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# *Short reports*

## Cystic fibrosis in 3 Pakistani children

For Caucasians of European origin, cystic fibrosis (CF) remains the commonest recognized autosomal recessive disorder, but it appears to be a rarity among the coloured races. For a time, records may have suggested an association between CF and whiteness; in recent years, however, instances of CF children have been described whose racial origins are Negroid (Kulczycki, Guin, and Mann, 1964), Mongoloid (Harris and Riley, 1968; Wang *et al.*, 1968; Wright and Morton, 1968), and non-European Caucasoid (Asian Indian) (Mehta *et al.*, 1968; Reddy *et al.*, 1970), though clinical descriptions and biochemical data for the latter children are not wholly convincing. Immigration to the United Kingdom provides a further opportunity for assessment of the racial incidence of this disease.

The present case reports concern 3 Pakistani children born in Birmingham, in whom CF has been confirmed. 2 of the 3 (Cases 1 and 2) were brother and sister.

### Case reports

**Case 1.** The third child of healthy, unrelated Pakistani parents was born prematurely, weight 1·78 kg, estimated gestation 32 weeks. Respiration was established immediately. 4 hours after birth, respiratory distress with cyanosis occurred and there was metabolic and respiratory acidosis. Treatment was with intravenous sodium bicarbonate, oxygen, and intramuscular ampicillin and cloxacillin, to which intramuscular kanamycin was added 2 days later. After two profound apnoeic attacks when the baby was 10 hours old, positive pressure respiration was started using a Loosco ventilator. A chest *x*-ray showed some right-sided opacity with reticulation in both lungs. 2 days later an air bronchogram was present. Repeated *x*-rays showed progressive infiltration. The baby died on the 26th day of life.

This child failed to pass meconium until he received a rectal washout 5 days after birth. However, this did not suggest a diagnosis of CF at the time, as many small, immature babies show delay in the passage of meconium. 2 or 3 days later there was diarrhoea with frequent loose frothy motions. Reducing substances were present and the child was started on a lactose-free milk but, though the reducing substances disappeared, the diarrhoea persisted.

*Necropsy findings.* The macroscopical changes were restricted to the respiratory system and to the liver and bile ducts. There was severe purulent bronchopneumonia. The liver was firm and congested and the gallbladder and bile ducts contained viscid bile. Histology of the lungs showed three striking changes: areas of interstitial fibrosis with thickening and hypercellularity of the alveolar septae; alveolar hyperdistension in the nonfibrotic areas and at the edges of the fibrous zones, many of the alveolae containing acute inflammatory exudate; enlargement and distortion of the bronchial mucous glands which were distended with mucin-rich acid mucopolysaccharide. Bronchopneumonia was related predominantly to the areas of fibrosis. The degree of fibrosis was out of proportion to the degree of damage seen in other parts of the lungs.

The liver showed severe fatty change: many of the bile canaliculi were dilated and contained bile plugs. There was no bile duct proliferation. The pancreas (Fig.) showed uniform distension of the ducts with mucin, which was P.A.S.-positive, and Alcian blue negative. The lobular architecture was preserved. There was a slight but diffuse increase in the stromal fibrous tissue. Some of the ducts were damaged and contained mucinous plugs. The interlobular septae were thickened and contained focal collections of lymphocytes.

The salivary glands showed distension of the mucin-containing cells and occasional acini were dilated. The contents of these acini stained with both Alcian blue and P.A.S. in many instances, while in others only the Alcian blue stain was taken up. Examination of the large intestine showed the deeper parts of the glands to be plugged with mucus.

These histological findings are compatible with those of CF.

**Case 2.** A girl, the sister of Case 1, was born at term, birthweight 2·6 kg. Abdominal distension was noted at birth and *x*-ray of the abdomen showed evidence of small gut obstruction consistent with a diagnosis of meconium ileus. An enema, using gastrografin under fluoroscopic control, showed that the colon was collapsed and that the terminal loops of ileum contained small plugs of meconium. A further gastrografin enema on the third day of life passed up through the ileum into a distended segment containing meconium. The hygroscopic effect of the gastrografin effectively stimulated peristalsis to overcome the obstruction, while intravenous fluids effectively prevented systemic dehydration.

This baby then had repeated respiratory infections in the first 2 years of life, initially with staphylococci and later with *Pseudomonas pyocyanea*. A number of these infections required hospital admission for intravenous antibiotic therapy and, on one occasion, intubation and bronchial lavage were required to overcome diffuse

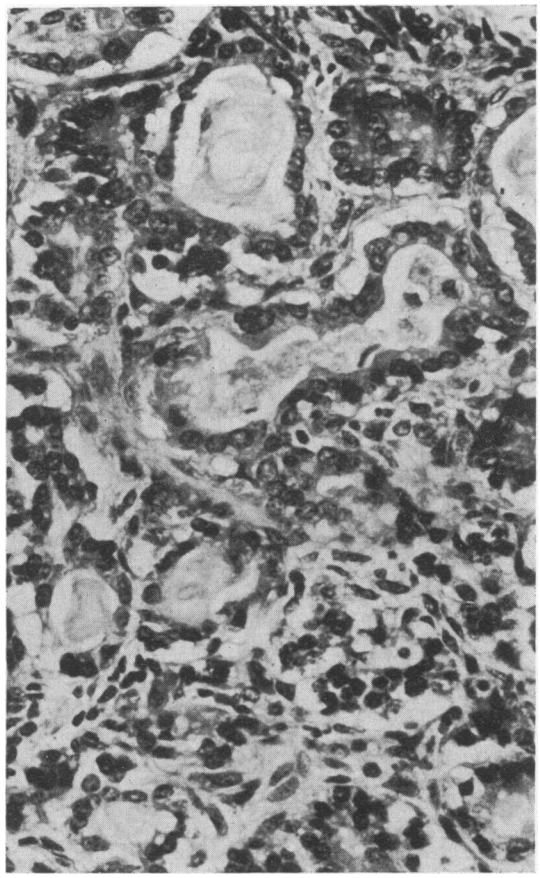

FIG.—*Case 1. Pancreas showing distension of ducts with mucin and an increase in stromal fibrous tissue. (P.A.S. ×200.)*

obstructive emphysema. Repeated *x*-rays were consistent with a diagnosis of CF. A sweat sodium was 72 mEq/l. and sweat chloride 120 mEq/l. from a specimen of sweat weighing 386 mg. She was treated with Pancrex-V, appropriate oral antibiotics, and inhalations of n-acetyl cysteine, neomycin, and polymyxin.

The diagnosis of CF in these 2 children is based upon the clinical features and necropsy findings in Case 1, the clinical features and sweat test results in Case 2, and on the family history.

**Case 3.** A girl, the only child of healthy, unrelated West Pakistani parents, was born after a normal pregnancy and delivery at term, weighing 2·62 kg. Rapid breathing and a continuous precordial murmur were noted soon after birth. She was treated for heart failure from the tenth day of life. Shortly after a normal cardiac catheterization at 5 weeks, the murmur disappeared and the congestive cardiac failure resolved.

Intermittent harsh cough and loose offensive stools were observed from the age of 2 months. She was breathless, wheezed, and failed to thrive. At 3 months her height and weight lay below the 3rd centile for British children. CF was suspected and a sweat sodium level of 120 mEq/l. (144 mg sweat) was in keeping with this diagnosis. She continued with antibiotic therapy, physiotherapy, and pancreatin supplements.

Subsequent investigations at the age of 6 months confirmed CF; sweat electrolyte values for sodium and chloride were 81 and 101 mEq/l., respectively (weight of sweat 206 mg), and enzyme analysis of duodenal fluid showed no measurable tryptic activity and a very low lipase content of 27 IU (normal value >100 IU). The mean 24-hour faecal fat excretion over a 3-day period when no pancreatic supplements were given was 10·2 g. She was still small, and examination of the chest showed an increased anteroposterior diameter. On chest *x*-ray there was some degree of bronchial wall thickening, but no localized infection. At 14 months she is a vigorous child, whose height has reached the 25th centile and whose weight is on the 10th centile.

## Discussion

The reasons underlying the high gene frequency for CF among white Europeans remain a topic for philosophical discussion, but estimates of incidence of the disease lie between 1:2000 and 1:2500. The data for other racial groups are scanty, but suggest at present that it is very rare in non-whites. A study by Kramm *et al.* (1962) pointed out that only 2% of 2652 CF patients in three New England states were Negro, though Negroes made up 13% of the population sampled. The admixture of blood from white forebears (with a high gene frequency for CF) prevents meaningful interpretation of these percentages. With regard to the Mongolian races, Wright and Morton (1968) conducted an interesting survey over a 15-year period on the Hawaiian Islands, the population being part Caucasian and part Mongolian. They identified 24 CF children, of whom 21 were Caucasian, 1 a Japanese-Caucasian hybrid, and 2 Mongolian, giving incidence of 1:3800 for the Caucasian group, and 1:90,000 for the Mongolian. The incidence in India and Pakistan is unknown, but as Reddy *et al.* (1970) stated in their survey of necropsy material, 'the disease has not been suspected before death as we were under the impression that CF does not occur in this part of the world'.

As the 3 cases described here appear at present to be the only ones known to West Midland paediatricians, all of whom replied to a questionnaire on this matter, and the number of Asian immigrants under the age of 15 years in this population appears

to be approximately 30,000 (from figures provided by the Medical Officers of Health in the region and extracted from the 1971 census), a very rough estimate of the incidence of CF in this region among Asians is 1:10,000. No attempt has been made to determine gene frequency, because the data are so scanty and the immigrant groups have come mainly from small, well-defined areas of India and Pakistan where consanguineous marriages are common, though not always recognized as such.

Pakistanis are Caucasian by race, as are most of the inhabitants of the Indian subcontinent. If the high incidence of CF among populations of European origin is associated with their Caucasian race, then with increased awareness of the disease further cases may be found in India and Pakistan.


## Summary

Three children, 2 of them brother and sister, whose parents were natives of West Pakistan, had cystic fibrosis. The present incidence of this disease among Asian immigrants in the West Midlands is approximately 1:10,000.


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# Assessment of gestational age in twins

The reliability of a scoring system for the estimation of neonatal gestational age, based on 10 neurological and 11 external criteria, devised by Dubowitz, Dubowitz, and Goldberg (1970), has been confirmed by Brueton, Palit, and Prosser (1973), Jaroszewicz and Boyd (1973), and Singer, Blake, and Wolfsdorf (1973). In the original study by Dubowitz *et al.* (1970), 23 small-for-dates and 14 large-for-dates babies were included. The distribution of total score against gestational age of these infants seemed to fit the regression line and not to differ from that of appropriate weight-for-dates infants, though the authors did not specifically comment on this finding. In order to test the reliability of the method, this study was undertaken to estimate the gestational age of twins, with particular emphasis on pairs of twins with marked differences in birthweight.

## Material and methods

Gestational age was estimated in 33 pairs of consecutive twins by the method of Dubowitz *et al.* All the estimations were done by one experienced examiner (A.M.J.) during the routine estimation of gestational age of newborns, as previously described (Jaroszewicz and Boyd, 1973). It was unavoidable that the examiner would sometimes know that twins were being examined. True gestational age was unknown in many of these pregnancies due to uncertainty about the date of the last menstrual period. The difference in birthweight between members of a twin pair was calculated as a percentage of the weight of the heavier twin.

## Results

The results are shown in the Table where the pairs have been arranged in order of increasing birthweight differences in percent. The difference in the estimated gestational age (EGA) between the lighter and heavier of the twins varied between 0·0 and 2·0 weeks, with one exception, where the difference was 2·5 weeks (pair no 24). The lighter twin was not necessarily the one to show a lower EGA. The mean EGA of the 33 lighter twins was 36 weeks and of the 33 heavier twins 36·4 weeks. The difference between these two means is not significant ($P<0·001$). In 7 pairs (pairs no. 27 to 33) the birthweight difference was more than 20%: the mean EGA of the lighter twins in this group was 37·2 weeks, and the mean EGA of the 7 heavier twins 37·5 weeks. This difference, too, is not significant ($P<0·001$).