

Neonatal Hypoglycaemia—A Critical Reappraisal

Few would deny that neonatal hypoglycaemia is a pathophysiological reality, but doubt still exists regarding the causes and consequences, and therefore the management, of the condition. The association between hypoglycaemia and abnormal neurological manifestations was first emphasized by Cornblath, Odell, and Levin (1959) who suggested that the brain damage suffered subsequently by some of the infants had been caused by the hypoglycaemia. Other work (Chance and Bower, 1966; Pildes *et al.*, 1967; Haworth and McRae, 1967) corroborated these findings and showed that hypoglycaemia associated with clinical abnormality was followed more often by brain damage than was asymptomatic hypoglycaemia. The causal relation between hypoglycaemia and abnormal clinical signs was proven by the rapid correction of the abnormality by intravenous glucose (Cornblath *et al.*, 1959); and this was illustrated in neuropathological terms by showing that infants dying from symptomatic hypoglycaemia had histological changes that differed, particularly in extent and distribution, from those associated with perinatal asphyxia, but that were similar to those reported in adults or experimental animals dying from hypoglycaemia (Anderson, Milner, and Strich, 1967).

If it is accepted that hypoglycaemia *per se* can cause neuronal damage in the newborn, the problem facing the paediatrician can be defined. By elucidating the pathogenesis of the low blood glucose level, a plan of rational investigation and treatment can be formulated and infants at risk can be characterized so that adequate prophylaxis may be offered. In drawing up plans for the detection, investigation, and treatment of hypoglycaemia it is important to devise a scheme which is generally applicable and not one which can be applied only in units with a high staff-patient ratio.

For simplicity, causes of hypoglycaemia in a newborn infant can be subdivided into those which result in deficient hepatic glucose production, and those acting via hyperinsulinism. Deficiency of hepatic glycogen stores has been incriminated in infants who are thought to be malnourished *in utero* (Shelley and Neligan, 1966), but this is probably not the most important factor in their hypogly-

caemia. The main energy source of the normal infant switches from carbohydrate to lipid in the early hours of life, and it is reasonable to infer that, as in the fasting adult, this change is accompanied by depletion of hepatic glycogen. Thus the normal and the abnormal baby both use up their hepatic carbohydrate reserves within hours of birth. Hypoglycaemia probably develops in the small-for-dates infant and in the normally developed baby born very prematurely because of deficient hepatic gluconeogenesis from lipids and amino acids, lack of substrate delivery, particularly lipid, to the liver or to a combination of the two (see review by Adam, 1971). Subnormal hepatic glucose production may also be responsible for hypoglycaemia in rare metabolic errors such as glycogen storage disease. Deficient catecholamine secretion has been proposed as a cause of subnormal glycogenolysis (Broberger and Zetterström, 1961; Stern, Sourkes, and Riihää, 1967). This hypothesis needs to be re-examined in the light of recent work suggesting that glycogenolysis in the newborn rat is governed hormonally more by glucagon than by catecholamines (Girard, Bal, and Assan, 1972), and that the main effect of glucagon is not to stimulate glycogenolysis but gluconeogenesis (Coke, Yeung, and Oliver, 1971). For a given rate of hepatic glucose production the efficiency of utilization is an important modulating factor in the genesis of hypoglycaemia. Hypoxia dramatically reduces the energy produced per unit of glucose and probably has an additive effect with hypoglycaemia in the production of neuronal damage.

Hyperinsulinism is best understood as a cause of hypoglycaemia in infants born to diabetic mothers. The frequency and severity of symptomatic hypoglycaemia in these babies depends on the quality of maternal diabetic control (see Pedersen, 1967). Infants of gestational diabetics are less affected than those whose mothers are treated with insulin (McCann *et al.*, 1966). Babies born to women treated with oral sulphonylureas have a slight but very real chance of intractable hypoglycaemia, for in addition to abnormal intrauterine development they are born with therapeutic levels of an insulinotropic drug in the circulation (Kemball *et al.*, 1970).

It is not generally appreciated that erythroblastosis fetalis is probably the second commonest cause of hyperinsulinism (see review by Milner, 1971) which may cause symptomatic hypoglycaemia in the early hours of life or after exchange transfusion (Barrett and Oliver, 1968; Schiff *et al.*, 1971). Rarer causes of hyperinsulinism are leucine-sensitive hypoglycaemia and abnormal development of the pancreatic islets. Frank insulinomas (Garces, Drash, and Kenny, 1968; Salinas *et al.*, 1968; Grant and Barbor, 1970; Schwartz and Zwiren, 1971) and disorganized development of the islets (Yakovac, Baker, and Hummeler, 1971; Harken *et al.*, 1971) are now being reported more frequently, which suggests that they may not be so rare a cause of hypoglycaemia as had been thought.

The lower limit of normal blood glucose levels is 30 mg/100 ml in term infants and 20 mg/100 ml in infants born prematurely (Cornblath and Schwartz, 1966). The incidence of hypoglycaemia with or without abnormal clinical signs will obviously depend on how energetically the condition is sought. The figure of 17 hypoglycaemic infants per 1000 in a neonatal population selected for admission to a special care unit is probably representative (Griffiths, 1968). Obviously the incidence of subgroups known to be at risk is greater. In small-for-dates babies the incidence of hypoglycaemia with abnormal signs correctable by intravenous glucose is approximately 6% (Pildes *et al.*, 1967). About half the infants born to insulin-dependent diabetics and 20% of those born to gestational diabetics become hypoglycaemic. In these groups approximately one-fifth of the hypoglycaemic infants have abnormal signs (Beard *et al.*, 1971). Remembering that permanent brain damage or death is a probable consequence of untreated symptomatic hypoglycaemia, it is easy to estimate from the above figures a minimum incidence of brain damage which will result from failure to diagnose and treat neonatal hypoglycaemia in a given hospital.

The abnormal signs caused by hypoglycaemia have been described in detail (Cornblath and Schwartz, 1966). Such signs may result also, and more frequently, from other disturbances of the central nervous, cardiovascular, or respiratory systems. The causal relation of hypoglycaemia to the signs can be proven only by giving glucose intravenously. It is possible in most hospitals to nurse infants known to be at risk from hypoglycaemia in a special area where the nursing staff can monitor blood glucose levels frequently with 'Dextrostix'. Prophylaxis against hypoglycaemia should also be provided in these circumstances by

early feeding (Smallpeice and Davies, 1964; Wharton and Bower, 1965). The management of the infant found to have a low blood glucose by 'Dextrostix' will vary from centre to centre. Three possibilities arise when the blood glucose level is checked in the laboratory: the baby may be symptomless and be normoglycaemic, have symptoms and a low blood glucose level, or have symptoms and a normal blood glucose level. A simple but effective approach to the clinical problem arising from a low 'Dextrostix' reading is to confirm the blood glucose level in the laboratory before taking action if the infant is symptomless, but if symptoms are present to give intravenous glucose promptly. The decision to start a glucose or hexose infusion should be based more on the clinical response to intravenous glucose than the blood glucose level. In this way effective treatment can be given with minimum delay and the rare contingency of a baby suffering from neuroglycopenia who is normoglycaemic at the time of blood sampling is also covered. The risk of iatrogenic harm from intravenous glucose is slight provided a peripheral vein is used.

If facilities are available the initial glucose injection can be used as an intravenous glucose tolerance test to estimate the glucose disappearance rate and thereby the severity of the hypoglycaemia (Gentz, Persson, and Zetterström, 1969). Le Dune (1972a) has shown in this way that hypoglycaemia in small-for-dates babies has a more complex aetiology than had been thought. Some infants had a rapid glucose disappearance with normal plasma insulin levels, due presumably to an intracellular glucose deficit, but in 6 of 18 small-for-dates hypoglycaemic infants the babies were hyperinsulinaemic also. To maintain an adequate caloric intake and blood glucose levels without overloading the baby with water, hypertonic solutions must be used. It has been argued that a mixture of glucose (10%), fructose (5%), and galactose (5%) is preferable to glucose (20%) (J. A. Davis, 1970, personal communication), the mixture of hexoses being thought to cause less irritation to the vein and both immediate and delayed rise in the blood glucose level after hepatic conversion of fructose and galactose to glucose. Against this must be set the risks of the baby being intolerant of galactose or fructose. Intravenous therapy must be discontinued gradually, hypertonic solutions being replaced with isotonic glucose to avoid the risk of rebound hypoglycaemia which is particularly likely in hyperinsulinaemic states.

Though other drugs have been used in the management of symptomatic hypoglycaemia, none

has an established place in the management of the condition. Glucagon has been used to stimulate hepatic glycogenolysis. The blood glucose response to glucagon alone has been variously reported to be independent of the clinical state of the baby (Blum *et al.*, 1969) or to be correlated with the fasting blood glucose level of hypoglycaemic small-for-dates infants (Le Dune, 1972b). Glucagon stimulates insulin secretion in the newborn (Milner and Wright 1967) and, as reported elsewhere in this issue of the *Archives*, Le Dune (1972b) has shown that a proportion of hypoglycaemic small-for-dates infants has an exaggerated plasma insulin response to intravenous glucagon. The use of glucagon alone in the treatment of neonatal hypoglycaemia is not recommended, but in view of the fact that glucagon may stimulate both glycogenolysis and gluconeogenesis, the therapeutic use of the hormone in combination with intravenous hexose should be studied further. Glucocorticoids have been recommended (see Klevit, 1970; Beard *et al.*, 1971) but no critical study of the results of such treatment has been performed. The use of steroids may be irrational since adrenocortical function in the normal newborn is as active or more active than in the adult (Okuno, Nishimura, and Kawarazaki, 1972), but Kenny and Preeyasombat (1967) did report that 4 of 8 infants suffering from transient neonatal symptomatic hypoglycaemia had low cortisol production rates. As for glucagon, a scientifically valid study of cortisol secretion and of the therapeutic use of cortisol in the treatment of neonatal hypoglycaemia is needed. Diazoxide has been used successfully to suppress insulin secretion in older children but has been generally ineffective in the management of neonatal hypoglycaemia due to insulinoma. Therapeutic trials of a long-acting catecholamine are being performed (Beard *et al.*, 1971), but this drug, like the others, has other actions besides raising blood glucose levels which may be of more harm than benefit to the baby.

The management of hypoglycaemia is a satisfying facet of neonatal medicine because the condition can be diagnosed readily and treated effectively. Some of the confusion about the clinical significance of neonatal hypoglycaemia has stemmed from work in which the association of abnormal signs and hypoglycaemia has not been clearly differentiated from abnormal signs correctable by intravenous glucose (Griffiths, 1968; Griffiths and Bryant, 1971). The infrequency with which hypoglycaemia causes clinical neurological abnormality should not lull the paediatrician into complacency, for the end results of untreated symptomatic hypogly-

caemia are permanent cerebral damage or death. Therefore, the emphasis must be on prophylaxis and, when indicated, rapid restoration of normoglycaemia.

R. D. G. MILNER

*Department of Child Health,
University of Manchester,
St. Mary's Hospital,
Manchester 13 OJH.*

REFERENCES

- Adam, P. A. J. (1971). Control of glucose metabolism in the human fetus and newborn infant. In *Advances in Metabolic Disorders*, Vol. 5, p. 183. Ed. by R. Levine and R. Luft. Academic Press, New York and London.
- Anderson, J. M., Milner, R. D. G., and Strich, S. J. (1967). Effects of neonatal hypoglycaemia on the nervous system: a pathological study. *Journal of Neurology, Neurosurgery and Psychiatry*, **30**, 295.
- Barrett, C. T., and Oliver, T. K., Jr. (1968). Hypoglycemia and hyperinsulinism in infants with erythroblastosis fetalis. *New England Journal of Medicine*, **278**, 1260.
- Beard, A., Cornblath, M., Gentz, J., Kellum, M., Persson, B., Zetterström, R., and Haworth, J. C. (1971). Neonatal hypoglycaemia: a discussion. *Journal of Pediatrics*, **79**, 314.
- Blum, D., Dodion, J., Loeb, H., Wilkin, P., and Hubinont, P. O. (1969). Studies on hypoglycaemia in small-for-dates newborns. *Archives of Disease in Childhood*, **44**, 304.
- Broberger, O., and Zetterström, R. (1961). Hypoglycemia with an inability to increase the epinephrine secretion in insulin-induced hypoglycemia. *Journal of Pediatrics*, **59**, 215.
- Cake, M. H., Yeung, D., and Oliver, I. T. (1971). The control of postnatal hypoglycaemia. Suggestions based on experimental observations in neonatal rats. *Biology of the Neonate*, **18**, 183.
- Chance, G. W., and Bower, B. D. (1966). Hypoglycaemia and temporary hyperglycaemia in infants of low birth weight for maturity. *Archives of Disease in Childhood*, **41**, 279.
- Cornblath, M., Odell, G. B., and Levin, E. Y. (1959). Symptomatic neonatal hypoglycaemia associated with toxemia of pregnancy. *Journal of Pediatrics*, **55**, 545.
- Cornblath, M., and Schwartz, R. (1966). *Disorders of Carbohydrate Metabolism in Infancy*. Saunders, Philadelphia and London.
- Garces, L. Y., Drash, A., and Kenny, F. M. (1968). Islet cell tumor in the neonate. *Pediatrics*, **41**, 789.
- Gentz, J., Persson, B., and Zetterström, R. (1969). On the diagnosis of symptomatic neonatal hypoglycaemia. *Acta Paediatrica Scandinavica*, **58**, 449.
- Girard, J., Bal, D., and Assan, R. (1972). Glucagon secretion during the early postnatal period in the rat. *Hormone and Metabolic Research*, **4**, 168.
- Grant, D. B., and Barbor, P. R. H. (1970). Islet cell tumour causing hypoglycaemia in a newborn infant. *Archives of Disease in Childhood*, **45**, 434.
- Griffiths, A. D. (1968). Association of hypoglycaemia with symptoms in the newborn. *Archives of Disease in Childhood*, **43**, 688.
- Griffiths, A. D., and Bryant, G. M. (1971). Assessment of effects of neonatal hypoglycaemia. A study of 41 cases with matched controls. *Archives of Disease in Childhood*, **46**, 819.
- Harken, A. H., Filler, R. M., AvRuskin, T. W., and Crigler, J. F., Jr. (1971). The role of 'total' pancreatectomy in the treatment of unremitting hypoglycaemia of infancy. *Journal of Pediatric Surgery*, **6**, 284.
- Haworth, J. C., and McRae, K. N. (1967). Neonatal hypoglycaemia: a six year experience. *Journal-Lancet*, **87**, 41.
- Kemball, M. L., McIver, C., Milner, R. D. G., Nourse, C. H., Schiff, D., and Tiernan, J. R. (1970). Neonatal hypoglycaemia in infants of diabetic mothers given sulphonylurea drugs in pregnancy. *Archives of Disease in Childhood*, **45**, 696.
- Kenny, F. M., and Preeyasombat, C. (1967). Cortisol production rate. VI. Hypoglycaemia in the neonatal and postneonatal period, and in association with dwarfism. *Journal of Pediatrics*, **70**, 65.
- Klevit, H. D. (1970). Corticosteroid therapy in the neonatal period. *Pediatric Clinics of North America*, **17**, 1003.

- LeDune, M. A. (1972a). Intravenous glucose tolerance and plasma insulin studies in small-for-dates infants. *Archives of Disease in Childhood*, **47**, 111.
- LeDune, M. A. (1972b). Response to glucagon in small-for-dates hypoglycaemic and non-hypoglycaemic newborn infants. *Archives of Disease in Childhood*, **47**, 754.
- McCann, M. L., Chen, C. H., Katigbak, E. B., Kotchen, J. M., Likly, B. F., and Schwartz, R. (1966). Effects of fructose on hypoglycemia in infants of diabetic mothers. *New England Journal of Medicine*, **275**, 1.
- Milner, R. D. G. (1971). The development of insulin secretion in man. In *Metabolic Processes in the Foetus and Newborn Infant*, p. 193. Ed. by J. H. P. Jonxis, H. K. A. Visser, and J. A. Troelstra. Stenfort Kroese, N.V., Leiden.
- Milner, R. D. G., and Wright, A. D. (1967). Plasma glucose, non-esterified fatty acid, insulin and growth hormone response to glucagon in the newborn. *Clinical Science*, **32**, 249.
- Okuno, A., Nishimura, Y., and Kawarazaki, T. (1972). Changes in plasma 11—hydroxycorticosteroids after ACTH, insulin and dexamethasone in neonatal infants. *Journal of Clinical Endocrinology and Metabolism*, **34**, 516.
- Pedersen, J. (1967). *The Pregnant Diabetic and her Newborn*, p. 219. Munksgaard, Copenhagen.
- Pildes R., Forbes, A. E., O'Connor, S. M., and Cornblath, M. (1967). The incidence of neonatal hypoglycemia—a completed survey. *Journal of Pediatrics*, **70**, 76.
- Salinas, E. D., Jr., Mangurten, H. H., Roberts, S. S., Simon, W. H., and Cornblath, M. (1968). Functioning islet cell adenoma in the newborn. Report of a case with failure of diazoxide. *Pediatrics*, **41**, 646.
- Schiff, D., Aranda, J. V., Colle, E., and Stern, L. (1971). Metabolic effects of exchange transfusion. II Delayed hypoglycemia following exchange transfusion with citrated blood. *Journal of Pediatrics*, **79**, 589.
- Schwartz, J. F., and Zwiren, G. T. (1971). Islet cell adenomatosis and adenoma in an infant. *Journal of Pediatrics*, **79**, 232.
- Shelley, H. J., and Neligan, G. A. (1966). Neonatal hypoglycaemia. *British Medical Bulletin*, **22**, 34.
- Smallpeice, V., and Davies, P. A. (1964). Immediate feeding of premature infants with undiluted breast-milk. *Lancet*, **2**, 1349.
- Stern, L., Sourkes, T. L., and Rähä, N. (1967). The role of the adrenal medulla in the hypoglycemia of foetal malnutrition. *Biologia Neonatorum*, **11**, 129.
- Wharton, B. A., and Bower, B. D. (1965). Immediate or later feeding of premature babies? A controlled trial. *Lancet*, **2**, 969.
- Yakovac, W. C., Baker, L., and Hummeler, K. (1971). Beta cell nesidioblastosis in idiopathic hypoglycaemia of infancy. *Journal of Pediatrics*, **79**, 226.