Discussion

There are only 20 patients with megacystis-microcolon-intestinal hypoperistalsis syndrome in the published reports, and almost all were born at term and were girls.¹⁻⁵ The syndrome encompasses anomalies of two organ systems. In the gastrointestinal tract, shortening and fixation are noted, with a microcolon and diffuse hypoperistalsis. Considerable postnatal abdominal distention with bilious vomiting resembling the clinical picture of mechanical intestinal obstruction called for an early exploratory laparotomy in most reported cases. In the urinary system, a large bladder without bladder neck obstruction is described. In some cases this is accompanied by hydronephrosis and hydroureters.

The pathogenesis of the syndrome remains obscure with no satisfactory explanation for the absence of peristalsis and the flaccid bladder. This syndrome may be a variant of a group of diseases that affect the motility of the gastrointestinal tract. These come under the heading of idiopathic intestinal pseudo-obstruction.⁶ In these disorders ultrastructure examination of the ileum and the urinary bladder showed vascular degenerative changes in the smooth muscle cells.^{5,6} Both patients described here were boys. This is important when the differential diagnosis is considered. Prune belly syndrome predominately affects boys, but neonates with prune belly syndrome have no hypoperistalsis of the gut. In our second patient, decompression of the bladder caused abdominal wall flaccidity that later disappeared.

The megacystis-microcolon-intestinal hypoperistalsis syndrome may be accurately diagnosed by abdominal sonography, cystography, and a barium

enema. A combination of an enlarged bladder without bladder neck obstruction together with a typical 'microcolon' with no radiological evidence of mechanical intestinal obstruction is diagnostic, and should prevent an unnecessary exploration. This was the case in the second patient described. This syndrome was lethal in all the reported patients and only two patients survived for more than one year.^{2,4} Treatment was symptomatic with long term total parenteral nutrition and adequate drainage of urine. Attempts to induce intestinal peristalsis by pharmacological means have so far failed to improve the poor outcome of the disease.³

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Haemophilia and T lymphocyte subsets

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SUMMARY Number of circulating lymphocytes and T cell subsets were assessed in 13 boys with severe haemophilia and 12 age matched controls. There was no significant difference between the two groups. This conflicts with previous findings in adults where lymphopenia and changes in T cell subpopulations have been found frequently.

Lymphopenia with reversal of the ratio of T cell subpopulations defined by the monoclonal antibodies OKT4 and OKT8 (or their equivalents) are constant findings in the acquired immune deficiency syndrome (AIDS),¹ and have been taken as an indicator of latent AIDS when found in asymptomatic subjects.² The disease is thought to be transmissible in blood products, and screening of groups at risk has led to the discovery of the characteristic

lymphocyte disturbances in 50–75% of adult haemophiliacs.^{2–4} We wondered if children might be similarly affected.

Patients and methods

Twelve boys with severe haemophilia A and one with haemophilia B were studied. All had received freeze dried large pool factor VIII (or IX) concentrate at some stage. Twelve age matched control children, without infection were also examined; blood being taken with the parents' consent either at the time of venepuncture before elective surgery or for investigation of conditions unlikely to affect immune status.

T cell subsets were estimated using standard techniques with appropriate OKT antisera (3, 4, and 8, Ortho Diagnostic Systems). Statistical analysis was performed with the unpaired Student's *t* test, using absolute numbers of cells counted.

Results

There was no significant difference between the groups in either mean lymphocyte counts, or in T cell subset numbers or ratios (see Tables 1 and 2). One boy with haemophilia, the oldest (case 14, Table 2), had a reversed OKT4:OKT8 ratio on one of two occasions when he was assessed. He also had the highest accumulative exposure to factor VIII and had progressive liver disease, described previously.⁵ Another 3 year old patient also had a reversed ratio on the first assessment, but was suffering from sunstroke at the time and this pattern had returned to normal within 10 days.⁶ Only the older boy's abnormal findings were included in the analysis.

Table 1 *T lymphocyte subsets in the control group*

Case No	Age (yrs)	Lymphocyte count ($\times 10^9/l$)	OKT3 ($\times 10^9/l$)	OKT4 ($\times 10^9/l$)	OKT8 ($\times 10^9/l$)	OKT4:8 ratio
1	8	1.94	1.4	0.88	0.45	1.96
2	10	1.28	0.74	0.57	0.18	3.17
3	13	2.05	1.55	1.09	0.5	2.18
4	9	2.17	1.53	1.01	0.47	2.15
5	6	2.46	1.14	0.87	0.43	2.02
6	4	2.5	1.7	1.2	0.48	2.5
7	3	5.41	3.52	2.49	1.43	1.74
8	3	3.32	2.16	1.36	0.8	1.7
9	13	1.4	1.0	0.57	0.45	1.27
10	1.8	3.16	2.2	1.25	0.92	1.36
11	11	2.16	1.31	0.8	0.76	1.12
12	8	1.61	0.8	0.5	0.23	2.4
$\bar{x}$		2.45	1.59	1.05	0.59	1.96

Table 2 *T lymphocyte subsets in children with haemophilia*

Case No	Age (yrs)	Lymphocyte count ($\times 10^9/l$)	OKT3 ($\times 10^9/l$)	OKT4 ($\times 10^9/l$)	OKT8 ($\times 10^9/l$)	OKT4:8 ratio
13	9	1.85	1.38	0.9	0.41	2.2
14	12	1.74	1.3	0.63	0.7	0.9
15	9	2.5	1.97	1.11	0.76	1.46
16	7	2.1	1.5	0.89	0.63	1.41
17	8	1.78	0.91	0.71	0.37	1.9
18	11	2.28	1.41	1.02	0.48	2.13
19	12	2.33	1.5	0.96	0.53	1.81
20	11	2.13	1.34	0.89	0.7	1.27
21	6	3.68	2.76	1.3	0.85	1.53
22	3	4.29	2.23	1.63	0.79	2.06
23	1.9	3.84	2.4	1.52	0.81	1.88
24	3	4.85	3.18	2.09	1.41	1.48
25	7	2.1	1.68	1.07	0.5	2.2
$\bar{x}$		2.73	1.81	1.13	0.687	1.71

Discussion

Despite the fact that very few haemophiliacs have actually developed overt AIDS,⁷ it has been repeatedly shown that many, if not most, have at least one hallmark of the disease—a lymphopenia associated with a reversal in the ratio of T cell subpopulations defined by the monoclonal antibodies OKT4 and OKT8, or their equivalents.^{2–4} Although these subpopulations are frequently assumed to be synonymous with helper and suppressor cells respectively, they are not, and contain other smaller functional subsets as well.

Whether the abnormalities found in haemophiliacs are related to AIDS is far from clear, but as no other explanation has been found it is perhaps encouraging that the children we studied were, with one exception, normal. Why they should differ from adults is not, however, clear. It could simply be that they have not yet had enough clotting factor concentrate for a long enough period, and the one abnormal boy (case 14), who was the oldest and had had the most factor VIII, would support this.

Time may be more important than dose: Saidi *et al* found no relation between the amount of factor VIII received and lymphocyte disturbances in their adult study.⁴ Nonetheless, an AIDS-like syndrome has been described in infancy, shortly after a transfusion from a donor who later developed the disease.⁸ Until more information becomes available this is further reason, in addition to the risk of hepatitis, to minimise donor exposure in young haemophiliacs.

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Familial erythrophagocytic reticulosis

Complete response to combination chemotherapy

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SUMMARY Two infants with familial erythrophagocytic reticulosis attained a durable complete remission after combination chemotherapy including intrathecal methotrexate. Though both later died, neither child had definitive evidence of tumour at necropsy.

Familial erythrophagocytic reticulosis (FER) is a rare, rapidly progressive disorder, inherited as an autosomal recessive trait,¹ and presenting between 3 and 6 months of age. There have been reports of responses to single agent chemotherapy² but, with one exception,³ remissions were short. We report two infants treated with combination ('CHOP') chemotherapy and intrathecal methotrexate (IT MTX). Both attained complete clinical remissions, for 18 months and 38 months, respectively.

Case 1

This infant, the second child of unrelated parents, presented at 2 months of age with fever and vomiting. Her brother had died at age 14 months after an illness characterised by fever, hepatosplenomegaly, and pancytopenia, and necropsy had showed histiocyte proliferation with phagocytic activity in the liver, kidneys, lymph nodes, marrow, and meninges. On examination she was pale and had hepatosplenomegaly. Her haemoglobin value was 6.6 g/dl, white blood count $4.7 \times 10^9/l$ and platelets $96 \times 10^9/l$; blood film showed a

leukoerythroblastic anaemia. Cerebrospinal fluid was normal. Her fasting serum triglycerides value was raised at 2.82 mmol/l (normal range 0.35-1 mmol/l). Bone marrow aspirate showed no obvious increase in histiocytes or erythrophagocytosis but immunological studies showed a population of cells bearing Fc (32%) and C3 (21%) receptors. Immune function including phytohaemagglutinin response, yeast opsonization, and immunoglobulins was normal. Serology for herpes simplex, cytomegalovirus, Epstein-Barr virus, toxoplasmosis, and syphilis was negative, as were bacterial and urine cultures for cytomegalovirus.

FER was diagnosed and 'CHOP' chemotherapy was begun. Intrathecal methotrexate was given with courses 2-7 (Table). Within one month the hepatosplenomegaly and pancytopenia resolved, and apart from one episode of fever and neutropenia she remained well and developed normally. Adriamycin was stopped at a cumulative dose of 450 mg/m². When chemotherapy was stopped after one year her

Table CHOP treatment regimen* (Courses repeated 3-4 weekly, depending on blood count)

Drug	Dose	Route	Timing
Adriamycin*	2.00 mg/kg	IV	Day 1
Cyclophosphamide	30.00 mg/kg	IV	Day 1
Vincristine	0.05 mg/kg	IV	Day 1
Prednisolone	4.00 mg/kg	Oral	Day 1-5

* COP=CHOP without adriamycin, which has stopped at a total dose of 450 mg/m².