Discordance in Monozygotic Twins: One Diabetic, the Other an Idiot with Neurological Abnormalities*

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While our knowledge of aetiology remains incomplete, the reporting of examples of discordant monozygotic twins continues to be of value. Cases where the difference has been present from birth also serve to remind us of a fact, commonly overlooked, that in exceptional circumstances the intra-uterine environment may be significantly different for monozygotic twins.

The few case reports available are of considerable interest but often of limited value. In the earlier papers zygosity could not be established to the satisfaction of workers today, and in almost every study the particular prenatal factor could not be determined.

The pair to be described, though looking identical for the first few months of life, were distinctly different in health, and with time this difference became more exaggerated. Now, at 19 years, one is a bed-ridden idiot with small head and spastic diplegia, subject to frequent *grand mal* seizures, while his twin, a farm labourer of dull normal intelligence, suffers from diabetes. Neither twin shows any features of the other's condition.

Case Report

The proband (Twin A) was included in an unselected series of twins attending the Maudsley Hospital Children's Department. He was referred in 1957 for an opinion as to whether he was epileptic. The twins were conceived 5 years after the mother's only other pregnancy, which resulted in a healthy female child, and were born in the summer of 1944; the mother was then aged 30 and the father 31. The only incident during the nine-month pregnancy was a fall at 8 weeks which resulted in a broken finger, but no *per vaginam* loss. The mother can recall no minor illnesses while she was carrying the twins; there were no signs of toxæmia nor any suggestion of threatened abortion. The only

radiological examination was two weeks before the confinement to confirm the multiple pregnancy, and she was taking no drugs.

After a labour lasting 8 to 10 hours Twin A presented as a vertex and was born without difficulty, weighing 6 lb. 9 oz. (2976 g.). Ten minutes later Twin B presented as a breech and was also delivered without any trouble; he weighed 4 lb. 6 oz. (1984 g.). The first-born was a healthy baby, but the second was 'slightly shocked' and jaundiced, and was placed in an oxygen cot; the mother did not see him until 10 days later. The only information available about the afterbirth is from the midwife's record, which refers to, 'binovular placenta and membranes complete'.

The twins were both on bottles when they were taken home from hospital at 3 weeks of age, and their subsequent progress was recorded by the health visitor. Twin B was a lazy placid baby, and great difficulty was experienced in getting him to suck; it was realized from the outset that something was wrong, and after getting opinions from several doctors the parents took him to the Hospital for Sick Children, Great Ormond Street, when he was 14 months old. The consultant there considered he was microcephalic, obviously retarded, and possibly with impaired vision, and recommended re-examination after a lapse of twelve months. Before this time, however, his management had become such a problem that he was admitted to hospital; he was then 21 months old. He was diagnosed as a 'microcephalic idiot with spastic paralysis of the lower limbs' and transferred to a colony for mental defectives four years later; and there he has remained. On admission to the colony he was a 'helpless incontinent bedridden microcephalic idiot' who had no awareness of what was going on around him, and his mental age was assessed at about 3 months.

The only change in his condition has been in the character of his frequent epileptic seizures; at first these were *petit mal*, but since the age of 15 years tonic and *grand mal* seizures have predominated. Due to his complete inability to co-operate, he is still fed on a liquid diet, and is taking phenobarbitone and primidone mysoline. His only illnesses have been mild attacks of measles at 9 months, chicken-pox at 21 months, and otitis media at the age of 8 years. At no time have reducing substances been found in his urine, and a glucose tolerance test is within normal limits. Examina-

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TABLE I
DETAILS OF CLINICAL EXAMINATION IN TWIN A AND TWIN B

Character	Twin A	Twin B
Birth weight	6 lb. 9 oz. (2976 g.)	4 lb. 6 oz. (1984 g.)
Clinical examination	No abnormal physical features; well-built and well-nourished	Sloping forehead and small head; severe spastic paresis of lower extremities with generalized hyperreflexia; sternum slightly deviated to right; mid-thoracic scoliosis
<i>Investigations</i>		
Glucose tolerance test	Diabetic	Normal
Chromosome analysis	—	No abnormalities
Electroencephalogram	No abnormality	—
Intelligence quotient	78-84	Approx. 20
<i>Measurements</i>		
Weight	10 st. 1 lb. (64 kg.)	6 st. 6 lb. (39 kg.)
Head circumference	21½ in. (55.1 cm.)	19 in. (48.2 cm.)
length	18.4 cm.	15.5 cm.
breadth	16.6 cm.	14.2 cm.
Cephalic index	0.90	0.92
Height	173 cm.	170 cm.
Sitting height	80.2 cm.	89.2 cm.
Bi-acromial diameter	41.6 cm.	35.5 cm.
Bi-iliac diameter	30.7 cm.	24.2 cm.
Androgyny score	94.1	82.3

tion of a blood culture revealed no chromosome abnormality and details of a recent clinical examination are summarized in Table I.

Twin A was developing normally and reaching milestones at the average ages; all went well until his second year when he developed diabetes. This proved extremely difficult to control, and his admission to hospital in coma was such a frequent occurrence that he was sent at the age of 7 years to a special institution for severe diabetics where he remained until the age of 16. Since his return home he has been in regular employment as a farm labourer and his diabetes is now well stabilized. He was given the Terman Merill Intelligence test on three occasions (Table II).

TABLE II
TERMAN MERILL INTELLIGENCE TEST
ON THREE CONSECUTIVE YEARS ON TWIN A

Year Tested	Mental Age	Actual Age	I.Q.
1956	9.6	12.1	79
1957	10.3	13.1	78
1958	11.6	14.1	84

These results were consistent with his school reports and general behaviour, and place him in the dull normal range.

An electroencephalogram in 1957 showed no abnormalities, and there is nothing in the history to indi-

cate a diagnosis of epilepsy. The turns that led to his referral at the age of 13 were in all likelihood symptoms of hypoglycaemia, and there has been no subsequent suggestion of an epileptic seizure.

The family history has been carefully checked, and the only positive feature is the development of diabetes in the maternal grandmother when she was in her eighties. The father's sister had monozygotic twins, but there is no other record of multiple pregnancies. No relatives have suffered from epilepsy, none have been mentally retarded, and there is no history of consanguinity. Their mother has kept in good health and has had no miscarriages. Both she and the father are of above average intelligence, and he now has a responsible clerical job in a Shire Council after having successfully managed a large grocery store. His only illness was pulmonary tuberculosis which necessitated sanatorium treatment when the twins were 2 years old. Their sister was a shorthand typist before her marriage, and has had no other illnesses apart from mild tuberculosis.

Zygosity

As a common chorionic membrane was not demonstrated it cannot be absolutely stated that the twins are monozygotic, and cross skin grafting could not be arranged. Blood grouping of the twins, their parents, and sib was carried out by Dr Ruth Sanger at the Lister Institute and is summarized in Table III. The

TABLE III
BLOOD GROUPING OF TWINS, PARENTS, AND SIB

	O	MMS	P ₁ +	R ₁ r	Lu (a -)	K -	Le (a + b -)	Fy (a -)	Xg (a +)
Father	A ₁	MsMs	P ₁ +	R ₁ R ₁	Lu (a -)	K -	Le (a + b -)	Fy (a +)	Xg (a +)
Mother	A ₁	MMS	P ₁ +	R ₁ R ₁	Lu (a -)	K -	Le (a + b -)	Fy (a + b +)	Xg (a +)
Sister	A ₁	MsMs	P ₁ +	R ₁ R ₁	Lu (a -)	K -	Le (a + b -)	Fy (a +)	Xg (a +)
Twin A	A ₁	MsMs	P ₁ +	R ₁ R ₁	Lu (a -)	K -	Le (a + b -)	Fy (a +)	Xg (a +)
Twin B	A ₁	MsMs	P ₁ +	R ₁ R ₁	Lu (a -)	K -	Le (a + b -)	Fy (a +)	Xg (a +)

FIG. 1. Appearance of twins at 12 months. Twin B is being propped up on the left.

FIG. 2. Appearance of twins at 19 years. Twin B on the left.

TABLE IIIA

Character	Independent Relative Chance	
	Parental and Sibship Data Included	Parental Data Excluded
Initial odds	2.3333	2.3333
Likeness in sex	0.5	0.5
Likeness in ABO	0.6113	0.6470
Likeness in MNS	0.5	0.4116
Likeness in Rhesus	0.5	0.5021
Likeness in Fy	0.7072	—
Likeness in P, Lu, K, Le, and Fy	—	0.3375
Likeness in Xg	0.8303	0.7380
Total relative chance pD	0.1047	0.0389
Total chance pD/(1 + pD)	0.0947	0.0374

calculated relative chance in favour of their being dizygotic on these blood findings, based on the method of Smith and Penrose (1955), is given in Table IIIA.

Their similarity in morphological traits provides added empirical evidence to support the argument that they are monozygotic. Both have the same medium brown iris colour; the texture, colour, and distribution of hair is identical; eyebrows are the same shape; and both have numerous moles on the trunk and face. People had difficulty in identifying them during their early months (Fig. 1), though their differing health has produced such a divergence in physique and appearance that they now have little in common (Fig. 2).

Palm prints were examined by Dr S. B. Holt of the Galton Laboratory. The palmar main lines and the type-

FIG. 3. Palm prints. Twin A at the top and Twin B at the bottom.

lines of the fingers are shown in Fig. 3. Dr Holt reports:

'The palms of the two twins show various features in common, and the configurations are not inconsistent with monozygosity. On all the four palms there is a rather highly placed axial triradius, in the position t' , suggestive of growth disturbances during the period of ridge differentiation (that is in the third and fourth foetal months). Large hypothenar patterns are present on both palms of twin B and on the left palm of twin A. On the left palm of both twins the A main line termi-

nates at the base of the thumb, a feature that is uncommon in the general population. In the distal area of both right palms the arrangement of the main lines B , C , and D is similar, with C forming a fourth interdigital loop. On the left palm of both twins there are fourth interdigital loops but they differ in that on twin B the loop is formed by main line D , while in twin A the loop is formed by line C .

'Values of the maximal atd angles and $a-b$ ridge counts are given in Table IV:

TABLE IV

	Maximal <i>atd</i> Angle			<i>a-b</i> Ridge Count		
	Left	Right	Sum (both hands)	Left	Right	Sum (both hands)
Twin A	52	51	103	38	40	78
Twin B	46	40	86	44	38	82

'The values of the maximal *atd* angles on right and left palms of twin B are deceptively low, considering the position of the proximal, *t'*, triradius on each. These are due to the distances between triradii *a* and *d* on both hands being less than the corresponding distances in twin A, presumably because the hands of twin B are narrower than those of his twin.

'Although there are some discrepancies between the twins with respect to finger pattern types (the most marked being the presence of two radial loops on the fingers of twin B and the absence of this type of pattern in twin A), their total ridge counts (single) are very similar, differing only by 4 ridges'.

Details of finger ridge counts are tabulated in Table IVA. As described in Slater (1963), one of the two terminal points has been counted in every case, rather than neither terminal point as described by Holt (1961).

TABLE IVA

FINGER RIDGE COUNTS IN TWIN A AND TWIN B

Finger		Twin A		Twin B	
		Pattern	Ridge Count	Pattern	Ridge Count
<i>Right hand</i>					
1	r.	UL	19	UL	19
	u.		—		—
2	r.	UL	19	RL	—
	u.		—		11
3	r.	W	13	RL	—
	u.		6		16
4	r.	W	19	W	20
	u.		14		11
5	r.	UL	19	UL	17
	u.		—		—
<i>Left hand</i>					
1	r.	UL	21	UL	18
	u.		—		—
2	r.	UL	12	W	14
	u.		—		18
3	r.	UL	17	W	14
	u.		—		12
4	r.	UL	19	UL	19
	u.		—		—
5	r.	UL	15	UL	17
	u.		—		—
Total (double count)			193	206	
Total (single count)			173	169	

r. = radial side.

u. = ulnar side.

UL = ulnar loop. RL = radial loop. W = whorl.

Probability dizygotic (Slater's method, 1963) = 0.64.

Relative chance dizygotic (Smith and Penrose method, 1955) = 0.23.

This does not, of course, affect the intra-pair difference or the probability of dizygosity by the Smith and Penrose method. The probability of zygotity, based on these data, varies considerably, depending on the technique of analysis used. As disturbance of growth in the early foetal months may bring about extreme modifications in dermal patterns (Walker, 1957), it would not be surprising to find differences in pattern and count in these twins irrespective of zygotity.

Discussion

Microcephaly, cerebral palsy, epilepsy, and idiocy are all heterogeneous groups of disorders, and, occurring together, indicate an underlying abnormality in cerebral development but do not add up to any specific syndrome. Each condition, taken separately, has presented difficulties in establishing a clear-cut aetiological classification, and the relative importance of genetic factors in each one varies considerably.

Microcephaly, a purely descriptive term, was considered until recently to be due either to a recessive gene, or to the effects of irradiation. Böök, Schut, and Reed (1953), when reviewing the published reports, referred to asphyxia at birth, to brain infection, to encephalitis, to maternal rubella, and to some other maternal infections as possible causes, but concluded that the evidence for this was not soundly based. Komai, Kishimoto, and Ozaki (1955) also took the view that the evidence for non-genetic agents other than irradiation was not convincing. Since then Hinden (1956) has described a case of microcephaly in one of monozygotic twins and showed that as the twins were grossly different at birth, and there was no subsequent illness associated with brain damage, the difference must have been due to some intra-uterine factor. The affected twin had, in addition, central blindness and adducted thumbs, but was not spastic; the pregnancy was reported as being normal.

Brandon, Kirman, and Williams (1959a) have also described two discordant monozygotic pairs. Although it was difficult to exclude 'birth injury' in the broad sense of the term as a causal factor in both cases, the balance of evidence favoured the view that the microcephaly was due to factors operating during pregnancy.

In their survey of microcephaly at the Fountain Hospital, Brandon, Kirman, and Williams (1959b) found that in 131 cases, 70 had spastic diplegia, and 57 were also epileptic. Their material showed more evidence of the familial incidence in the form of microcephaly with spastic diplegia than in the

uncomplicated form. Allen and Kallmann (1962) in their extensive survey of mental subnormality in twins report three pairs of monozygotic twins, and all were concordant for microcephaly alone.

Twin B reported in this paper has a small head and slanting forehead and, though measurements of cranial circumference were not recorded in the various hospital notes, all doctors who saw him consistently made a diagnosis of microcephaly. This case supports the conclusion of Hinden (1956) and Brandon *et al.* (1959a) that intrauterine factors, other than irradiation, may be responsible for microcephaly, and further suggests that cases associated with spastic diplegia may also be included in this aetiological group. Like the other three case reports, the causative factor did not produce any obvious disturbance of the mother's pregnancy.

Cerebral palsy is also the end-product of a variety of disease processes, and twin studies have thrown light on the problem of aetiology. Thums (1939) reported 90 pairs of twins where at least one had cerebral palsy, and concluded that genetic factors played only a minor role, while birth injury was a very frequent cause. Allen's data (1955) supported these findings by also showing that twins were rarely concordant for cerebral palsy; however, there was a high rate of stillbirth or neonatal death in twin partners in his cases.

Only one of his three monozygotic twin pairs was concordant. Kernikterus had affected another pair in differing degrees, and only one was spastic, while in a third pair, with an inherited bleeding tendency, trauma had produced a cerebral haemorrhage in one twin and so explained their discordance. Birth trauma can be excluded in the present case; it is, however, in agreement with the current opinion that genetic factors are of minor importance in the production of cerebral diplegia.

Although in the minority, there is nothing exceptional in reporting discordance for epilepsy in monozygotic twins. Conrad (1935) found 20 of 30 uniovular twin pairs to be concordant, and other studies have been in agreement with this figure of 67% (Rosanoff, Handy, and Rosanoff, 1934; Harvald, 1951; Lennox, 1951).

Concerning *idiocy*, Allen and Kallmann (1962) showed that when low-grade mental defect was associated with clinical abnormalities other than cerebral palsy, monozygotic twins were nearly always concordant for mental defect, if not for the other clinical findings. When mental deficiency was associated with cerebral palsy and epilepsy, discordance was the rule, thus suggesting the operation of accidental agents rather than a genetic

basis. The present case is in keeping with their findings.

There is a strong hereditary background to *diabetes*, as illustrated by twin data, but environmental factors, as with epilepsy, have prevented the expression of the gene or genes in one-third of the monozygotic twins reported (Berg, 1939; Joslin, 1940; Verschuier, 1958).

The present case is thus of no exceptional interest in being discordant. Twin B's other disabilities have possibly protected him against his genetic potentiality to develop diabetes, by enforcing a simple and unvaried diet and environment.

Price (1950) suggested that differences in placental circulation may account for divergent development in monozygotic twins. The reported cases of discordant pairs, however, are just as commonly dichorionic as monochorionic (Waardenberg, 1957). In the twins reported here, the midwife's brief comment suggests that such a factor was not operating to explain the difference between them. It is unlikely that the mother's fall at eight weeks could have contributed in any way to this developmental difference, but something operating at about that time and affecting only one of the twins must be held responsible.

Summary

A pair of twins discordant for microcephaly, cerebral palsy, epilepsy, idiocy, and diabetes is described.

The high probability of their being monozygotic is supported by identical blood groups and other characteristics.

This case supports the belief that intrauterine factors, other than irradiation, can produce microcephaly even in association with cerebral palsy.

Severe incapacity protected one of the twins from developing diabetes.

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