ANAEMIAS OF MARASMUS AND KWASHIORKOR IN KENYA

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(RECEIVED FOR PUBLICATION OCTOBER 4, 1962)

The purpose of these investigations is to describe the incidence and type of anaemia in marasmus and kwashiorkor, its aetiology and response to treatment.

Marasmus and kwashiorkor and their associated anaemias in Kenya are complicated conditions. Besides the usual low serum proteins on admission, infections such as measles, pneumonia, diarrhoea, otitis and intestinal and blood parasites were generally present and unless these were treated haematological response was incomplete; protein treatment alone produced no improvement in blood values.

The anaemias were not usually severe, were mostly hypo- or normochromic and were unrelated to the serum protein values. They had low mean corpuscular haemoglobin concentration, in spite of high iron stores. Hypo- and aplasia were common and developed either early or late in the course of the illness (Foy, Kondi and MacDougall, 1961).

The blood findings in marasmus and kwashiorkor were indistinguishable although the clinical picture was different.

Subjects and Methods

Forty-seven children between the ages of 12 months and 4 years entering the King George VI Hospital, Nairobi, during 1960-1962, were diagnosed by clinical assessment as either marasmus, marasmic-kwashiorkor or kwashiorkor (Jelliffe and Dean, 1959; Trowell, Davies and Dean, 1954). They were under observation for from six to 16 weeks and at least fortnightly blood and marrow examinations were made. All were nursed in the same ward and received similar diets.

Haematological examinations were done by standard techniques on blood taken from the internal jugular and marrows from the spinous processes of the lumbar vertebrae. The marrow smears were stained with Leishman and Giemsa and determination of the marrow haemosiderin was by the direct method (Rath and Finch, 1948; Wallerstein and Pollycove, 1958). Sideroblasts were stained by Dacie's (1956) method and calculated as a percentage of the normoblasts. The unsaturated

iron binding capacity was done by Ventura's technique (1952) previously calibrated as recommended by Gitlow, Beyers and Colmore (1952). Absolute eosinophil count was done by Dacie's (1956) method. Serum iron was estimated by the method of Bothwell and Mallett (1955).

Serum proteins were determined by the biuret method (Gornall, Bardawill and David, 1949). The albumin was salted with 27.2% sodium sulphate to avoid carrying over α_1 globulin into the albumin fraction thus giving falsely high albumin values (Yeoman, 1960a, b and c). Some workers have either not stated the concentration of sodium sulphate used or have used 22.5%, thus yielding falsely high albumin values and lowered globulins. The globulins were separated by low voltage paper electrophoresis with barbiturate buffer at pH 8.6, ionic strength 0.075 and the number of strips in each run kept constant (Yeoman, 1960b and c). To compensate for the wide variations in the serum protein content of marasmus and kwashiorkor the amount of serum seeded on the paper was calculated according to the formula

$$\mu\text{l.} = \frac{35}{\text{g./Total Protein/100 ml.}} \quad (\text{Sunderman and Sunderman, 1957; 1960}).$$

The strips were run for 16 hours, dried at 100° C., stained with bromophenol blue and scanned with a reflectance scanner (Yeoman, 1960b and c; Walsh, Humoller and Dunn, 1955). Quantitation was done by the square counting technique from which Gaussian curves were built (Wallner, 1955; Grassmann and Hannig, 1954). These refinements are considered necessary if reproducible results are desired. The comparison between the albumin content by the chemical and electrophoretic methods yielded results that were within 0.1-0.2 g./100 ml.

Aminoaciduria was determined on 24-hour specimens by two-dimensional ascending or descending chromatography in isopropanol-ammonia water and butanol-acetic acid and sprayed with Ehrlich's or other specific reagents. In some cases, a third separation was carried out in phenol water to separate more distinctly anthranilic acid, 3-hydroxyanthranilic acid, 5-hydroxy indol acetic acid, 3-indol acetic acid and 3-indolyl acrylic acid. Xanthurenic acid was stained with sulphanilic after separation in isopropanol and butanol-acetic.

Treatment

The patients were given 'Casilan', skimmed milk and vegetable oil, as recommended by Jelliffe and Dean (1959). As appetite improved a mixed diet of meat, maize meal and vegetables was started. The patients were covered during the first week with either tetracycline or penicillin and streptomycin. Intercurrent infections such as helminths, giardia, malaria, measles, diarrhoea and respiratory complaints when present were appropriately treated. All cases were given potassium chloride to correct electrolyte disturbances which are common in marasmus and kwashiorkor (Hansen and Brock, 1954).

The majority of the anaemias were hypochromic with high iron stores but required therapeutic iron later as haemopoiesis increased and the marrow haemosiderin was exhausted. The hypo- and aplastic anaemias occurring early in the disease and associated with infection and giant pro-erythroblasts usually remitted spontaneously; those developing later and not associated with infection responded to prednisone or riboflavin. Four patients showing no haemoglobin improvement on iron or other therapy over several weeks and having initially grade 4 haemosiderin in the marrow made a dramatic response to pyridoxine. The patients that had megaloblasts and/or giant stab cells required folic acid to produce full haematological response, although in some the giant stab cells disappeared spontaneously, perhaps because of improved gut vascularity and absorption.

Clinical and Laboratory Findings

When admitted all the patients exhibited the clinical picture of marasmus and kwashiorkor with characteristic hair and skin changes. Some had pyrexia or developed it in hospital from intercurrent infections. Most of them had a previous history of enteritis, respiratory infection, measles, chicken-pox or developed them while they were in hospital; some had malaria and many had intestinal helminths and protozoa. Of the 47 cases investigated, 15 had malaria pigment—one with trophozoites, one had hookworms, 14 had roundworms, 12 had giardia, two had strongyloides and two had tuberculosis. The helminth findings were not different from those found in non-marasmus and kwashiorkor children. Five patients had megaloblastosis when admitted and three developed it during treatment. Eleven had giant stab cells and four developed them later. Ten became aplastic during the first 14 days in hospital, three with giant pro-erythroblasts, all these cases remitted without haematinics as the infection subsided or was treated. Nine other patients (Foy *et al.*, 1961; Kondi, Mehta and Mbaya, 1962b) developed erythroid aplasia or hypoplasia during the later stages of their recovery, which was not associated with infection or giant pro-erythroblasts. Seven of these aplasias responded to riboflavin or prednisone.

The two others left hospital with erythroid aplasia; one died suddenly at home, perhaps associated with acute adrenal dysfunction, and the other was lost sight of.

Blood. In Table 1 are shown the haematological changes that take place during the course of the illness. The anaemia was rarely gross, the mean haemoglobin being 9.0 g./100 ml. Five patients had haemoglobins below 7 g./100 ml. on entrance. In a considerable number the haemoglobin fell during the first eight to 10 days associated with decreased marrow activity (Table 2).

The packed cell volume was low on entrance, fluctuated during the following weeks with the haemoglobin and reticulocytes, to reach normal level on discharge. The serum iron was reduced with a mean value of 47.0 µg./100 ml. The unsaturated iron binding capacity was greatly below normal with a mean of 120 µg./100 ml. (range 0-267). The saturation index ranged from 8-100% with a mean of 35%. On discharge the mean haemoglobin was 12 g./100 ml. with a range of 10.5-13.0 g./100 ml., but the mean corpuscular haemoglobin concentration showed little change. The mean serum iron level and the saturation indices on discharge were below the entrance level in spite of iron treatment. The unsaturated iron binding capacity in every case showed a great increase during the first 10 days of the illness, the mean exit value being more than twice the entrance level.

Marrow and Reticulocytes. Approximately 17% of the patients had megaloblastic marrows on entrance or developed them during the course of the illness; 32% had giant stab cells or developed them later. These are thought to be associated with folic acid deficiency and their appearance during treatment may be a result of increased erythropoiesis making greater demands on limited folic acid stores.

The erythroid activity of the marrow varied in the different patients and was highly labile during the course of the illness. On entrance it was either active, hypo- or aplastic with red cell precursors, ranging from 3-50%, mean 21%. During the next two weeks the activity was very varied. Punctures done two weeks after admission frequently showed decreased activity or even aplasia. Since, however, the reticulocytes usually rose four to six days after entrance there was probably also a spurt in marrow activity at this time which was missed as it was impracticable to do daily marrow punctures. This erythroid aplasia was generally accompanied by infection and high temperature, was always of

TABLE 1
HAEMATOLOGICAL VALUES DURING ILLNESS

	Hb (g./100 ml.)	Packed Cell Volume (%)	Mean Corpuscular Haemo- globin Concen- tration (%)	Unsaturated Iron Binding Capacity (μ g./100 ml.)	Serum Iron (μ g./100 ml.)	Total Iron Binding Capacity (μ g./100 ml.)	Sat. Index (%)	Red Cell Precursors (%)
<i>On Admittance:</i>								
Mean	9.0	30	30	120	47	153	35	21
Range	4.2-12	15-37	24-37	0-267	13-112	56-346	8-100	3-50
<i>2nd Observation:</i>								
Mean	8.9	36	29	314	34	370	11	24
Range	4.2-10.6	17-38	23-34	101-460	10-108	185-574	3-37	3-57
<i>3rd Observation:</i>								
Mean	10.0	34	29	350	27	390	8	24
Range	6.2-12.6	27-43	23-37	166-514	10-44	129-533	3-16	2-78
<i>4th Observation:</i>								
Mean	11.0	37	30	323	37	370	7	26
Range	7.7-12.8	29-42	26-33	184-505	13-90	206-525	4-20	1-40
<i>5th Observation:</i>								
Mean	11.0	37	29	323	38	350	8	22
Range	8-13.1	26-42	25-34	175-505	16-50	274-498	4-22	0-42
<i>6th Observation:</i>								
Mean	12.0	40	30	288	26	270	16	14
Range	10.5-13	37-41	27-32	230-368	15-44	116-401	4-38	0-33

short duration and was followed by greatly increased reticulocytosis. The marrow remained normal unless another infection developed and this might be followed by a further hypo- or aplastic condition. During the latter stages of recovery an aplasia sometimes occurred that was not associated with infection (Figs. 2 and 3).

During the aplastic crisis the white cell series in the aplasias of infection had 19% lymphocytes and 65% neutrophils while in those not associated with infection they were 50% and 45% respectively. In

the non-aplastic cases the percentage of lymphocytes on entrance was 26% and neutrophils 53% changing on discharge to 34% and 30%.

Haemosiderin. Marrow haemosiderin on admission to hospital was usually high, generally in the form of aggregates, the finer pepper-like granules were only rarely seen. Graded according to the notation of Rath and Finch (1948), 17 were grade 4, six grade 3, two grade 2, three grade 1, and four had no haemosiderin. Twelve had malaria pigment

FIG. 1.—Variation in absolute eosinophils (17 cases) mean/c.mm. The left-hand figures under Range refer to weeks.

TABLE 2
HAEMOGLOBIN VARIATIONS

Date (1961)	Hb (g./100 ml.)	P.C.V. (%)
October 6	12.0	36
October 18	8.0	30
November 2	10.4	35
November 3	11.0	33
November 23	10.0	32
December 15	11.4	36
May 6	10.9	37
May 18	8.8	28
May 29	8.8	28
May 27	7.8	27
June 10	4.5	17
June 21	8.4	31
June 7	8.5	35
June 30	6.9	26
July 5	8.4	34
July 9	11.4	37
July 23	9.2	31
August 9	10.1	34

FIG. 2.—Variations in marrow activity. The left-hand figures under Range refer to weeks.

alone and three malaria pigment and haemosiderin. On discharge marrow haemosiderin was present in only nine cases.

Absolute Eosinophil Count. The absolute eosinophil count was low on admission (0-120/c.mm., mean 14/c.mm.). During the next two weeks it rose (0-1,100/c.mm., mean 227/c.mm.) unless an infection was present in which case it usually fell. In the following four weeks eosinophils fell to normal values (44-200/c.mm.) (Fig. 1).

Sideroblasts. On admission these were sometimes high and sometimes low, generally decreasing

FIG. 3.—Variation in reticulocytes.

during treatment. There seemed to be little or no relation between the variations in the haemosiderin content, marrow activity and the sideroblast counts (Hansen and Weinfeld, 1959; Fridman, 1960).

Proteins. The serum proteins showed the usual picture common in marasmus and kwashiorkor. On entrance the total protein albumin and total globulins had means of 4.8, 1.6 and 3.2 g./100 ml. respectively (Table 3). This reversal of the albumin:

TABLE 3
PROTEIN VARIATIONS DURING THE ILLNESS

	Total Protein	Albumin	α_1	α_2	β	γ	Total Globulin
On Admission:							
Mean (g./100 ml.)	4.8	1.6	0.40	0.80	0.70	1.3	3.20
Mean (%)		33.0	9.0	16.0	13.0	28.0	67.0
Range (%)		21-45	4-13	9-23	5-18	17-35	55-74
2nd Observation:							
Mean (g./100 ml.)	6.7	2.4	0.40	1.07	1.19	1.82	4.24
Mean (%)		37.0	6.0	16.0	17.0	23.0	63.0
Range (%)		26-46	3-10	11-24	13-23	11-32	53-72
3rd Observation:							
Mean (g./100 ml.)	7.2	2.8	0.38	1.07	1.22	1.70	4.35
Mean (%)		38.0	5.0	15.0	17.0	25.0	62.0
Range (%)		30-54	2-10	11-19	13-23	17-33	53-70
4th Observation:							
Mean (g./100 ml.)	7.3	2.8	0.41	1.12	1.14	1.77	4.46
Mean (%)		37.0	5.0	16.0	16.0	25.0	63.0
Range (%)		34-45	2-10	12-21	13-23	15-32	57-73
5th Observation:							
Mean (g./100 ml.)	7.4	2.8	0.36	1.12	1.29	1.78	4.5
Mean (%)		38.0	5.5	16.0	17.0	24.0	65.0
Range (%)		25-55	2-8	13-27	9-21	16-30	45-74
6th Observation:							
Mean (g./100 ml.)	7.6	3.0	0.33	1.19	1.22	2.08	4.95
Mean (%)		38.0	5.5	16.0	14.0	27.0	64.0
Range (%)		35-44	4-7	13-17	13-17	23-29	61-65

globulin ratio is usual in these diseases, is common in Africans and due either to infections, to diet or is genetically determined (McGregor and Gilles, 1960). The exit values showed a rise in all fractions except α_1 . Albumin on entrance formed 33% of the total proteins and globulins 67% changing to 37% and 63% respectively on discharge. Although the absolute values change the percentage of the various fractions to the total proteins showed no significant alteration with the exception of α_1 globulin. There was a rapid rise in the serum proteins during the first five to 10 days, thereafter changes were less marked. The serum protein pattern and its changes bore no relation to the degree and type of anaemia, and the fluctuations in the haemoglobin and protein during the course of the illness were unrelated.

Folic Acid and B₁₂ Levels. The serum B₁₂ levels were within normal range as previously found by MacDougall and Ross (1960). Sometimes they were high and associated with liver damage (Satoskar, Kulkarni, Mehta, Sanzgiri and Bamji, 1962). The serum folic acid levels (*L. casei* and *S. faecalis*) were below normal and often unmeasurable (Table 4). The folic acid values did not appear to be related in any way to liver damage.

TABLE 4
SERUM B₁₂ AND FOLIC ACID LEVELS IN
MARASMUS AND KWASHIORKOR

Case No.	B ₁₂ (μ g./ml.)	Folic Acid (<i>L. casei</i>) (μ g./ml.)	Folic Acid (<i>S. faecalis</i>) (μ g./ml.)
1	200	1.1	0.7
2	500	3.5	0.0
3	1,000	3.2	0.0
4	140	2.9	0.0
5	900	3.6	0.0
6	1,500	1.8	1.8
7	330	Much above normal	Much above normal

Urine. Two-dimensional chromatography revealed abnormal aminoaciduria with kynurenine, anthranilic and 3-hydroxyanthranilic acids, as well as 5-hydroxy-indol-acetic and xanthurenic acids, present without prior tryptophan loading (Foy *et al.*, 1961; Kondi *et al.*, 1962b).

Anthranilic acid was present in about 50% of all the cases, mostly transient, but remaining very much longer in the aplastic patients. Prednisone used in the treatment of non-infectious aplasias did not clear the anthranilic acid from the urine, although it remitted the aplasia.

Four patients studied specifically had xanthurenic acid in the urine. Pyridoxine was given in two of these resulting in haemoglobin improvement and

the disappearance of xanthurenic acid, perhaps indicating a block in tryptophan metabolism due to deficiency of pyridoxine.

Discussion

The results of these investigations show that the anaemias of marasmus and kwashiorkor are not usually severe (Scragg and Rubidge, 1960). They are predominantly hypochromic or normochromic with low mean corpuscular haemoglobin concentration in the former, although they have abundant haemosiderin in the form of massive aggregates in the marrow. Some had megaloblasts and/or giant stab cells, indicating deficiency of B₁₂ or folic acid. Since these megaloblastic anaemias have normal to high serum B₁₂ levels and do not usually respond to B₁₂, it is unlikely that deficiency of this vitamin is a factor in their genesis (Adams and Scragg, 1962). Their high serum B₁₂ levels and low liver values are probably associated with liver damage. During treatment the serum B₁₂ returned to normal (Satoskar *et al.*, 1962).

Serum folic acid levels in these megaloblastic anaemias were low, sometimes having no detectable amounts, and they usually responded to folic acid. It appears then that there is a deficiency of folic acid.

In about half the patients during the first eight to 15 days the haemoglobin values usually fell due to reduction in erythroid activity that frequently occurs at this period. Changes in the oedema are probably not an important factor in these haemoglobin variations.

Hypo- or aplastic anaemias frequently developed either early on in the illness or later during the recovery period. These hypo- and aplasias of the marrow would be more commonly found were it practicable to do more frequent marrow punctures. Marrow activity is subject to wide and frequent variations and punctures done at infrequent intervals of seven to 14 days will give little indication of its state in the intervening periods, hence the poor correlation that is sometimes found between erythroid activity and reticulocytosis. Mean red cell precursor values will not reveal the actual state of marrow activity in any given patient at a particular moment or its relation to reticulocytosis. We found no evidence that the spleen was involved in these aplasias (Crosby, 1961).

The low reticulocytosis on entrance was sometimes associated with marrow hypoplasia or failure of maturation. This was followed by rising reticulocytes accompanying increased marrow activity. In many instances there was a subsequent fall in the reticulocytes as well as marrow activity. This was later followed by another increase in reticulocytes

and marrow activity. It is generally assumed that the degree of reticulocytosis can be used as an index of erythropoiesis, but variations in the rate of release of reticulocytes from bone marrow, or their maturation in the peripheral blood will vitiate this relation, and reticulocytosis will give only an approximate index of marrow activity (Seip, 1953; Wintrobe, 1961; Foy *et al.*, 1961; Morgan, 1962). Erythroid and reticulocyte activity followed the presence and treatment of infections. In addition, improved gut vascularity may increase absorption and influence haemopoiesis. This in turn may result in more rapid depletion of limited stores of haemopoietic factors and be followed by reduced marrow activity unless they are replaced therapeutically.

The extreme marrow lability was generally associated with infection. In a few cases where there was no obvious infection the marrow was nevertheless hypoplastic, but in these the absolute eosinophil count was high and the marrow inactivity may have been allergic (Gasser, 1957). It is our opinion that these hypo- and aplastic marrows that occur early on in the disease, that sometimes have giant pro-erythroblasts and that remit spontaneously within the first week are different from those that develop later (Lien-Keng, 1957; Gasser, 1957; Foy *et al.*, 1961; Kondi *et al.*, 1962b). These latter are not associated with obvious infection, have no giant pro-erythroblasts, remain inactive longer, usually have excess amounts of anthranilic acid in the urine and do not readily remit unless treated with prednisone or riboflavine. These two types have recently been found by Neame and Naude (1961) and Neame (1962) in Durban. The responses to prednisone and riboflavine may be associated with adrenal dysfunction—riboflavine taking part in corticosteroid metabolism (Foy *et al.*, 1961; Kondi *et al.*, 1962b). Trowell (1937), Gillman and Gillman (1951) and Chatterji and Sen Gupta (1960) have shown that at autopsy the adrenals were abnormal in marasmus and kwashiorkor. Lurie and Jackson (1962) found that in some of their cases 17-ketosteroid and 17-hydroxy-corticosteroid metabolism was not abnormal, but it is likely that there are wide variations in different patients.

In the aplasia of infection the neutrophils are raised, but in those aplasias unaccompanied by infection the lymphocytes predominate and rise as the red cell precursors fall, and as the erythroid series increase so the lymphocytes fall. This association we think indicates that the small lymphocyte is acting as a multipotent stem cell (Yoffey and Courtice, 1956; Stohlman, 1961; Goodman and Hodgson, 1962a and b; Kondi, Mehta and Foy, 1962a; Kondi *et al.*, 1962b; *Lancet*, 1962). Neither

of these types of aplasia appears to be associated with folic acid deficiency since they frequently occur while the patient is having folic acid.

Lien Keng and Tembelaka (1960) have recently described three types of aplasia—acute, chronic and subacute. Perhaps their acute form corresponds to our early ones that are usually associated with infection or allergy; their chronic and subacute ones may be equivalent to the aplasias that appear later on in the course of the disease and are not associated with infection.

The failure of haematological response in four cases until pyridoxine was given indicates that this vitamin deficiency without any characteristic clinical features is common in kwashiorkor (Theron, Pretorius and Joubert, 1961).

As previously reported, abnormal aminoaciduria is common in both marasmus and kwashiorkor (Schendel, Antonis and Hansen, 1959; Schendel and Hansen, 1959, 1962; Foy *et al.*, 1961; Kondi *et al.*, 1962b). Such compounds as kynurenine, anthranilic, 3-hydroxyanthranilic and xanthurenic acids as well as 5-hydroxy-indol-acetic acid and 3-indolyl-acrylic acid are frequently present without prior tryptophan loading. When riboflavine was given the anthranilic acid disappeared and the aplasia remitted; prednisone had no effect on the anthranilic acid but treated the aplasia. Those patients who had xanthurenic acid in their urine responded only to pyridoxine, which resulted in a disappearance of the xanthurenic acid and a rise in the haemoglobin. The presence of these amino acids and their clearance with riboflavine or pyridoxine is probably associated with upsets in tryptophan metabolism. We do not think that these aminoacidurias are associated with renal tubular changes or deficiency of protein (Edozi and Udezo, 1960). Details of this work are being reported separately.

The absolute eosinophil count showed great variations in marasmus and kwashiorkor. Aschkenasy (1961) has shown that in rats eosinopenia is related to low serum proteins. In our patients on admittance there was eosinopenia which may have been due to a combination of low serum proteins and infection. The eosinopenia that occurred later on in the disease followed the pattern of the infectious process and not that of the proteins. These eosinopenias were usually associated with a neutrophilia (Simons septic factor, Wintrobe, 1961) and perhaps related to adrenocortical hormone system. As recovery from the infection sets in there is a fall in the neutrophils and an increase in the eosinophils and lymphocytes.

It is difficult to assess the relative importance of proteins and infection in the aetiology of the hypo-

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TABLE 5
COMPARISON OF HAEMOGLOBIN AND PROTEIN LEVELS (g./100 ml.) IN
KWASHIORKOR, MARASMUS AND ANAEMIAS

	Entrance					Discharge				
	Haemo- globin	Total Protein	Albumin	Total Globulin	A/G Ratio	Haemo- globin	Total Protein	Albumin	Total Globulin	A/G Ratio
<i>Kwashiorkor:</i>										
Mean	10.3	4.4	1.4	3.0	0.47 : 1.0	10.3	6.6	2.9	3.7	0.78 : 1.0
Range	8.4-12.0	3.6-5.0	1.0-1.9	2.6-3.3		9.2-11.0	5.4-7.1	2.8-3.5	3.3-4.4	
<i>Marasmus:</i>										
Mean	10.8	6.0	2.5	3.5	0.71 : 1.0	10.7	6.7	3.3	3.4	0.97 : 1.0
Range	7.2-13.5	4.4-8.0	1.7-4.0	2.6-4.4		9.5-11.5	5.9-7.4	2.3-4.6	2.7-4.6	
<i>Anaemia (megaloblastic):</i>										
Mean	5.2	6.5	3.2	3.3	0.97 : 1.0	13.0	7.7	4.0	3.7	1.1 : 1.0
Range	2.2-8.5	5.9-7.5	1.9-4.4	1.5-4.0		10.0-15.0	6.7-9.4	2.9-5.0	1.8-5.8	
<i>Anaemia (iron-deficient):</i>										
Mean	5.2	7.1	3.2	3.9	0.82 : 1.0	13.0	7.8	3.5	4.3	0.81 : 1.0
Range	3.3-7.5	6.0-7.8	2.3-4.3	3.3-5.2		10.6-15.5	5.4-8.8	1.5-4.8	3.1-5.2	

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chromic and normochromic anaemias in marasmus and kwashiorkor. Scrimshaw, Wilson and Bressani (1960) considered that nutrition and infection acted synergistically in the genesis of these diseases. We think that infection is an important factor in the aetiology of these types of anaemia and intimately connected with variations in haemopoiesis. Treatment of infection results in increased marrow activity and rapid utilization of the iron stores and it is at this stage that therapeutic iron is required both in the hypochromic and megaloblastic anaemias. Proteins given alone will not improve the blood picture (Table 5).

The fall in the haemoglobin values occurred at a time when the serum proteins were rapidly rising; this, together with the failure of protein treatment alone to raise haemoglobin, indicates that proteins and haemoglobin changes are not closely associated in marasmus and kwashiorkor (Table 5).

Shahidi, Diamond and Schwachman (1961) have described an anaemia of 'protein deficiency' associated with cystic fibrosis of the pancreas that remitted when treated with high quality protein, no iron being necessary. No unsaturated iron binding capacity or marrow haemosiderin estimations were, however, done on their patients, and it is difficult to decide what type of anaemia was being dealt with.

Low mean corpuscular haemoglobin concentration associated with abundant iron stores suggests that there is a block in iron utilization due to infection or low serum proteins or both, which hinders haemoglobin synthesis (Heilmeyer, Keiderling and Wöhler, 1959; Foy *et al.*, 1961). The serum iron on

admission was usually reduced (Edozien and Udeozo, 1960), but the saturation index was normal perhaps because the relative amount of iron was high in comparison with the very reduced protein values as indicated by the low unsaturated iron binding capacity. The well-filled marrow iron stores and normal-to-high saturation indices imply an absence of iron deficiency although the serum iron was low, to be expected with such low protein and transferrin values. Edozien and Udeozo (1960) have suggested that the low serum iron in marasmus and kwashiorkor is the result of dietary iron deficiency or disturbance in absorption or storage. However, the presence of high iron stores with low mean corpuscular haemoglobin concentration seems to point to a block in Fe utilization due to decreased erythropoiesis, infection or reduced serum proteins which hinder haemoglobin synthesis (Heilmeyer *et al.*, 1959; Foy *et al.*, 1961). During treatment the saturation index, serum iron and marrow haemosiderin all fell, no doubt due to increased haemopoiesis.

Hathorn, Canham and Gillman (1961) found the serum iron levels unrelated to nutrition; Gerritsen and Walker (1953) found high values in normal Africans. Normal plasma iron values for Africans in South Africa range from 120-147 $\mu\text{g./100 ml.}$, with saturation index of 33-40% and total iron binding capacity, 358-380 $\mu\text{g./100 ml.}$, so that our figures for saturation index, serum iron and total iron binding capacity appear to be low when compared with these, in spite of our high marrow haemosiderin (Table 1). The marrow on discharge was free of haemosiderin in all patients in spite of the therapeutic iron that

was given throughout the illness, an indication of rapid haemopoiesis. The malaria pigment was still present in all those who had it on entrance.

There were considerable fluctuations in the unsaturated iron binding capacity, which on entrance was usually low, suggesting low transferrin values. As the serum protein rose the unsaturated iron binding capacity increased very considerably in all cases. Changes in the saturation index, serum iron, marrow haemosiderin and unsaturated iron binding capacity seem to be associated with infection, haemopoiesis and serum protein changes.

The usually extremely low unsaturated iron binding capacity on admission implies an absence of iron deficiency, confirmed by the high marrow haemosiderin but not by the low serum iron and mean corpuscular haemoglobin concentration. The rise in the unsaturated iron binding capacity that occurred during the first week or 10 days closely paralleled the increased serum proteins and marrow activity in those patients who did not develop an aplasia. Perhaps the low entrance unsaturated iron binding capacity may have been due to insufficient transferrin associated with the low serum proteins (Foy *et al.*, 1961), there being sufficient iron available to saturate the reduced amount of transferrin (Morgan and Brackenridge, 1962). Similarly low values for the unsaturated and total iron binding capacities have been found by Lahey, Behar, Viteri and Scrimshaw (1958) in kwashiorkor. Most workers have given values for total iron binding capacity only, but it is more satisfactory to use serum iron and unsaturated iron from which the total iron binding capacity can be derived, because rises in the total iron binding capacity may be due to either increases in the serum iron binding capacity or the unsaturated iron binding capacity, which the total iron binding capacity alone will not disclose.

Morgan (1962) found that in rats and rabbits the variation in the total iron binding capacity was dependent on tissue oxygen supply and demand; whether this is so in human anaemias is not known (Awai and Brown, 1961). There appears to be a dynamic relation between serum iron, oxygen erythropoiesis, serum proteins, iron stores and absorption (Hyde, 1957; Gupta, Kumar, Devi and Mangalik, 1959; Hallberg, Sölvell and Brise, 1959; Sölvell, 1960).

The lack of relation between sideroblastosis, marrow activity and marrow haemosiderin has been investigated by a number of authors (Pappenheimer, Thompson, Parker and Smith, 1945; Mills, Huff, Krupp and Garcia, 1950; Remy, 1952; Kaplan, Zuelzer and Mouriquand, 1954; Mouriquand, 1958; Björkman, 1956), and there is little

agreement concerning the factors that contribute to their rise and fall. Hutchinson (1953) believes that they can be used to differentiate between hypochromic anaemia associated with iron deficiency and those due to infection. Our own experience is limited and agrees with those authors who consider that there is little relation between marrow haemosiderin, erythropoiesis and sideroblast counts (Weinfeld and Hansen, 1962).

Summary

The haematological findings in 47 children with marasmus and kwashiorkor are presented and the aetiology and response to treatment is discussed.

The anaemias were mostly hypochromic or normochromic and were rarely severe. No association was found between the degrees of anaemia and the serum protein levels.

Erythropoietic activity of the bone marrow was extremely variable both on entrance to hospital and during recovery. Hypoplasia or aplasia was found in a considerable number of cases and was of two distinct types. One, occurring early, of short duration, associated with giant pro-erythroblasts, neutrophilia and infections and responding without haematinics as the infection subsided. Two, occurring late in recovery, of longer duration, unassociated with giant pro-erythroblasts or infections with a lymphocytosis and responding to riboflavine or prednisone. These aplasias are not associated with folic acid deficiency.

Of patients with anaemias refractory to all other therapy, 8% eventually responded to pyridoxine. The significance of excessive urinary indolic compounds and their relation to blocks in tryptophan metabolism and response to prednisone, riboflavine and pyridoxine is discussed.

Megaloblastic anaemia responding to folic acid was present in 17% of the cases and associated with low serum folic acid and normal vitamin B₁₂ levels.

Marrow haemosiderin was increased in the majority of patients on admission, although the mean corpuscular haemoglobin concentration, serum iron and unsaturated iron binding capacity levels were low. During recovery, as the serum proteins and unsaturated iron binding capacities increased, the serum iron, saturation index and marrow haemosiderin fell. Iron therapy was then required to effect full haematological remission.

On entrance the absolute eosinophil count was low and fluctuated during the course of the illness, with infections.

The possibility of the small lymphocyte being a multipotent stem cell in relation to erythropoiesis is discussed.

The effect of intercurrent infections on erythropoiesis was a notable feature of these anaemias and the lack of response to haematinics in the presence of active infection is stressed.

We are indebted to Professor Rachmilewitz and Dr. Izaak for the B₁₂ and folic acid estimations and to the medical and nursing staff of the King George VI Hospital, Nairobi, for their help and co-operation throughout these studies.

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