

## Discussion

Holoprosencephaly implies a whole or undivided forebrain. It includes a broad spectrum of abnormalities ranging from complete failure of differentiation of the telencephalic vesicles to a partial fusion of otherwise well developed hemispheres. According to DeMyer,<sup>1</sup> three cerebral types can be recognised: alobar, semilobar, and lobar. As a result of diencephalic dysgenesis, endocrine disorders are sometimes present.<sup>2</sup>

There is often an association with a range of facial midline deformities,<sup>3</sup> probably resulting from a failure of embryonic interaction between the notochordal plate, the neuroectoderm of the brainplate, and the oral plate.<sup>4</sup>

The correlation shown by DeMyer *et al*<sup>3</sup> and summarised as 'the face predicts the brain' is illustrated by the reported cases. The least affected sib (case 3) had a cleft lip, flat nose, hypotelorism, and lobar holoprosencephaly on CT scan. The next (case 1) had hypotelorism with microphthalmia of the left eye and semilobar holoprosencephaly. The most severely affected (case 2) had cyclopia with alobar holoprosencephaly. We were unable to find any published report describing a comparable variation in one family.

The aetiology of holoprosencephaly is heterogeneous. Most cases are sporadic. Environmental factors, maternal disease, and several distinct chromosomal syndromes are associated with it.<sup>1,5</sup> Autosomal dominant inheritance with incomplete penetrance and wide variability, sometimes with minimal involvement, as well as autosomal recessive inheritance have been described.<sup>5</sup>

Although in most disorders with autosomal recessive inheritance the extent of the malformation is usually similar, the absence of minor signs in the parents, the negative medical history in all the pregnancies, and the fact that three out of four

children in one sibship were affected makes autosomal recessive inheritance in this family most likely.

In a study of 30 families in which a child with a severe form of holoprosencephaly was born, Roach *et al*<sup>6</sup> found that two out of 35 subsequent children of 18 of the mothers had holoprosencephaly. The empirical recurrence risk was estimated as 6% ( $\pm 4$ ). Because of the wide variation in expression of this disorder, extensive examination of sibs and parents for minor manifestations, such as anosmia, single central incisor, hypo- and hypertelorism, and hypothalamic-pituitary dysfunction, is essential for genetic counselling. If Mendelian patterns of inheritance are established for particular families, the recurrence risk increases accordingly.<sup>1,6</sup>

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## Thanatophoric dysplasia in identical twins

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**SUMMARY** Female twins concordant for thanatophoric dysplasia are presented. Monozygosity was confirmed using minisatellite DNA genetic fingerprinting. The evidence

supporting new dominant mutations as the likely cause of thanatophoric dysplasia is reviewed.

Conflicting conclusions have been reached regarding the mode of inheritance of thanatophoric dysplasia.

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sia. Early reports of affected sibs born to healthy parents<sup>1,2</sup> prompted Bouvet *et al*<sup>3</sup> to suggest autosomal recessive inheritance, whereas Pena and Goodman<sup>4</sup> favoured a polygenic mechanism with a recurrence risk of approximately 1 in 50. Reassess-

ment of early reports of allegedly affected sibs resulted in revision of the diagnosis in many instances,<sup>5</sup> leading to the suggestion that thanatophoric dysplasia is likely to result from a new dominant mutation in many if not all cases.<sup>6,7</sup> In this

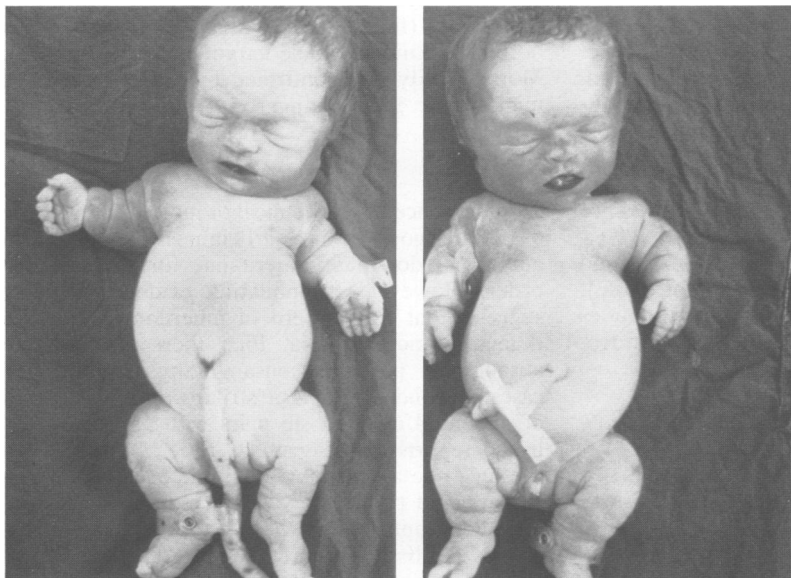


FIG 1 *Post mortem view of the twins.*

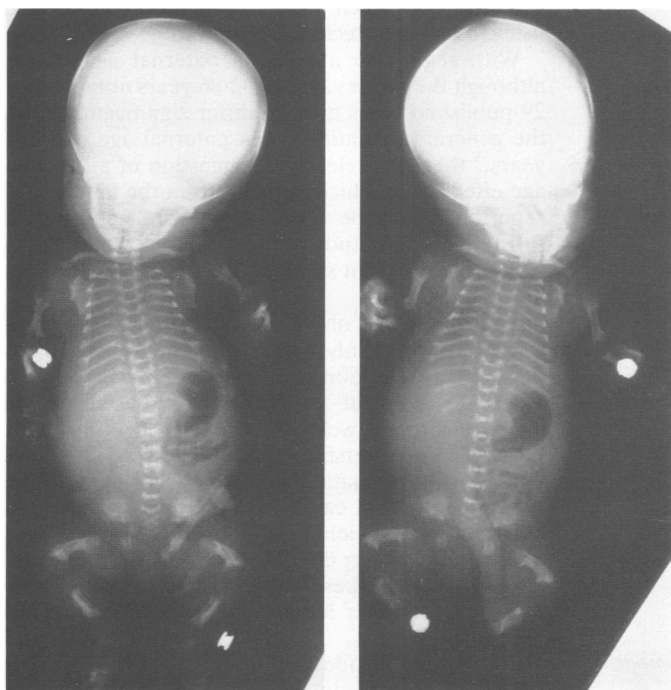


FIG 2 *Radiographs of the twins.*

paper we describe monozygotic twins, concordant for thanatophoric dysplasia, and review the accumulating evidence in favour of autosomal dominant inheritance.

### Case reports

The twins, both female, were the product of the second pregnancy of a healthy 27 year old mother and her healthy, unrelated 46 year old husband. Delivery occurred after spontaneous onset of labour at 34 weeks' gestation. Both twins died within one hour.

Twin 1 weighed 1680 g (3rd centile), was 37 cm long (<3rd centile), and had a head circumference of 32.0 cm (75th centile). Twin 2 weighed 1790 g (10th centile), was 37 cm long (<3rd centile), and had a head circumference of 32.5 cm (90th centile). Clinical examination showed identical abnormalities in both twins, consisting of depressed nasal bridge,

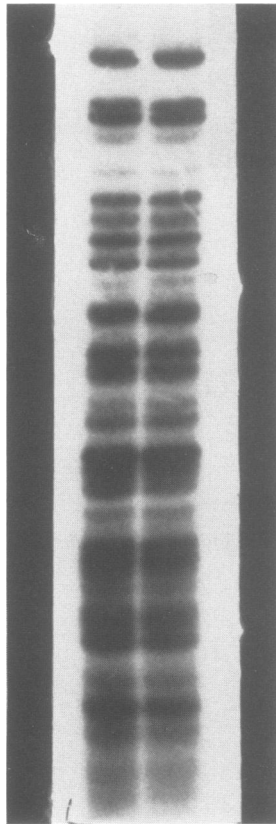


FIG 3 Demonstration of monozygosity. DNA minisatellite fingerprints obtained using probe 15.1.11.4.

short neck, narrow chest, and short limbs (fig 1). No other external or internal abnormalities were found at necropsy.

Radiographs of both babies showed marked platyspondyly with H shaped vertebral bodies on AP projection, flat acetabular roofs, and short tubular bones with 'telephone receiver' bowing of the femora (fig 2). Chromosome studies showed a normal G banded female karyotype in both babies. Monozygosity was confirmed by analysis of DNA minisatellite genetic fingerprint patterns<sup>8</sup> (fig 3).

### Discussion

In the absence of biochemical or molecular evidence of heterozygosity, it is clearly impossible to confirm autosomal dominant inheritance for a lethal disorder. However, accumulating evidence strongly suggests that this pattern of inheritance underlies thanatophoric dysplasia. First there is a notable absence of parental consanguinity in published cases. Second, there is a striking paucity of well documented affected sib pairs with only two published reports standing up to close scrutiny.<sup>3 9</sup> To these can be added four published accounts of like sex affected twins,<sup>3 6 10 11</sup> with monozygosity having been confirmed in only one pair using blood groups and tissue typing.<sup>11</sup> The present cases constitute the fifth report of concordant affected twins and the first for which monozygosity was confirmed using molecular techniques.

With regard to a possible paternal age effect, although the mean value of 32.86 years obtained for 29 published cases did not differ significantly from the general population mean paternal age of 31.05 years,<sup>3</sup> there was clearly a suggestion of a paternal age effect, with which the data from the family now reported would be consistent. Such an effect, if substantiated by study of further cases, would be an additional factor in support of autosomal dominant inheritance.

The final piece of supportive evidence for autosomal dominant inheritance comes from estimates of the likely mutation rate ( $\mu$ ). Connor *et al*<sup>7</sup> derived a value for  $\mu$  of  $11.8 \pm 4.1 \times 10^{-6}$  based on an incidence in the west of Scotland of 1 in 42 221 births. In Leicestershire, where details of all babies dying in the perinatal period are recorded,<sup>12</sup> these twins are the first cases of thanatophoric dysplasia born since 1982, yielding a comparable incidence of approximately 1 in 60 000 births. As Connor *et al*<sup>7</sup> have indicated, these values are similar to those observed for other lethal autosomal dominant disorders.

Thus we conclude that these twins add further weight to an already substantial body of evidence

supporting autosomal dominant inheritance in thanatophoric dysplasia. Rare examples of recurrence in a sibship may well result from parental gonadal mosaicism, as has been established for several lethal cases of osteogenesis imperfecta.<sup>13</sup>

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