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THE NATURAL HISTORY OF ANAEMIA ASSOCIATED WITH PROTEIN MALNUTRITION*

BY

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During the past three decades it has become clear that protein malnutrition is a major cause of death and disability throughout the Tropics. Its severest effects are on infants and young children, but there are reasons for believing that older children and adults, and particularly pregnant women, are affected by it. The term "protein malnutrition" has been discussed by Platt (1953); its meaning is wider than simple dietary protein deficiency, and includes disturbances produced primarily by under-feeding but aggravated by zymotic agents and infection which may convert borderline nutrition into malnutrition.

The study on which these lectures are based began in 1950 in Nigeria when I was confronted with a number of severely anaemic pregnant women. Anaemia in pregnancy is common in Nigeria and throughout the Tropics, and difficulties were encountered in finding an effective remedy for it. Similar difficulties were experienced by Napier (1940) in treating anaemia in pregnancy in India. Earlier work (Woodruff, 1951) has indicated that protein malnutrition plays an important part in the causation of this anaemia, and there is prevalent in Nigeria, as in the Tropics generally, the disease variously known as malignant malnutrition, kwashiorkor, and fatty liver disease. This has recently been referred to as the protein malnutrition syndrome in childhood. It is associated with an anaemia, and, in view of this, further investigations were undertaken to answer the question whether the anaemia in protein malnutrition in childhood is similar to or different from that encountered in pregnant women. There were obvious similarities between both sets of patients in that they were living on poor diets; in the children there was a special demand for protein imposed by the growth of their own body, and in the pregnant women a similar demand imposed by the foetus.

In considering the anaemias associated with protein malnutrition it is necessary to take into account many facts relating to the persons affected, their disease, and their environment. Thus the local foods are of obvious importance; so are the parasites and other causes of locally prevalent diseases, and the habits and social customs of the people.

The patients were all studied at hospitals associated with University College, Ibadan, Nigeria, a town which has grown rapidly during the last 50 years and in which the social and economic conditions prevailing have previously been described (Woodruff, 1951).

Although poverty plays a part in the causation of malnutrition, Trowell *et al.* (1954) have drawn attention to the fact that malnutrition often depends more on the type of crops grown in the patients' neighbourhood than on monetary wealth. Thus in a cassava-growing region wealthy people may live on an unbalanced and poor cassava diet. Certainly the parents of grossly malnourished children often are sufficiently well off to wear costly clothing. Taboos are important causes of malnutrition in some regions. Thus in Western Nigeria a common taboo prohibits the eating of eggs, so although hens are numerous no use is made of the valuable source of protein their eggs supply.

Methods of Investigation.—The haematological methods used were standard and have previously been described in detail (Woodruff, 1951). The electrophoretic studies of plasma proteins were made with paper as described by Flynn and de Mayo (1951). Reticulocyte ripening was studied by the method described by Nizet and Robscheit-Robbins (1950).

ANAEMIA AND MALNUTRITION IN PREGNANT WOMEN

These patients, numbering 45, all complained of lassitude and weakness, and many of dyspnoea. Only two gave a history of having had soreness of the tongue. The most outstanding clinical findings were hepatomegaly and splenomegaly. The liver was palpable in 30 and the spleen in 32 cases. In 10 the liver reached 3 in. (7.5 cm.) or more below the costal margin, and the spleen did so in nine. Subcutaneous oedema was present in 10 cases and ascites in one. No evidence of cardiac failure was found to explain the hepatosplenomegaly or oedema. A trace of albumin was present in the urine of several patients, but there were no casts.

The haematological findings for 40 patients are shown in Table I; in the remaining five cases either the patient was first seen in convalescence or full haematological indices were not obtained. It is apparent that these anaemias are of considerable severity; about 50% are normocytic, 25% macrocytic, and 25% microcytic, as judged by the mean corpuscular volume (M.C.V.). The mean corpuscular

*Being the text of the Goulstonian Lectures delivered before the Royal College of Physicians of London on February 23 and 25, 1954.

TABLE I.—Haematological Values at Initial Examination in 40 Cases of Anaemia in Pregnancy

Type of Anaemia	Haemoglobin (g. per 100 ml.)		Red Blood Cells (millions per c.mm.)		M.C.V. (cu.μ)		M.C.H.C. (%)		Reticulocytes (% of R.B.C.)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Macrocytic (M.C.V. >95 cu.μ) (11 cases) ..	6.93	5.18-8.70	2.23	1.81-2.90	102.76	95.30-120.40	30.33	26.60-33.30	4.51	1.2-9.5
Normocytic (M.C.V. 82-95 cu.μ) (19 cases)	5.55	4.62-9.18	2.00	0.89-3.98	86.88	82.30-93.46	33.04	26.20-38.00	4.49	0.5-16.5
Microcytic (M.C.V. <82 cu.μ) (10 cases) ..	6.66	4.14-9.62	2.60	1.38-3.36	74.26	57.70-81.81	33.47	28.60-37.68	3.30	0.5-6.0

haemoglobin concentration (M.C.H.C.) in the majority of cases is satisfactory, and evidence of iron deficiency was infrequent.

Reticulocyte counts at initial examination averaged 4%, indicating that the marrow was active, and this was borne out by microscopical examination of the marrow films, which with two exceptions showed macronormoblastic hyperplasia. In two cases Ehrlich megaloblasts were present. Dr. D. S. Ridley has kindly examined the marrow films and reports that the principal features are: (1) the cells are larger than normal, but not so large as those of the megaloblastic series, the pronormoblasts being 15-21 μ and early normoblasts up to 17 μ in diameter; (2) normal coarsely marked nuclei are found; (3) there is premature haemoglobinization; (4) primitive forms predominate in relation to the scanty late normoblasts; and (5) erythropoiesis is active.

The sickle-cell trait was found in only six cases, thus this abnormality could not be held responsible for the characteristics of the anaemia.

The gastric juice was examined in 39 cases, and histamine-fast achlorhydria was found in 11. Among these 11 patients were the two with megaloblastic marrow.

Schumm's test was positive in 21 cases, so that in these there was a haemolytic process at work. Fairley *et al.* (1938) described such a process in pregnant women suffering from nutritional macrocytic anaemia, and in his cases, too, there was hepatomegaly. Fairley thought it probable that this haemolytic process was initiated by malaria, but continued in the absence of an overt infection. Such a mechanism may be at work in these cases, although haemolytic anaemia in liver disease has been described by Davidson and Fullerton (1938) and by Coleman (1948), and this affords another possible basis for this feature.

In 1950 it was suspected that the anaemia in these cases might respond to liver extract, vitamin B₁₂, or folic acid, for it is associated with a macronormoblastic marrow in which the cells are sometimes difficult to distinguish from megaloblasts. Megaloblastic anaemia in pregnancy has been reported in the Tropics by many workers, and Wills (1931, 1932, 1933), Manson-Bahr (1951), and others have found it to respond to specific haemopoietic substances. Vitamin B₁₂ in doses of 100 and 120 μg. failed, however, to bring about a reticulocyte crisis or improvement in the haematological picture. Maximal doses of liver and of folic acid also failed. The therapeutic failure of vitamin B₁₂ is understandable in the light of estimations of the vitamin in the serum which Dr. G. I. M. Ross has kindly carried out in five cases, the concentrations ranging from 470 to 1,000 μμg. per ml. The normal range was found by Mollin and Ross (1952) to be from 100 to 720 μμg., with a mean of 358 μμg. per ml. of serum. Thus the values in these women were all normal or slightly above normal.

In macrocytic, normocytic, and microcytic groups iron administered before delivery failed to evoke a reticulocyte crisis or haematological improvement. In one of the cases the M.C.H.C. was as low as 26.6%. Five of the patients improved spontaneously after delivery without treatment. In others, however, this tendency towards spontaneous remission was absent.

The problem, therefore, was of an anaemia often of considerable severity, occurring late in pregnancy, refractory to treatment with iron, folic acid, liver extract, and vitamin B₁₂, and associated with a macronormoblastic marrow and hepatosplenomegaly.

Investigations Concerning the Cause of the Anaemia

Role of Helminths

Of the many questions posed by this anaemia one of the first is whether parasites such as intestinal worms are important aetiological factors. Accordingly stools were searched in all cases; ova of *Ancylostoma duodenale* were found in 14, and ova of *Ascaris lumbricoides* in 34. Treating both worm infections did not, however, influence the anaemia. In many of the cases the infection was light, only very few ova being present. Infection with *A. lumbricoides* is not recognized as a cause of anaemia, though the nutritional demands of this parasite have to be met from the patient's diet and may aggravate any malnutrition present. Infection with *A. duodenale*, where present, no doubt aggravated the anaemia, but the extent to which it did so was probably small, for the characteristics of the anaemia in infected and non-infected persons were similar.

Malaria

One or more blood films from the patients were examined on admission, and subsequently whenever there was fever. Patients found to have overt malaria were excluded from the study. Ibadan is, however, in a highly malarious region, and probably all the patients had been infected in the past but their infections had been adequately dealt with by their immune processes. Malaria may have played a part in the causation of the anaemia and malnutrition, but there is abundant evidence that other very important factors were also at work. Thus patients, and particularly pregnant women, with malarial parasites in the blood and anaemia not uncommonly failed to improve haematologically when given adequate antimalarial treatment.

In well-nourished persons, even when severe anaemia is caused by malaria, the anaemia improves rapidly after adequate antimalarial treatment has been instituted. To one of the pregnant women in this series 600 mg. of mepacrine had been given empirically daily for three days before she was seen for the purpose of this study. Her haemoglobin content was 5.03 g., and her total plasma protein level 5.93 g. per 100 ml. (albumin 1.95 and globulin 3.45 g. per 100 ml.). During the subsequent eight weeks she was delivered, received 2 pints (1.1 litres) of blood by transfusion and 0.9 g. ferrous gluconate daily for three weeks, yet at the end of this period her haemoglobin level was unchanged. She was given a supplement of 4 oz. (113 g.) casein daily, and in two weeks the haemoglobin had risen to 6.2 g., and the total plasma proteins to 7.08 g. per 100 ml. (albumin 3.11 and globulin 3.60 g. per 100 ml.). In cases such as this it is clear that conditions other than malaria are important in preventing recovery from the anaemia.

Significance of the Hepatomegaly

The next question is, what is the significance of the hepatomegaly: is it possible that it is related to the anaemia? Syphilitic disease of the liver was excluded, as the Kahn test, performed in 36 cases, gave a positive result in only one case.

A biopsy of the liver was taken in 42 of the 43 patients, and histological examination showed fatty infiltration in about a quarter of these, and in almost all an increase in fibrous tissue. The fat, when present, was usually in the peripheral portions of the liver lobules, but in some cases it was irregularly distributed; it was never gross, but simulated that seen in mild cases of fatty liver disease in malnutrition of childhood (Woodruff, 1951). The fibrous tissue was

increased in the portal tracts and also occurred diffusely between liver cells. Staining with Wilder's silver method showed that reticulin, instead of being a fine strand between parenchymal cells, was thicker than normal and in multiple strands, often appearing like teased-out rope or lacework. In most cases the cytoplasm of the parenchymal liver cells was thin, vacuolated, and stained badly; in some cells only filaments of cytoplasm were present. Biopsies were repeated after treatment in eight cases, and the late Dr. W. Silveira (who kindly examined the sections) found that in the second specimens the cytoplasm invariably stained better than in the first, and fat where originally present had diminished or disappeared. No change in reticulin was, however, noted. Dr. D. S. Ridley has stained several of these sections for glycogen and found this greatly increased. Certainly the cells are not filled with their normal complement of healthy cytoplasm.

This liver damage has much in common with that found in children suffering from protein malnutrition, and is also similar to that which can be produced in animals by feeding them on diets low in protein and adequate in carbohydrate or fat. Accordingly the question arose whether the anaemia in these cases is the result not of deficiency of a specific haemopoietic factor but of protein, and whether protein malnutrition causes the liver damage and both contribute to the production of anaemia.

Plasma Proteins

The plasma proteins were estimated chemically in 34 cases. The mean values are shown in Table II, from which it will be found that the albumin fraction is reduced and the globulin fraction increased as compared with normal

TABLE II.—*Plasma Proteins (g. per 100 ml.) in 34 Cases of Anaemia in Pregnancy*

	Total Protein	Albumin	Globulin	Fibrinogen	A/G Ratio
Mean	7.37	3.15	3.76	0.46	0.84/1
Range	4.9-8.7	1.9-4.1	2.6-4.9	0.1-1.2	0.48/1-1.48/1
Normal range (Harrison, 1947)	5.8-8.8	3.4-6.7	1.2-2.9	0.2-0.4	4.0/1-1.2/1

TABLE III.—*Electrophoretic Separation of Serum Proteins in Cases Studied*

	Albumin (%)	Globulin (%)			
		α_1	α_2	β	γ
Mean of 9 women with anaemia in pregnancy	38.23	10.60	7.33	10.03	33.81
Mean of 5 young children with severe protein malnutrition	27.89	13.59	15.07	15.99	27.46
Mean of 11 older children, adult males, and non-pregnant females with protein malnutrition and anaemia	25.72	8.99	15.64	12.58	37.07
Normal average:					
Ricketts <i>et al.</i> (1949)	60.30	4.00	9.70	12.80	13.20
Taylor <i>et al.</i> (1949)	64.10	4.10	7.70	11.40	12.70
Mean of 12 patients with malaria (Taylor <i>et al.</i> , 1949)	55.90	6.80	8.10	13.70	15.30
Mean of 7 patients with cirrhosis of liver and ascites (Ricketts <i>et al.</i> , 1949)	35.20	4.20	7.20	7.70	35.70

values. Serum was examined electrophoretically in nine cases to determine the type of globulin responsible for the increased amounts present. Typical electrophoretic patterns are shown in Figs. 1 and 2 and may be compared with that from a healthy Syrian woman living in Ibadan (Fig. 3). The mean values of the various protein fractions are summarized in Table III and compared with figures from other patients studied and with those of healthy persons, patients with malaria, and patients with cirrhosis of the liver.

It is clear from a review of the literature on the plasma proteins in malaria (Maegraith, 1948) that in this disease the albumin is reduced and the globulin increased. It is not clear, however, which globulin fraction becomes increased. Taylor *et al.* (1949) infected 12 healthy volunteers with malaria and permitted them to have five to eight paroxysms of fever. The electrophoretic protein patterns before and after the experiment are shown in lines 5 and 6 respectively in Table III. The albumin fraction decreased by 14.5%, the α_1 globulin increased by 62%, and the γ globulin by 19%. Similar changes have been reported by Ganzin (1954).

There is a large literature on the changes in the plasma proteins which may occur in liver disease. The figures given in Table III are those obtained by Ricketts *et al.* (1949) in seven patients with hepatic cirrhosis and ascites, and it is seen that there is nearly three times the normal amount of γ globulin present. The position thus far, therefore, was that these women were anaemic, they were not suffering from deficiency of any known specific haemopoietic factor, and the anaemia appeared not to be caused by the presence of parasites but was associated with liver damage and to some extent also by malaria.

The position thus far, therefore, was that these women were anaemic, they were not suffering from deficiency of any known specific haemopoietic factor, and the anaemia appeared not to be caused by the presence of parasites but was associated with liver damage and altered levels of various protein fractions in the blood. The next question which arose was whether there was any evidence that the patients' diets were deficient in protein. Answering this was fortunately facilitated by the fact that the hospitals at Ibadan, like the great majority of those in tropical Africa, do not provide patients with food except in special cases. Food must be brought by relatives or friends, who visit the hospital thrice daily for this purpose. It was thus possible, by weighing and charting the food brought, to obtain an indication of what the patients eat in their homes. In 1950 this was done in 13 cases, and the protein, carbohydrate, and calorie content estimated. The mean daily protein consumption worked out at approximately 50 g., and the total calories provided about 2,000. Miss M. W. Grant, of the Department of Nutrition at the London School of Hygiene and Tropical Medicine, has carefully

FIG. 1

FIG. 2

FIGS. 1 and 2.—Protein pattern obtained by electrophoresis of serum of two of the patients with anaemia in pregnancy. In this and in subsequent similar diagrams figures under Alb. indicate percentage of albumin present, those under α_1 , α_2 , β , and γ the percentages of the various globulin fractions.

FIG. 3.—Protein pattern obtained by electrophoresis of serum of a healthy Syrian woman living in Ibadan.

checked the diets and these figures, and considers that the values were probably all over-estimated by as much as 30%, the reason being that the water content of the flour used in Ibadan is greater than the figure given in the tables used. Even so, the protein content of the diets was just over half that usually recommended for pregnant women, whereas their calorie value appeared to be adequate. This fitted in with the appearance of the patients, who were fairly well covered. In 1953 more accurate dietary data were obtained, not only by weighing and recording food eaten but by collecting representative samples for analysis. The exact counterpart of food eaten by the patients was placed in a container, aliquots were dried and brought back to this country, and Professor B. S. Platt kindly had these analysed. With the data obtained from these analyses and the records of the patients' diets Miss M. W. Grant and Miss Dare have been able to estimate accurately the calorie, protein, fat, and carbohydrate values of the diets. These are shown in Table IV, and support the suggestion that the

TABLE IV.—*Constituents of the Diet of 14 Patients*

Case No.	Calories	Protein (g.)	Fat (g.)	Carbohydrate (g.)
Pregnant women:				
5/53	1,900	56.9	53.3	297.3
6/53	1,303	35.7	59.8	155.2
22/53	1,145	30.0	29.2	190.6
23/53	1,097	43.5	39.3	141.9
27/53	1,439	35.6	56.6	195.6
28/53	1,579	36.7	51.5	241.8
33/53	1,022	26.1	43.2	132.9
34/53	1,112	36.1	34.7	164.7
40/53	1,209	29.5	41.2	179.7
47/53	1,625	33.4	54.6	251.0
Mean	1,343	36.4	46.3	195.1
" % calories	100	10.9	31.0	58.1
Non-pregnant adults:				
29/53	2,740	62.6	77.0	448.3
44/53	976	27.4	32.1	143.6
Adolescents:				
36/53	1,132	30.3	35.2	173.4
48/53	1,432	37.2	45.0	219.3

earlier figures were over-estimates. Thus the mean daily protein intake was 36.4 g. The calorie value was adequate for patients lying in bed.

In the League of Nations *Report on the Physiological Basis of Nutrition* (1936) it is recommended that women between the fourth and ninth months of pregnancy should have 1.5 g. protein per kg. body weight. For the women in this series this would have been 77.3 g. per day. In 1950 the Committee on Nutrition of the British Medical Association recommended that at least 14% of a pregnant woman's calories should be supplied by protein. Thus by either of these standards the women in this series were living on a diet grossly deficient in protein.

A further question which now suggested itself was whether the patients who developed anaemia were those who had an excessive demand on their already poor supplies of dietary protein. This arose from the fact that there seemed to be an extraordinary proportion of twins born of the women studied. Accordingly the obstetric history of the patients was gone into. Much of this has previously been reported (Woodruff, 1951), but, in brief, it has been found that among 45 women studied there was one twin pregnancy in five pregnancies. Ross (1952) states that the ratio throughout the world is 1 in 90. In the United States of America among white persons it is 1 in 88, and among coloured citizens 1 in 67; among Africans in Rhodesia, where Ross was working, the rate is 1 in 35. At Ibadan in 1953 the ratio in 1,000 consecutive hospital deliveries was found to be 1 in 20. Twin pregnancies therefore were four times as common among the anaemic women as they were in non-anaemic pregnant women delivered in hospital at Ibadan. This suggests that those who have heavy nutritional demands imposed by twin pregnancy and are living on this deficient diet are more likely to develop anaemia than are women bearing only one child. The people of Nigeria recognize

that to bear twins imposes a greater risk to maternal health than does a single pregnancy, and for this reason have an elaborate ritual following their birth. It is considered that evil spirits are brought by the twins and are responsible for this ill-health. Two wooden idols are therefore made, into which it is hoped the spirits will enter, thus preventing harm to mother or children. As in much folklore, there is some basis for the belief, for certainly anaemia in pregnancy with its associated risks to health is more common among women bearing twins.

Cytological Appearances

There seemed, therefore, to be good evidence that this anaemia was associated with protein malnutrition and with liver damage. Further, this liver damage was of the kind

TABLE V.—*Cell Diameter and Thickness (in μ) in 34 Cases of Anaemia in Pregnancy*

Type of Anaemia	M.C.D.		σ		M.C.A.T.	
	Mean	Range	Mean	Range	Mean	Range
Macrocytic (9 cases)	7.87	7.46-8.51	0.76	0.60-0.93	2.07	1.55-2.49
Normocytic (17 cases)	7.61	7.06-8.20	0.90	0.52-2.63	1.94	1.61-2.62
Microcytic (10 cases)	7.52	6.32-8.10	1.06	0.51-2.79	1.76	1.37-2.13
Normal values	7.20	6.70-7.70*	0.46	0.40-0.50†	2.10	1.70-2.50‡

* Whitby and Britton (1950). † Larsen (1948). ‡ Price-Jones, Vaughan, and Goddard (1935).

reported by Himsworth (1950) in animals deprived of protein and given adequate calories in the form of fat or carbohydrates—namely, diffuse fibrosis and fatty infiltration. Larsen (1948) found that in patients with acute or chronic liver disease the red blood cells have an increased diameter but diminished thickness. Thus the ratio of their diameter to their thickness is greater than normal. Glynn, Himsworth, and Neuberger (1945) have also reported this type of red blood cell in rats suffering from hepatic disease induced by methionine deficiency. The next question therefore was whether the cells in these cases were also broader and thinner than normal. Their characteristic appearance in thin films suggested that they were. The cells were larger than those of microcytic anaemia, yet they had the pale, vacuolated appearance of those found in that disease. Trowell has called them "foam" or "bubble" cells, and many resemble target cells. There is polychromasia due to the slight increase in reticulocytes and there is also well-marked anisocytosis—a point which is brought out by the wide base of the Price-Jones curves in such cases.

FIG. 4.—The ratio of red blood cell diameter to thickness in 36 women with anaemia in pregnancy. In all but five cases this ratio is greater than the average in health—that is, the cells are thinner than average.

Price-Jones curves were constructed in 36 cases. A shift to the right was present in 24 cases, to the left in only two, and a centrally placed curve was found in 10 cases. In all cases the base was broader than normal. Normal values and the figures obtained from these curves are summarized in Table V. The mean cell diameter (M.C.D.) was increased

even in most cases which were microcytic when classified according to the M.C.V. It was greater than normal in 15 cases, and in the upper half of the normal range in 15 cases. The standard deviation (σ) of the M.C.D., which Larsen (1948) finds is constantly raised in liver disease, was also raised in all cases. The range was 0.51-2.79 μ . The mean corpuscular average thickness (M.C.A.T.) was below normal average in 34 cases. Haden (1935) has shown that normally the diameter of the red blood cell is 2.4-4.2 times its thickness, and that when the diameter is more than 4.2 times the thickness the cell is abnormally thin. The diameter-thickness ratio in the pregnant anaemic women is shown in Fig. 4; it will be seen that in 13 cases the cells were pathologically thin, and in all but five they were thinner than average.

Response to Treatment

In view of the evidence of protein malnutrition, five patients were given daily supplements of 2-4 oz. (56.5-113 g.) casein after a control period of 10 days. This was followed by steady improvement without the development of a well-marked reticulocyte crisis (Fig. 5). In these cases, and in others in which improvement took place on a good diet only, the haematological improvement was invariably accompanied by increase in plasma albumin and by the albumin-globulin ratio becoming less abnormal. In Table VI the values in nine cases before and after treatment are shown and attention is drawn to the fact that albumin has increased in every case.

There is a further important piece of evidence suggesting that protein malnutrition causes liver damage in pregnant women. Following the demonstration of what appeared to be liver damage due to protein malnutrition in anaemic

mothers, Silvera and Jelliffe (1952) at Ibadan examined the livers of infants who died within a few hours of being born of malnourished mothers. They found that in several instances the infant's liver was grossly infiltrated with fat and even contained an increased amount of fibrous tissue. This fatty infiltration and fibrosis is of very great interest in that it cannot have been caused by parasites. In two instances vascular or congestive damage arising during childbirth could be excluded by the fact that the two mothers from whose infants the specimens were obtained were delivered by caesarean section. A nutritional cause was the only one likely. It appears that in tropical parts some infants may be born with the handicap of a damaged liver.

Comment

The evidence thus far therefore suggests that anaemia in pregnant women in Nigeria might be associated with protein malnutrition and liver damage, in some cases no doubt aggravated by parasitic infection. Further, this malnutrition is more likely to develop in those who have heavy demands on their protein supplies. If this hypothesis is correct, then the anaemia of these pregnant women and that of children and non-pregnant adults suffering from protein malnutrition ought to have much in common, and to test the hypothesis a comparison was made of the anaemia in these three types of patients.

ANAEMIA ASSOCIATED WITH PROTEIN MALNUTRITION IN EARLY CHILDHOOD

This series of nine children were studied by courtesy of, and with much help from, Dr. A. Tompkins. All presented with classical clinical manifestations of protein malnutrition or kwashiorkor. They were oedematous, each had a dermatosis and liver damage, and eight had ascites. Their hair, instead of being crisp and curly as it should be in Africans, was soft and straight. One might ask how children are allowed to become so ill, and the answer to that question in part lies in local folklore and superstition. The child affected is commonly believed to be possessed of a spirit or devil, and the advice of an indigenous practitioner is first sought. His usual treatment is to tie the head of a snake, lizard, or rat on to the patient, and it is only when this has failed that help is sought from a hospital or a medically qualified person. Thus we have another example of how ignorance and spurious beliefs play a part in the causation of this disorder.

The age at which this florid clinical condition occurs varies considerably, but the commonest is some months after the cessation of breast-feeding; this takes place much later than in Europe, usually between the ages of 2 and 3 years. At this time the child is given a diet of starchy gruels high in carbohydrate and relatively low in protein. Though the disease is commonest at

FIG. 5.—Improvement in haematological values in anaemia in pregnancy following treatment with casein. Rectangles labelled A and G indicate albumin and globulin values respectively.

TABLE VI.—Serum Proteins Before and After Treatment in 9 Cases of Anaemia in Pregnancy

Case No.	Before Treatment					After Treatment				
	Total Protein (g.%)	Albumin (g.%)	Globulin (g.%)	A/G Ratio	Haemoglobin (g.%)	Total Protein (g.%)	Albumin (g.%)	Globulin (g.%)	A/G Ratio	Haemoglobin (g.%)
28/53	5.40	1.95	3.45	0.57/1	3.96	6.71	3.11	3.60	0.86/1	6.22
33/53	6.90	2.22	4.68	0.48/1	5.03	6.26	2.78	3.48	0.80/1	6.96
38/53	6.24	2.62	3.62	0.72/1	4.29	6.63	3.12	3.51	0.89/1	7.25
39/53	6.44	1.70	4.74	0.36/1	6.81	7.75	2.95	4.80	0.62/1	9.77
47/53	6.17	2.31	3.86	0.60/1	7.70	7.10	2.71	4.39	0.62/1	9.18
51/53	7.26	3.18	4.08	0.78/1	6.07	7.73	3.33	4.40	0.74/1	7.55
53/53	6.14	2.47	3.67	0.68/1	5.18	6.12	3.00	3.12	0.96/1	9.18
53/53	5.61	3.00	2.61	1.15/1	7.55	6.00	3.37	2.63	1.28/1	8.58
55/53	7.27	2.84	4.43	0.64/1	4.14	7.60	3.35	4.25	0.79/1	6.66
Mean	6.38	2.47	3.90	0.55/1	5.63	6.88	3.08	3.79	0.84/1	7.93

this age, it may occur in a modified form at any time in childhood, and it seems probable that a variety of it is found in adult life. The ages of the children in this series ranged from 2½ to 6 years. In two of the cases the illness had started after the mother had left the child in the care of a grandparent while she was preoccupied with a later addition to the family. This is not uncommon history, and it is probable that the grandparent, by reason of age or incapacity, is unable to provide more than the cheapest and most readily available foods. These are cassava, yams, and maize, all of which are rich in carbohydrate and poor in protein.

Anorexia was usual, and this is an important symptom as it leads to aggravation of the dietetic deficiency. Oedema, when it first appeared, often affected the most dependent parts of the body, and therefore the side on which the child had been lying during sleep (Fig. 6). Later all the subcutaneous tissue becomes oedematous, and in addition to ascites there may be pleural or pericardial effusions.

FIG. 6.—Unilateral oedema of face following sleep in child suffering from protein malnutrition.

The skin is at first affected in the body flexures, where small folds appear; superficial portions become loose and later drop off, taking with them the pigmented layer. Depigmented patches remain, and soon a condition develops which has been likened to crazy pavement (Fig. 7). It is difficult to avoid the conclusion that most of this shedding of superficial dermis is due to the inter-

FIG. 7.—“Crazy-pavement” dermatosis in an African child suffering from protein malnutrition.

ference with the nutrition of the superficial layers which results from the oedema beneath pressing on capillaries and restricting blood supply. In addition to this “crazy-pavement” dermatosis, however, there may be generalized depigmentation of the skin and hair, which, instead of being the normal black of the African child, assumes a light-brown colour. Nagchaudhuri and Platt (1954) have investigated this and found that there are chemical changes in the pigment in the hair of these cases. Such generalized depigmentation was present in one case.

In this group of nine children with oedema and skin changes the liver was palpable in seven, the greatest distance below the costal margin being 1½ in. (3.7 cm.). The spleen was palpable in only two cases; in one of these it was just tipped on inspiration, and in the other it was 1 in. (2.5 cm.) below the left costal margin.

Results of Investigations

Haematological Values

Detailed haematological observations were made in six cases. The bone marrow was uniformly macronormoblastic, but megaloblasts were not found and sickling was not detected in any of the six cases.

The haematological indices at initial examination are shown in Table VII. The anaemia, it will be noted, is well

TABLE VII.—Haematological Values in 6 Children with Protein Malnutrition

Case No.	Hb (g.%)	R.B.C. (Millions/c.mm.)	M.C.V. (cu.μ)	M.C.H.C. (%)	M.C.D. (μ)	M.C.A.T. (μ)
25/53	6.66	2.07	106.28	30.00	8.82	1.74
30/53	8.88	3.62	71.82	34.15	7.84	1.49
31/53	8.14	3.35	80.59	30.15	8.14	1.55
37/53	8.88	3.21	81.00	34.15	7.84	1.68
42/53	8.58	3.72	69.89	32.61	7.58	1.46
61/53	7.84	2.76	86.96	32.70	7.02	2.24
Mean	8.16	3.12	82.76	32.29	8.04	1.58

marked, though not severe. Schumm's test was negative in all six cases. The M.C.V. is on the low side of the normal range in most cases, but the M.C.D. is abnormally increased in four cases and at the upper limit of the normal range in one case. The M.C.A.T. is below the normal range in all but two cases. There is little evidence of iron deficiency, the lowest M.C.H.C. being 30%. The Price-Jones curves showed a shift to the right in four cases, and in two the curve was centrally placed; in all it was flatter than normal. The standard deviation of the M.C.D. was increased just as it was in the pregnant women, the mean being 0.916 and the range 0.369–1.513. The values for the ratio of cell diameter to thickness in these cases are shown in Fig. 8, from which it is obvious that the cells are very much thinner than normal. This anaemia is therefore orthochromic and, as judged by cell volume, normocytic, but on the basis of cell diameter it is macrocytic. The cells, however, like those of the pregnant women, are thinner than normal and the ratio of cell diameter to cell thickness is increased.

FIG. 8.—The ratio of red blood cell diameter to thickness in six children with anaemia and protein malnutrition. In five cases the cells are pathologically thin.

Parasites

Particular attention has been paid to examination for parasites in these as in all cases in the study. Ova of *A. duodenale* were not found in the stools of any of these children, but in two cases ova of *A. lumbricoides* were found. Blood films were examined for malarial parasites both on admission and subsequently whenever there was fever; in two cases *Plasmodium falciparum* rings were found on admission. Trowell, Davies, and Dean (1952) find that those affected by kwashiorkor usually harbour some parasites, but the same syndrome may occur in the absence of parasitic infections. The findings in this series support this statement.

TABLE VIII.—*Plasma Proteins and Corresponding Haemoglobin Values and Red Blood Cell Counts in 5 Children Suffering from Protein Malnutrition*

Case No.	Date	Total Protein (g.%)	Albumin (g.%)	Globulin (g.%)	Fibrinogen (g.%)	A/G Ratio	Plasma Colloid Osmotic Pressure (mm. Water at 0° C.)	Hb (g.%)	R.B.C. Millions/c.mm.
30/53	2/9/53	3.85	1.24	2.42	0.19	0.51/1	103.6	8.88	3.62
	29/10/53	7.55	3.88	3.41	0.26	1.14/1	309.4	9.47	3.31
37/53	9/9/53	4.97	0.71	3.96	0.30	0.18/1	115.6	8.88	3.21
	22/10/53	5.94	1.29	4.33	0.32	0.29/1	163.0	10.80	3.94
42/53	26/9/53	4.56	0.91	3.23	0.42	0.28/1	108.2	8.14	3.46
	25/10/53	5.30	1.55	3.70	0.05	0.42/1	154.6	10.66	3.59
31/53 (serum)	29/8/53	4.10	0.20	3.90	—	0.05/1	85.4	8.14	3.35
61/53 (serum)	26/10/53	6.57	3.88	2.69	—	1.44/1	278.0	7.84	2.76
Normal range (Harrison, 1947)		5.8–8.8	3.4–6.7	1.2–2.9	0.20–0.40	4/1–1.2/1	247–342*		

* Keys *et al.*, 1950a.**Plasma Proteins**

The plasma proteins were estimated in five of the six cases, and the values obtained, together with the corresponding haemoglobin and red blood cell counts, are shown in Table VIII. In three cases the figures obtained after treatment are also given. By comparison with normal values the albumin fraction before treatment is low and the globulin fraction greater than normal in all but two cases, so that there is a striking inversion of the albumin–globulin ratio. The albumin, it will be noted, increased with treatment. This increase is most marked in the first case, where after eight weeks' treatment with a good diet and a supplement of 56 g. milk protein daily the figures approximated to those at the lower end of the normal range.

The colloid osmotic pressure of the plasma in these cases is shown in Table VIII, the figures for Case 61/53 being obtained during convalescence. These pressures have been calculated from the formula propounded by Keys (1938), who in a series of 40 normal young men found the range to be from 247 to 342 mm. water (Keys *et al.*, 1950a). Thus the values were lower than normal in all four cases in which they were calculated before treatment. The development of oedema is dependent on several factors, of which the plasma colloid osmotic pressure is only one. In nephritis with hypoproteinaemia, Muntwyler *et al.* (1933) found that oedema usually developed when the plasma colloid osmotic pressure dropped below 160 mm. water, and that patients with pressure above this figure had no oedema. His findings accord well with those in this series, in which all the patients had gross oedema and a plasma colloid osmotic pressure below 160 mm. water when first observed. The oedema became less with treatment; when the second reading was obtained, it had disappeared altogether from Case 30/53 and in Cases 37/53 and 42/53 was just perceptible.

Electrophoresis of the Plasma Proteins

In view of the abnormal globulin values found in these children the question again arose as to what globulin fraction predominated. Serum was examined electrophoretically in five cases, a typical curve being shown in Fig. 9; the combined results obtained are shown in Table III and are compared with those in normal serum. Electrophoresis confirmed that in all these malnourished children the albumin fraction was grossly reduced and the α_1 and γ globulin increased. In cirrhosis of the liver the reduction in albumin and increase in β and γ globulins closely parallel the changes in these malnourished children.

FIG. 9.—Protein pattern obtained by electrophoresis of serum of child with protein malnutrition and anaemia.

In Taylor's malaria experiment (Taylor *et al.*, 1949) the increase in γ globulin was proportionately less, and that of α_1 globulin proportionately greater, than in the children or in cirrhosis. It is of course difficult to compare Taylor's experiment with malaria in volunteers and the findings in these children, who probably had been chronically infected most of their lives. Nevertheless, if the changes were due only to malaria one would expect them to be of the same qualitative kind as in Taylor's experiment. Again, the interpretation which, though provisional, best fits the facts is that the increase in γ globulin is the one that is associated with liver damage and the increase in α_1 globulin is brought about as part of the development of immunity to malaria. Liver damage, malaria, and a low-protein diet probably all contribute to the low albumin values.

Liver Pathology

Liver was obtained for histological examination in all cases. In two this was at necropsy, in the remainder by biopsy. The outstanding features were infiltration with fat and some increase in fibrous tissue in the portal tracts and between the parenchymal cells as in the pregnant women.

Response to Treatment

Regarding treatment in these cases, there is general agreement that best results are obtained with well-balanced diets rich in protein. On admission, therefore, all the patients were given a balanced diet and a 50 g. supplement of casein daily. It was not possible to observe the children during a control period before giving them this diet, as their condition on admission was critical. This was emphasized by the fact that two of them died within a few hours.

The responses of these cases were similar to one another, and in brief this meant a gradual improvement in the clinical condition over a period of weeks or months and a coincident rise in haemoglobin and plasma protein levels. As in the pregnant women, no marked reticulocyte crisis occurred, and this is understandable if there is a deficiency of protein rather than of specific haemopoietic substances. The anaemia would thus be unlike that present in pernicious and similar anaemias, where microquantities of a haemopoietic substance are deficient, the other requirements of haemoglobin production being available. Here it is probable that the materials from which haemoglobin is made are defective or deficient, and this can be corrected only gradually.

The slowness of the therapeutic response in malnutrition and undernutrition has been commented on by many workers. Keys *et al.* (1950b), reviewing the literature on starvation during and after the two world wars, state that the plasma protein level in malnourished persons given a liberal diet increases at only a slow rate. This is understandable on the basis of work done by Elman *et al.* (1942), who from experiments on dogs found that a deficiency of 1 g. of plasma protein is equivalent to one of approximately 30 g. of body protein. Thus by computing the plasma protein deficit and multiplying by 30 a rough indication of the total body protein deficit can be reached. In protein-deficient dogs Elman *et al.* noted that, although infusion of

plasma or amino-acids temporarily raised the plasma protein level, it was only after the total body protein deficit had been replaced that permanent elevation of plasma protein level occurred. On the basis of the plasma protein values and the estimated plasma volume the mean total initial body protein deficit in children in this series can be computed as approximately 450 g. per child. According to the League of Nations (1936) standards the mean daily protein requirement for growth and metabolism of those children worked out at 41 g. It is thus clear that, with these large deficits to make good, a diet containing more than 41 g. of protein daily would be needed for a considerable period before normal plasma protein values could be obtained and maintained.

Reticulocyte Ripening

The rate at which reticulocytes ripened was studied in two children. In the first the estimations were made at an interval of three weeks, during which the haematological values of the plasma proteins had not changed significantly. The rate at which reticulocytes ripened also remained virtually constant, the percentage present in the blood diminishing by increments of 0.5 and 0.6 per hour respectively. In the other case estimations were made at the beginning, in the middle, and at the end of a six-week period, during which the haemoglobin level had risen from 8.88 g. to 10.80 g. per 100 ml., and the plasma protein level from 4.97 g. (albumin 0.71 g.) to 5.94 g. (albumin 1.29 g.) per 100 ml. The successive rates at which reticulocytes ripened also improved, the percentage present in the blood diminishing by increments of 0.5, 0.6, and 1.0 per hour. Similar results were obtained in three pregnant women. In one whose plasma proteins had not changed significantly during three weeks the percentage of reticulocytes present in the blood decreased by 0.4 per hour at the beginning and at the end of the period. In two others whose plasma proteins had respectively improved from 7.45 g. (albumin 2.22 g.) and 6.62 g. (albumin 2.23 g.) to 7.9 g. (albumin 2.80 g.) and 7.53 g. (albumin 2.62 g.) per 100 ml., the rate of reticulocyte ripening also improved. Before treatment the percentage of reticulocytes in the blood decreased by increments of 0.64 and 0.5 per hour respectively, and after treatment in each case by increments of 1% per hour.

Nizet and Robschey-Robbins (1950) have shown that in dogs with simple anaemia the reticulocytes ripen at the normal rate, but in those with anaemia and hypoproteinaemia ripening is delayed. They found that this delay can be overcome by adding various amino-acids or plasma proteins to the suspension, and conclude that the red blood cell at the reticulocyte stage is able to incorporate plasma proteins into itself or synthesize proteins from amino-acids. Thus if the plasma proteins are abnormal or deficient, some disturbance may take place in the ripening of reticulocytes and therefore in the formation of the mature red cell. These workers state that it is at present not clear whether man is ever subjected to protein depletion severe enough to bring about this effect. The present investigations in children and adults suggest, however, that in protein malnutrition of the kind here being discussed the disturbance is sufficient to delay reticulocyte ripening.

Comment

These children with protein malnutrition therefore have an anaemia. They have histological evidence of liver damage, there is gross abnormality of their plasma proteins with reduction in albumin and increase in globulin, and there is evidence of arrest in the ripening of reticulocytes. The condition responds slowly to a good diet rich in protein.

Thus protein malnutrition and anaemia occur in acute or subacute forms during two phases of life in which growth is rapid: in children when the growth is that of their own body, and in pregnant women when it is that of the foetus. The question arises as to what extent protein malnutrition occurs in association with anaemia at other times of life, and, if it occurs, what are the characteristics of the anaemia.

ANAEMIA AND PROTEIN MALNUTRITION IN OLDER CHILDREN AND ADULTS

Of 21 anaemic older Nigerian children and adults studied, all complained of lassitude, weakness, and inability to carry on with their work; most of them also complained of dyspnoea. In 15 the abdomen was distended by hepatomegaly, splenomegaly, or ascites. In most instances the swelling was of considerable extent, as can be seen from Fig. 10. The liver was palpable in 13 cases and the spleen

FIG. 10

FIG. 11

FIG. 10.—Older child with ascites and cirrhosis of the liver. FIG. 11.—The ratio of red blood cell diameter to thickness in 19 older children, adult males, and non-pregnant females suffering from anaemia and chronic protein malnutrition.

in eight. The liver was 3 in. (7.6 cm.) or more below the costal margin in four cases; the spleen reached for a similar distance in three. In 11 patients there was ascites, and in 10 clinically detectable oedema. One patient complained of sore tongue. Some fever was present from time to time in most cases, but there were periods of several weeks without any rise in temperature.

TABLE IX.—Haematological Values in 17 Older Children, Adult Males, and Non-pregnant Females Suffering from Protein Malnutrition

	Macrocytic (M.C.V. >95 cu.μ) (6 Cases)		Normocytic (M.C.V. 82-95 cu.μ) (2 Cases)		Microcytic (M.C.V. <82 cu.μ) (9 Cases)	
	Mean	Range	Mean	Range	Mean	Range
Hb (g.%)	6.76	2.88-10.36	8.84	6.07-11.62	7.37	2.66-11.84
R.B.C. (millions/c.mm.)	2.18	1.06-3.75	3.27	2.14-4.40	3.40	1.37-4.59
M.C.V. (cu.μ)	107.84	96.24-131.03	88.98	84.50-93.46	67.94	50.50-78.29
M.C.H.C. (%)	29.37	24.00-32.66	30.87	30.35-31.40	31.91	28.27-35.39
M.C.D. (μ)	8.22	7.49-9.75	7.52	7.30-7.74	7.88	7.13-8.69
σ	1.37	0.77-2.10	0.73	0.59-0.88	0.86	0.66-1.15
M.C.A.T. (μ)	2.28	2.03-2.69	1.68	1.35-2.02	1.46	1.18-1.82
M.C.D./M.C.A.T.	3.68	2.93-4.82	4.66	3.61-5.71	5.44	4.02-7.34
Reticulocytes (% of R.B.C.)	4.20	0.50-12.00	0.50	0.50-1.00	1.56	0.50-4.00

Results of Investigations

Haematological Findings

The initial haematological values in 17 of these cases are summarized in Table IX; four are excluded as complete haematological investigation was not possible in these cases. Once again the anaemia was well marked, there was no great tendency to hypochromia, the M.C.D. was increased, and the M.C.A.T. diminished in almost all cases. The bone marrow was macronormoblastic, but megaloblasts were not found. Schumm's test was positive in three cases.

The Price-Jones curves were displaced to the right in all but two of the cases, in which they were centrally placed. The curves were broader than normal in all cases. The ratio M.C.D./M.C.A.T. is shown in Fig. 11, and it is apparent that in almost all cases the cells were thinner than normal.

Here, then, were a set of anaemias of considerable severity and almost all associated with hepatosplenomegaly, ascites, or oedema, and a macronormoblastic bone marrow. It was again important to exclude sickle-cell disease and parasites as causes of anaemia, and accordingly appropriate searches were made.

Parasites and the Sickle-cell Trait

Of the 17 cases subjected to detailed haematological studies the sickle-cell trait was present in one-fifth. The characteristics of the anaemia in these cases were similar to those of the others in which the trait was not present, and sicklaemia was accordingly thought not to be an important aetiological factor. Cases of anaemia in which overt malaria were found have been excluded.

Ova of *Ancylostoma duodenale* were found in the stools of eight patients, and ova of *Ascaris lumbricoides* in five, a double infection being present in three. The faeces were free from helminthic ova in seven cases. In a further case the only parasite found was *Taenia saginata*, which can be discounted as a cause of anaemia; in yet another, fatal case a single *A. lumbricoides* was found at necropsy. In most of the cases the infections were light as judged by the number of eggs present in the faeces. It is unlikely that a light infection with *A. lumbricoides* plays an important part in the causation of protein malnutrition or anaemia. If to the three cases in which this parasite alone was present are added the seven without intestinal parasites, and the one infected with *T. saginata* only, it will be seen that in 11 of the 21 cases intestinal parasites could be excluded as a cause of the malnutrition and anaemia. In more than half of the patients, therefore, it seemed unlikely that parasites were playing a part in the causation of the disease at the time of their admission to hospital.

Plasma Proteins

Analysis of the plasma proteins both chemically and electrophoretically gave similar results to those found in the children and pregnant women, the albumin invariably being reduced and the globulin greatly increased. The values in

TABLE X.—Plasma Proteins (g. per 100 ml.) in Older Children, Adult Males, and Non-pregnant Females

	12 Patients		7 Patients (Means)	
	Means	Range	Before Treatment	After Treatment
Total protein	6.07	3.93-7.30	5.84	6.34
Albumin	1.96	0.62-3.34	1.94	2.49
Globulin	3.82	2.49-5.02	3.64	3.60
Fibrinogen	0.29	0.14-0.50	0.26	0.25
A/G ratio	0.46/1	0.13/1-1.06/1	0.55/1	0.71/1
Haemoglobin	—	—	6.08	7.71

12 cases are shown in Table X, in which figures obtained before and after treatment are also given. In each of the cases the albumin content improved after treatment with a high-protein diet.

A curve typical of those obtained by electrophoretic separation of the serum proteins in the series is shown in

Fig. 12. Mean values estimated electrophoretically in 11 cases are shown in Table III. In these older children and adults the albumin deficit, and the amount of γ globulin present, were greater than in either of the other groups. This and the advanced liver changes found suggested that malnutrition was of longer standing in cases in this group than in the children and pregnant women.

One point which is clearly brought out by the figures is that the total protein value may give little indication of the disorganization which may be present in the various constituents. Thus one patient's plasma proteins amounted to 7.30 g. per 100 ml., but in that total there was only 1.87 g. albumin compared with 5.02 g. globulin. In an oedematous young male adult who died shortly after admission the figures were: total 5.48 g. (albumin 0.62 g., globulin 4.86 g.) per 100 ml. serum.

Proteins in Ascitic Fluid

The electrophoretic pattern of the proteins in ascitic fluid and the rate at which fluid accumulated were determined in two cases. It was found that in one approximately 4.6 g.,

FIG. 12.—Protein pattern obtained by electrophoresis of serum of a child aged 8 years who was oedematous and anaemic.

FIG. 13.—Frozen section of liver from a child who died at the age of 8 with cirrhosis of "hobnail" type. Note fibrous strands and fatty infiltration. The fat appears black in the photograph. (Stain Sudan III and haematoxylin. $\times 35$.)

and in the other 7.5 g., of protein were being lost into the fluid daily. Thus the onset of ascites in one of these malnourished persons may constitute a serious drain on protein supplies. In one case the rate of production of fluid fell from 200 ml. daily after the institution of a high-protein diet. No emphasis is placed on this observation in a single case, but it fitted in well with the hypothesis that protein malnutrition was the most important factor in the causation of the ascites.

Liver Histology

Specimens of liver were obtained either by biopsy or at necropsy in all cases. Again, either fat or fibrosis was a constant finding, and in two cases cirrhosis was gross and

advanced. In one child who died at the age of 8 the liver was found at necropsy to be of the typical "hobnail" type, and in addition to being cirrhotic it was also grossly infiltrated with fat (Fig. 13). Such changes are almost certainly later chronic manifestations of the process which is seen in its early acute form in younger children and pregnant women.

One adult male who died had a primary carcinoma of the liver in addition to gross cirrhosis. On the primary nature of this growth the late Dr. W. D. Silvera and Dr. D. S. Ridley were agreed.

Hippuric Acid Excretion Test

In view of the histological and naked-eye evidence of liver damage obtained it is hardly surprising that abnormally small quantities of hippuric acid were excreted after the usual test doses of 6 g. sodium benzoate had been given. In the five cases in which this was done the mean amount of hippuric acid excreted in four hours and expressed as benzoic acid was 0.946 g., range 0.471–1.973 g. Harrison (1947) considers values below 2.5 g. to be abnormal.

Response to Treatment

In this group treatment was even more difficult than in the children or pregnant women. In general the results were poor, but small increases in haemoglobin with coincident improvement in plasma albumin were usually obtainable after the patient had been on a good diet with a supplement of casein for at least two weeks. In those having a treatable infection, such as ankylostomiasis, the outlook was more favourable. The remainder, however, all had advanced chronic liver disease and belonged to a class of patient notoriously unresponsive to treatment. The evidence pointed to the disease in these cases having reached an irreversible stage. Three of the patients died within a few weeks of admission to hospital; all had grossly cirrhotic livers.

DISCUSSION

There is, therefore, evidence that anaemia in some African older children, adult males, and non-pregnant females may be associated with chronic protein malnutrition and liver damage, and this anaemia has the same characteristics as that found in young children and pregnant women. This type of disease is very much more common in the Tropics than in temperate regions. When it occurs it seems to be more chronic than that in children and pregnant women, and unless there are aggravating parasitic factors it is even less amenable to treatment.

Thus protein malnutrition may develop in acute form in childhood and in pregnancy, both periods of rapid growth. It may occur at other times in chronic form if there is a prolonged drain on protein supplies. Some individuals are probably always bordering on this state of malnutrition, and this might be expected to affect their growth and development and to disturb their metabolic and physiological processes. Thus it has been shown by Burke, Harding, and Stuart (1943) that protein deficiency in pregnancy may lead to a low birth weight of the infant. In Nigeria infants born of women with anaemia weigh, on an average, 2 lb. (0.907 kg.) less than those of healthy women (Woodruff, 1954). Platt (1939) has shown that in malnourished children there is a stunting of growth; the growth curves begin to fall away from normal at 6 months of age, and full physical development may never take place. Anaemia and liver damage appear to be other aspects of this malnutrition syndrome.

There is another way in which the disease may manifest itself on a large scale in the Tropics, and this is in

the development of gynaecomastia. Several of the male patients in the series suffered from this, and it is a common condition in Africans, Trowell (1948) finding 25 (5%) of 500 East African railway workers so affected. Figs 13 and 14 are photographs of two of the patients

FIG. 14

FIG. 15

FIGS. 14 and 15.—Gynaecomastia, probably resulting from liver damage caused by protein malnutrition.

studied. In these cases once again liver biopsy showed fatty infiltration or fibrosis. It seems that the gynaecomastia results from damage which renders the liver incapable of inactivating oestrogens normally produced, and this damage also is probably caused by prolonged protein malnutrition. Disturbances of this kind illustrate the gross changes in bodily functions which may occur in the syndrome.

CONCLUSIONS

This study indicates that the natural history of anaemia associated with protein malnutrition may briefly be summed up as follows:

Evolution of Nutritional Macrocytic Anaemia Associated with Liver Damage

Among certain communities children may be born with livers already damaged by maternal malnutrition. If they survive they again pass through a period following weaning during which the demand for protein imposed by growth is greater than the supply, and the liver is liable to be damaged. At these times an anaemia and other signs of malnutrition may develop. The anaemia is associated with a macronormoblastic marrow and with red cells which are broader and thinner than normal. Many succumb while passing through this stage in childhood; others recover, but probably the majority of these latter are left with some hepatic damage and fibrosis. Nevertheless the functional reserve of the liver is such that, in spite of this, the patient manages until he or she passes through a period in which demands for protein are again in excess of the available supply. In women this state may occur in acute form during pregnancy, foetal growth being the precipitating factor. In adult males and non-pregnant females the disease is less common, but when seen in hospital practice in Nigeria it usually represents a late stage of a chronic process. It develops if the diet is markedly and chronically deficient in protein, and particularly if parasites impose an additional drain on deficient supplies of nutrients. In these cases one of the factors in the causation of the anaemia may be that haemoglobin in its production can draw on plasma proteins, as has been shown by Whipple (1948), and thus when these proteins are abnormal or deficient the production of haemoglobin may be affected. In these cases abnormality, as distinct from deficiency, of plasma proteins may arise from the production of antibodies containing protein, or from liver disease, it being established that the liver plays an important part in protein synthesis.

The characteristics of protein malnutrition in Nigerians are similar whether it occurs in childhood, in pregnancy, or in adult life unassociated with pregnancy. In many cases the disease starts in early life, or even in intrauterine life, and progresses as it is aggravated during periods of growth or deprivation until finally it ends in advanced hepatic cirrhosis with all its concomitant haematological and other features. This stage may even be reached in childhood.

Many of the clinical and pathological states considered in this work are gross and unlikely to be encountered in Great Britain. Nevertheless they provide an insight into the function of various organs and tissues, and into processes which may affect the body in a less florid form in the temperate zones in conditions—such as nephrosis, exudative dermatoses, burns, alcoholism, and cirrhosis of the liver—resulting from non-nutritional causes.

Finally it should be added that Dr. Goulston clearly wished these lectures to illustrate disease processes, for he directed that they should be read "on some dead body, if possibly it can be procured, which shall then and there be dissected for the diseases treated of, and shall afterwards be buried." It is hoped that this study of the natural history of anaemia associated with protein malnutrition may have applications which extend beyond the syndrome seen in the Tropics to disease processes encountered in other regions of the world.

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A plea for more enlightened treatment of criminals was made by Sir DAVID HENDERSON in the Morison lecture on "Society and Criminal Conduct," which he delivered last December at the Royal College of Physicians of Edinburgh. He declared that further research must be devoted to the causation and motivation of abnormal conduct. By the time criminal behaviour had been fully established it was often irremediable. The law must be sufficiently elastic to take cognizance of all the data, hereditary, physical, and social, surrounding criminal behaviour. Society must take care that the law is not merely a system of revenge. "We may extol the reformatory outlook, but the spirit of revenge and retaliation, of hate and anger, and resentment, has its roots dug deep." His analysis of 150 "lust cases" shows the difficulty of reconciling the legal with the medical approach; a disturbing feature of homosexual cases was the inconsistency of the sentences imposed. Of 129 reprieved murderers, 112 had made a satisfactory readjustment to society. The 150 lust cases showed 81 sane, 17 insane, 26 defective, and 26 psychopathic. Sir David said he had come to believe that abnormality and unsoundness of mind could not be accepted as synonymous. Abnormality demanded an individual approach which could be effected only through clinical research. There was a close parallel between mental illness and the disorders that resulted in crime; both were best treated at a preventive level.