Papers and Originals

Observations on the Aetiology and Treatment of Anaemia in Kwashiorkor*

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Anaemia has been shown to develop in experimental animals deprived of proteins or essential amino-acids (Cartwright, 1947), but there is little evidence that protein deficiency is ever the cause of anaemia in man. Though protein is the major deficiency in kwashiorkor, there is an inadequate supply of other nutrients and infection is common. It might be expected, therefore, that anaemia in kwashiorkor is multifactorial. Morphological descriptions support this view. In the considerable body of literature which has accumulated its features are reported as normocytic, hypochromic, macrocytic, megaloblastic, or hypoplastic—singly or in combinations—but as yet there is little clear evidence regarding causation, and treatment is largely empirical.

We report here the results of an investigation of the part played in the production of this anaemia by infection and by deficiencies of iron, vitamin B_{12}, and folic acid; speculate on the role of protein deficiency as an aetiological factor; and make recommendations about treatment.

Clinical Materials and Methods

Sixty African children suffering from kwashiorkor were investigated in a ward used specially for this purpose. All had oedema, dermatosis, and lowered plasma proteins (mean albumin 1 g./100 ml.). They were admitted to the series if their haemoglobins were less than 10.5 g./100 ml., without any other form of selection. As controls we used 40 African infants of comparable age and apparently in good nutritional health.

On admission, Heaf tests and *x*-ray examination of the chest were carried out in all cases. Other infections were diagnosed on clinical grounds and confirmed by appropriate pathological tests. Twenty patients were found to be suffering from acute concomitant infection when first seen—namely, pneumonia, which was the commonest, gastroenteritis, and bacillary and amoebic dysentery. All 60 infants were given tetracycline in a dose of 125 mg. six-hourly whether or not there was evidence of acute infection. Despite this, three developed pneumonia in hospital and one later had amoebic dysentery. In seven infants the course of the disease was complicated by measles.

Our haematological methods have been reported elsewhere (Adams and Scragg, 1965), with the exception of serum folate estimations, which were carried out as described by Waters and Mollin (1961), and neutrophil lobe averages, for which we adopted the method of Herbert (1962). Clinical and haematological progress was observed for at least four weeks while the children were on a high-calorie diet of full-strength cow's milk with added glucose and potassium acetate. Feeds were offered four-hourly in unlimited amounts. Supplements of folic acid and vitamin B_{12} were not given except in two infants who required treatment with folic acid during the course of their illness. Six patients needed blood transfusion.

By random selection 32 infants received intramuscular iron dextran (Imferon) in six injections during the first two weeks, the total dose being 9 ml. When comparing the results of this group with those of the remainder we excluded the two patients who were given folic acid and the six who were transfused.

Results

Severity of the Anaemia

The mean haemoglobin on admission and the mean of the lowest levels reached in all cases, together with the controls for comparison, are given in Table I. In most of the infants the haemoglobin level dropped shortly after admission, the biggest fall among those who survived being 3.3 g./100 ml. In almost a quarter of the series (14) the lowest haemoglobin was below 6 g./100 ml. Severe anaemia must therefore be regarded as a common feature of kwashiorkor.

TABLE I.—*Severity of the Anaemia (Hb g./100 ml.)*

Haemoglobin	Controls (40)	Kwashiorkor (60)	
		Admission	Lowest
Mean	10·7	8·0	6·8*
Range	6·5–12·4	4·5–10·4	3·7–10·4
Under 9 g. ..	2	45	60
„ 6 g. ..	0	6	14

* Mean of 39 patients (10 died. Hb did not fall in 11).

Role of Infection

The mean haemoglobin on admission in infants with infection was the same as in those without infection, and there was no significant difference between the means of the lowest haemoglobin levels recorded in the two groups (Table II). It may be concluded, therefore, that infection played no part in the

TABLE II.—*Haemoglobin on Admission in Relation to Infection (Hb g./100 ml.)*

	Mean Hb on Admission	Mean Lowest Hb
Patients with infection (20)	8·0	6·7
„ without „ (38)	8·0	7·0

2 patients who died have been excluded because necropsies were not done and infection was in doubt.

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production of anaemia. This is not surprising, since the infections were mostly acute, whereas it is chronic infection which is likely to cause anaemia.

The presence of infection on admission did not affect subsequent haematological progress. The mean rise in haemoglobin over four weeks in such patients was 1.1 g./100 ml., as compared with 0.82 g./100 ml. in infants without infection. In a group of six suffering from intercurrent infection during treatment, however, the rise in haemoglobin was negligible. As would be expected, the presence of infection decreased the chances of survival: among the 20 infants admitted with infection six died (30%), but only two deaths (15%) occurred in the remainder.

Iron Deficiency

Examination of marrow specimens for haemosiderin showed that iron-deficiency anaemia was uncommon before treatment started (Table III). Stainable iron was present in all patients except two in whom iron-deficiency anaemia was confirmed by the absence of sideroblasts and by the plasma iron patterns. A striking feature of the common plasma iron pattern in kwashiorkor is the diminution of total iron-binding capacity and the high percentage saturation—above 70% in a third of the infants, and complete in one case. The number of controls with apparent iron deficiency (judged on percentage saturation) is also worth noting (Table III).

TABLE III.—*Iron Status on Admission. Bone Marrow Haemosiderin Present in 58 Out of 60 Cases*

	Plasma Iron Patterns	
	Plasma Iron (μg. per 100 ml.)	Saturation (%)
Controls (20) Mean	46	22
Controls (20) Range	8–112	3–58*
Kwashiorkor (59) Mean	51	57
Kwashiorkor (59) Range	12–152	8–100†

* 7 under 16.
† 19 out of 59, 70% saturated or more.

We previously drew attention to the characteristic plasma iron pattern in kwashiorkor and the infrequency of iron-deficiency anaemia before treatment is started (Adams and Scragg, 1965). We pointed out that after treatment with high-protein diet the picture of iron deficiency commonly emerges, presumably because there is a rise in total red cell mass and the stores are drained of iron. It was for this reason that we divided the 60 infants in this series into two groups by random selection on admission, treating about half with iron. The results are summarized in Table IV. It will be seen that the use of iron prevented the development of iron deficiency and produced a much better mean rise in haemoglobin at the end of an observation period of four weeks.

TABLE IV.—*Results of Randomized Clinical Trial*

Diet Only	Iron-treated
28 patients, 5 died	32 patients, 5 died
1 iron-deficient on admission	1 iron-deficient on admission
9 iron-deficient after 4 weeks	0 iron-deficient after 4 weeks
Mean Hb rise, 0·28 g./100 ml.	Mean Hb rise, 1·42 g./100 ml.

Iron deficiency diagnosed by absence of haemosiderin and sideroblasts in the marrow and saturation less than 16%.

Incidence of Megaloblastic Anaemia

Examination of the bone marrow for morphological changes showed partial megaloblastic erythropoiesis in 17 infants (28%). In these cases erythropoiesis was predominantly normoblastic in type, but giant metamyelocytes were present in all, and in some there were intermediate megaloblasts as well. None was fully megaloblastic. In this group the neutrophil lobe average was slightly higher (2.93) than it was in those with fully normoblastic erythropoiesis (2.64) and in the controls (2.60).

It is noteworthy, however, that the mean haemoglobin on admission was almost the same (7.9 g./100 ml.) in patients with these bone marrow changes as it was when erythropoiesis was entirely normoblastic (8.1 g./100 ml.), suggesting that megaloblastic erythropoiesis plays no significant part in determining the severity of the anaemia of kwashiorkor before treatment with protein is started.

A point worth noting is the fact that where partial megaloblastic change in the marrow was present on admission the mean haemoglobin rise after four weeks' treatment was virtually the same as in the normoblastic group (see Table V). This occurred irrespective of whether iron had been given or not. Furthermore, the presence of these bone marrow abnormalities on admission did not significantly alter the prognosis: there were 3 deaths among 17 infants with partial megaloblastic erythropoiesis (18%) compared with 7 in the remaining 43 (16%).

TABLE V.—*Effect of Partial Megaloblastic Erythropoiesis on Mean Hb Rise After Four Weeks*

	Mean Hb Rise (g./100 ml.)	
	Iron-treated	Diet Only
Partial megaloblastic erythropoiesis ..	1·83 (7)	0·56 (5)
Normoblastic erythropoiesis	1·18 (17)	0·05 (13)

Number of cases in parentheses.

Vitamin-B_{12} Deficiency

Table VI gives the results of serum vitamin-B_{12} estimations, from which it is apparent that deficiency of this substance seldom occurs in kwashiorkor, confirming our previous observations (Adams and Scragg, 1962). The high values before treatment are probably related to fatty infiltration of the liver.

TABLE VI.—*Serum Vitamin-B_{12} Levels (μμg./100 ml.)*

	Mean	Range
Controls (22)	519	160–1,500
Kwashiorkor patients:		
On admission (48)	1,089	185–4,000
„ discharge (40)	532	135–1,710

Folic Acid Deficiency

Table VII, which gives the serum folate results, shows that folate deficiency was a common finding. Compared with the controls, a much higher proportion of patients with kwashiorkor had subnormal values, one-fifth being less than 3 mμg./ml. while more than half were under 5 mμg./ml., the upper limits of definite and probable folate deficiency according to Herbert (1966).

TABLE VII.—*Serum Folate Levels (mμg./100 ml.)*

	Mean	Range
Controls (39)	10·7	2·8–24·8 (1 under 3; 4 under 5)
Kwashiorkor patients:		
On admission (54) ..	5·6	0·4–19·0 (10 under 3; 31 under 5)
At 4 weeks (44)	5·2	0·7–13 (11 under 3)

There was a broad correlation between folate levels and the appearance of the bone marrow. Partial megaloblastic erythropoiesis was observed in 5 out of 10 cases in which the folate was under 3 mμg./ml., in 7 out of 21 with values between 3 and 4.9 mμg./ml., and in 3 out of 23 with normal serum folate activity. The neutrophil lobe average was slightly higher (2.83 mμg.)

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among those with low folate levels than it was in the group with normal values (2.6 mμg.) and in the controls (2.6 mμg.).

Nevertheless there was no evidence that the degree of anaemia on admission was related to folate deficiency. The mean haemoglobin in 10 cases in which the folate level was less than 3 mμg./ml. was 8.1 g./100 ml.; in 21 cases with serum folate activity between 3 and 4.9 mμg./ml. the mean haemoglobin was 8.3 g./100 ml., and the same mean was found among the 23 cases with normal folate levels. Moreover, the mean haemoglobin rise over the first four weeks of treatment in those infants who had low serum folate values on admission compared favourably with the mean rise in those infants with normal serum folate levels (see Table VIII). There were no deaths among the 10 patients with serum folates less than 3 mμg./ml., though only one was treated with folic acid.

TABLE VIII.—*Effect of Serum Folate Levels on Mean Hb Rise After Four Weeks*

	No.	Mean Hb Rise (g./100 ml.)
Serum folate on admission <3·0 mμg./ml. ..	9	1·05
" " " " >5·0 " ..	14	0·80

Discussion

Role of Protein Deficiency

This is by no means an exhaustive study of the many possible factors which might lead to anaemia in kwashiorkor. We have not, for instance, investigated in depth the role of haemolysis, and we cannot express an opinion on the therapeutic value of vitamin E, for which claims have been made (Majaj *et al.*, 1963; Marvin and Audu, 1964; Sandstead *et al.*, 1965). Nor have we attempted to assess the place of riboflavin, deficiency of which may give rise to anaemia and reticulocytopenia due to red cell hypoplasia (Lane and Alfrey, 1965) though its therapeutic use in kwashiorkor is disputed (Allen and Dean, 1965). We are impressed, however, by the similarity between the anaemia found in protein-deficient Rhesus monkeys (Sood *et al.*, 1965) and our own observations in kwashiorkor, and we believe we have circumstantial evidence to support the opinions of Ghitis *et al.* (1963b) and Allen and Dean (1965) that protein deficiency is the main cause of the anaemia in this disease.

Allen and Dean investigated 100 infants with kwashiorkor in Uganda. Though some of their patients, unlike ours, were infested with hookworm and malaria, the series as a whole was similar. They showed a definite relation between the lowest haemoglobin and the total plasma protein. Though we cannot confirm this from our experience, the facts all seem to link the anaemia with lack of protein. The relation must of necessity remain speculative, since definitive proof is clearly impossible in humans, though in animals the evidence is strong (Bethard *et al.*, 1958; Ghitis *et al.*, 1963a). In the present paper we show that there is no reason to attribute the anaemia found on admission to deficiencies of iron or vitamin B_{12}; and though partial megaloblastic erythropoiesis may be seen on examining the bone marrow, and folate deficiency is not uncommon, it has been pointed out that the degree of anaemia is comparable to that observed among the rest of the patients in whom erythropoiesis was normoblastic and folate levels were within the normal range. Infection has also been ruled out as a major cause of anaemia. Moreover, in this series, and in others we have previously reported (Adams, 1954; Adams and Scragg, 1962, 1965), we have noted a common haematological pattern after treatment with high protein diets, whether there was evidence of concomitant deficiencies or not. The underlying pattern was not related to the use of iron, folic acid, or vitamin B_{12}. The reticulocyte count rises shortly after protein feeding begins; in the present series this occurred as frequently in patients on diet only as it did in those receiving additional iron. The haemoglobin level often drops at first but later rises steadily over a period of many weeks to reach a normal or near-normal value, provided deficiencies of iron or folic acid do not manifest themselves. A typical example of uncomplicated progress to recovery is shown in Fig. 1.

Fall in Haemoglobin and Need for Blood Transfusion

The drop in haemoglobin which occurs soon after protein feeding starts is generally slight, but it may be severe and abrupt. We have assumed, with some justification (Cronje *et al.*, 1961; Adams and Scragg, 1965), that this is partly the result of the expansion in blood volume which follows the rise in plasma proteins. When the fall in haemoglobin is small and anaemia only moderate in degree it can be ignored. An abrupt drop, however, is an indication for immediate blood transfusion. Such episodes are alarming and sometimes herald death. To obviate them requires awareness of their occurrence and constant vigilance, and we therefore advise regular estimations of haemoglobin every five days in all cases. When the initial haemoglobin is less than 6 g./100 ml. transfusion is also a wise precaution. Falls in haemoglobin of 3 g./100 ml. were observed in some infants who survived, and prompt transfusion may have saved their lives. In one case delay in giving blood probably contributed to the patient's death.

It is unlikely that change in blood volume is the only cause of increasing anaemia. In some cases of kwashiorkor the haemoglobin drops because of the development of hypoplasia of the bone marrow (Lien-Keng and Tumbelaka, 1960; Neame and Simson, 1964). Reticulocytes disappear from the peripheral blood and red cell precursors from the marrow, but after a few days or a week the marrow recovers spontaneously, reticulocytosis occurs, and the haemoglobin rises. Such episodes give a double reticulocyte peak to the haematological pattern with a trough of reticulocytopenia in between. In the present series there were five examples, one of which is shown in Fig. 2. Their occurrence raises the question of haemolysis as an aetiological factor, since similar hypoplastic crises are found in haemolytic anaemias. We have not studied this aspect of the problem fully.

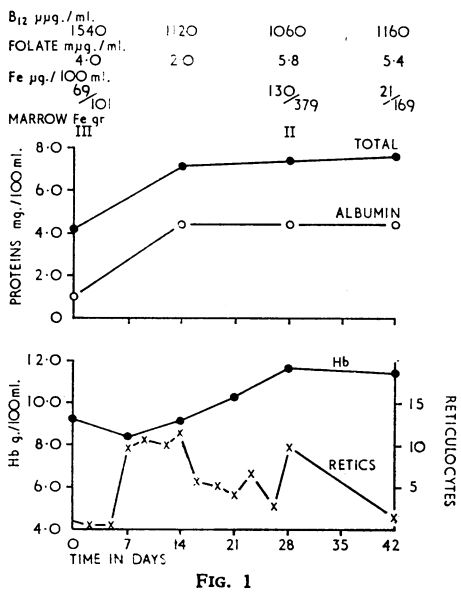

FIG. 1

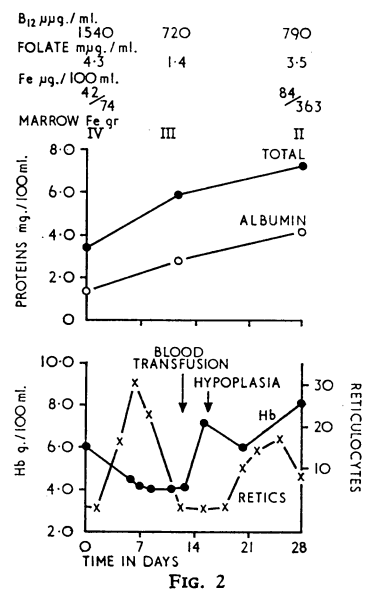

FIG. 2

FIG. 1.—Patient on diet only. FIG. 2.—Patient on diet and given blood transfusion.

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In the 60 infants reported here the mean serum bilirubin on admission was within the normal range (0.82 mg./100 ml.) and the initial reticulocyte count was usually only slightly raised (mean 3%), both values being little higher than corresponding control means of 0.54 mg./100 ml. and 1.6%. For this reason it seemed unlikely that the anaemia was predominantly haemolytic. When temporary marrow hypoplasia occurs, however, it does not affect the haemoglobin appreciably unless the red cell survival time is considerably reduced, which has been shown by Hoffenberg (1967, personal communication) to be the case in kwashiorkor. A haemolytic element should therefore be added to the factors which may contribute to the anaemia in this disease, though its importance remains to be clarified.

Iron and Folic Acid as Supplements During Treatment

We previously demonstrated (Adams and Scragg, 1965) that iron deficiency may occur in the recovery phase of kwashiorkor and we have now shown that it can be prevented by administration of iron. Since the detection of iron deficiency with any degree of certainty may require sophisticated tests which are not practicable except as research procedures, we recommend the administration of intramuscular iron to all infants with this disease, a total of 9 ml. of iron dextran being given over the first two weeks. In view of the high proportion of controls who appeared to be iron-deficient, judged on plasma iron patterns, it may well be that the occurrence of iron deficiency in kwashiorkor is not related to the disease itself but to the general iron status of infants in the age group at risk.

The case for supplements of folic acid is less easy to substantiate. It has been seen that partial megaloblastic erythropoiesis and subnormal serum folate levels are not uncommon findings on admission. Though they do not appear to limit haematological progress over the first four weeks, their existence can hardly be regarded with complacency. We have incomplete information about their long-term effects, but occasionally have observed the full picture of megaloblastic anaemia emerging later on. We therefore believe that the addition of folic acid to protein feeding is sound therapy in kwashiorkor, and recommend a routine supplement of 5 mg. thrice daily in all cases.

Summary

From a controlled clinical trial evidence is submitted in favour of the addition of iron to treatment with high-protein diet in kwashiorkor. Though iron-deficiency anaemia is seldom present on the patient's admission, routine treatment with iron prevents its development during the recovery phase.

No evidence was found that vitamin-B_{12} deficiency plays a part in the production of anaemia in kwashiorkor, and there was little support for the view that its severity may be related to the presence of infection, though this complication undoubtedly affects prognosis adversely.

Partial megaloblastic erythropoiesis and folate deficiency are shown to be common findings without playing a major part in the aetiology of the anaemia. Nevertheless, reasons are given justifying the use of folic acid supplements in all cases.

The common haematological pattern during recovery from kwashiorkor, no matter whether haematinics are added or not, suggests that protein deficiency is the main cause of the anaemia.

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The Liver after Kwashiorkor*

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In many tropical areas a widespread belief persists that malnutrition in infancy often predisposes to hepatic cirrhosis. Evidence has been put forward for a progression from the fatty liver of kwashiorkor (Trowell *et al.*, 1954) to the development of cirrhosis (Davies, 1948; Ramalingaswami, 1964). There is a considerable weight of opinion against such a course of events in man (Gillman and Gillman, 1951; Higginson *et al.*, 1957; Waterlow and Bras, 1957; Brock, 1966). This last view is, however, supported by only one adequate long-term follow-up investigation, which included liver histology (Suckling and Campbell, 1957). In that study, which was carried out in a non-tropical country—South Africa—there was no evidence of cirrhosis in liver biopsy specimens obtained from 20 children five years after recovery from kwashiorkor.

The present investigation was designed to study liver structure and function in 50 African children four years or more after they had had kwashiorkor.

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Patients and Methods

Details of the 50 patients investigated are given in Table I. Fifty-five households were visited, but five children were found

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