Paediatric Haematology

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Preface

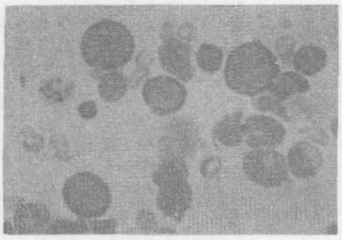
This book is written for all those concerned with the diagnosis and management of blood disorders in children, whether they are primarily paediatricians or haematologists. I have tried to integrate the fundamental molecular, genetic and cell kinetic aspects of each group of disorders with their clinical and haematological manifestations where this is contributory to an understanding of their pathogenesis and management.

A considerable body of documented information has accumulated in these fields over the past few years and I have attempted to provide access to this by reference to key papers and selected reviews or annotations throughout the text, together with a bibliography designed to give 'the way in' to the literature for the worker wishing to pursue some point in greater depth. Where there are divergent or currently unresolved views on a particular topic I have indicated this. On most issues, however, I have stated my own opinion and practice.

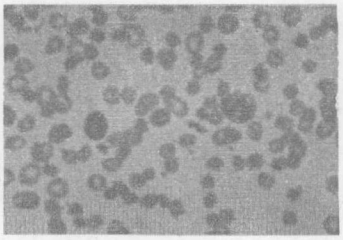
The bibliography also serves to give acknowledgement to the many investigators who have contributed to our better understanding of this complex and rapidly changing subject, including in particular that small band of paediatric haematologists whose contributions recur in chapter after chapter throughout the book.

I am personally indebted to Dr Rosemary Biggs, Professor R. G. Macfarlane and Dr A. A. Sharp of the Radcliffe Infirmary, Oxford, who initiated my interest in haematology, and to my colleagues at the Royal Hospital for Sick Children, Glasgow, who have taught me a little paediatrics! Mr J. Devlin and members of his department of Medical Illustration have generously given much time and effort in the preparation of the original clinical photographs and charts, as well as assisting in the preparation of the photomicrographs. The original X-ray plates have been reproduced by the courtesy of Dr Phillip Rawson and Dr Elizabeth Sweet of the department of Radiology. I especially wish to thank my secretary Mrs Catherine Walker who meticulously decoded my illegible notes into the text which follows.

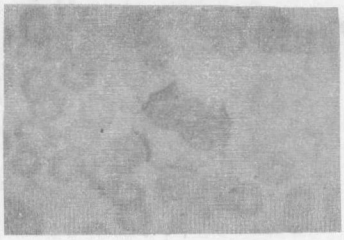
Glasgow, 1976 M.L.N.W.



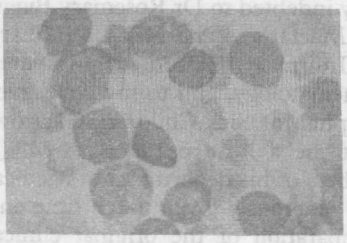
A. Megaloblastic Marrow in Juvenile Pernicious Anaemia × 540



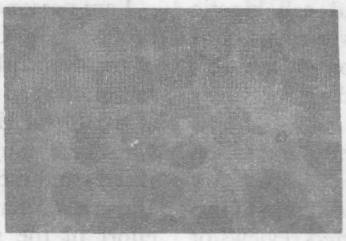
B. Infantile Pycnocytosis. Peripheral blood ⁄ 540



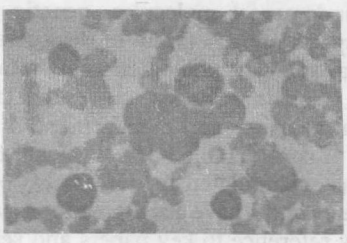
C. Glandular Fever Cell. Peripheral blood ⁄ 1,000



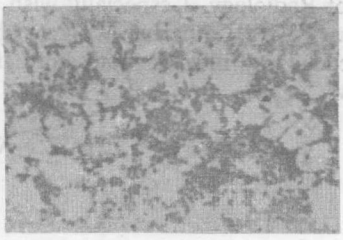
D. Leukaemic Lymphoblasts. Marrow ⁄ 1,000



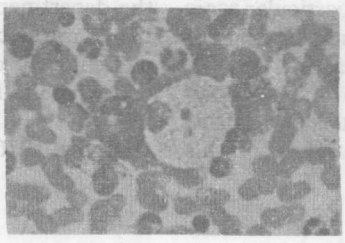
E. PAS positive Leukaemic Lymphoblasts. Marrow ⁄ 1,000



F. Neuroblastoma Cells in Marrow ⁄ 540

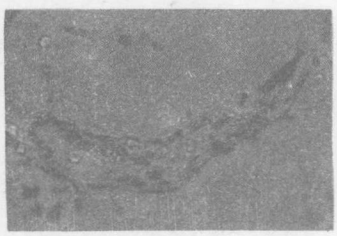


G. Reticulum Cells in Marrow. Histiocytosis X. ⁄ 100

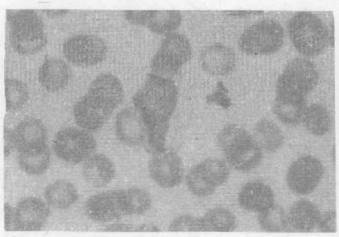


H. Sea-blue Histiocyte (Lt.) and Nieman-Pick-like Cell (Rt.) in Marrow of child with bizarre neurological syndrome. × 540

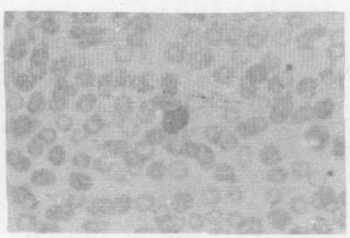
I. Gaucher-like Cell in Marrow ⁄ 540



J. Cystine Crystals. Marrow in Cystinosis. ⁄ 540



K. Reilly Bodies in Lymphocytes in Hurler's syndrome. Peripheral blood ⁄ 1,000



L. Vacuolated Lymphocytes in Gm1 Type 1 Gangliosidosis. Peripheral blood × 540

Leishman's stain, apart from PAS stain in E and Neutral Red

Introduction

HAEMATOLOGICAL ASSESSMENT IN CHILDHOOD

Intrinsic handicaps in the practice of paediatric haematology are that 'clean' venepunctures are less dependable than in adults and that it is seldom justifiable to use radioactive isotope techniques to study red cell survival or iron metabolism. In fact almost all haematological investigations can be performed on capillary blood samples including coagulation tests such as the thromboplastin screening test or Factor VIII Assay (Hardisty and Ingram, 1965) providing the technical staff are adequately trained and the laboratory properly orientated to paediatric work. The relative ease of capillary blood sampling makes sequential observations more practical whether at intervals of hours, in monitoring the correction of coagulation disorders, at intervals of days, in assessing the response to haematinics, or at intervals of weeks in the surveillance of chemotherapy as in leukaemia. Many such children can be followed both in remission and relapse for periods of 3 to 5 years with frequent blood tests without recourse to a single diagnostic venepuncture. This policy permits the reservation of veins for therapeutic purposes. A further advantage is that the artefacts of red cell and white cell morphology often seen in anticoagulated blood collected some hours previously is avoided when freshly made blood films from capillary blood are used, and the spurious thrombocytopenia frequently found in 'difficult' venepuncture specimens is obviated. A modification of capillary blood collection using small plastic tubes containing EDTA rather than pipettes has recently been described for paediatric work by Stuart, Barrett and Pragnell (1974). It permits the use of automated cell counting as well as ESR determination by a micromethod. Only 0·5 ml of blood is collected for a number of tests.

It is strikingly informative to graph the therapy and relevant haematological measurements in patients with blood diseases; for example the platelet count in idiopathic thrombocytopenic purpura (ITP), the granulocytes, blast cells and platelets in leukaemia, and the reticulocytes plus haemoglobin in haemolytic or deficiency anaemias. Consideration of the graph may disclose trends and relationships not otherwise apparent, at the same time giving a better guide as to the appropriate intervals at which future tests should be performed; for instance reticulocyte peaks, response to Factor VIII·therapy or the existence of cyclic neutropenia could be entirely missed by haphazard timing of tests.

Marrow examinations are frequently needed in the elucidation of abnormalities of the peripheral blood including all cases of thrombocytopenia, neutropenia, unexplained anaemia or leucoerythroblastic anaemia. It is seldom profitable to examine the bone marrow before considering the peripheral blood findings since few diseases extensively involve the marrow without producing some abnormality of the peripheral blood. Also it may be impossible to evaluate the significance of the marrow findings without a knowledge of the peripheral blood picture and the clinical features (e.g. in ITP). Particularly in leukaemia repeated marrow examinations are of value to assess the response to therapy. The posterior iliac crest is the most consistently useful site over the age of 6–8 weeks; below this age the tibial puncture is used, taking great care to avoid damaging the upper tibial ossification centre.

Normal values

Table 1 shows the range of normal haemoglobin, PCV and MCV over the first 12 weeks of life. At 9 weeks the haemoglobin may fall as low as 9·5 g/100 ml in full-term infants. In premature infants even lower levels are seen viz. mean 9·4 g/100 ml ±1·0 (S.D.) at 10 weeks (Gorten and Cross, 1964). In a recent annotation on the subject Oski and Stockman (1974) state that apparently healthy premature infants weighing 1·2 kg or less show average haemoglobin levels of 8·0 g/100 ml between 6 and 8 weeks, and that values of 7·0 g/100 ml are frequently seen without recognizable haematological or other disease. From 6 months to puberty there is a gradual rise in haemoglobin and PCV to adult levels (Table 2).

Table 1 Haemoglobin, PCV and MCV in normal full-term infants

Days	No. Cases	Hb g/100 ml ± S.D.	PCV per cent ± S.D.	MCV μ^3 ± S.D.
1	19	19·0 ± 2·2	61 ± 7·4	119 ± 9·4
2	19	19·0 ± 1·9	60 ± 6·4	115 ± 7·0
3	19	18·7 ± 3·4	62 ± 9·3	116 ± 5·3
4	10	18·6 ± 2·1	57 ± 8·1	114 ± 7·5
5	12	17·6 ± 1·1	57 ± 7·3	114 ± 8·9
6	15	17·4 ± 2·2	54 ± 7·2	113 ± 10·0
7	12	17·9 ± 2·5	56 ± 9·4	118 ± 11·2
Weeks				
2nd	32	17·3 ± 2·3	54 ± 8·3	112 ± 19·0
3rd	11	15·6 ± 2·6	46 ± 7·3	111 ± 8·2
4th	17	14·2 ± 2·1	43 ± 5·7	105 ± 7·5
5th	15	12·7 ± 1·6	36 ± 4·8	101 ± 8·1
6th	10	11·9 ± 1·5	36 ± 6·2	102 ± 10·2
7th	10	12·0 ± 1·5	36 ± 4·8	105 ± 12·0
8th	17	11·1 ± 1·1	33 ± 3·7	100 ± 13·0
9th	13	10·7 ± 0·9	31 ± 2·5	93 ± 12·0
10th	12	11·2 ± 0·9	32 ± 2·7	91 ± 9·3
11th	11	11·4 ± 0·9	34 ± 2·1	91 ± 7·7
12th	13	11·3 ± 0·9	33 ± 3·3	88 ± 7·9

Note the physiological macrocytosis at birth.

Data reproduced by permission of Professor Matoth and the editor, from the paper by Matoth et al. (1971) Acta Paediat. Scand., **60**, 317.

Table 2 Haemoglobin and PCV in children after the age of 6 months

Age	Hb g/100 ml ± S.D.	PCV per cent ± S.D.
6 Months	11·5 ± 0·7	38 ± 2
12 ,,	11·9 ± 0·6	39 ± 2
1½–3 Years	11·8 ± 0·5	39 ± 2
5 ,,	12·7 ± 1·0	37 ± 3
10 ,,	13·2 ± 1·0	39 ± 3
14 ,,	16·0 ± 2·0	40 ± 3
Adult male	16·0 ± 2·0	47 ± 5
Adult female	14·0 ± 2·0	42 ± 5

Data from Lascari (1973), p. 112.

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Table 3 Normal leucocyte values and differential counts in childhood

Age	Total WBC $10^3/mm^3$	Mean per cent Neutrophils Bands	Neutrophils Segmented	Lymphocytes	Monocytes	Eosinophils
Birth	9–30	9	52	31	6	2
12 hours	13–38	10	58	24	5	2
1 week	5–21	7	39	41	9	4
6 months	6–18	4	28	61	5	3
1 year	6–18	3	28	61	5	3
2 years	6–17	3	30	59	5	3
4 years	6–16	3	39	50	5	3
6 years	5–15	3	48	42	5	3
12 years	5–14	3	52	38	4	3
16 years	5–13	3	54	35	5	3

Data from Lascari (1973), p. 112, and Dittmar and Altman (1961).

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White cell counts show an absolute and relative lymphocytosis until the age of 4 years, after which adult proportions pertain (Table 3). The absolute number of neutrophils, however, normally remain above 1,500/mm^3 during the first 4 years in spite of the relative lymphocytosis at this time.

Platelet counts are normal throughout infancy and childhood (Chap. 16).

Marrow findings are essentially normal throughout childhood apart from a marked erythroid depression with as low as 7 per cent of normoblasts at the age of 1 month rising to 15 per cent at 3 months, 16 per cent at 6 months and 19 per cent at 1 year, thereafter being indistinguishable from normal (Gairdner *et al.*, 1952; Glaser *et al.*, 1970). Marrow plasma cell counts are low in normal infants and young children, but approach adult levels at 5 years (Steiner and Pearson, 1966).

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Contents

1. Iron Deficiency Anaemia

Pathogenesis, *Iron endowment at birth, Iron in the diet, Gastrointestinal function* / Incidence of iron deficiency / Clinical features / Diagnosis and laboratory findings, *Additional haematological findings, Biochemical tests of iron deficiency, Tests for intestinal blood loss* / Treatment

This is the commonest form of anaemia seen in paediatric practice. The maximum incidence occurs between 6 months and 3 years of age.

PATHOGENESIS

The prime cause is exhaustion of the neonatal iron stores at a time when the demands of an increasing blood volume and red cell mass are exceeding dietary intake and absorption.

Iron endowment at birth

Over 75 per cent of the total body iron of the newborn is accounted for by its circulating haemoglobin (Table 1.1). This in turn is dependent upon two factors: (a) the blood volume, which is proportional to the birth weight (85 ml/kg body wt.), and (b) the haemoglobin concentration at birth, polycythaemic by normal standards. Either low birth weight or a low haemoglobin concentration in the neonatal period result in a proportionately impoverished iron endowment for the newborn infant. Instead of the neonatal iron stores being adequate to meet haemopoietic requirements for 4–6 months, as in the normal infant, they become prematurely exhausted leading to iron deficiency.

In premature or multiple births the iron stores are diminished in direct proportion to the birth weight (75 mg of elemental iron per kg body weight, Osgood, 1955). After birth there is a relatively more rapid growth rate and increase in blood volume in premature as compared to full-term infants (e.g. the birth weight is doubled much earlier in the premature infant). Schulman (1961) has calculated (Table 1.2) that the full-term infant requires a total of 156 mg of absorbed iron over its first year if it is to have an 'ideal' haemoglobin level 12·3 g/100 ml at the age of 1 year. A premature infant of 1·5 kg would require nearly twice this amount of iron over the year in order to achieve the same level of haemoglobin. (The figure of 12·3 g haemoglobin/100 ml used in this calculation was derived from earlier work by Sturgeon (1956) showing that this was the mean haemoglobin level at one year in a group of children rendered iron-sufficient by the administration of 250 mg parenteral iron at 9 months.)

Table 1.1 Total body iron at birth in term and premature infants

Maturity	B.wt.	Hb g/100 ml	Hb mass	Hb Fe	Storage Fe	Tissue Fe	Total Fe
Full term	3·3 kg	19·0	55 g	185 mg	34 mg	23 mg	242 mg
Premature	1·5 kg	19·0	30 g	97 mg	15 mg	10 mg	122 mg
						Deficit at birth =	120 mg

From Schulman (1961) *J.A.M.A.*, **175**,, 118.

In fact there are two main periods when the premature infant may experience a fall in haemoglobin concentration. The early phase begins in the first week of life and may last to 4 months of age. Very little erythropoiesis is occurring during the first two months of either normal or premature infants and this 'early' anaemia of prematurity is caused by the disproportionately rapid increase in blood volume occurring at a time when there is little red cell production (Gairdner, Marks and Roscoe, 1955). The red cells are normochromic and normocytic (Hadley and Chinnook, 1954).

Table 1.2. Total body iron at 1 year compared to endowment at birth

B.wt.	Hb g/100 ml	Hb mass	Hb Fe	Storage Fe	Tissue Fe	Total Fe
10·5 kg	12·3	103 g	325 mg	0	73 mg	398 mg
	Full-term infant required 398 — 242 = 156 mg over year					
	Premature infant required 398 — 112 = 276 mg over year					

From Schulman *J.A.M.A.*, **175**, 118 (1961).

The second fall in haemoglobin concentration begins in the fourth or fifth months and has the features of a hypochromic iron deficiency anaemia. This 'late' anaemia of prematurity can be prevented by prophylactic iron supplementation (Gorten and Cross, 1964).

A low haemoglobin level in the neonatal period, similarly leading to a reduced endowment of iron stores, can be caused by a large foeto-maternal haemorrhage at delivery, by haemorrhage from one twin to another (twin transfusion syndrome between monochorial foetuses) or by intrapartum foetal blood loss from such causes as rupture of the umbilical cord, anomalous placental vessels, *placenta previa* or *abruptio placentae*. Exchange transfusion may also cause a reduction in the infant's red cell mass by replacing the normally polycythaemic infant's blood by banked blood having a lower haematocrit. Over-enthusiastic diagnostic venepunctures may occasionally cause anaemia, bearing in mind that the blood volume of the newborn is in the region of 250 ml. Chronic foeto-maternal haemorrhage is the unique cause of a hypochromic anaemia due to established iron deficiency at birth. Maternal iron deficiency probably never causes anaemia in the newborn infant (Lanzkowsky, 1961), although extreme degrees of maternal iron deficiency anaemia, e.g. 5·2 g/100 ml, may be associated with the development of anaemia in the infant at about one year (Strauss, 1933), presumably due to a reduction of foetal storage iron in these exceptional circumstances.

The Committee of Nutrition of the American Academy of Paediatrics (1969) have emphasized that it is a simple matter to identify the infants who are poorly endowed with iron stores from a consideration of (a) their birth weight and (b) their haemoglobin levels at the age of a few days. There is a greater need for iron supplements in the poorly endowed infant than in the well-endowed infant and therapeutic recommendations are given for these two groups (*vide infra*).

Iron in the diet

Milk, the natural food of the infant, contains negligible amounts of iron. The concentration is 0·5 mg/l for cow's milk and 1·5 mg/l for human. About 15 litres (or US Quarts) of milk per day would have to be consumed to provide for the iron requirements of normal infants during their first year of life. (Committee on Nutrition, 1969). Most of the naturally occurring dietary iron is derived from fruit, eggs, meat and vetetables and it is only when mixed feeding is introduced that natural

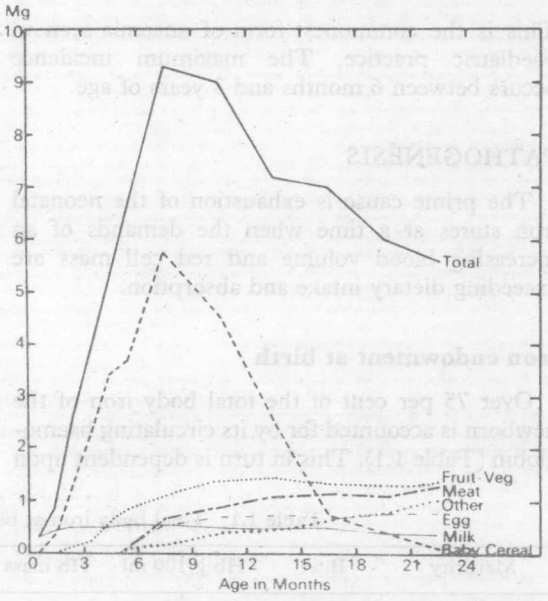

Fig. 1.1 Median total daily dietary iron intake and amounts contributed by various foods during infant development. (Reproduced by permission of Dr Beal and the Editor from the paper by Beal, Myers and McCammon (1962) *Paediatrics*, **30**, 518).

dietary iron becomes appreciable (Fig. 1.1). Only approximately 10 per cent of this dietary iron is absorbed (Schulz and Smith, 1958). The dietary requirement of elemental iron at 6 months has been estimated at 7–8 mg per day by Schulman (1961). This is similar to the recommendation of 1·0 mg/kg per day for well-endowed normal infants (Committee on Nutrition, 1969). It can be seen that this figure is seldom achieved from natural sources alone (Fig. 1.1). The current availability of iron-fortified infant cereals and milk formulae (Table 1.3) simplifies the satisfaction of these iron requirements. Up to 80 per cent of the total iron ingested over the first 6 months of life may be

Table 1.3 Iron content of certain infant feeds

Milk product	Iron in mg/100 ml*
National Dried Milk (½ cream or full cream)	0·66
Cow and Gate Babymilk 1 and 2	0·50
Cow and Gate 'Premium'	0·65
Cow and Gate 'Ready to Feed' (½ cream or full cream)	0·40
Ostermilk One	1·03
Ostermilk Two or 'Golden'	1·20
Ostermilk 'Ready to Feed' ('Golden' or 'New')	1·00
SMA 'Ready to Feed' or SMA S26	0·80
Human milk	0·15
Cow's milk	0·10

* Made up according to manufacturer's instructions. Around 150 to 200 ml/kg body wt./day taken in first 5–6 months.
Data largely from D.H.S.S. Report No. 9 (1974) 'Present-Day Practice in Infant Feeding'. London: H.M.S.O.

derived from these enriched sources. Although these products are available they are not always used. Ordinary cow's milk is often given instead. In the opinion of Diamond and Naiman (1967) continued or excessive milk administration, 'milkomania', due to poverty or ignorance, is the single most important cause of iron deficiency developing in the full-term infant.

An excellent recent commentary upon iron-fortified formulas in infancy, the incidence of iron deficiency and inter-relation between iron therapy and vitamin E deficiency is that of Pearson (1971).

Gastrointestinal function and iron deficiency

Occult gastrointestinal blood loss, accompanied by hypoproteinaemia, hypocupraemia and microscopic changes in the duodenal villi have been shown to occur in association with iron deficiency anaemia by the use of ^{51}Cr or ^{59}Fe-labelled red cells, this technique being more sensitive than direct chemical tests on the stools (Hoag, Wallerstein and Pollycove, 1961). Such blood loss may be attributed to the diffuse enteropathy described in children with nutritional iron deficiency by Naiman, Oski, Diamond, Vawter and Schwachman (1964). These authors demonstrated that children with iron deficiency had a high incidence of achlorhydria, impaired absorption of xylose and vitamin A with steatorrhoea and histological evidence of chronic duodenitis and mucosal atrophy. Following treatment with oral iron most of the abnormalities disappeared, suggesting that these were the effect rather than the cause of the iron deficiency.

An alternative theory has followed from the work of Wilson, Heiner and Lahey (1962) who found precipitins to milk protein in the sera of 75–80 per cent of iron deficient infants aged 6–24 months, together with loss of serum proteins into the gut. Subsequently Lahey and Wilson (1966) have presented evidence that gastro-intestinal blood loss may be induced by ingestion of whole cow's milk in infants possessing antibodies to milk proteins. In some of their patients the administration of milk was the triggering factor leading to a recurrence of blood loss in spite of previous correction of the anaemia by iron therapy. Milk-induced gastrointestinal loss of ^{131}I-labelled serum albumen was similarly found in 7 of 12 iron deficient infants (7–17 months) by an independent group (Woodruff, Wright and Wright, 1972). Further observations by Wilson, Lahey and Heiner (1974) suggest that enteropathy induced by cow's milk occurs in about 50 per cent of young children (6–25 months) with severe iron deficiency anaemia (Hb 2·4–7·7 g/100 ml). Transient allergy to bovine serum protein related to development of gastrointestinal immunity appears to be the cause. This subject has recently been reviewed (*B.M.J.*, 1972).

An unexpected role of acute gastroenteritis in the genesis of infantile anaemia and iron deficiency has been suggested by Elian, Bar-Shani, Liberman and Matoth (1966). Using ^{51}Cr-labelled red cells they found considerably greater blood loss in infants with gastroenteritis (0·7 to 4·8 ml/day, mean 1·85 ml) compared to controls (mean 0·64 ml) or infants with other infections (mean 0·43 ml). (One ml of blood contains approximately 0·5 mg of elemental iron.) They found that anaemia at the age of 1 year was more closely correlated with a history of recurrent diarrhoea than with a poor diet. Intestinal infestation, particularly with hookworm in appropriate geographical areas, can similarly be an important cause of blood loss and anaemia.