abnormal motility, at least in infancy, and the very slow passage of barium in the barium follow-through at age 18 months supports this. The abnormality in motility would be the main factor that predisposed to small intestinal bacterial overgrowth, but the secondary acquisition of achlorhydria would exacerbate this. At the time of her acute admission at age 15 months a secondary acute enterocolitis was present too. We have not been able to demonstrate a primary immune defect. It seems likely that some malabsorption will be a permanent feature of this child's life, but at the moment her increased appetite enables her to absorb enough to thrive despite persistent steatorrhoea.

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Delayed separation of the umbilical cord, severe widespread infections, and immunodeficiency

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SUMMARY Three of 4 children in a family died from infection before age one year. All 3 had delayed separation of the umbilical cord in the third week. One child was found to have defects both in specific antibody production and in neutrophil function; these were not improved by treatment with ascorbic acid or levamisole.

Hayward *et al.*¹ described a new familial syndrome of delayed separation of the umbilical cord, widespread infections, and defective neutrophil mobility. They suggested that the isolated defect in neutrophil mobility could be corrected *in vitro* and *in vivo* by ascorbic acid. We report a family with an apparently similar clinical syndrome; however, in the child studied the immunological defect was more extensive and affected both neutrophil function and specific antibody production, and was not improved by treatment with ascorbic acid or levamisole.

Case report

A girl weighing 3 kg was born by caesarean section. She was the fourth child of healthy unrelated white

parents. After slight neonatal asphyxia, she fed poorly from birth, and developed diarrhoea during the first week of life. The umbilical cord did not separate until the third week, leaving an imperfectly healed stump. At age 4 weeks she developed an axillary abscess which healed spontaneously, followed by a staphylococcal abscess on the chest wall requiring surgical incision and a course of flucloxacillin. She had a mild anaemia with a total white cell count of $45 \pm 10^9/l$, of which 90% were neutrophils.

The family history is remarkable. The first child had died suddenly after 10 weeks, having previously been well; necropsy examination showed clostridial septicaemia due to gangrenous ileo-caecitis. The second child had died at age 7 weeks from overwhelming staphylococcal infection and necropsy had shown peritonitis complicating necrotising enterocolitis. The umbilical cords of both children had failed to separate until the third week of life. Both parents and the third sibling, whose cord separated normally, are well.

In view of this family history of unusual infection, the patient was transferred for immunological investigation at age 2 months, as a possible case of

Table 1 Tests of humoral and cell-mediated immunity

Age (months)	Serum immunoglobulin (g/l)			Antibody activity		Peripheral blood lymphocyte count ($\times 10^9/l$)	Lymphocyte subpopulations* (%)			Lymphocyte transformation ratio†	
	IgG	IgA	IgM	<i>E. coli</i>	Isoagglutinins		E-rosetting cells	EAC-rosetting cells	Smlg-rosetting positive cells	PHA	PWM
2	6.10 (2.70-7.60)	0.05 (0.05-0.55)	0.45 (0.15-0.65)	Negative	Negative	9.70	52 (60-80)	28 (15-30)	16 (5-15)	13(6)	4(3)
5	9.30 (2.10-11.25)	0.15 (0.10-0.95)	1.70 (0.15-0.85)	Negative	Negative	11.80	69			91(58)	
8	16.35 (4.80-15.50)	0.15 (0.20-1.00)	1.70 (0.25-1.45)	Negative	Negative						

Immunoglobulin levels shown in brackets represent normal values for age.

* Results expressed as a percentage of lymphocytes forming non-immune rosettes with sheep erythrocytes (E rosettes), bearing receptors for C3b (EAC rosettes), or expressing surface membrane immunoglobulin (Smlg) by direct immunofluorescence.⁷ Normal range shown in brackets.

† Results expressed as a ratio of radioactive counts/minute obtained by incubating lymphocytes in the presence of phytohaemagglutinin (PHA) or pokeweed mitogen (PWM) to the counts obtained in culture medium alone.² Values for a healthy adult control shown in brackets.

Table 2 Tests of neutrophil function

Age (months)	Neutrophil mobility*		NBT reduction†		Staphylococcal bactericidal index‡	Leucocyte iodination test§
	Medium alone	Casein-stimulated	Unstimulated	Endotoxin-stimulated		
2			26 (NR < 10)	45 (NR > 30)	0.10 (NR < 0.20)	
5	25 (37)	28 (148)	27	44		0.70 (2.70)
6	18 (17)	30 (90)				
7	17 (37)	25 (129)				
8	26 (55)	43 (127)			0.04	0.77 (3.35)

NR = normal range.

* Distance moved in μ m by leading front method² in medium alone and in the presence of casein (5 mg/ml) as a chemoattractant. Value for a healthy adult control shown in brackets.

† Percentage of neutrophils showing reduction of nitroblue tetrazolium (NBT) before and after endotoxin stimulation.²

‡ Ratio of ingested staphylococcal colony count after 140 minutes' incubation to colony count after 20 minutes' incubation.²

§ Results expressed as the percentage of radiolabelled inorganic iodide converted to an intracellular protein-bound form during the phagocytosis of zymosan.⁴ Value for a healthy adult control shown in brackets.

severe combined immunodeficiency. This diagnosis was excluded by the normal or raised proportions and absolute numbers of T- and B- lymphocytes in peripheral blood, normal lymphocyte transformation to non-specific plant mitogens (phytohaemagglutinin and pokeweed mitogen), and normal serum immunoglobulin levels (Table 1). The absence of serum isohaemagglutinins (blood group O Rh-positive) and lack of antibodies to *Escherichia coli*, were not considered unusual at this age. After a further course of intravenous antibiotics she was discharged home on oral fusidic acid, but her white cell count remained $>50 \times 10^9/l$.

By age 5 months, she had suffered further staphylococcal abscesses, a possible bacterial meningitis (organism not isolated), and had a chronic umbilical discharge. She was persistently pyrexial, unwell, and had gained no weight. To eradicate any possible anaerobic organisms in the umbilical discharge, she was treated with intravenous clindamycin and metronidazole, but although the discharge

dried up and the fever subsided, her white cell count remained $>50 \times 10^9/l$. Further immunological investigations (Table 2) showed impaired neutrophil mobility but a normal capacity to reduce nitroblue-tetrazolium (NBT). Both parents and her sibling had normal neutrophil mobility. Her serum IgM level was raised but serum IgA was in the low normal range for age (Table 1). Functional haemolytic activity of the classical complement pathway (CH50), and immunochemical C3 and C4 component levels were normal.

Because of the similarity of this case to the syndrome described by Hayward *et al.*,¹ the *in vitro* effect of ascorbic acid on neutrophil mobility was investigated. Preincubation of the patient's polymorphs in ascorbic acid at concentrations ranging from 1 to 50 mmol/l failed to enhance their migration towards a standard chemoattractant² (casein 5 mg/ml). Despite this negative *in vitro* response, the patient was given a therapeutic trial of ascorbic acid (500 mg/day) for 6 weeks. Because levamisole may

improve neutrophil mobility in certain disorders of phagocytic function,³ she was also given levamisole (30 mg/week) for 3 months. There was no reduction in the severity or frequency of infections and immunological reassessment (Table 2) confirmed the persistent impairment of neutrophil mobility although the patient's serum generated adequate cytotoxicity in crossover experiments. Staphylococcal bacteriocidal activity was within normal limits. However, the defect was not confined to neutrophil mobility since leucocyte iodination⁴ was impaired compared with control cells. This test measures the percentage of radiolabelled inorganic iodide converted to an intracellular protein-bound form during the phagocytosis of zymosan and is thought to reflect neutrophil myeloperoxidase activity.⁴ In healthy adults between 2.1 and 5.2% of the administered radioiodine is incorporated into the polymorphs. We have no comparable normal range for age-matched subjects but infants studied to date, in whom a neutrophil defect was eventually excluded after a battery of tests, all had values in excess of 1.7%.

At 9 months, her serum IgA was low despite recurrent infections at mucosal surfaces; in contrast serum IgG and IgM were raised (Table 1). Antibodies to blood group substances, *E. coli*, and staphylococcus were still absent at an age when specific antibody activity is generally detectable. Replacement of intramuscular immunoglobulins was added to her treatment but despite further courses of antibiotics and a blood transfusion her condition deteriorated and she died. At necropsy she was found to have a mediastinitis and a perforated oesophagus, a partially patent urachus, and evidence of previous peritonitis. Apart from macroscopic thymic atrophy and hepatosplenomegaly, there were no specific histological abnormalities in the peripheral or intestinal lymph nodes, thymus, liver, spleen, or bone marrow.

Discussion

Hayward *et al.*¹ identified 6 infants from two families with delayed separation of the umbilical cord; severe bacterial infections developed in 5 of them. The two infants they tested had defective neutrophil mobility with normal NBT reduction, and normal staphylococcal phagocytosis and killing. Subsequently, Bowen *et al.*⁵ reported 2 unrelated patients with a similar problem: each had difficult cord separation and impairment of neutrophil chemotaxis but additionally showed defective leucocyte adherence and abnormal monocyte chemotaxis. Our patient had clinical features in common with these reports—

namely the probable family history of recurrent infection associated with delayed cord separation and defective neutrophil mobility in the proband. In contrast however, there was (a) a lack of an *in vitro* or *in vivo* response to high dose ascorbic acid therapy for 6 weeks, (b) an additional impairment of the leucocyte iodination test suggesting abnormal leucocyte myeloperoxidase activity, (c) probable selective IgA deficiency, and (d) lack of specific antibody synthesis.

Macrophages have an important role both in antigen processing for induction of a specific immune response and in T- and B-lymphocyte co-operation. Although formal tests of macrophage function are not readily available, the poor antibody responses in the presence of normal lymphocyte subpopulations and normal serum IgG and IgM levels may reflect a failure in macrophage function similar to that proposed in the Wiskott-Aldrich syndrome.⁶ Finally, the abnormal leucocyte iodination found in our patient and the defective leucocyte adherence reported by Bowen *et al.*⁵ suggest a more generalised abnormality of phagocytic cells. In our view, therefore, the immunological component of the syndrome is not restricted solely to neutrophil mobility as first suggested.¹

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