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ANAEMIA OF PREGNANCY AMONG AFRICANS IN NIGERIA

BY

A. W. WOODRUFF, M.D., M.R.C.P., D.T.M.&H.

(From the Department of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, and the Department of Medicine, University College, Ibadan, Nigeria)

Severe anaemia frequently complicates pregnancy in Africans as it does in other inhabitants of the Tropics; it is often refractory to treatment, and among the babies born of anaemic mothers the neonatal mortality is high. The management and treatment of these cases are difficult, as their cause is not known with certainty. The frequency with which they were encountered in Nigeria, and the severity of the illness, prompted this investigation into the aetiology, pathology, and treatment of the condition.

Anaemias in Africans

In order that the cases of anaemia forming the basis of this study may be viewed in their proper perspective it is desirable that nutritional anaemias in general and the anaemias of Africans in particular should be briefly reviewed; these form the background against which the investigation was made.

The frequent occurrence of hypochromic microcytic anaemia among Africans has long been noted, and there is a close association between it and the incidence of infection with ankylostomes and schistosomes. Present knowledge regarding this type of anaemia has been reviewed by Trowell (1939).

Nutritional macrocytic anaemias have also been described in Africa, early reports coming from Summerhayes (quoted by Wills, 1932), Trowell (1939), and Anderson and Roberts (1940), while Russell (1941) drew attention to the high incidence of macrocytic anaemia in pregnant women on the Gold Coast. More recently, further studies have been reported (Trowell, 1947; Lehmann, 1949; Beet, 1949). Anaemias similar in type to the African nutritional anaemias have been described in detail in India (Balfour, 1927; McSwiney, 1927; Mackie, 1929; Wills, 1931, 1932, 1933). In a comprehensive review of the subject, Napier (1940) draws attention to the importance of anaemia as a cause of maternal and infantile mortality in that country. By comparison, anaemias in Africans have received less attention, and, as stated by Trowell (1947), "nowhere is the focus clear, and the picture lacks precision." The deficiencies of haematological data relating to Africans have also been commented upon by Beet (1949).

An important contribution to knowledge of nutritional anaemias was made by Fairley, Bromfield, Foy, and Kondi (1938), who described a haemolytic variety of nutritional macrocytic anaemia occurring among pregnant women in Macedonia. The spleen was invariably and the liver frequently enlarged in these cases. Two

necropsies were carried out, and in the livers were found marked activity of the reticulo-endothelial cells, passive venous congestion with considerable damage to the parenchymal cells, proliferation throughout the sinusoidal system, and moderate deposition of iron-reacting pigment in the periportal zone—changes attributed to chronic malarial infections. The haemolytic tendency was thought to be due to phagocytosis of newly formed red blood cells by hypertrophied reticulo-endothelial tissue.

The varieties of anaemia occurring among Africans have recently been studied by Foy and his collaborators (1950). They conclude that there are at least four, namely:

(1) Those with hypochromic microcytic blood pictures, no megaloblasts in the bone marrow, acid in the gastric juice, and negative Schumm and indirect van den Bergh reactions. These patients usually have ankylostomes or schistosomes in the faeces, and respond to worming and/or iron therapy.

(2) Those with a normochromic normocytic blood picture, a megaloblastic marrow, and acid in the gastric juice. The serum bilirubin is between 0.5 and 2.5 mg. per 100 ml., and Schumm's test is sometimes positive. These cases respond to liver extracts, pteroylglutamic acid, or "marmite."

(3) Those with a normochromic normocytic blood picture, red-cell counts between 1.5 and 2.5 millions, and a marrow containing no megaloblasts but some giant stab cells. There is acid in the gastric juice, the serum bilirubin is between 0.4 and 0.8 mg. per 100 ml., and Schumm's test may or may not be positive. Such cases respond to liver extracts, pteroylglutamic acid, or marmite.

(4) Macrocytic anaemias with megaloblasts and giant stab cells in the marrow, achlorhydria, a positive Schumm's test, and a serum bilirubin of between 0.9 and 4 mg. per 100 ml. These cases respond to liver extracts, pteroylglutamic acid, and marmite.

To these must be added the anaemia observed to accompany malignant malnutrition or kwashiorkor in young children. This syndrome, first described by Williams (1933), has been the subject of much study in the past 17 years, particularly by Trowell (1949) in East Africa, Gillman and Gillman (1944, 1945a, 1945b, 1945c) in South Africa, and Waterlow (1948) in the West Indies. Present knowledge concerning the syndrome has been outlined by Waterlow (1948) and by Trowell (1949). It is characterized by oedema, dermatoses, hepatomegaly and splenomegaly, disturbed plasma proteins with inversion of the normal albumin/globulin ratio, and by an anaemia which may be of either the normocytic or the macrocytic variety. It has been

suggested by Lehmann (1949) and Trowell (1949) that the macrocytosis in these cases is due to the presence in the peripheral blood of reticulocytes, and that the anaemia is partly due to coincident ankylostome infections.

Among similar cases in which helminthic infections could be excluded Altmann and Murray (1948) nevertheless found anaemia usually normocytic but occasionally macrocytic, and this they concluded was due to protein deficiency and to be an "expression of the generally abnormal metabolism in a malnourished organism." These findings are of considerable importance in connexion with the anaemias in the present study. Trowell (1947) stated that when cases of macrocytic anaemia and dimorphic anaemia in African men and non-pregnant women are investigated in Uganda a large number are found to show one or more of the features of the kwashiorkor syndrome. He further states: "It remains for the future to see if the macrocytic anaemia seen in pregnancy in either the tropical or the temperate regions shows any of these signs of malnutrition; at present there has been almost no investigation along these lines."

The patients in this series were all studied in the hospitals associated with University College, Ibadan, Nigeria, and it seems desirable, therefore, to outline briefly the social and economic background and the habits of the population from which they were drawn.

Social and Economic Background of Population from which Patients were Drawn

The town of Ibadan is situated within the coastal tropical rain-forest belt approximately 40 miles (64 km.) south of its northern fringe; vast tracts of forest in the region have been cleared and the land has been cultivated. The town has become a bustling business and administrative centre of an area from which the principal products are cocoa, maize, cassava, yams, and groundnuts. Of these, the cocoa and most of the groundnuts are exported, and the remaining three form the staple diet of the indigenous population. Meat is expensive, fish very expensive, fresh milk virtually unobtainable, and eggs are scarce. Many Africans will not eat eggs because of religious scruples. The town has grown rapidly in the last 50 years and now with half a million inhabitants has the largest African population of any town in the world. This population is mainly composed of members of the Yoruba, Ibo, and Hausa tribes. The majority of the inhabitants of Ibadan are petty traders, clerks, or labourers, whose respective average weekly income is approximately 10s., £1, and 9s. Almost all live in small mud-walled, tin-roofed huts. By European standards there is gross overcrowding, and sanitary arrangements are primitive.

Polygamy is usual, and wives are procured by payment to the girl's father of a sum of approximately £20. Few can afford this amount without borrowing, and an exorbitant rate of interest is often charged. In many families, therefore, a load of debt absorbs income which might otherwise be spent on food. The possession of several wives is regarded as a mark of prosperity and social distinction, and many accordingly become committed to debts they can ill afford. Under the social code prevailing the husband is required to provide his wives with shelter and food only, and severe economies are often effected at the expense of the latter. It is customary for the wife to undertake some petty trading

to augment her needs, but many subsist in poverty and want. A further mark of social distinction is the possession of many voluminous brightly coloured garments, and the budget in poor families is often further strained by extravagant buying in this connexion. The community from which the patients are drawn is therefore poor, and financial distress is aggravated by many of the prevailing social customs.

Methods

On admission patients were examined in detail and the findings recorded, a sample of oxalated venous blood was obtained, and the following examinations made.

The haemoglobin was estimated by the method of King, Gilchrist, and Delory (1944), using an Eel photoelectric absorptiometer. In three cases and for the four estimations made on children of the patients, Sahli's method as described by Whitby and Britton (1946) was employed. Red-cell and white-cell counts were made, using a Bürker-Türk counting chamber. The packed cell volume (P.C.V.) of the blood was determined by the method of Wintrobe (1933a, 1933b), and Schumm's test for methaemalbumin was carried out as described by Fairley (1941). Estimations of haemoglobin red cells and P.C.V. were repeated at intervals of five days. Sternal marrow was aspirated, and marrow and two blood films simultaneously obtained were stained with Leishman's stain. The films were examined for parasites as well as from the haematological viewpoint. Price-Jones curves were constructed in 21 cases, using the method of Price-Jones (1933) and measuring 500 cells. Platelets were estimated by the indirect method, and reticulocytes were stained supravitaly with cresyl blue and counted daily throughout the period spent in hospital. The sickle-cell trait was searched for by placing a drop of fresh blood on a slide, covering with a coverslip, ringing with petroleum-jelly, and inspecting at 24-hour intervals for three days. The red-cell fragility was assessed, using standard saline solutions of concentrations ranging from 0.28 to 0.72%.

Plasma was preserved in sealed glass ampoules at 2° C. and brought back to the London School of Hygiene and Tropical Medicine, where the proteins were estimated by the Johnston and Gibson (1938) modification of the method of Wu (1922). Van den Bergh quantitative tests were carried out by the method of King (1946); and thymol turbidity tests and the colloidal gold reaction by the methods of McLagan (1944a, 1944b).

In 24 out of the 25 cases a liver biopsy was done. The technique adopted was that described by Gillman and Gillman (1945a), but either a Gillman or a Vim Silvermann needle was used. In five patients the biopsy was repeated when the blood picture, though improved, was still not normal, the interval between the two examinations varying from 10 to 56 days. No untoward sequelae to the biopsies were encountered. The specimens of liver were fixed in 5% formal-saline immediately on withdrawal from the body. Paraffin sections were stained with haematoxylin and eosin; Van Gieson; and for reticulin by Wilder's (1935) modification of Laidlaw's (1929) method. Frozen sections were stained for fat with Sudan III.

The hippuric-acid test of liver function was done in five cases; the method employed was that described by Kolmer and Boerner (1945), 5.9 g. of sodium benzoate being given and the urine collected for four hours. Analyses were made of fasting gastric juice removed before and after the injection of 0.5 mg. of histamine phosphate.

After admission a system of dietary control was established: liver, red meats, and eggs were forbidden, although few patients had been in the habit of consuming more than 1 oz. (28 g.) of meat weekly. Consumption of other protein-containing foods was permitted. A control period of at least five days was allowed to elapse before any treatment was given. Although a longer period would have been preferred, Nigerians, even if very ill, often refuse to stay in hospital

for more than two to three weeks, so that early treatment was essential if its results were to be observed. To follow up Africans after they have left hospital is often impossible; nevertheless a number did attend regularly as out-patients, and their progress was studied. Methods employed in dietary analysis are discussed in the section on the nutritional status of the patients.

Symptoms and Clinical Findings

The commonest symptoms of which the patients complained were lethargy and weakness, these becoming progressively worse as pregnancy advanced. Those with severe anaemia often complained of some dyspnoea and palpitation. Soreness of the tongue and dysphagia were not encountered.

Apart from the clinical evidence of anaemia often clearly apparent, the most outstanding findings were hepatomegaly and splenomegaly. In 16 out of 25 patients the liver reached more than $\frac{1}{2}$ in. (1.25 cm.) below the costal margin during inspiration, while a further three had livers of which the edge only was palpable. In nine the liver reached 3 in. (7.5 cm.) or more below the costal margin. The spleen was palpable below the left costal margin in 19 cases, in three its edge only was clearly felt, in 15 it extended below the costal margin for a distance of 1 in. (2.5 cm.) or more, in eight for 3 in. (7.5 cm.) or more, and in four for 4 in. (10 cm.) or more. Neither the liver nor the spleen was tender in these patients.

No evidence of cardiac failure was detected, and this condition could be excluded as a cause of hepatomegaly and/or oedema.

Oedema of the feet and shins was present only in seven patients, all of whom were pregnant. It disappeared in three of these after delivery, in the other four parturition had not occurred by the time the investigation had to be concluded. In all the patients in whom oedema was observed the plasma proteins were not sufficiently diminished of themselves to account for its presence, so that pressure from the uterus was probably an important causative factor.

Among Africans a yellow colour of the conjunctivae in the regions around the cornea is common, but, as the fornices in these patients are usually clear, the discoloration is due to causes other than jaundice, most probably to local irritation from dust. A slightly yellow tinge in the conjunctival fornices was noticed in three patients, while in a fourth marked jaundice developed.

Among the patients with haemolytic nutritional macrocytic anaemia occurring in pregnancy described by Fairley and others (1938) bronchitis was common; in this series, however, neither it nor other respiratory diseases were encountered. Fissures at the angles of the lips were seen in only three patients, and were probably due to secondary deficiencies not associated with the anaemia. Ulceration of the tongue and buccal mucous membrane was not encountered. No neurological or renal abnormalities were detected.

Obstetric and Neonatal Findings

A remarkable feature of the obstetric history of these patients is the high incidence of twin pregnancies among them. Six out of 21 women who had given birth to children had borne twins, two of them on two separate occasions. Evidence is later brought forward of protein deficiency and liver damage as possible aetiological factors in connexion with the anaemia in these cases. Twin

pregnancies, by imposing a more than usually severe drain on available protein, might aggravate both the deficiency and the liver damage.

Of the 25 patients in the series 13 were primiparae, and of the 12 others eight had borne children who died in the first month of life. Mr. J. G. Dumoulin delivered six of these eight patients during the present investigation, and only one of them bore a child who lived longer than 12 days (Table I). Of the patients in the whole series, 18 were delivered during this investigation; there were no obstetric complications, yet only eight of the children born survived the first 12 days of life. It therefore seems that the children of patients with anaemia of pregnancy in Nigeria frequently die in the neonatal period, and series of pregnancies may terminate unsuccessfully in this way.

TABLE I.—Data Relating to Children of the Present and of Previous Pregnancies

Case No.	No. of Previous Pregnancies Following which			Present Pregnancy		
	Child Died in First Month of Life	Child Died at Age of 1-12 Months	Child Lived More Than 1 Year	Duration at Delivery (Weeks)	Child's Neonatal History	Birth Weight of Children
1	3	0	0	30	Died on 6th day	lb. 4 3, oz. 1 11, kg. 1.90
2	0	0	0	23	Stillborn	1 11, 0.76
3	0	0	0	28	Died on 7th day	Unknown
4	0	0	0	36	Healthy child	5 6, 2.44
5	3	0	0	32	Died on 6th day	4 11, 2.13
6	0	0	0	36	Healthy child	5 8, 2.49
7	0	0	0	26	Stillborn	2 4, 1.02
8	0	1	3	36	Twins: 1 healthy, 1 stillborn	5 1½, 4 2, 2.31, 1.87
10	1	0	3	24	Stillborn	Unknown
11	0	1	0	36	Healthy child	6 0, 2.72
12	1	0	0	36	Twins: 1 healthy, 1 stillborn	3 14, Unknown, 1.76
13	0	1	1	32	Died on 3rd day	3 0, 1.36
14	1	0	0	28	Died on 10th day	4 3, 1.90
15	1	0	0	34	Died on 12th day	4 3, 2.46
16	0	0	0	36	Stillborn	4 12, 2.15
19	0	0	0	36	Healthy child	6 7, 2.92
23	0	0	0	36	" "	6 5, 2.86
24	0	0	0	36	" "	" "
9	1	0	0	17	Term not reached when patient left hospital	
17	1	0	1	18		
18	0	0	0	20		
20	0	0	0	21		
21	0	1	1	22		
22	0	0	0	25		
25	0	0	0			

. In Cases 1, 5, 8, 9, 12, and 15 there was a history of twins among the previous pregnancies.

Shaw (1933) gives the following figures as the mean birth weights of 299 East African children:

	Male	Female
First child ..	6 lb. 11.17 oz. (3.04 kg.)	6 lb. 9.71 oz. (3.00 kg.)
Second child ..	7 " 4.3 " (3.30 ")	6 " 15.7 " (3.16 ")
Third and subsequent children ..	7 " 4.4 " (3.30 ")	6 " 15.6 " (3.16 ")

Reference to Table I reveals that, compared with these, all the 18 women delivered bore infants of whom the birth weight was abnormally low, and half the pregnancies terminated prematurely. Figures for Nigerian children are not available.

In four of the healthy children born at term the haemoglobin and red blood cells were estimated. The values obtained were:

Child of Case	4	11	12	13
Haemoglobin	10.51 g. per 100 ml.	18.25 " " "	14.60 " " "	17.52 " " "
R.B.C.s	3.5 millions per cmm.	5.1 " " "	5.0 " " "	6.4 " " "

With the possible exception of the child of Case 4 there is no evidence of anaemia in the offspring of these anaemic mothers.

Nutritional Status of the Patients

Signs of gross malnutrition as indicated by severe wasting or symptoms of a clear-cut deficiency disease were not encountered among the patients in this series or indeed among the adults in the hospitals in Ibadan at the time of the study. Approximately one-half of the children admitted, however, were suffering from malignant malnutrition, and one of the commonest conditions seen in adults in the medical wards of the hospitals was cirrhosis of the liver with or without ascites. As the result of work by Himsworth (1950), Gillman and Gillman (1945b, 1945c), Gillman *et al.* (1945), Trowell and Muwazi (1945a, 1945b), Waterlow (1948), and others it is now generally believed that diffuse fibrosis of the liver in the Tropics is most commonly produced by a diet deficient in protein. There was good reason to suspect, therefore, that the diets of the local inhabitants were deficient in protein but contained enough carbohydrate to prevent marked wasting. Unfortunately, a weighing machine did not become available till the last few days of the investigation, and only the patients referred to in Table II could be weighed.

TABLE II.—Heights and Weights of Seven Patients

Case No.	When Weighed	Height		Weight	
		ft.	in.	lb.	kg.
1	2 months after delivery	5	2	157	97
3	2½ " " "	5	1½	155	86
5	2 " " "	4	11½	152	104½
18	7th month of pregnancy	4	11½	151	103½
20	5th " " "	5	0	152	108
22	8th " " "	5	0	152	127
25	7th " " "	5	2	157	111

Height and weight standards for healthy women in Nigeria are not available, but those for Gambia were found by Dean Smith (1950, personal communication) to be: height, 5 ft. 2.1 in. (157 cm.), standard deviation ± 1.76 in. (4.4 cm.); weight, mean 115 lb. (52.2 kg.), standard deviation ± 15.9 lb. (7.2 kg.). Green-Armytage and Dutta (1936) found that pregnant women in India seldom increase much in weight during the first three months, but from that time till term an increase of 16–20 lb. (7.3–9.1 kg.) is to be expected, or approximately 3 lb. (1.4 kg.) a month. If for each month of pregnancy subsequent to the third 3 lb. (1.4 kg.) is deducted from the weight given in Table II it is seen that Cases 5, 20, and 22 come into the lowest portion of the normal range while the remainder are distinctly though not grossly underweight. In Cases 5, 18, 20, and 22 growth appears to have been stunted.

The diets of the patients were studied, and in 13 cases all food eaten in hospital during a 1–4 days' period was weighed. The hospitals did not supply meals to patients, and these were therefore brought thrice daily by relatives. Although there is reason to believe that persons in hospital are in this way given rather more to eat than they would obtain in their own homes, the amounts are a useful guide to the individual's normal diet. The staple foods in this region—namely, maize pap, yams, and gari made from cassava—are all prepared according to recipes which do not vary materially from family to family. These recipes were procured and from them the quantities of the basic ingredients determined. With the aid of the tables compiled by Platt (1945), the protein and carbohydrate contents of these ingredients were calculated. Fat was not estimated, as without the imposition of special ill-tolerated conditions

considerable inaccuracies would result from the patients' eating habits. A quantity of oil, sometimes enough for several days, is kept, and into this portions of food are dipped during the meal. Oil being relatively expensive, the amounts used in this way and also added in cooking vary with the financial status of the individual. The fat content of popular dishes therefore cannot be accurately assessed from standard recipes. The amount of protein and carbohydrate consumed daily is shown in Table III. The daily protein intake recommended for

TABLE III.—Constituents of the Diets of 13 Patients

Case No.	Daily Protein Consumption (g.)	Daily Carbohydrate Consumption (g.)	Total Calories Provided by Dietary Protein and Carbohydrate	No. of Days Food Weighed
5	38	362	1,600	2
6	66	390	1,824	1
9	65	626	2,764	2
11	63	727	3,160	2
13	69	619	2,752	2
14	86	716	3,208	2
17	26	216	968	2
18	55	513	2,272	2
20	56	480	2,144	2
21	47	396	1,772	4
22	73	591	2,656	2
24	56	358	1,656	3
25	40	315	1,420	2

pregnant women by the Food and Nutrition Board of the National Research Council (U.S.A.) is 85 g., or 1.5 g. per kg. of body weight, and of this it is suggested that one-half to three-quarters should be of animal origin. The dietary history of these patients revealed that they never had more than 1 oz. (28 g.) of meat or fish a day, and only the exceptions among them had more than 1 oz. (28 g.) every three to four days. Several stated that they normally had only one piece weighing about 1 oz. (28 g.) weekly. Most of the dietary protein was supplied by maize. This is deficient in tryptophan and lysine, without which essential amino-acids it is probable that some of the protein ingested could not be utilized by the body. There seems to be little doubt that all the patients in this series were living on a diet grossly deficient in animal protein, and markedly deficient in non-animal protein. Clinical evidence points to such deficiencies being common among the general population of Nigeria.

The fat content of the diets of these patients probably averages not more than 30 g. a day and therefore provides approximately 270 calories. If this figure is added to the calories provided by protein and carbohydrate shown in Table III, an approximation to the total daily calorie value of the diets is obtained. Nicholls (1938) has recommended that the diet of pregnant women in the Tropics should supply 2,800 calories daily. The Committee on Foods of the National Research Council (U.S.A.) (*Bull. nat. Res. Coun., Wash., 1945*) gave 2,500 as the minimum figure. If the former recommendation is accepted, then reference to Table III shows that 8 of the 13 patients whose diets were analysed have an inadequate calorie intake; if the latter standards are accepted seven are inadequate. Except in one patient (Case 17), who was very ill and suffering from anorexia, the deficiency of calories is not gross—a finding which accorded with the general appearance of the patients.

Wilson and Mitra (1938) surveyed the diets of a section of the population of Assam among whom nutritional anaemias in pregnancy were common. Their findings were almost identical with those in the present survey.

Haematological Data

The following values were found at initial examinations of patients in the series. As one patient was not seen till convalescent the figures for that case are excluded. *Haemoglobin*: mean, 5.7 g./100 ml.; range, 2.66–8.7 g. *Red blood cell count*: mean, 1.58 millions per c.mm.; range, 0.59–3.04 millions. *Mean corpuscular volume (M.C.V.)*: mean $91.1 \mu^3$; range, 74.9 – $120.4 \mu^3$. *Mean corpuscular haemoglobin concentration (M.C.H.C.)*: mean, 32.01%; range, 26.6–38%. *Mean corpuscular haemoglobin (M.C.H.)*: mean, $28.7 \mu\mu\text{g.}$; range, 21.9–36.2 $\mu\mu\text{g.}$

The anaemias can be divided into three main groups as follows:

Group 1.—Microcytic and Hypochromic: M.C.V. less than $82 \mu^3$ and M.C.H.C. less than 32%—two cases.

Group 2.—(a) Normocytic and Hypochromic: M.C.V. 82 – $95 \mu^3$, M.C.H.C. less than 32%, four cases. **(b) Normocytic and Normochromic:** M.C.V. 82 – $95 \mu^3$, M.C.H.C. 32–38%—11 cases.

Group 3.—Macrocytic: M.C.V. greater than $95 \mu^3$ —seven cases.

It is apparent that anaemias of pregnancy in Nigeria do not form a homogeneous group. If an M.C.H.C. value of below 32% is taken to indicate hypochromia then hypochromia is encountered among macrocytic, normocytic, and microcytic anaemias. Fairley *et al.* (1938) found a similar position among nutritional macrocytic anaemias in pregnant women in Macedonia, while Wintrobe (1932) and Britton (1936) pointed out that in pernicious anaemia the M.C.H.C. is often lower than normal. The various absolute values for the anaemias of malnutrition in infants studied by Altmann and Murray (1948) were not dissimilar from those in the present series.

The reticulocyte counts in patients first seen before delivery and before treatment had been given were: Group 1 (microcytic and hypochromic), mean 1.2%; Group 2a (normocytic and hypochromic), 2.3%, range 0.5–4.1%; Group 2b (normocytic and normochromic), 1.9%, range 0.5–4.2%; Group 3 (macrocytic), 4.2%, range 3.0–7.0%.

A reticulocyte crisis may occur spontaneously in the puerperium, so that figures from patients first seen then are excluded.

The platelets were significantly reduced in all groups, mean 228,000 per c.mm., range 72,000–350,000 per c.mm. This finding accords well with that of Fairley *et al.* (1938) in cases of nutritional anaemia in pregnant women in Macedonia. In that series thrombocytopenic purpura was observed in approximately 25% of the patients; in these it seems the platelet count was below 55,000 per c.mm. Neither platelet counts as low as this nor purpura were observed in this study.

The white blood cells were reduced to 5,000 per c.mm. or less in 11 cases. Again similar changes were observed by Fairley *et al.* (1938). The reduction in these patients not only of the red cells but of the white cells and platelets they attributed to a pancytopenia.

The sickle-cell trait was found in 3 out of 19 cases. These were divided equally among the three types of anaemia, and, apart from the presence of the trait, the clinical, haematological, and pathological characters in these cases and their response to treatment did not differ from those of the other members of their group—points suggesting that the presence of the trait was an incidental finding only and was not aetiologically related to the anaemia.

The red-cell fragility was determined in 14 cases. All were within the normal range.

The sternal marrow was examined in 23 cases. The almost universal appearance was one of hyperplasia of the myeloid

elements with a macro-normoblastic picture. True Ehrlich megaloblasts were observed in only two cases, though there were many cells which resembled megaloblasts very closely. There appeared to be little correlation between the marrow findings and those in the peripheral blood, and in this respect as well as in the prevalence of the macro-normoblastic appearances these cases are strikingly similar to those of malnutritional anaemia in infants studied by Altmann and Murray (1948). This dissociation between the marrow and the peripheral blood picture has also been reported by Foy *et al.* (1950).

Price-Jones curves were constructed for 21 cases. In each, 500 cells were measured. A shift to the right and broadening of the base was present in 13, a shift to the left was

FIG. 1.—Typical Price-Jones curve.

FIG. 2.—Typical Price-Jones curve.

found only in one case—one of the two in Group 1. A broad base in a centrally placed curve was found in seven cases. No normal curves were obtained. Typical curves are shown in Figs. 1 and 2.

The mean corpuscular diameter (M.C.D.) (normal 6.7μ to 7.7μ , average 7.2μ , Whitby and Britton, 1946) was in the upper half of the normal range in all but three cases and greater than normal in 11 cases, range 7.068μ – 8.606μ . The standard deviation of the M.C.D. (σ) and the coefficient of variation (V) were increased in all cases, the range for the former being 0.6μ – 1.08μ (normal 0.4μ – 0.5μ , Price-Jones, 1933), and for the latter 7.74%–14.67% (normal 5.3%–7.3%, Price-Jones, 1933).

The mean corpuscular average thickness (M.C.A.T.) (normal 1.7 to 2.5 μ , Price-Jones, Vaughan, and Goddard, 1935) was in the lower half of the normal range in 18 cases, below 2.0 μ in 11 cases, and below 1.7 μ in three cases, the range being 1.374 μ –2.486 μ . The ratio of M.C.D. to the M.C.A.T. has been shown (Haden, 1935) to average 3.4/1 in healthy persons, the normal range being 2.4/1 to 4.2/1. A value of more than 4.2/1 indicates an abnormally flat cell. In the present series the mean value was 4.04/1, range 3/1 to 6.26/1. In 18 cases the value was greater than 3.4/1 and in six cases greater than 4.2/1.

These findings are of special interest in view of the work of Larsen (1948), who found the red cells in acute and chronic hepatitis to be abnormally broad and thin, the M.C.V. in such patients often being normal, and the standard deviation of the M.C.D. increased.

The Gastric Juice

This was examined in 23 cases; in 15 of these free acid was present after histamine, while a histamine-fast achlorhydria was found in eight. Both patients who had a megaloblastic marrow had achlorhydria. Achlorhydria appeared to be equally common in the macrocytic and normocytic groups.

Stool Findings

Stools were examined in 23 cases. Sixteen patients were found to be infected with *Ascaris lumbricoides*, four with *Trichuris trichuria*, and four with *Ankylostoma duodenale*. Infection with the two former worms has not been reported as a cause of anaemia, and from the haematological viewpoint may be ignored. In this series it is considered that ankylostomiasis is also unrelated to the anaemia. This view is based on the following facts: (1) That in only 4 cases out of 23 was the infection present. (2) Those infected were distributed in a random way among the normocytic and macrocytic groups, whereas the anaemia produced by ankylostome infections is typically microcytic. (3) Of the four patients infected two were given anthelmintic treatment immediately on admission, yet the anaemia did not materially improve. (4) Of the other two cases the anaemia in one rapidly improved after delivery and in the other some improvement with marmite was obtained before delivery. No attempt was made to expel the worms in either case until investigations of the anaemia were concluded.

Cysts of *Entamoeba histolytica* were present in only one case and the anaemia responded satisfactorily before anti-amoebic treatment was given.

Evidence of Malaria

Overt malaria was not detected in any of the patients, although blood slides were examined from them all. None complained of symptoms suggestive of malaria, though the region in which they live is highly malarious. The absence of clinical evidence of malaria and of parasitaemia demonstrable by examination of blood films suggested that malarial infections, if present, were unlikely to be severe enough to cause anaemia, though they may have added to the strain on the blood-forming tissues.

Evidence of Syphilis

The high incidence among the patients in this series of hepatomegaly and of pathological changes in the liver as revealed in the biopsy material rendered it necessary to exclude syphilis as an aetiological factor. No clinical

evidence of the infection was detected by examination of the nervous, cardiovascular, or other systems, and the Kahn test was positive in only one case out of 21 in which it was done. The anaemia in this patient underwent a spontaneous remission after delivery and before any antisyphilitic treatment was given. There is no evidence, therefore, that syphilis is responsible for the anaemia or the condition of the liver in these patients.

Biochemical Data

The *van den Bergh* test was done in 15 cases, and only in two was the bilirubin content of the serum significantly raised.

Schumm's test was positive in 16 out of 24 cases. Positive reactions were found among all types of anaemia. The test has been demonstrated by Fairley (1941) to be a very sensitive index of intravascular haemolysis, so that this process seems to occur in some cases of all types of anaemia of pregnancy encountered in this study.

Plasma Proteins.—In view of the evidence of dietary protein deficiency and of liver damage in the patients the plasma proteins were determined as often as possible. They were fractionated and estimated individually in 15 cases, while only the total was determined in a further seven instances. The totals were found to be within normal limits in all but one case, in which it was reduced (range 4.9–8.7 g. per 100 ml.) but an outstanding feature of the values was the almost universal increase in the globulin fraction (range 2.6–4.7 g. per 100 ml., mean 3.64 g. per 100 ml.). The other values, expressed in grammes per 100 ml., were albumin, mean 3.48, range, 2.2–4.1; fibrinogen, mean, 0.48, range, 0.1–1.2. Expressed in grammes per 100 ml., Harrison (1947) gives the following as the normal figures for the plasma proteins: Total, 5.8–8.8; fibrinogen, 0.20–0.40; albumin 3.4–6.7, average 4; globulin 1.2–2.9, average 2; albumin/globulin ratio (A/G), 4/1 to 1.2/1, average 2/1. If these standards are accepted, then of the 15 patients in whom estimations were made the albumin fraction was below the average in 13, the globulin above the average in all, and the globulin values were greater than those of the normal range in 11 cases. The A/G ratio was below the normal range in 11 cases (range 0.58/1 to 1.48/1, mean 0.99/1). Similar protein values were noted by Holmes (1945) in a study of oedema in nutritional macrocytic anaemia, while a fall in plasma albumin and rise in globulin has been reported in liver disease by many authors, notably Filinski (1922), Post and Patek (1942), Higgins *et al.* (1944), and Maizels (1946).

Liver Pathology

Histology

A specimen of liver was obtained by biopsy in 24 patients. In the paraffin sections stained with haematoxylin and eosin the outstanding features were that in many sections the cytoplasm of the parenchymal cells was pale, and there was an obvious increase in fibrous tissue within the portal tracts and also a considerable amount of pale staining material between individual liver cells (Fig. 3). In places, embedded in this substance, were small round cells which were perhaps lymphocytes. The appearance after special staining suggested that much of the material was reticulin. Two sections were treated with Best's carmine at the suggestion of Dr. D. S. Ridley; the pale cells were then seen to be loaded with glycogen granules. Waterlow (1948)

FIG. 3.—Liver section from Case 23. (Stain haematoxylin and eosin.) The parenchymal cells are pale, and between many of them are clumps of material containing reticulin. ($\times 200$.)

FIG. 4.—Case 3. Section showing diffuse increase in reticulin network between parenchymal liver cells. ($\times 200$.)

found large amounts of glycogen in the livers of infants suffering from malignant malnutrition.

When stained by Wilder's method almost every section showed some increase in reticulin fibres. Exceptions were three cases in which the anaemia was among the least severe of any in the series. Little increase in reticulin was found in two other patients whose anaemia also was not severe. In the remainder a mild or moderate degree of diffuse fibrosis was present (Fig. 4). Strands of reticulin between individual liver cells were increased in thickness and number, often appearing like the ends of teased-out rope, while in the portal tracts and around the central veins of the liver lobules the tissue was

invariably increased. In those patients in whom the biopsy was repeated the second samples did not materially differ from the first. The longest interval between the two, however, was only 56 days.

In seven patients fatty infiltration of the liver was demonstrable in frozen sections stained with Sudan III. In two the infiltration was mild or moderate (Fig. 5), but uniformly distributed in the periphery of the liver lobules. In the remaining five cases only a few scattered cells were affected.

In almost all of these anaemic patients, therefore, there was either fibrosis or fatty infiltration of the liver. It is difficult to ascertain how long the fibrosis had been present, but Dr. J. C. Waterlow, who kindly examined a number of sections, thinks the appearance more consistent with a long-standing than with a recent infiltration of fibrous tissue.

FIG. 5.—Fatty degeneration of the periphery of liver lobule. Frozen section stained with Sudan III and methylene blue. ($\times 120$.)

Biochemical Tests of Liver Function

As a guide to liver function the thymol turbidity, colloidal gold, and hippuric-acid tests were carried out whenever possible.

The thymol turbidity test was performed in 19 cases; in these it was positive in 11 and at the upper limit of the normal range (0–4 units) in a further three.

The colloidal gold reaction was done alongside the thymol turbidity test; the results confirmed those of the latter. In no case was a positive reaction obtained in one and a negative in the other.

The hippuric-acid test was carried out in five cases, and was positive in them all. In four hours the normal excretion by women is 3.36–5.5 g., amounts below 2.5 g. being distinctly abnormal (Harrison, 1947). Amounts of hippuric acid in grammes excreted in four hours by these patients were, respectively, 1.90, 2.30, 1.23, 2.20, and 2.25.

Course of the Anaemia

It was found that the anaemia is most likely to develop in the last three to four months of pregnancy. It may improve with rest and with increase in the protein content of the diet; and it had a distinct tendency to remit spontaneously after delivery.

Treatment

In all types of case the results of treatment before delivery were disappointing, while, in the puerperium, assessment of the therapeutic efficiency of different substances was largely invalidated by the natural tendency to remit.

In the microcytic group iron given before delivery failed to evoke a reticulocyte crisis.

In the normocytic group deworming, "marmite," folic acid, iron, and vitamin B₁₂ similarly failed during pregnancy. Marmite was given in doses of 3 oz. (85 g.) daily for 15 and 8 days respectively to two patients, but no reticulocyte crisis or increase in the red blood cells or haemoglobin occurred. In other cases folic acid in doses of 20 mg. daily for six days failed, as did ferrous sulphate in doses of 3 gr. (0.2 g.) thrice daily. In another case a single injection of 80 μ g. of vitamin B₁₂ ("cytamen") was given without response.

Among those with macrocytic anaemia, two patients had natural remissions after delivery, another was given 3 oz. (85 g.) of marmite daily for 10 days during the puerperium, and another received 100 μ g. of vitamin B₁₂ (cytamen) intramuscularly six days after delivery. All improved at approximately the same rate. One patient had failed to respond to iron given during pregnancy, though her M.C.H.C. was only 26.6%. Two patients were given vitamin B₁₂ during pregnancy in doses of 100 μ g. and 120 μ g. respectively. No significant response to treatment occurred in one, though small increases in the reticulocyte count and haemoglobin were observed in the other. Large doses of vitamin B₁₂ were used, as Patel and Kocher (1950) suggested that some of the reports of ineffectiveness of vitamin B₁₂ in macrocytic anaemia of pregnancy and the puerperium were due to the use of too small a dose. The amounts here employed were respectively 10 and 12 times greater than those producing maximal responses in Addisonian anaemia. In both cases folic acid was also ineffective. Two patients who were critically ill on admission were each given a transfusion of 1½ pints (850 ml.) of blood to help them over this period. After

parturition the anaemia improved rapidly. Another patient, after deworming and a control period lasting 21 days, was given 3 oz. (85 g.) of marmite daily. Over the ensuing eight days the reticulocytes rose 4%, the red cells 0.6 million per c.mm., and the haemoglobin 1.45 g. per 100 ml.

The two patients with megaloblastic bone marrows were first seen on the day on which they were delivered. They were ill and had haemoglobin values of 2.66 and 4.48 g. per 100 ml. respectively. Both were treated immediately—one with liver extract, the other with marmite. They developed satisfactory reticulocyte responses and made good recoveries.

This group of macrocytic anaemias in pregnancy appear to be different from those of the temperate zone in their failure to respond to folic acid, as regards the marrow findings, and in the presence of methaemalbumin in the circulating plasma, though in their response to vitamin B₁₂ they are similar to those reported by Ungley and Thompson (1950).

Napier (1940) stated that "anaemia of pregnancy is amenable to suitable treatment in the early months of pregnancy and in some cases in the later months, but in the majority it is only possible to stop or slow down the deterioration of the blood picture until after parturition." For the macrocytic variety of anaemia in pregnant Nigerian women this statement still appears to hold good in spite of the advent of vitamin B₁₂ and folic acid.

Discussion

The outstanding features of these cases of anaemia in pregnancy appear to be the high incidence among them of liver damage, a haemolytic tendency, a disturbance of the plasma proteins, and an increase in the diameter and a decrease in the thickness of the red blood cells, with a shift to the right or a broadening of the base of the Price-Jones curve. The diets of the patients are deficient in protein but only mildly deficient in carbohydrate. The increase in the diameter of the red cells was noted even in anaemia which, when judged by the M.C.V. alone, would be classed as microcytic. The anaemias in the series have so many points in common that, even though the M.C.V. varies, it seems possible that they have certain similar aetiological features.

Macrocytic anaemia with haemolytic features associated with liver disease was described by Davidson and Fullerton (1938), though anaemia in patients with cirrhosis of the liver is more common, and was recognized by Wintrobe (1933a, 1933b). Since that time several accounts have been published, and Wintrobe (1936) reviewed 132 cases. Jarrold and Vilter (1949) state that such patients usually have not a megaloblastic but a macro-normoblastic marrow. Coleman (1948) described further cases of haemolytic anaemia in liver disease. The occurrence, therefore, of haemolytic features in patients with anaemia in pregnancy and liver damage takes on a fresh interest when viewed against the background of this work. Larsen (1948) finds that the standard deviation of the M.C.D. is invariably increased in patients with liver damage, and both he and Himsworth (1950) state that the cells in these cases are abnormally broad and thin, so that the M.C.V. may be within the normal range—findings in common with those of the present series.

Himsworth (1950) further points out that growth, by imposing on the body demands for protein, may

result in hepatic injury in childhood and pregnancy. He states (p. 97) that "if rats are given a diet containing just sufficient casein and choline to prevent fat accumulating in the liver, and then allowed to become pregnant, gross fatty infiltration of the liver develops. After parturition the fat content returns to normal." It seems at least possible that such a mechanism is at work in the patients studied in this investigation. Some of them no doubt begin pregnancy with livers damaged in childhood by malignant malnutrition and ensuing diffuse fibrosis, while in others living on a protein-deficient diet pregnancy is the final stress leading to fatty infiltration and/or fibrosis with disturbance of liver function. This process probably in part explains the development of anaemia which the work already referred to has shown to occur in patients with liver damage.

The other main factor concerned is protein deficiency. This of itself may cause anaemia. Himsworth and Glynn (1944) have demonstrated this experimentally in animals deficient in methionine when a macrocytic anaemia with macro-normoblastic marrow developed. As protein deficiency may also damage the liver some interplay of these two factors seems highly probable. Parasitic infections, including malaria, may impose a further drain on the patient's available protein. Liver damage and dietary protein deficiency both appear to be common among the population from whom these patients were drawn. Hepatic enlargement, however, was very much more common among these anaemic patients than among non-anaemic pregnant women in Ibadan. Splenic enlargement in these patients may in part be due to chronic malaria, but it is more probably associated with the liver damage. Himsworth (1950) has discussed this point in detail, and it seems possible for the spleen to enlarge as the result of liver damage with or without portal hypertension. The conclusion tentatively suggested from the findings in this investigation is that dietary protein deficiency, liver damage, the demands of pregnancy, and particularly of twin pregnancies, impose a combined strain on bodily metabolism of which the development of anaemia is a result.

This hypothesis would explain the failure to exert any therapeutic action in these cases of known haemopoietic substances, including vitamin B₁₂, folic acid, and liver extract in normal doses, the disturbance of blood formation and the development of macrocytosis here being the result of protein lack and liver damage. There is no evidence of any deficiency of haemopoietic principle. It is possible that the very large doses of liver extract found effective by some workers may benefit the anaemia through the action on a damaged liver of their contained protein and lipotropic substances. Marmite, too, may perhaps owe some of its therapeutic efficiency to its known content of lipotropic substances rather than to the extrinsic haemopoietic factor which it contains.

The possible relationship of this type of anaemia of pregnancy in the Tropics to those of pregnancy in the temperate zone, cirrhosis of the liver, so-called Banti's disease, and particularly to haemolytic anaemia occurring in association with liver disease, appears to be worthy of further investigation. There seem to be good grounds for believing that the anaemias of pregnancy in Nigeria are related to those found in malignant malnutrition or kwashiorkor.

The most helpful therapeutic measure in these patients once the latter months of pregnancy have been reached

appears to be blood transfusion, repeated as required until natural remission takes place after parturition. The patient should be given a high-protein diet supplemented by 2 to 3 oz. (57 to 85 g.) of marmite daily—a preparation which the African takes with relish.

To make pregnancy safe for tropical peoples and to prevent the occurrence of these anaemias, the aim must be an adequate diet, particularly during the years of growth and child-bearing, so that at neither of these periods does the liver become damaged or protein deficiency develop.

Summary

Anaemia in pregnancy in Nigeria is often encountered among those living on a protein-deficient diet.

There is a marked tendency for labour to be premature in these cases, and the neonatal mortality is high.

The anaemia is characterized by an increase in the diameter of the red blood cells, and diminution in their thickness. A haemolytic tendency is common.

The patients frequently have enlarged livers and spleens.

The bone marrow almost invariably shows a macro-normoblastic picture.

The total plasma proteins are normal, though the globulin is usually increased.

Liver biopsy has shown the liver to be diffusely fibrosed in many cases and infiltrated with fat in others.

Biochemical tests reveal an impairment of liver function.

The anaemia tends to become most severe in the last three months of pregnancy and to remit spontaneously after parturition.

It is usually refractory to treatment before parturition. The therapeutic measures that seem most useful, however, are a high protein diet and blood transfusion, repeated as necessary till the natural remission develops.

In pregnant women in the Tropics a vicious circle may be established by the demands of the foetus for protein aggravating the effects of dietary protein deficiency and liver damage due to protein deficiency. It is suggested that anaemia of the type described is the result of this process.

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Each month the United States Information Services issue a medical newsletter prepared by the American Medical Association as a guide to developments in American medical research. The November copy is an eight-page quarto booklet containing abstracts on 10 different subjects. A brief mention of four items will show the scope of the newsletter. The first note describes the treatment of lobar pneumonia with bacitracin, an antibiotic produced by a strain of *Bacillus subtilis*, and suggests that it is effective against pneumococcal pneumonia, though toxic to the kidneys (*Annals of Internal Medicine*, May, 1951). The second (*Annals of Allergy*, May, 1951) suggests that khellin may have a useful place in the treatment of bronchial asthma, particularly in patients with hypertension. Khellin is obtained from a plant known in Arabic as khella and in English as bishop's weed, and belongs to the carrot family. A report from the *International Journal of Leprosy*, March, 1951, discusses the somewhat limited value of streptomycin and dihydrostreptomycin in treating leprosy. Fourteen patients with hepatic insufficiency, with onset of coma, were treated with large doses of aureomycin, and eight showed definite improvement. The authors (*Gastroenterology*, May, 1951) conclude that the antibiotic has a beneficial action worth further trial.