (1937). Permanent experimental diabetes produced by pituitary (anterior lobe) injections. *Lancet*, **2**, 372.

C. G. THEODORIDIS, G. W. CHANCE,* B. T. RUDD, and G. A. BROWN.
Institute of Child Health, Francis Road, Birmingham 16.

*Present address: Hospital for Sick Children, Toronto, Canada.

Maternal Histidinaemia

The hazards of maternal phenylketonuria are well documented (Stevenson and Huntley, 1967; Allan and Brown, 1968). A maternal blood phenylalanine above 15–20 mg/100 ml is almost invariably followed by impaired intelligence. Growth retardation, microcephaly, and abnormalities of the skeleton, heart, and eyes are also found. Next to phenylketonuria and homocystinuria, histidinaemia is probably the most common inborn error of amino acid metabolism. We present here what we believe is the first case of maternal histidinaemia to be recorded.

Case Report

The mother was aged 23 and the father 21 years at the birth of the patient. The father, a guardsman, was healthy, but the mother had *grand mal* epilepsy from the age of 15 years. Her parents are alive and well, as are one brother and one sister. A second sister with spina bifida died at 7 weeks. A younger brother aged 16 years is mildly retarded (IQ 80) and at a school for epileptic children. He was found to have histidinaemia, and when members of his family were examined the disorder

was also diagnosed in his epileptic sister, the mother of our patient, who was then 26 years old. Her urine contained an excess of imidazole pyruvic acid, 390 mg/24 hr, and 720 mg/24 hr in two samples. On three occasions her blood histidine was more than three times normal (7, 8, and 10 mg/100 ml). A histidine load test was characteristic of histidinaemia. Skin histidase (Whitfield and Shepherd, 1970) was less than 0.1 μ moles/g per hr. Her IQ (WAIS) is 100.

The mother had attended irregularly for antenatal care during this, her first, pregnancy. She had no significant nausea but her blood pressure was intermittently raised, the highest recorded value being 150/88 mm Hg. Her protein intake appears to have been normal. Her epilepsy was treated with phenytoin and phenobarbitone. Between the 11th and 19th week she was twice admitted to hospital with an overdose of barbiturate and received psychiatric treatment. Labour started 17 days past term. A first stage of 17½ hours and a second stage of 1 hour 10 minutes were followed by a normal vertex delivery. The male infant weighed 3.46 kg and was in good condition at birth. His subsequent progress was uneventful. According to his mother he walked and said single words by the age of 1 year, fed himself with his left hand at 18 months, and spoke in sentences by the age of 2 years. He is still left-handed.

On examination at 4½ years he was an alert, ginger-haired boy, with normal speech. The head circumference was 50 cm, within 2 SD of the mean for his age. His weight and height were above the 25th centile for his age. Cranial nerves and fundi were normal. No measurable wasting, weakness, or incoordination was detected in the limbs; the deep tendon reflexes were symmetrically normal. He was strongly left-handed and left-footed but able to perform fine manipulations with both hands and hop on either foot. The cardiovascular, respiratory, and alimentary systems were normal.

Investigations. Serum histidine measured with the Technicon Amino Acid Analyser was 2 mg/100 ml, a normal result. Sweat was collected on filter paper by pilocarpine iontophoresis, eluted with 0.1M phosphate buffer, pH 7.4, and the urocanic acid estimated spectrophotometrically at 277 m μ . The level was 10.8 mg/100 ml, well within the normal range. No excess of imidazole derivatives was detected in the urine by paper chromatography. The ferric chloride and 'phenistix' tests were negative.

In the electroencephalogram a symmetrical alpha rhythm was seen at 8 c/sec, blocked by eye opening. Rhythmic activity at 6–8 c/sec was sometimes recognizable over the anterior part of the head unrelated to eye opening. A moderate amount of 4–7 c/sec activity was seen over both hemispheres. No marked change was seen during overbreathing and the response to photic stimulation was well formed and symmetrical. The record showed no signs of a focal lesion or paroxysmal features and was judged normal for age.

The child was assessed psychologically at 3 years 11 months. He responded well to test items. On the Stanford-Binet Intelligence Scale, Form L-M, he

obtained a mental age of 4 years 3 months (IQ 107). No discrepancy was apparent between his verbal and non-verbal development. His speech was clear. In all he was a normal little boy of average intellectual potential.

He manages satisfactorily at his nursery school and relates well to other children, though his concentration is sometimes poor and he is on occasion rather excitable.

Discussion

Timely dietary treatment of phenylketonuric infants is generally accepted to be beneficial. Furthermore, a phenylketonuric mother who had three retarded children while on an unrestricted diet gave birth to a normal infant after a low phenylalanine diet during a subsequent pregnancy (Allan and Brown, 1968). Treatment is therefore also indicated in maternal phenylketonuria, at least if the maternal blood phenylalanine is above 15–20 mg/100 ml. The evidence that a diet low in histidine benefits histidinaemics is inconclusive (van Sprang and Wadman, 1967; Corner *et al.*, 1968; Gatfield *et al.*, 1969). The link between the biochemical abnormality and mental retardation is less direct than in phenylketonuria. In addition to the enzyme defect other factors were probably involved in some severely affected cases (Waisman, 1967; Corner *et al.*, 1968). Blood histidine is lower in histidinaemia than phenylalanine in phenylketonuria, due perhaps to the lower histidine content of dietary protein, higher renal clearance of histidine, or increased efficiency of alternative pathways (Seakins and Holton, 1969). This may account for the lower incidence of mental retardation observed in histidinaemia. The risk in maternal histidinaemia would also be expected to be lower than in maternal phenylketonuria. The blood histidine in the mother of our case is about average for the disease. We could find no evidence of damage to the fetus at this level. Though he is the child of a broken marriage and his mother is often depressed, he is intellectually normal and has no obvious emotional difficulties.

We tentatively conclude from our case that treatment of a histidinaemic mother with a blood histidine below 10 mg/100 ml is probably not necessary. Some histidinaemics, however, have much higher levels than this, and it is possible that, as in phenylketonuria, the risk to the fetus increases dramatically above a certain level. At present it may therefore be safest to treat during pregnancy a histidinaemic with a blood histidine greater than about 10 mg/100 ml.

Summary

A boy aged 4½ years, born to a mother with

histidinaemia, is described. No adverse effects were detected of the maternal metabolic disorder on the physical and intellectual development of the child.

We thank Mr. T. D. Anderson, Dr. R. C. P. Bradley, Mrs. V. G. Classon, Mrs. G. Fletcher, Miss M. K. Jeffrey, Mrs. J. Messenger, Dr. E. H. Reynolds, Mrs. J. Shepherd, Dr. G. T. West, Dr. A. Whitfield, and Dr. K. J. Zilkha for help in this study, and the South West Metropolitan Regional Hospital Board for a grant.

REFERENCES

- Allan, J. D., and Brown, J. K. (1968). Maternal phenylketonuria and foetal brain damage: an attempt at prevention by dietary control. In *Some Recent Advances in Inborn Errors of Metabolism*, p. 14. Ed. by K. S. Holt and V. P. Coffey. Livingstone, Edinburgh.
- Corner, B. D., Holton, J. B., Norman, R. M., and Williams, P. M. (1968). A case of histidinemia controlled with a low histidine diet. *Pediatrics*, **41**, 1074.
- Gatfield, P. D., Knights, R. M., Devereux, M., and Pozsonyi, J. P. (1969). Histidinemia: report of four new cases in one family and the effect of low-histidine diets. *Canadian Medical Association Journal*, **101**, 465.
- Seakins, J. W. T., and Holton, J. B. (1969). Histidinaemia. *Biochemical Journal*, **111**, 4P.
- Stevenson, R. E., and Huntley, C. C. (1967). Congenital malformations in offspring of phenylketonuric mothers. *Pediatrics*, **40**, 33.
- van Sprang, F. J., and Wadman, S. K. (1967). Treatment of a patient with histidinemia. *Acta Paediatrica Scandinavica*, **56**, 493.
- Waisman, H. A. (1967). Variations in clinical and laboratory findings in histidinemia. *American Journal of Diseases of Childhood*, **113**, 93.
- Whitfield, A. E., and Shepherd, J. (1970). Measurement of L-histidine ammonia-lyase activity and urocanic acid content of human skin. *Clinica Chimica Acta*, **29**, 181.

B. G. R. NEVILLE, RUTH F. HARRIS, DIANA J. STERN, and J. STERN

National Hospital, Queen Square, London W.C.1,
Queen Mary's Hospital for Children, Carshalton,
Surrey, and Sutton Child Guidance Clinic, Sutton,
Surrey.

Correspondence to Dr. J. Stern, Queen Mary's Hospital for Children, Carshalton, Surrey.

Favism in Breast-fed Infants

There is a wide spectrum of disease associated with deficiency of erythrocyte glucose-6-phosphate-dehydrogenase (G6PD). It includes favism, cases of acute haemolytic anaemia associated with the intake of some oxidant drugs, such as primaquine (Tarlov *et al.*, 1962), one variety of congenital non-spherocytic haemolytic anaemia (Wintrobe, 1967), and jaundice usually occurring during the first week of life (Shahidi and Diamond, 1959; Zinkham, 1963).

Favism is an acute haemolytic anaemia caused in a susceptible individual by eating the *Vicia fava* beans or inhaling their pollen, and is well recognized throughout the Mediterranean area, particularly in Southern Italy and Greece (Marks and Gross, 1959). A few cases have been described in the United States of America (Larkin, 1953), Great Britain (Holt and Sladden, 1965), and Germany (Gasser, 1953), as well as many countries in the Middle East. In Iraq an acute haemolytic anaemia known as Baghdad spring anaemia (Lederer, 1941) was later proved to be identical with favism, and deficiency of the enzyme G6PD was demonstrated in the affected children (Taj-Eldin, Al-Samarrae, and Al-Aboosi, 1963). In Iraq, children are the usual victims of favism, the syndrome being rare in adults (Zaki and Taj-Eldin, unpublished data). Thus, there must be factors contributing to the aetiology of this disease in addition to G6PD deficiency, inherited susceptibility, and exposure to the plant or its pollen.

During the period from 1962 until 1968 we found 4 cases of favism in exclusively breast-fed infants. Only 3 such cases have previously been reported (Emanuel and Schoenfeld, 1961; Casper and Schulman, 1956; Joannides, 1952).

Method

In Case 1 the deficiency of the enzyme G6PD was demonstrated by Motulsky's cresyl blue dye test (Motulsky and Kampbell-Kraut, 1961), and in the other 3 cases by the reduction of the tetrazolium dye spot test, as described by Fairbanks and Beutler (1962).

Case Reports

Case 1 only is described in detail; the findings in the other 3 cases are summarized in Tables I and II.

Case 1. This male infant aged 4 months, the first child of healthy Arab parents living in Baghdad, was the outcome of a normal pregnancy and labour, and had no significant previous history.

He was exclusively breast-fed. Four days before his admission in November 1962 his mother had eaten boiled, dried fava beans. Two days later he became pale and drowsy, and passed dark urine. On admission he was ill, apathetic, pale, and icteric. The heart rate was 160 per minute, respiratory rate 50 per minute, rectal temperature 37.2 °C. There were no enlarged lymph glands, the spleen was not palpable, and the liver was 2 cm below the costal margin. The mother denied taking any drugs.

Red cell count was 1,480,000/mm³, Hb 3.8 g/100 ml, PCV 12%, reticulocyte count 7%, and white cell count 18,000/mm³, with 55% polymorphs and no immature white cells. Total bilirubin was 4.2 mg/100 ml (indirect reacting 3.6 mg/100 ml); the direct Coombs