again improved rapidly. A daily reticulocyte count showed a peak of 20% on days 4 and 5 and his haemoglobin gradually rose to 13 g/dl by 7 January 1977.

Comment

The very low serum folate value may have been exaggerated by sulphasalazine interfering with the microbiological assay, but the rapid clinical and haematological improvement, including the prompt reticulocyte response to treatment with folic acid, leaves little doubt that folate deficiency was the cause of the megaloblastic anaemia in this patient.

There are several causes of folate deficiency in the elderly. Dietary deficiency was unlikely in this patient because he had been on the same mixed hospital diet without any major changes for 22 years without ill effect. His primary intestinal disease, probably some form of colitis, was not sufficiently severe to have caused gross folic acid deficiency, and, moreover, he had been suffering from it for over two years with no effect on his haematological status until drug treatment was started. Coeliac disease may cause folate deficiency but there was no evidence of this disease in this patient. His stools never showed the typical frothy appearance of the coeliac stool, and the values for faecal fat and xylose absorption were within normal limits. A small-intestinal biopsy, therefore, did not seem justified.

Levodopa and carbidopa are not known to affect the haemopoietic system, nor is diazepam, the only other drug he was given. In 1973, however, Franklin and Rosenberg[4] reported a significant reduction in serum folate levels in 10 patients with inflammatory bowel disease who were being treated with Azulfidine (sulphasalazine) compared with values in a control group of 16 similar patients not on this drug, and in 1976 Juhl *et al*[5] showed that sulphasalazine interferes with the absorption of digoxin. Therefore treatment with sulphasalazine seems the most likely cause of this patient's megaloblastic anaemia.

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Chondrodysplasia punctata and maternal warfarin treatment

In March 1975 Becker *et al*[1] reported from the United States two cases of children with chondrodysplasia punctata whose mothers had taken warfarin during the first trimester of pregnancy. Since then there have been reports from the United States and South Africa of five further cases[2-5] of this syndrome, the main features of which are nasal hypoplasia and epiphyseal stippling. We report here a similar case to alert obstetricians, physicians, and paediatricians in the United Kingdom to the likely teratogenic effect of warfarin.

Case report

A 1200-g boy was born to a 28-year-old woman in December 1976. The mother had been started on continuous oral anticoagulation with warfarin (6-7 mg daily) six months before becoming pregnant, when she was diagnosed as having thromboembolic pulmonary hypertension possibly related to the oral contraceptives that she had taken for the preceding year. The oral contraceptives were discontinued after this episode. She had had three previous pregnancies, the first two resulting uneventfully in full-term, normal deliveries and the third resulting in the spontaneous delivery of a 1000-g stillborn infant at home. There was no consanguinity, no family history of short stature, and skeletal survey radiographs of both parents were normal.

In her fourth pregnancy she was first seen at nine weeks' gestation, when she expressed a wish to continue with the pregnancy. Her only drug treatment at that time was warfarin. She received no other medication, apart from an iron and folic acid preparation, until she was admitted to hospital at 24 weeks' gestation with a history of vaginal bleeding. The warfarin was discontinued and she was given heparin. She had further vaginal bleeding

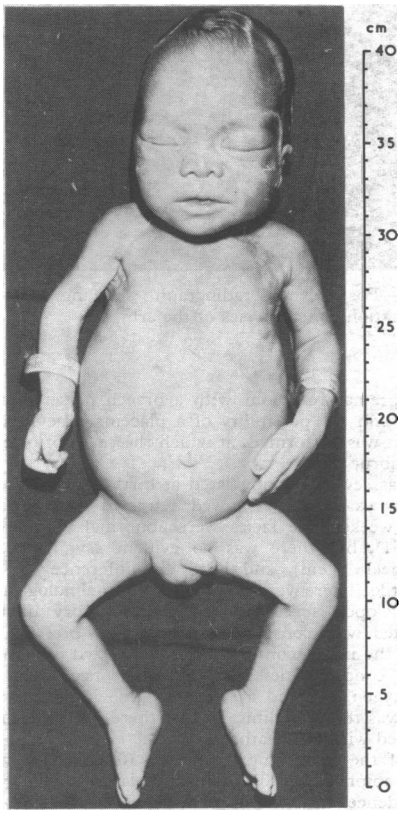

FIG 1—Wasted infant with abnormal facies and nasal hypoplasia.

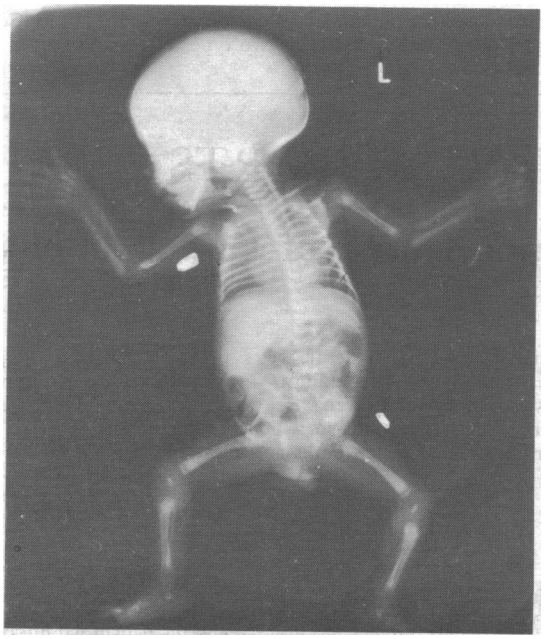

FIG 2—Radiograph on 10th day showing stippling of all epiphyses.

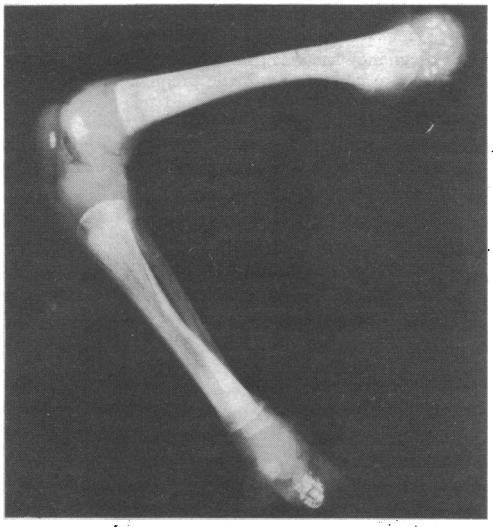

FIG 3—Postmortem radiograph showing punctate calcifications in epiphyses of the arm.

and went into premature labour with a breech presentation at 29 weeks. In view of this and the possibility of a placenta praevia a lower-segment caesarean section was performed, at which the cause of bleeding was found to be placental abruption.

The infant was severely asphyxiated at birth and required active resuscitation. Physical examination showed a wasted infant with a gestational maturity of 31 weeks. The facies were abnormal with pronounced nasal hypoplasia (fig 1), but there was no evident asymmetry. Birth weight, length (crown-heel 35 cm), and head circumference (27·5 cm) were on the 10th percentile. There were no obvious ophthalmological abnormalities. The infant developed severe idiopathic respiratory distress syndrome, which was treated with constant positive airway pressure. Although this largely resolved the infant continued to need added oxygen. When he was 18 days old his condition deteriorated and he needed an increased concentration of oxygen. He had a series of apnoeic attacks and died when 21 days old. It was thought clinically that there was an element of tracheal collapse associated with the death.

Radiograph of the infant (fig 2) on the 10th day showed pronounced stippling of all epiphyses, and chondrodysplasia punctata was diagnosed. Histological evidence and postmortem radiographs (fig 3) confirmed the punctate calcifications in all epiphyses. There was calcification in the larynx. Histological examination of the lungs showed changes of resolving severe hyaline membrane disease.

Comment

Chondrodysplasia punctata was first described in 1914 by Conradi.[6] Spranger[7] distinguished between two types of the disease—a milder, probably dominantly inherited, type (Conradi-Hunermann) with a good prognosis; and a lethal, probably recessively inherited, form with a poor prognosis (Rhizomelic). Radiologically our patient had the features of the Conradi-Hunermann form of chondrodysplasia punctata. He also had the laryngeal calcification and coronal cleft vertebrae of the recessive form of chondrodysplasia punctata. Nevertheless, his strong similarity to the other infants,[1–5] whose mothers had taken warfarin during the first trimester of pregnancy make it likely that his condition was a phenocopy of the genetic syndrome induced by the teratogenic effect of this drug.

Our patient died from respiratory problems, possibly related to his being preterm, or possibly to tracheal collapse associated with its skeletal dysplasia. Of the seven patients reported previously two developed normally, two were retarded and blind, one died in the neonatal period, and there was no information on follow-up in the other two. Hall[8] considers it likely that the hypoplastic nose and stippled epiphyses are features of first-trimester warfarin usage while mental retardation and opthalmological abnormalities are associated with second- and third-trimester use. Our patient is the only one so far described whose mother had taken only warfarin in the first trimester. Our report strengthens the evidence that warfarin should not be used in pregnancy and that women should be advised not to conceive while taking the drug.

We thank Professor O P Gray and Mr J F Pearson for allowing us to report this case and Dr M L Lawrence and Dr G M Roberts for their help and their postmortem and radiological information respectively.

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SHORT REPORTS

Demonstration of candida in blood smears

The diagnosis of candidaemia rests primarily on obtaining blood cultures in Sabouraud's medium, the growth taking a minimum of ten days to appear and often three weeks or longer.[1] Here we report a patient with candidaemia in which the diagnosis was made rapidly by identification of blastospores and pseudohyphae in blood smears.

Case report and methods

A 74-year-old man was admitted to hospital on 19 December 1975 with signs of intestinal obstruction, from recurrence of a carcinoma of the sigmoid colon. The carcinoma was resected in a two-stage procedure. Postoperatively a subclavian venous catheter was inserted and the patient fed intravenously with amino-acids and glucose. On 14 January 1976 his general condition deteriorated and his temperature rose suddenly to 39·5°C. Because blastospores and pseudohyphae were seen on blood smears (fig 1) prepared from blood samples obtained by venepuncture, treatment with amphotericin B and 5-fluorocytosine was started as early as nine hours after the fever started. Co-trimoxazole was added on the same day. The patient was discharged 2 February, and was doing well at follow-up seven months later.

Haematological investigations were done by standard laboratory methods on a blood sample collected in EDTA; blood smears were made immediately and stained with Wright's blood stain on automatically operating Hema-Tek slide stainer.

Growth of *Staphylococcus aureus* as well as *Candida albicans* was seen, respectively, after one day and five days on blood cultures (Hemobact media) prepared at the time of the rise in temperature. Candida were also cultivated in Sabouraud's medium blood culture prepared several hours after fever began. Serum obtained on 21 January showed a hemagglutinin titre to *Candida* (Candida-HA-Test, Roche) as high as 1/320 (normal: <1/160).

Discussion

Undoubtedly this patient had typical candidaemia. Concomitant bacterial infection, which was observed in this case, is a known feature