

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.<sup>6</sup> Spranger<sup>7</sup> 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,<sup>1-5</sup> 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<sup>8</sup> considers it likely that the hypoplastic nose and stippled epiphyses are features of first-trimester warfarin usage while mental retardation and ophthalmological 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.

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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.<sup>1</sup> 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 blasto-

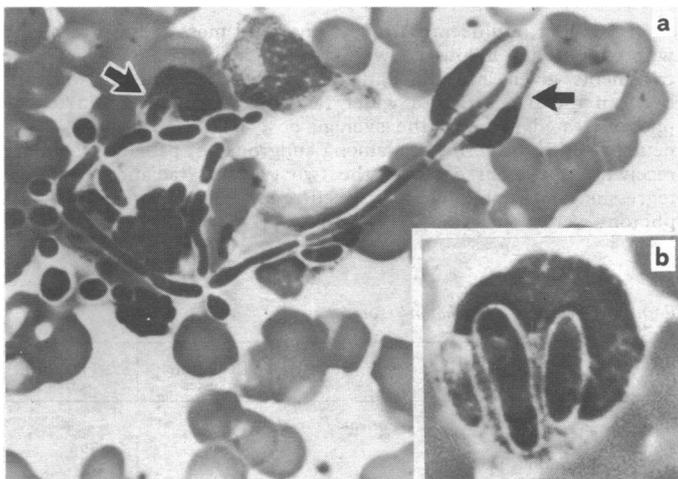
spores and pseudohyphae were seen on blood smears (fig 1) prepared from blood samples obtained by venepuncture, treatment with amphotericin B and 5-fluorocytosine was started as early as nine hours after the fever started. Co-trimoxazole was added on the same day. The patient was discharged 2 February, 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



*Candida* pseudohyphae and blastospores in blood smear (Wright's stain; (a)  $\times 325$ , (b)  $\times 651$ ). (a) There are at least six neutrophils around pseudohyphae phagocytizing fungal elements are seen (arrows). (b) Pseudohyphae in a neutrophil. The clear space surrounding the basophilic organisms represents the cell wall, which does not take Wright's stain.

of candidaemia.<sup>2</sup> Strikingly, the microscopical examination of the blood smears prepared by a widely used laboratory method disclosed the first evidence of candidaemia, and, because of the rapid diagnosis, we could start treatment only a few hours after fever began, which was his first symptom of the infection. *Candida* has also been seen in blood smears in three other reported cases<sup>3,4</sup> and this method of diagnosis needs to be considered in a possible case. Fever is the most common symptom in candidaemia,<sup>2</sup> and, since *Candida* blastospores and pseudohyphae are phagocytosed by leucocytes (and therefore their number may be diminished by destruction), the blood smears should be prepared at the time the temperature rises, as we did in this patient.

We thank Mr A Regenss for the haematological investigations.

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## Effect of wholemeal and white bread on iron absorption in normal people

Two aspects for consideration in studies of bread and iron absorption are the effect of bread on absorption of dietary iron and the relative merits of wholemeal and white bread as sources of iron. Reports on iron absorption from bread<sup>1-4</sup> are conflicting, but none of the recent ones<sup>2-4</sup> have compared absorption of iron from white and wholemeal bread in the same person. It is important to determine the effect of dietary fibre on iron absorption because of the popularity of high-fibre diets. We report a comparison of the effects of both white and wholemeal bread on the absorption of physiological amounts of iron in 13 normal subjects.

### Subjects, methods, and results

The subjects were healthy, non-anaemic (haemoglobin  $> 12\text{g/dl}$  in women and  $13.8\text{g/dl}$  in men) volunteers from an obesity clinic who were taking a 3.3 MJ (800 kcal) diet. The bread was given as a standard meal after a 12-hour fast. No tea or coffee was drunk for 12 hours after the meal. No subject had blood loss, or took aspirin or iron treatment during the study. Eight of the nine women were postmenopausal, the other having had a hysterectomy.

The iron was given as  $5\ \mu\text{Ci}\ ^{59}\text{Fe}\ \text{Cl}_3$  in solution with 250 ml distilled water, and the meal consisted of  $100 \pm 5\text{g}$  of wholemeal or white bread. Both breads were made from the same batch of Manitoba flour, the wholemeal being of higher extraction, and the white was not supplemented with iron. In addition to the two types of bread, the subjects received a third test containing the same amount of iron with 100 mg ascorbic acid as fresh orange juice.

The absorption of  $^{59}\text{Fe}$  was measured with a whole-body counter using a multiple-dose technique similar to that of Callender and Warner.<sup>2</sup> Repeat counts were close at 30 minutes after the test meal, and again 48 hours later, retention being measured at 14 days. Absorption tests were given according to a random block design. Thirteen subjects volunteered so that all the six possible orders of three tests were given at least twice.

The table shows that the absorption of iron with wholemeal bread was significantly less than with white bread ( $P < 0.01$ ). Ascorbic acid enhanced absorption in all but one subject. Analysis of variance confirmed a difference between treatments ( $P = 0.002$ ) and showed no significant difference between the orders in which the treatments were given ( $P = 0.16$ ) or any significant interactions ( $P = 0.99$ ).

#### Effect of orange juice, wholemeal, and white bread on absorption of iron

No	Sex	Age (yrs)	Iron absorption (%)*		
			Orange juice (OJ)	White bread (WB)	Wholemeal bread (BB)
1	M	44	10.3	1.2	0.0
2	F	52	41.9	25.2	6.0
3	F	62	5.6	2.7	0.5
4	F	52	21.0	7.2	0.0
5	F	35	30.2	19.9	0.1
6	F	41	20.6	16.6	0.0
7	M	50	9.9	0.0	0.0
8	M	56	1.1	0.0	0.5
9	F	62	17.0	2.6	0.2
10	F	71	19.0	5.3	1.4
11	F	57	20.1	4.9	0.4
12	M	47	42.9	19.5	27.1
13	F	54	9.5	5.5	0.3
Mean $\pm$ 1SEM			19.16 $\pm$ 3.58	8.51 $\pm$ 2.39	2.81 $\pm$ 2.07

Paired *t* tests (DF = 12) showed: OJ *v* WB, *t* = 5.97;  $P = 0.0001$ ; OJ *v* BB, *t* = 6.08;  $P = 0.0001$ ; WB *v* BB, *t* = 2.52,  $P = 0.01$ .

\*Iron given as  $5\ \mu\text{Ci}\ ^{59}\text{Fe}\ \text{Cl}_3$  in 250 ml distilled water.

### Discussion

We used small amounts of inorganic iron labelled with  $^{59}\text{Fe}$  as an "extrinsic tag" to study the effects of fibre on dietary iron, wholemeal bread being used as a high-fibre meal and white bread as a low-fibre meal. Layrisse and Martinez-Torres<sup>5</sup> showed a high correlation between the absorption of extrinsic tag given with the food of native iron biosynthetically labelled ("intrinsic tag") in vegetable food. They postulated that the extrinsic iron mixes with the non-haem iron pool and may be used as a marker for non-haem iron in food. Orange juice, containing about 100 mg ascorbic acid, was added to the iron to measure "augmented" iron absorption.<sup>3</sup> Other dietary factors such as eggs and tea, which inhibit iron absorption, were avoided on test days.

Our results confirm that wholemeal bread significantly inhibits the absorption of non-haem iron. Iron may be rendered less available for absorption by constituents of the wholemeal, such as phytate.<sup>1</sup> The over-enthusiastic consumption of bran—for example, in breakfast cereals—may increase the long-term risk of iron deficiency by inducing negative balance. Vegetarians tend to eat wholemeal bread rather than white and this may inhibit iron absorption. They are also deprived of haem iron, which is an important source and doubles the absorption of vegetable iron.<sup>5</sup> If other types of fibre inhibit the absorption of non-haem iron, a high-fibre diet taken over long periods may cause negative iron balance and encourage the development of anaemia, particularly if there is associated chronic blood loss, as in diverticular disease.

Wholemeal flour contains more iron than white bread. The iron content of white bread is supplemented with iron to bring it to that of 80% extraction flour. According to the Layrisse/Martinez-Torres model<sup>5</sup> the extrinsic iron mixes with that of bread and acts as a label