MEGALOBLASTIC ANAEMIA IN INFANCY WITH SPECIAL REFERENCE TO TREATMENT WITH VITAMIN B_{12}

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Megaloblastic anaemia in malnourished Bantu infants was first reported by Altmann and Murray (1948), who detected megaloblasts in the bone marrow of 3 anaemic patients suffering from kwashiorkor. In 1 of their cases the megaloblasts disappeared from the bone marrow on ward diet alone; a secondary reticulocyte response, however, occurred with folic-acid therapy. Adams (1954) reported varying degrees of megaloblastic change in 8 cases suffering from kwashiorkor. Of 6 cases with mild changes in the bone marrow, 2 responded to crude liver extract together with vitamin B_{12}, while the effect of diet alone was found to be unpredictable.

Walt *et al.* (1956) reported 42 cases of megaloblastic anaemia in Bantu infants. Kwashiorkor was present in 22, but the state of nutrition in the remaining 20 cases was not defined. Folic acid, 15 mg. daily, was administered to 38 cases, 2 of whom received additional vitamin B_{12}. A reticulocyte response of 8% or more was observed in 30 of the 38 cases. In many of their cases the reticulocyte response was delayed for periods up to 22 days. Recovery with reversion of the bone marrow to normal occurred in 2 cases in whom folic acid was not administered. Walt *et al.* (1957) reported on a further 18 cases who on folic acid therapy developed a reticulocyte response above 11%. Kwashiorkor was present in 16 of these patients. Megaloblasts had disappeared from the bone marrow in those cases in whom the marrow examination was repeated within 96 hours of commencing folic-acid therapy.

Of the megaloblastic anaemias in infancy reported from the USA and various parts of Europe, all acceptable cases treated with folic acid or citrovorum factor have shown a substantial response (Zuelzer and Rutzky, 1953). Therapy with vitamin B_{12} has, however, produced inconsistent results. Lushby and Doan (1949) and Zuelzer and Rutzky (1953) have reported degenerative bone-marrow changes in patients treated with vitamin B_{12}. Where a partial response occurred, a second response could be induced with either folic acid or citrovorum factor. A satisfactory response to vitamin-B_{12} therapy has, however, been reported by Sturgeon and Carpenter (1950) and McPherson *et al.* (1949). It would appear that the cases seen in Italy, Switzerland, Germany and Algeria, unlike those in the USA, respond to vitamin-B_{12} therapy (Gerbasi 1958). In Italy megaloblastic anaemia in infancy frequently responds to the injection of highly purified liver extracts (Amato, 1946; Pecorella *et al.*, 1947). Gerbasi (1958) states that in Italy megaloblastic anaemia of infancy is more often than not associated with a deficiency of vitamin B_{12} in the diet.

As there is but scanty reference in the literature to the effect of vitamin-B_{12} therapy on the megaloblastic anaemia in infancy in Africa, it is the purpose of this paper to report the results of this form of treatment, and to describe some of the clinical and haematological features of the condition.

MATERIAL AND DIAGNOSTIC CRITERIA

The present study was conducted over a period of 35 months during which time 5,500 children, mostly Bantu, were admitted to one of the paediatric wards. The haemoglobin level, which was measured as oxyhaemoglobin in a Klett-Summerson photo-electric colorimeter, was determined in those children under 3 years of age who showed the slightest evidence of clinical anaemia. An iliac-crest marrow puncture was performed when the haemoglobin value was below 9·0 g. per 100 ml.

Protein malnutrition (kwashiorkor) was diagnosed when sparse, straight and depigmented hair, cheilosis or angular stomatitis, dermatosis and oedema were present. Those cases who were 60% or less of their expected weight (Harvard School of Public Health, 1954), but who showed none of the aforementioned signs of malnutrition, were classified as marasmic.

The routine dietetic treatment in this series consisted of 10 feeds a day of a preparation of skimmed or half-skimmed milk, given every 2 hours. When anorexia was present the feeds were given through an intragastric tube for the first 2 days. When the oedema subsided and the child showed evidence of clinical improvement, meat and vegetables were added to the diet.

Megaloblastic anaemia was diagnosed when megaloblasts or numerous giant myeloid cells were present in the marrow. Zuelzer and Rutzky (1953) regard the presence of numerous giant myeloid cells in the marrow as indicative of deficiency of anti-megaloblastic factors, and the diagnostic criteria have been broadened to include those cases in whom only changes in the granulocyte series were evident.

RESULTS

There were 68 children in whom the diagnosis of megaloblastic anaemia was made. Of these, 22 cases were discarded on account of inadequate documentation. One further case was discarded because the marrow became megaloblastic during the course of a haemolytic type of anaemia. The features of the remaining 45 cases are presented below.

Age and Seasonal Incidence

The age of the cases ranged from 6 to 30 months, with a mean age of 20 months; 5 were aged 6–9 months, 26 10–18 months, and 13 19–24 months; 1 case was aged 30 months.

There was no seasonal variation of the incidence, cases occurring evenly throughout the year.

Feeding History and State of Nutrition

Accurate information on the dietary history was often difficult to obtain. All the children had received a diet rich in carbohydrates in the form of maize meal, potatoes and pumpkin. There were 20 children who had received inadequate amounts of milk as part of their diet. No child in this series had received breast feeds or green vegetables, and only 2 had received meat in their diet.

There were 29 cases who showed the features of protein-deficient malnutrition, and 13 others were marasmic. The remaining 3 children were fairly well nourished. An analysis of the weights of the children expressed as a percentage of the expected weight for age indicated that 36 of the 45

children were 60% or less of their expected weight (Mitchell and Nelson, 1954).

The serum-protein values were estimated in 18 patients. The total protein varied from 3·4 to 7·8 g. per 100 ml., and the serum albumin from 1·3 to 3·8 g. per 100 ml. The mean values were: total protein 4·85 g., albumin 2·20 g.

Presence of Infection

Of the 45 cases, 29 showed evidence of one or more types of infection. These were salmonella and Flexner dysentery (6 cases), pneumonia (13 cases), tuberculosis (6 cases), herpes simplex of the mouth (3 cases), pyrexia of unknown origin (3 cases), otitis media (2 cases) and upper-respiratory-tract infection (1 case). A further 9 cases were suffering from diarrhoea but no pathogenic organism was isolated from their stools.

Peripheral Blood

The haemoglobin value ranged from 2·9 to 8·8 g. per 100 ml. (mean 6·3 g.). The mean corpuscular haemoglobin concentration varied from 28 to 37%, and in 14 patients was 31% or less. The initial reticulocyte count ranged from less than 1% to 7%, and in 17 patients it was greater than 2%. Anisocytosis was marked in 27 cases, moderate in 15, and mild in 3, while poikilocytosis was marked in 22, moderate in 12, and mild in 11. Macrocytes were noted in 29 cases, and megaloblasts in 8. Anisochromia was detected in 6 patients; in the remainder the red cells appeared normochromic.

The total leucocyte count varied from 3·3 to 35·2 thousands per c.mm. Neutrophils were less than 2·0 thousand per c.mm. in 9 cases and a shift to the right was noted in 8 patients. Platelets were reduced in number in 14 cases.

Bone marrow

The marrow specimens were all of normal or increased cellularity. An erythroid reaction was present in 14 out of 31 cases in whom the myeloid erythroid ratio was calculated. In 14 specimens the changes in the marrow were mild; erythropoiesis was predominantly normoblastic, but numerous giant myeloid cells were present. Moderate changes were present in 20 specimens, where the predominant cell was the intermediate megaloblast; in the other 11 specimens numerous classical megaloblasts were present, and the picture was indistinguishable from that of pernicious anaemia in relapse.

Treatment

All the children received dietary therapy. In addition, vitamin B_{12} was given to 22 cases, folic acid to 6, and both to 3. Ward diet was the sole treatment in 13 cases.

(*a*) *Ward diet only.* Of the 13 children who were treated with ward diet alone: no response to therapy could be assessed in 6 of the cases. Of the remaining 7 (Table I), 4 showed a reticulocyte response greater than 5%, and in 2 of these the peak was greater than 10%. In 1 case the reticulocyte count rose from 1 to 5%, and 2 cases failed to show any reticulocyte response to ward diet. In the cases which responded, the maximum observed reticulocyte response occurred between the 15th and 23rd day after the commencement of therapy. The haemoglobin level rose by more than 2·0 g. per 100 ml. in 3 patients, was not significantly changed in 2, and fell in the remaining 2.

(*b*) *Folic acid.* In 6 cases 15 mg. of folic acid was given daily by mouth for periods ranging from 7 to 18 days (Table I). In 5 cases a reticulocyte response varying from 7·5% to 24% occurred between the 7th and 33rd day after commencing treatment. These 5 cases showed an increase in haemoglobin level greater than 2·0 g. per 100 ml. within 11–33 days of commencing treatment. There was no reticulocyte response in 1 case, who showed giant myeloid cells but no megaloblasts in the marrow.

(*c*) *Vitamin* B_{12}. An intramuscular injection of 100μg. of B_{12} was administered on alternate days to 24 patients for a total of 6 injections. Response to treatment as judged by a return of the bone marrow to normal, or a significant rise in the reticulocyte count or haemoglobin level, occurred in all the cases in whom the effect of therapy could be assessed (Table II). The maximum reticulocyte response was observed

TABLE I. THE EFFECT OF THERAPY WITH WARD DIET ALONE ON 7 CASES AND FOLIC ACID BY MOUTH ON 6 CASES

Case No.	State of nutrition	Degree of bone marrow change	Haemoglobin: Before treatment (g.%)	Haemoglobin: After treatment (g.%)	Haemoglobin: After treatment Day	Reticulocytes: Before treatment (%)	Reticulocytes: After treatment Max. retic count (%)	Reticulocytes: After treatment Day	Remarks
				Ward diet					
13	Marasmus	Mild	*6·5	7·4	30	5	<1	30	Received blood transfusion
19	Malnut.	Moderate	6·4	9·7	15	4·5	8	15	
21	Malnut.	Mild	8·1	10·2	28	1	5	28	
24	Malnut.	Mild	8·9	9·0	19	7	5·5	15	
28	Marasmus	Mild	6·9	5·5	13	2	12·5	13	
31	Malnut.	Mild	*7·5	6·9	10	<1	<1	10	Received blood transfusion
36	Marasmus	Moderate	7·1	10·7	21	5	18	21	
				Folic acid					
3	Malnut.	Moderate	5·8	9·9	18	4	12	14	
10	Malnut.	Mild	6·2	10·8	9	1·5	7·5	16	Marrow reverted to normal
37	Marasmus	Mild	8·6	9·9	14	2	<1	14	Died 17th day
42	Malnut	Moderate	5·8	10·0	14	2	9	11	Developed hypochromia
45	Malnut.	Moderate	4·5	11·5	33	<1	24	32	Developed hypochromia
46	Malnut.	Moderate	5·9	9·6	12	2	24	12	

* Post-transfusion haemoglobin level.

TABLE II. THE EFFECT OF THERAPY WITH INTRAMUSCULAR VITAMIN B_{12} IN 18 PATIENTS

Case No.	State of nutrition	Degree of bone marrow change	Haemoglobin: Before treatment (g.%)	Haemoglobin: After I.M. vit. B_{12} (g.%)	Haemoglobin: After I.M. vit. B_{12} Day	Reticulocytes: Before treatment (%)	Reticulocytes: After I.M. vit. B_{12} Max. retic count (%)	Reticulocytes: After I.M. vit. B_{12} Day	Remarks
6	Malnut.	Marked	*7·0	11·2	11	1	21	5	Received blood transfusion. Subsequent response to vitamin B_{12}
7	Marasmus	Marked	8·8	12·6	12	<4	22	5	
15	Marasmus	Marked	4·8	8·7	20	<1	26	7	Developed hypochromia
16	Malnut.	Marked	*11·0	12·5	28	<1	6	14	Received blood transfusion. Marrow reverted to normal on B_{12}
17	Malnut.	Mild	5·7	9·7	13	<1	19·5	4	
18	Malnut.	Moderate	6·5	10·5	28	3·5	7·5	4	Marrow reverted to normal
20	Malnut.	Moderate	8·4	10·4	29	1	13	10	Received blood transfusion.
22	Malnut.	Moderate	6·4	10·8	28	<1	15·5	6	Received blood transfusion Subsequent response to B_{12}
25	Marasmus	Mild	7·0	9·2	20	1	12·5	13	Developed hypochromia
27	Marasmus	Marked	4·0	7·5	15	2·5	36	8	
29	Malnut.	Moderate	4·6	8·1	18	1	10	8	Developed hypochromia
32	Malnut.	Moderate	4·0	11·4	22	3	7	7	Marrow revered to normal
33	Malnut.	Marked	4·0	11·4	16	<1	6	9	Marrow reverted to normal
34	Malnut.	Moderate	6·4	10·6	8	<1	22·5	8	
37	Marasmus	Moderate	4·2	9·0	14	3	25	9	
38	Malnut.	Moderate	5·4	11·2	15	3	26	3	
43	Malnut.	Moderate	*5·8	9·9	12	<1	43	6	Received blood transfusion. Subsequent response to B_{12}
44	Normal	Marked	*8·7	13·8	21	<1	17	8	Received blood transfusion. Subsequent response to B_{12}

* Post-transfusion haemoglobin level.

between the 3rd and 14th day after commencing treatment, with the majority of cases (61%) showing a maximum response between the 4th and 9th day. Treatment with B_{12} was given to 5 cases who had received blood transfusions previously and in whom haemoglobin levels had fallen subsequently; after treatment with vitamin B_{12} they all developed a reticulocyte response with a rise in haemoglobin levels. In 6 cases no response to treatment with vitamin B_{12} could be assessed. Two patients died shortly after treatment was begun, and in 3 cases follow-up studies were inadequate. One further case, with an associated severe iron deficiency, responded neither to vitamin B_{12} nor folic acid alone.

DISCUSSION

The age incidence in the present series is similar to that reported in children in the USA by Diamond (1953), and it is significant that the maximum incidence corresponds with the period of rapid growth. Of the present series of 46 cases, 42 showed evidence of disturbed nutrition, 36 being 60% or less of their expected weight for age. There was a close correlation between megaloblastic anaemia in infancy and disturbances in nutrition; the diets of these children were almost entirely devoid of green vegetables and were low in animal protein. During the period when the present series of 68 cases of megaloblastic anaemia were diagnosed, 800 malnourished children were admitted to hospital. This incidence of 8·5% in malnourished children is similar to that of 9% reported by Walt *et al.* (1957) in a similar group of children. Neither marasmus nor severe protein malnutrition is the sole cause of megaloblastic anaemia in infancy, for only 8–9% of children with kwashiorkor have been found to suffer from the disease.

The incidence of infection in this series was 86%, as compared with only 14% in a group of 105 cases of kwashiorkor investigated by Kahn (1958). It is possible that in children suffering from either malnutrition, undernutrition, or both, megaloblastic anaemia is precipitated by infection.

Of 7 cases receiving therapy with ward diet alone, the haemoglobin level rose significantly in only 3 patients. Response of the anaemia to ward diet is unpredictable, and when it occurs, the reticulocyte response and rise in haemoglobin value are generally less than in cases treated with folic acid or vitamin B_{12}. Blood transfusion alone will not induce haematological remission, as demonstrated by subsequent fall in haemoglobin value and a secondary response to vitamin-B_{12} therapy in 5 cases. The satisfactory response to folic-acid administration in this series confirms the results reported by Walt *et al.* (1957). The present series, however, demonstrates that the anaemia responds equally well to the administration of intramuscular vitamin B_{12}.

Malnourished children may be deficient in both vitamin B_{12} and folic acid, but owing to their nutritional state and slowing of their rate of growth, they may not show megaloblastic anaemia. It is suggested that some additional factor, possibly infection, is required to precipitate these marrow changes.

SUMMARY

The clinical and haematological features of 45 Bantu infants with megaloblastic anaemia are presented.

The association with malnutrition and infection is striking.

This form of megaloblastic anaemia in infancy responds to therapy with intramuscular vitamin B_{12} as well as to the administration of oral folic acid.

We wish to thank Prof. J. F. Murray, Drs. R. Cassel, H. B. W. Greig, E. Kahn and S. Wayburne for their help, the Director, South African Institute for Medical Research, for providing facilities for this study, and the Superintendent, Baragwanath Hospital, for permission to publish.

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