typical periventricular calcified lesions. No cardiac tumours were visible echocardiographically.

The parents were counselled that a future child was at a 1 in 2 risk of being affected by tuberous sclerosis, but that the manifestations of this were very variable. However, the mother unintentionally became pregnant soon afterwards and was offered fetal cardiac ultrasonography as a possible method of antenatal prediction of an affected child. Fetal echocardiography was performed on two occasions during the second trimester. The fetal heart was examined initially at 18 weeks' gestation and appeared normal. A second examination of the fetal heart during the 22nd week of pregnancy revealed the presence of a large tumour within the body of the right ventricle and at least one tumour on the surface of the heart (figure). As this fetus was almost certainly affected by tuberous sclerosis, termination of the pregnancy was offered. Necropsy confirmed the presence of a rhabdomyoma filling the body of the right ventricle with multiple smaller tumours in the left ventricle and on the external surfaces of the heart.

Discussion

The gene for tuberous sclerosis is notoriously variable in its expression. The frequency of associated rhabdomyomata large enough for echocardiographic detection is unknown. The family described may be unusual in that three out of four affected family members had echocardiographically detectable cardiac tumours. The tumours were large enough to cause circulatory obstruction in two of the four. Finding no evidence of cardiac tumours would not have excluded the diagnosis of tuberous

sclerosis in this case, but the positive identification of a cardiac tumour indicated a third affected child in this family. Even in the absence of a family history, a cardiac tumour in any patient found histologically to be a rhabdomyoma implies the diagnosis of tuberous sclerosis whether that disease is clinically manifest or not.³

The fetal heart can be well visualised echocardiographically between 16 weeks' gestation and term.⁴

As this case shows, cardiac tumours can be detected as a marker for tuberous sclerosis. As the technique gives rise to no fetal or maternal discomfort it should be offered for possible antenatal diagnosis in a pregnancy known to be at risk, although the absence of visible cardiac lesions would not exclude the presence of the disease. It is possible that in the future detailed ultrasonography of the fetal head may provide further evidence of the disease when it is present.

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Unusual ocular findings in an infant with cri-du-chat syndrome

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SUMMARY A newborn male with cri-du-chat syndrome, congenital nuclear cataracts, microspherophakia, and probably ectopic lenses is reported. Microspherophakia in cri-du-chat syndrome has not been previously described. The congenital cataracts were inherited from

his mother who had a balanced 5;13 translocation; the two events are considered to be coincidental and a possible 'position effect' was excluded, since the other members of her family with congenital cataracts, were chromosomally normal. This is the fourth case reported where familial cri-du-chat syndrome involves chromosomes 5p and 13q.

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Case report

The proband was the product of the first pregnancy of a 25-year-old mother and a 27-year-old father. The pregnancy was uneventful and delivery was at 39 weeks' gestation. There was no history of maternal infections, drug ingestion, or irradiation during the pregnancy.

The family history is significant in that the father had had postinfectious optic neuropathy since the age of 16 and the mother had congenital nuclear cataracts, with best corrected visual acuity 20/400 in each eye separately. Several maternal relatives had the same cataracts (fig 1).

Birth weight was 2700 g (between the 10th and 50th centile), length was 50 cm (50th centile), head

circumference was 35 cm (50th centile), and the Apgar score was 7 at 1 minute. Physical examination at 1 month of age revealed (fig 2): a high pitched mew-like cry, a round and thin face, epicanthal folds, slight downward slanting eyes, bilateral cataract, flat nasal bridge and philtrum, low set ears, high arched palate, microretrognathia, hypotonia, clinodactyly of the fifth fingers, partial syndactyly of the second and third toes bilaterally, and increased distance between the first and second toes bilaterally. During the neonatal period he had feeding difficulties associated with poor sucking.

Re-examination at 8 months of age showed a length of 65 cm (less than the 3rd centile), weight 4450 g (less than the 3rd centile), and head circumference 39 cm (less than the 3rd centile). He had the physical features of the cri-du-chat syndrome, and also a generalised hypotonia and hyporeflexia. He could not make sounds, roll over, control his head, sit briefly even with support of the pelvis, or transfer objects from hand to hand.

Repeated biomicroscopic examination of the eyes following pupillary dilation (at 1 week and 1, 4, and 6 months of age) showed nuclear cataract, microspherophakia, and probably ectopic lenses bilaterally. The latter finding could not be confirmed because, even after the use of the most potent mydriatics in combination (atropine 0.25%, phenylephrine 5%, cyclopentolate 2%, and tropicamide 1%), only partial pupillary dilation was obtained. At 8 months of age the 'methacholine test' was performed and the pupil constricted within 15 minutes after one drop of 2.5% methacholine was placed on the cornea. The ocular fundi could not be examined because of the central total opacity of the lenses (fig 3).

Titres for rubella, toxoplasmosis, and CMV viruses were negative. Radiographs of the skull, heart, bones, and upper gastrointestinal tract were normal. However, a retrograde cystourethrogram demonstrated a second grade vesicoureteral reflux.

FIG 1 Pedigree of the family.

FIG 2 The proband at 1 month of age.

FIG 3 The proband's nuclear cataracts.

FIG 4 Partial karyotypes of the proband (A) and his mother (B).

DERMATOGLYPHS

The proband had a unilateral simian crease with ulnar termination on his right palm, a Sidney crease on his left palm, bilateral distally located axial triradii (t'), and whorl patterns on all fingers and on all toes. His parents had unremarkable dermatoglyphs.

CYTOGENETICS

Chromosome studies using GTG banding were performed on cultured peripheral blood cells and fibroblasts from the proband and several members of his family (fig 1). The proband (IV·2) was monosomic for the terminal portion of the short arm of one chromosome 5 ($p14 \rightarrow pter$). The mother (III·4) carried a translocation (5;13)($p14;q33$). Therefore, the karyotype of the proband was 46,XY,der(5), $t(5;13)(p14;q33)$ mat (fig 4).

The proband's father (III·5) and maternal relatives (III·3, II·5, II·6, II·4, I·1) were shown to have normal chromosomes.

Discussion

The clinical delineation of the cri-du-chat syndrome was first established by Lejeune *et al* in 1963.¹ One year later it was proven to be associated with a partial deletion of one chromosome 5 by German *et al*.² Howard in 1972³ studied the ocular abnormalities in seven cases of cri-du-chat syndrome, but was unable to find a case with cataracts or microspherophakia. Niebuhr in 1978⁴ reviewed data on 331 cases and the ocular findings in cri-du-chat syndrome were: epicanthal folds (223/252), anti-mongoloid slanting (144/208), strabismus (87/156), cataract (6), and optic nerve atrophy (16/83).

The proband had most of the common clinical features of the syndrome, since the critical mid-portion of band 5p15⁵ is contained in the deleted portion of chromosome 5 ($p14 \rightarrow pter$). However, our patient had two interesting ocular findings, not

previously reported: bilateral microspherophakia and probably bilateral ectopic lenses. It should be noted, however, that the proband's congenital nuclear cataracts were inherited from his mother and may have no connection with the syndrome. According to the pedigree (fig 1), the cataracts appeared for the first time (de novo) in the maternal grandmother, who transmitted it to all her children by a presumed autosomal mode of inheritance.

The proband had a positive 'methacholine test', which is considered by Howard³ to be "specific in establishing the diagnosis in the cri-du-chat syndrome". This reaction of the pupil to methacholine, in addition to its considerable resistance to mydriatics, suggests a possible defective structure of the dilator muscle of the pupil in our proband.

The proband's 5p- was transmitted from the mother who is a balanced translocation carrier (5p;13q). This is the fourth familial cri-du-chat case to be reported with a translocation involving the short arm of chromosome 5 and the long arm of chromosome 13.⁵ The total frequency of familial cri-du-chat cases is 12.1%, out of which 11.2% is the estimated frequency of familial translocation.

Cytogenetic investigation of the proband's maternal relatives in three generations showed that

the translocation 5;13 in the mother was de novo. The normal karyotypes observed in her relatives with cataracts exclude any relationship between the chromosomal defect and the cataracts.

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Phenazopyridine induced methaemoglobinaemia associated with decreased activity of erythrocyte cytochrome *b₅* reductase

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SUMMARY A 25-year-old woman taking usual doses of phenazopyridine developed her third clinically significant episode of cyanosis. Life threatening methaemoglobinaemia was documented and was treated with methylene blue. The patient and several members of her family showed decreased activities of erythrocyte NADH-cytochrome *b₅* reductase, predisposing them to the development of clinically significant methaemoglobinaemia when challenged with oxidant drugs.

Phenazopyridine is a commonly used urinary

analgesic. Methaemoglobinaemia is a rare side effect of the drug, first reported by Crawford *et al*¹ in 1951 in an infant. Since then 11 cases have been reported, most associated with ingestion of many times the usual therapeutic dose. Only two cases have been reported with standard dosages,² and these occurred in patients with mild renal insufficiency. In none of the reported cases has an abnormality of erythrocyte cytochrome *b₅* reductase (NADH-methaemoglobin reductase) activity been documented. Decreased activity of this enzyme has been reported in subjects who are especially susceptible to toxic methaemoglobinaemia secondary to ingestion of oxidant drugs.^{3,4} We report a case of life threatening methaemoglobinaemia in a patient with decreased reductase activity after ingestion of near-therapeutic amounts of phenazopyridine.

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