Other Causes.—Heavy metals can cause renal tubular damage. In spite of a time relation between the decline in new cases of infantile renal acidosis and the withdrawal, in 1953, of mercury from teething powders (B.M.J., 1954), which quickly resulted in a virtual disappearance of pink disease, mercury intoxication has not been incriminated as a cause of infantile renal acidosis. Moreover, the carefully controlled metabolic studies of Williams *et al.* (1951) showed a normal range of plasma bicarbonate in 22 cases of pink disease. However, we are not aware of any published data on urinary excretion of mercury (or other heavy metals) in cases of primary renal tubular acidosis.

The decline reported from one Scottish, one Welsh, and five English university centres was matched by experience in Belfast and in Lyons. In Belfast 12 cases of infantile renal acidosis were diagnosed at Queen's University Paediatric Clinic between 1953 and 1955 inclusive, and none between 1956 and 1960 (F. M. Allen, personal communication, 1961); in Lyons no new cases were admitted to the paediatric clinic between 1956 and 1960, although 14 had been diagnosed during the preceding four years (M. Jeune, personal communication, 1961).

Summary

A ten-year survey (1950 to 1959 inclusive) of new cases of primary renal tubular acidosis of transient type (infantile renal acidosis) showed a sudden decline after 1954 in seven university teaching centres in England, Scotland, and Wales. Confirmatory evidence is presented from Belfast and Lyons. This decline and the transient nature of the disturbance point to an environmental causation not yet determined. The operation of certain exogenous factors which are known to damage the renal tubule—for example, vitamin D, sulphonamide, and mercury—is considered, but no one of these seems to explain the sudden change in the frequency of infantile renal tubular acidosis.

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REFERENCES

- Albright, F., Burnett, C. H., Parson, W., Reifstein, E. C., jun., and Roos, A. (1946). *Medicine (Baltimore)*, **25**, 399.
 Berlner, R. W., Kennedy, T. J., and Orloff, J. (1951). *Amer. J. Med.*, **11**, 274.
Brit. med. J., 1954, **1**, 265.
 Buchanan, E. U., and Komrower, G. M. (1958). *Arch. Dis. Childh.*, **33**, 532.
 Butler, A. M., Wilson, J. L., and Farber, S. (1936). *Pediatrics*, **8**, 489.
 Carré, I. J., Wood, B. S. B., and Smallwood, W. C. (1954). *Arch. Dis. Childh.*, **29**, 326.
 Doxiadis, S. A. (1952). *Ibid.*, **27**, 409.
 Ferris, T., Kashgarian, M., Leviten, H., Brandt, I., and Epstein, F. H. (1961). *New Engl. J. Med.*, **265**, 924.
 Galán, E. (1955). *Rev. cuba. Pediat.*, **27**, 199.
 Huth, E. J., Webster, G. D., jun., and Elkinton, J. R. (1960). *Amer. J. Med.*, **29**, 586.
 Joint Subcommittee on Welfare Foods (1957). Report. H.M.S.O., London.
 Lightwood, R. (1935). *Arch. Dis. Childh.*, **10**, 205.
 — (1955). *Rev. port. Pediat.*, **18**, 335.
 — MacLagan, N. F., and Williams, J. G. (1936). *Proc. roy. Soc. Med.*, **29**, 1431.
 — Payne, W. W., and Black, J. A. (1953). *Pediatrics*, **12**, 628.
 Neligan, G. A. (1955). *Arch. Dis. Childh.*, **30**, 301.
 Smith, L. H., and Schreiner, G. E. (1954). *J. Lab. clin. Med.*, **43**, 347.
 Williams, H., Macdonald, W. B., and Callow, V. (1951). *Med. J. Aust.*, **1**, 363.

POLYCYTHAEMIA AND ANAEMIA IN NEWBORN MONOZYGOTIC TWIN GIRLS

BY

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The occurrence of anaemia and polycythaemia at birth in monozygotic twins was first recorded by Herlitz (1941), who described two cases. Further instances were reported by Klingberg *et al.* (1955) and Bergstedt (1957). The first cases to be described in this country were the four reported by Kerr (1959). Differences in the haemoglobin levels of monozygotic twins have been noted by Seip (1956), and significant variations in the haemoglobin levels at birth in such pregnancies are probably commoner than previously reported cases would suggest.

History of Cases

The present example of monozygotic female twins (Fig. 1) is of interest because of the great difference in haemoglobin levels and the fact that the anaemic twin (II) was the larger. Complicating hyperbilirubinaemia was encountered in the

FIG. 1.—Twins 10 hours after delivery. The smaller twin (I) severely cyanosed; the larger twin (II) notably pale and limp.

FIG. 2.—Placenta showing sharp demarcation between the larger pale portion on the left and the smaller deeply congested portion on the right.

polycythaemic twin (I), and necessitated exchange transfusion. The general appearance of the placenta conformed to that described by Klingberg *et al.* (1955) and Kerr's first case, having a smaller, engorged part and a larger pale part (Fig. 2).

Haematological Findings

Table I gives details of the haematological findings.

TABLE I.—Haematological Findings

	Investigations	Twin I	Twin II
Cord blood ..	Hb	25.6 g. (175%)	7.8 g. (52%)
	Hb	27.0 g. (182%)	8.6 g. (58%)
	Reticulocytes	3.5%	15%
	P.C.V.	87%	34%
	M.C.H.C.	32%	25.5%
	W.B.C.	8,500	44,000
	Neutrophils	20%	14%
12 hours after delivery	Lymphocytes	32%	11%
	Normoblasts	48%	75%
	Film	Normal	Red cells: gross anisocytosis and polychromasia and slight hypochromasia. Normoblasts very numerous
	Serum bilirubin: Total	17 mg./100 ml.	1.7 mg./100 ml.
	Direct		0.5 „ /100 „

Clinical Findings

Obstetrical Background.—The mother, a 26-year-old primigravida, was admitted to hospital at 36 weeks' gestation with toxæmia, and at this time developed right-sided Bell's palsy. At 39 weeks rupture of the membranes was performed for increasing toxæmia. Subsequent labour was uneventful. An interval of 15 minutes elapsed between the birth of twin I and twin II.

Birth Weights.—Twin I: 5 lb. 10 oz. (2,551 g.). Twin II: 6 lb. 4 oz. (2,835 g.).

Immediate Post-natal Course.—Twin I was markedly cyanosed at birth (see Fig. 1). Respirations of intermittent gasping type were followed by regular respirations at 20 minutes. Oxygen, nalorphine hydrobromide, and nikethamide were administered. After onset of regular respirations cyanosis was still generalized and severe. Cord blood showed a haemoglobin of 25.6 g./100 ml. (175%). Twin II was pale and limp at birth but the heart beat was normal. Intermittent gasping respirations were followed by regular respirations at five minutes. Tone and cry were good, but marked pallor of skin and mucous membranes persisted (see Fig. 1). The cord-blood haemoglobin was 7.8 g. (52%).

Haematology and Serology.—The results of more extensive haematological and serological studies on both babies at 12 hours are summarized in Tables I and II. The direct antiglobulin test (Coombs test) was negative in both infants. Other serology on twin I showed no "mixed fields" with anti-A or any other grouping serum. The blood of polycythaemic twin I showed "no maternal ghosts by acid

TABLE II.—Blood Groups

Subject	ABO	Rh Phenotype	Probable Genotype	MN	P	K	F
Mother ..	A	ccDE	cDE/cde	MN	+++	—	—
Twin I ..	A	ccDE	cDE/cde	MN	—	—	+
„ II ..	A	ccDE	cDE/cde	MN	—	—	+

elution technique." The maternal blood (12 hours post partum) showed "only occasional foetal cells seen by acid elution technique—equivalent to about 3 ml. of foetal blood in the maternal circulation." There was no history of any hereditary haemoglobinopathy, and the maternal Wassermann reaction was negative.

Subsequent Progress

Twin I.—This infant remained lethargic and deeply cyanosed over the first 24 hours. Jaundice was clinically

evident at 10 hours. The serum bilirubin level at 24 hours was 23 mg./100 ml. (indirect). Exchange transfusion with 400 ml. of group O rhesus-negative blood was performed at 33 hours. On cutting the umbilical cord dark red viscid blood oozed from the vein. Venous pressure was 3½ in. (9 cm.). Definite reduction in jaundice occurred during the exchange transfusion and the infant became less cyanosed. Subsequent progress was interrupted by two generalized convulsions associated with a rectal temperature of 101° F. (38.3° C.) which was probably attributable to an incubator fault. On the third day the total serum bilirubin had fallen to 9.6 mg./100 ml. (direct 1.03 mg.) and the haemoglobin level fell, with the result that it was 23.8 g. (162%), 18 g. (122%), and 16.1 g. (109%) on the seventh, ninth, and sixteenth day respectively. Hepatosplenomegaly was never a feature. Slight generalized oedema was present for the first seven days, and the infant did not pass urine for some 79 hours after delivery.

Twin II.—At 12 hours physical examination and behaviour were considered to be within normal limits apart from pallor and enlargement of the liver (palpable 1½ in. (4.5 cm.) below the right costal margin); there was no other evidence of circulatory failure. A transfusion of 80 ml. of concentrated group A rhesus-positive blood was given via the umbilical vein, the pressure in which was normal. After transfusion the haemoglobin was 15.2 g. (103%) and physical examination showed nothing abnormal. Subsequent progress was uneventful.

Follow-up at 10 Weeks.—Twin I weighed 7 lb. 6 oz. (3,345 g.). Physical examination and developmental progress both normal. Hb 11.9 g. (82%); W.B.C. 8,000; platelets 270,000. Twin II weighed 8 lb. 9 oz. (3,885 g.). Physical examination and developmental progress both normal. Hb 9.5 g. (66%); W.B.C. 6,400; platelets 245,000.

Placental Findings

Naked-eye Examination.—The placenta was 20 cm. in diameter with two cords arising, one being 4 cm. from one edge, and the other 2 cm. from the opposite edge. Slightly more than half the placenta was pale in colour, and slightly less than half deeply congested. Demarcation between the two parts was extremely sharp (Fig. 2).

Histology.—The vessels of one part of the placenta were empty, while those of the other part were engorged. Demarcation between the anaemic and congested parts was very sharp. The two parts were otherwise quite normal. In the cord of the congested part the vein was dilated and full of blood clot. The vessel in the cord of the pale part was empty.

Aetiology

It has been recognized for many years that exsanguination of a second twin can occur via the unligated cut cord of the first twin. The first satisfactory demonstration of vascular anastomoses between the two parts of monozygotic twin placentas has been attributed to Schatz (1884), who considered that anastomoses were either superficial or deep, the latter being arteriovenous.

Potter (1961) states that communications between large blood-vessels supplying different foetuses and between smaller vessels of the villi are common with uniovular twins. They are rare with binovular twins. Browne and McClure Browne (1955) maintain that the circulations in uniovular placentas always communicate through the so-called third circulation and quote Schatz (1884) on the subject.

In the present case there appears to have been imbalance between the two foetal circulations involving the contribution of blood to the smaller polycythaemic twin by the larger anaemic twin. Significant foeto-maternal transfusion was excluded by examination of

maternal blood for foetal cells less than 12 hours after birth. Haemolysis as an explanation for the anaemia in twin II seemed unlikely, there being a normal bilirubin level, a negative Coombs test, and no haematological incompatibility between mother and infants.

The placental findings in the present case appear to be identical to those reported by Klingberg *et al.* (1955) and Kerr's (1959) Case 1, in that one part was grossly congested with dilated vessels and the other part pale with collapsed vessels.

Klingberg *et al.* (1955) suggest that the engorgement was the result of venous obstruction to the anaemic twin. In the present instance it seems likely that the smaller engorged part of the placenta supplied the smaller polycythaemic infant. The reasons for this view are that, firstly, there was no obvious site of venous obstruction either in the engorged cord or in the intra-abdominal part of the umbilical vein, a catheter passing easily up the vessel. Secondly, as the vascular imbalance was probably a comparatively recent occurrence, it seemed more likely that the smaller engorged placenta supplied the smaller twin. In uniovular twin pregnancies the relationship of placental weight to foetal weight is much the same as in a single pregnancy (Potter, 1961).

Pathology

Various techniques have been used to demonstrate the vascular connexions and are extensively reviewed by Gedda (1961). Prominent among studies are those of De Camellis and Tameo (1948), who showed by radiological methods that superficial anastomoses may be either arterio-arterial or veno-venous, while deep anastomoses are always between artery and vein. Superficial arterio-arterial anastomoses and deep arterio-venous connexions, if unbalanced, can produce unequal distribution of blood between the two fetuses.

In reported cases milk perfusion of the cord vessels (Bergstedt, 1957) and injection of coloured fluids (Klingberg *et al.*, 1955) have been used to demonstrate the vascular connexions. Failure to demonstrate a connexion between the two parts by perfusion in the present case was probably due to delay in examining the specimen after birth.

The occasional occurrence of polycythaemia in one and anaemia in the other of monozygotic twins has been effectively demonstrated (Herlitz, 1941; Klingberg *et al.*, 1955; Bergstedt, 1957; Kerr, 1959), and it has been shown that this occurrence can sometimes be explained by the nature of the vascular interplacental anastomoses (Klingberg *et al.*, 1955; Bergstedt, 1957).

As described, the placenta of the twins, the subject of this paper, was grossly abnormal on macroscopic examination, but technical difficulties prevented the demonstration of abnormal vascular anastomoses. There were no findings to suggest that the anaemia of twin II was due to bleeding from trauma of placenta or cord, or to foeto-maternal transfusion.

Treatment

Early recognition of the unequal distribution of blood between the two infants of a twin pregnancy has a direct bearing on management.

Colour changes of the infants have prompted investigation in the majority of reported cases. Pallor of the anaemic twin has been observed more frequently; however, in two instances (Kerr, 1959) persistent

cyanosis led to the correct diagnosis. A marked difference in the haemoglobin levels of twins affords additional evidence of the diagnosis, provided the anaemic twin has not been the subject of haemolysis, external bleeding, or foeto-maternal transfusion.

Treatment consists of simple transfusion to the anaemic infant and of reduction of the polycythaemia in the other baby by repeated small venesections or by exchange transfusion.

The occurrence of hyperbilirubinaemia in the polycythaemic baby in our case was an additional reason for exchange transfusion. Bergstedt (1957) reported the finding of hyperbilirubinaemia in similar circumstances (23.5 mg./100 ml. indirect).

Unexplained cyanosis or notable pallor in a newborn twin is an indication for haemoglobin estimation in both infants.

Summary

A case of monozygotic twins is reported, one being anaemic and the other polycythaemic at birth. Twin I, deeply cyanosed from birth, had a haemoglobin level of 175% and was given an exchange transfusion at 33 hours because of a rising indirect bilirubin level (23 mg./100 ml. at 24 hours). The cord haemoglobin level of twin II, who was markedly pale from birth, was 52%, and the baby was given a simple transfusion at the age of 10 hours.

Physical examination and developmental progress were considered to be normal in the case of both twins when followed up at the age of 10 weeks.

Macroscopically, one part of the placenta was pale and the other deeply congested, the line of demarcation being extremely sharp. Histologically, the vessels in the congested part were dilated and those in the pale part collapsed. Reasons are presented for considering that the engorged part of the placenta supplied the polycythaemic baby.

Haematological and serological findings would appear to exclude the possibility of haemolysis in and foeto-maternal transfusion from twin II and transplacental bleeding from the mother to the polycythaemic twin I.

It is suggested, therefore, that the findings in the present case are best explained by the presence of vascular anastomoses which are known to occur frequently between the two parts of monozygotic twin placentas.

Unexplained cyanosis or notable pallor in a newborn twin is to be regarded as an indication for haemoglobin estimation in both infants.

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REFERENCES

- Bergstedt, J. (1957). *Acta paediat. (Uppsala)*, **46**, 201.
- Browne, F. J., and McClure Browne, J. C. (1955). *Antenatal and Postnatal Care*, 8th ed. Churchill, London.
- De Camellis and Tameo (1948). Quoted by Gedda (1961).
- Gedda, L. (1961). *Twins in History and Science*. Thomas, Springfield, Illinois.
- Herlitz, G. (1941). *Acta paediat. (Uppsala)*, **29**, Suppl. 1, p. 211.
- Kerr, M. M. (1959). *Brit. med. J.*, **1**, 902.
- Klingberg, W. G., Jones, B., Allen, W. M., and Dempsey, E. (1955). *Amer. J. Dis. Child.*, **90**, 519.
- Potter, E. L. (1961). *Pathology of the Fetus and Infant*, 2nd ed. Year Book Medical Publishers, Chicago.
- Schatz, F. (1884). *Arch. Gynäk.*, **24**, 337.
- Seip, M. (1956). *Acta paediat. (Uppsala)*, **45**, 58.