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EFFECTS OF HEAVY AND REPEATED MALARIAL INFECTIONS ON GAMBIAN INFANTS AND CHILDREN

EFFECTS OF ERYTHROCYTIC PARASITIZATION

BY

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Since 1947, when the Medical Research Council established its laboratories in the Gambia, many workers investigating the importance of non-parasitic diseases in the African population have found great difficulty in assessing the contribution to the general picture of the inevitable malarial infection. McGregor and Smith (1952) and Walters and Waterlow (1954) found the twin threads of parasitization and malnutrition exceedingly complex and difficult to unravel. In no section of the community is this complication more in evidence than in infancy and early childhood—when plasmodial infection is severe and almost universal. This paper describes the result of an investigation in the Sukuta area of the Gambia that was undertaken to determine precisely the effects, both immediate and long-term, of repeated and heavy malarial infections on infants and young children.

Sukuta is one of the principal villages in the Kombo St. Mary District of the Gambia, and as such it possesses

an infant welfare centre which serves the surrounding villages within a radius of 10 miles. It is the centre of a dominantly agricultural Mandinka community which depends for food largely upon the cereals that are grown in the rainy season. Maize and digitaria are produced in small quantities in the early part of the rains, while staple cereals—rice, sorghum, and millet (*pennisetum* spp.)—are raised in the latter part. Groundnuts are grown principally as a cash crop, but some 10% of the yield is consumed annually as food. Cattle are kept in considerable numbers, but as they are seldom killed they contribute little to village food supplies. Milk yields are low, and when the requirements of calves are satisfied little remains for human consumption. Fish is relatively abundant in the coastal region, and considerable quantities are eaten even in the more inland villages.

In the area under consideration malaria is hyperendemic. Transmission declines in the dry months from December and May, when it becomes negligible, but rises dramatically with the onset of the rains in June, to reach a peak in October and November. *A. gambiae gambiae* is the dominant vector in the inland reaches, but in coastal villages associated with Avicennia mangrove swamps it is of secondary importance to *A. gambiae melas*. *P. falciparum* is by far the most commonly encountered parasite, but *P. malariae* and *P. ovale* are not infrequently seen.

In June, 1951, the investigation described here began with the creation of two experimental groups of newly born African infants at the Sukuta Infant Welfare Centre. The infants were assigned to either group by random selection. Infants in one group received 6 mg. of chloroquine base per kg. of body weight each week, while those in the other group received only a lactose placebo and were thereby maintained as controls. When each group contained 26 members no further infants were included. The sister in charge of the centre was advised to regard the experimental children as being in no way different from the other infants attending the clinic. If, in her opinion, an infant of the control series required antimalarial treatment, she was at complete liberty to administer any of the standard treatment courses that are used in Gambian dispensaries. Similarly, any non-malarious illness developing in members of either group had to be treated in accordance with her normal practice. An essential point of the experiment was that the established custom of infant-feeding in a rural Gambian community should not be modified: no supplements, such as skimmed milk, were therefore permitted.

When the children of the protected series reached the age of 2 years the weekly dosage level of 6 mg. of chloroquine base per kg. was discontinued and a flat rate of 150 mg. of base substituted. Both groups of children were regularly inspected and examined in the field, and in October, 1954, they were admitted to the research ward of the Medical Research Council's Laboratories at Fajara for detailed investigation and comparison. The methods used in the investigations and the results obtained are here reported.

First Investigation

Methods

Members of the two groups were visited weekly by a nursing sister who administered chloroquine to the protected and placebo to the unprotected series. The chloroquine, in powder form, was mixed in a teaspoon with water and care was taken to ensure that each infant swallowed its dose. Vomiting was noted to be a frequent sequel to treatment in the protected infants, and the practice of observing each baby for 30 minutes after drug administration was instituted. If vomiting did not occur within that period satisfactory retention was assumed. If, however, it occurred the dosage was repeated. As members of the protected series grew older the frequency of the vomiting decreased until it was no longer necessary to continue the observation period.

Thick and thin blood films were taken from each infant at each weekly inspection. The thick films were subsequently stained by Field's rapid method and examined microscopically under 1/12 in. oil immersion lens, 100 consecutive fields of each being examined. Thin films were fixed in methyl alcohol and stained by Giemsa's method.

At monthly intervals the members of both series were examined by a medical officer and details of weight, diet, and colour of hair were recorded. The sizes of liver and spleen were found by palpation, and haemoglobin values, as assessed by the Dare haemoglobinometer, were noted.

Results

Extreme difficulty was encountered throughout the investigation in preserving the size of the experimental groups, and, although each had contained 26 members initially, by the autumn of 1954 the number had dwindled through death and change of domicile to 20 protected and 13 unprotected children. Moreover, by this time 3 of the 20 protected children had each experienced a single short attack of malaria. These attacks originated in the failure, despite many attempts, to continue weekly chloroquine dosage. Mothers without warning would depart, taking their children with them on visits to distant relatives. On their return such children were examined closely for evidence of malaria contracted in their lapse from treatment, and, initially, all infected ones were excluded from the protected series. Ultimately these children who were known to have been infected for only a short period were retained. The three children referred to above were known to have been infected for less than 10 days.

By October, 1952, before movement of the parents had reduced the size of the groups, one child of the protected series and five of the controls had died, thus producing group mortality rates of 3.8% and 19.2% respectively. The difference in these rates is not statistically significant. All deaths took place in the first 16 months of life. The precise cause of death (acute gastroenteritis) could be established only in the case of the protected child. All the unprotected children who died were known to have been heavily infected with malaria immediately before death. From October, 1952, to November, 1954, no further deaths occurred, even in those whose regular drug prophylaxis had lapsed.

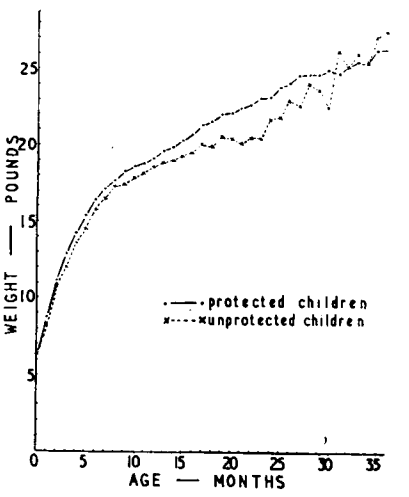

FIG. 1.—Average weight curves of protected and unprotected children during first three years of life.

Analysis of the dietary notes kept throughout the investigation showed that supplements to breast milk were started on the average at 4½ months. These supplements comprised paps of the common local cereals—rice, sorghum, and

millet. Weaning took place at the average age of 22 months, by which time the child was receiving a good mixed cereal diet with additions of meat and fish.

Fig. 1 expresses graphically the average weight curves of protected and unprotected children over the first three years of life. It will be noted that as age progresses and malaria infection becomes frequent the unprotected children lag behind their protected fellows. Nevertheless, at no time in the first three years is the weight difference statistically significant. By the end of the second year of life the unprotected children begin to make more rapid weight gains, and by the 36th month appear to have overtaken the protected children.

Figs. 2 and 3 contrast the weight development of a protected child with that of its control through successive wet and dry seasons. It is of interest to note that the subjects whose weights are recorded in Fig. 2 were homozygous (or uniovular) twin girls reared by their mother in identical circumstances.

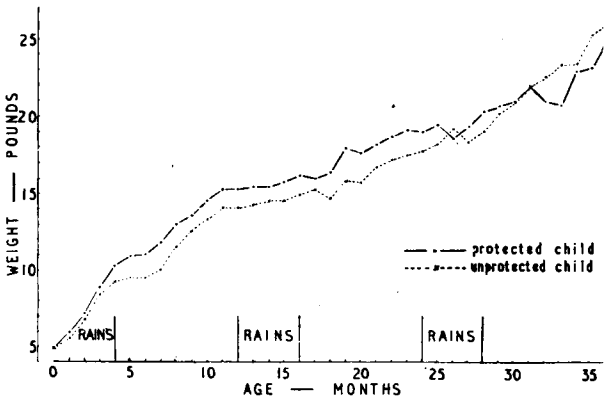

FIG. 2.—Weight development of a protected child and of its control. These two children were homozygous twins.

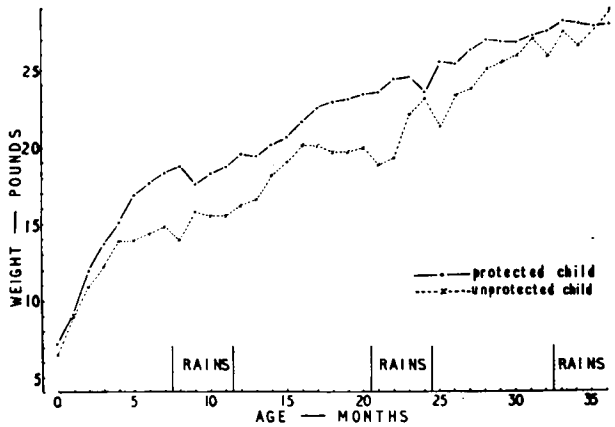

FIG. 3.—Weight development of a protected child and of its control.

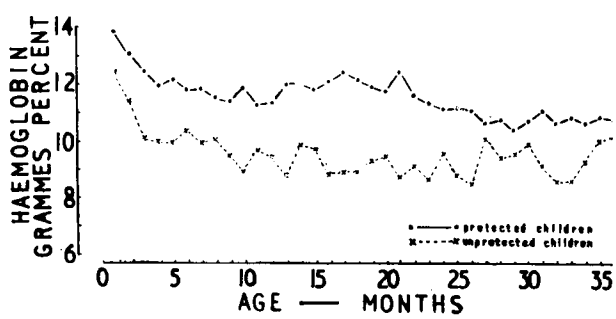

FIG. 4.—Mean Hb values of protected and unprotected children during first three years of life.

Both figures illustrate the tendency shown by all unprotected children to gain weight more slowly, and occasionally to lose weight in the wet malarious months than in the dry season.

Fig. 4 contrasts the mean haemoglobin values in children of both series from the end of the first month of life until the 36th month. The much lower level of the unprotected children will be noted.

In November, 1952, 25 protected children and 17 controls were examined. Table I contrasts the clinical findings.

TABLE I.—*Clinical Findings (November, 1952)*

	Protected Group	Unprotected Group
No. in group	25	17
Percentage with parasitaemia	0	100*
,, ,, splenomegaly	0	88·3*
,, ,, liver palpable below costal margin in mid-axillary line	4	88·3*
Percentage with hair dyspigmentation	32	53
Mean haemoglobin (g.%)	12·1 (S.D. 1·06)	9·5%* (S.D. 1·22)

* Values statistically significant.

Second Investigation

Methods

In October and November, 1954, 16 children of the protected series and 13 of the unprotected series were admitted to the ward of the Medical Research Council's Laboratories for detailed clinico-pathological investigation. Each child remained in hospital for five days, during which time liver biopsy was performed with the parents' sanction. Specimens of urine, stool, and blood from each child were examined in the following ways.

1. *Urine* was tested for specific gravity and the presence of protein, sugar, bile, blood, and casts.

2. *Stools.*—Microscopical examination of both fresh saline and salt-flotation preparations for protozoal and helminthic parasites. Densities of helminth ova were calculated by a modification of the Stoll technique.

3. *Blood.*—(*a*) Thick and thin films were examined for the presence of plasmodia. (*b*) Thick films, prepared at 11 p.m., were dehaemoglobinized, fixed in methyl alcohol, stained with haem-alum, and examined for the presence of microfilariae. (*c*) Haemoglobin values were assessed, using the M.R.C. Grey Wedge photometer. In each case the mean of ten readings was taken. (*d*) Erythrocyte sedimentation rates were obtained by Wintrobe's method. (*e*) Packed cell volume was read after centrifuging for thirty minutes at 6,000 revolutions a minute. (*f*) Red- and white-cell enumeration was performed on a Neubauer "bright ruling" haemocytometer. (*g*) Sickling tests were made, employing the sealed cover-slip technique and using a 2% solution of sodium metabisulphite as a reducing agent. (*h*) Samples of serum were forwarded by air to the United Kingdom for various treponemal tests. (*i*) Total serum proteins were estimated by a semimicro-Kjeldahl method, using a selenium-sulphuric acid catalyst. For the estimation of serum albumin, serum globulin was precipitated by 25% sodium sulphate. The difference between total serum protein and serum albumin results was taken as the serum globulin value. Non-protein nitrogen was estimated separately after the serum had been deproteinized by a modified Folin-Wu tungstic acid reagent. (*j*) Electrophoresis of serum proteins was effected in a horizontal tank containing a barbiturate buffer (*p*H 8.6) to which a small quantity of fungicide (sodium salicylanilide) had been added. Serum (10–20 μl.) was applied by coverslip to Whatman's No. 2 (chromatography) filter paper. A direct current (120 v.), obtained from a high-tension dry battery, was passed through the filter paper for 20–22 hours. Electrophoretograms were fixed by heat, stained with azocarmine "B" and "scanned" in a Joyce-Loebel densitometer.

Results

The results of the liver biopsy will be dealt with later in a separate publication. The detailed results of the other investigations are shown in Tables II–IX and Fig. 5.

All the children appeared fit and well, and no difference in physical agility or mental acuity could be detected between members of the two groups. The mean weight of protected children was slightly lower than that of the unprotected children, but the former were slightly the taller (Table II).

No marked nutritional deficiencies were found in any child, and both groups were assessed as being in good nutritional condition (Table III).

All children of the unprotected series showed considerable enlargement of both liver and spleen (Table IV). In only two of the protected children could the liver be palpated below the costal margin in the mid-axillary line, and in only one child of this series could the spleen be felt. In this latter case splenic enlargement was small and the child was known to have experienced a short attack of malaria a few months before.

Examination of thick and thin blood films revealed that all the unprotected children were infected with malaria (Table V). In every instance the children were apyrexial and the infection seemed to be completely asymptomatic. Parasite densities varied in individuals from 20 to 3,000 per 100 oil fields of thick blood films. The frequencies of infecting plasmodia were *P. falciparum* 100%, *P. malariae* 61.5%, and *P. ovale* 7.7%.

Examination of night films did not reveal the presence of microfilariae in the blood of any child. The incidence of infection with intestinal helminths was higher in the protected series, but the density of these infections appeared to be greater in the unprotected children. The mean egg loads per gramme of faeces in protected and unprotected children respectively were: hookworm, 600 and 900; ascaris, 12,400 and 23,800; tapeworm, 1,600 and nil.

In only one case, that of an unprotected child, could any gross urinary abnormality be detected. This child showed a marked proteinuria (Esbach 1.125 g.%) but seemed physically fit and well and the N.P.N. value of her serum was within normal limits. No evidence of oedema could be detected on clinical examination. Microscopy of the uncentrifuged urinary deposit revealed both granular and hyaline casts, epithelial cells, and a few blood cells of both the red and white series. The blood of the child showed a fairly dense *P. malariae* infection, and while it is clear that the urinary condition could easily have been completely independent of this the possibility that it was a sequel to quartan malaria must be borne in mind.

While the mean haemoglobin concentration of each group showed practically no difference the mean erythrocyte concentration and the mean haematocrit value of the unprotected children were considerably lower than those of the protected series (Table VII). Both groups showed a degree of normocytic anaemia, that of the unprotected children being the greater. Erythrocyte sedimentation rates in the malarious children were much higher, despite the asymptomatic nature of the infections, than those of the non-malarious group.

In the serum of only one child, positive results were obtained in the Wassermann, cardiolipin Wassermann, Kahn, and treponemal immobilization tests. A positive pallida reaction was also obtained. This child was one of the two protected children in whom enlarged livers were palpated, and the possibility that luetic disease was responsible for the enlargement must be considered.

The mean total serum protein values, as determined by chemical estimation, were found to be approximately 0.5 g.% higher in the unprotected children (Table VIII). Fractionation of the serum proteins revealed that mean

TABLE II.—*Mean Ages, Heights, and Weights (October–November, 1954)*

	Protected Children	Unprotected Children
No. in group	16	13
Average age (weeks)	161·68	161·15
Average birth weight (oz.)	103·75 (S.D. 19·92)	100·53 (S.D. 17·74)
,, weight in October–November, 1954 (oz.)	464·50 (S.D. 59·65)	466·15 (S.D. 45·03)
Average weekly weight gain since birth (oz.)	2·23	2·26
Average height in October, 1954 (in.)	35·82 (S.D. 1·39)	34·49 (S.D. 1·88)

1 oz. avoirdupois equals 28·35 g.; 1 inch equals 2·5 cm.

TABLE III.—*Clinical Nutritional Assessment (October–November, 1954)*

	Protected Children	Unprotected Children
No. in group	16	13
Skin changes: xerosis, crackling, P.G.F., follicular keratosis, dyssebacia	12·5%	15·38%
Muscle mass	Good	Good
Bone changes: genu valgum, frontal bossing, beaded ribs, enlarged epiphyses	25·0%	46·14%
Mucosal changes: angular stomatitis, cheilosis, tongue changes	12·5%	23·0%

TABLE IV.—*Incidence and Degree of Hepatomegaly and Splenomegaly (October–November, 1954)*

	Protected Children	Unprotected Children
No. in group	16	13
Hepatomegaly:		
1 F.B. below costal margin	12·5%	23·1%
2 ,, ,, ,, ,,	Nil	46·2%
3 ,, ,, ,, ,,	,,	30·8%
Splenomegaly:		
Just palpable	6·3%	Nil
1 F.B. below costal margin	Nil	7·7%
2 ,, ,, ,, ,,	,,	7·7%
3 ,, ,, ,, ,,	,,	30·8%
4 ,, ,, ,, ,,	,,	23·1%
5 ,, ,, ,, ,,	,,	23·1%
6 ,, ,, ,, ,,	,,	7·7%

TABLE V.—*Incidence of Parasitic Infection (October–November, 1954)*

	Protected Children	Unprotected Children
No. in group	16	13
Malaria	0	100%
Filariasis	0	0
Hookworm	68·8%	38·5%
Ascaris	68·8%	38·5%
Tapeworm	6·3%	0
E. histolytica	0	0

TABLE VI.—*Urinary Findings (October–November, 1954)*

	Protected Children	Unprotected Children
No. in group	16	13
Specific gravity (av.)	1019·6 (S.D. 11·89)	1017·6 (S.D. 6·59)
Albumin:		
Trace	18·8%	38·5%
Heavy	Nil	7·7%
		Esbach 1·125 g.%
Sugar	,,	Nil
Bile	,,	,,
Casts	,,	7·7%
Blood	,,	7·7%

TABLE VII.—*Mean Haematological Values (October–November, 1954)*

	Protected Children	Unprotected Children
No. in group	16	13
E.S.R.	31·1 (S.D. 12·05)	50·84 (S.D. 2·11)
Haemoglobin	11·28 g.% (S.D. 0·91)	10·88 g.% (S.D. 1·248)
R.B.C. per c.mm. (millions)	4·00 (S.D. 0·361)	3·688 (S.D. 0·416)
P.C.V.	34·37% (S.D. 1·61)	31·96% (S.D. 2·54)
M.C.V.	86·25 c.μ (S.D. 8·28)	86·92 c.μ (S.D. 5·48)
M.C.H.C.	32·81% (S.D. 1·83)	33·84% (S.D. 2·28)
W.B.C. (thousands)	9·288 (S.D. 2·84)	9·980 (S.D. 2·76)
Sickling trait	12·5%	Nil

TABLE VIII.—*Mean Serum Proteins and Non-protein Nitrogen Values (October–November, 1954)*

	Protected Children	Unprotected Children
No. in group	16	13
Chemical estimation:		
Total proteins	7·13 g.% (S.D. 0·4429)	7·59 g.% (S.D. 0·4309)
Albumin	3·92 g.% (S.D. 0·5295)	3·83 g.% (S.D. 0·3567)
Globulin	3·20 g.% (S.D. 0·4017)	3·76 g.% (S.D. 0·3640)
Non-protein nitrogen	20·85 mg.% (S.D. 6·33)	19·07 mg.% (S.D. 4·28)

albumin values for each group were almost identical but that the mean globulin value was higher in unprotected children. Non-protein nitrogen serum values were similar in both groups.

Fig. 5 shows the graphs obtained by "scanning" the electrophoretograms of an unprotected and a protected child. The strikingly high gamma-globulin fraction of the former will be noted.

When a pattern similar to the above had been prepared on standard graph paper for each child of both series it was cut out with scissors and weighed. A perpendicular to the baseline was then dropped from the lowest point of the trough between the curves representing the beta- and gamma-globulin fractions and, by cutting along this, the gamma portion of the pattern was severed from the remainder. This portion was then weighed and its weight as a percentage of the total graph calculated. In this way the mean serum gamma-globulin was estimated to be 24.43% (S.D. 5.74) of the mean total serum protein value in the protected children and 32.21% (S.D. 4.39) in the unprotected children. It is thus apparent that the gamma-globulin content of the serum of the malarious children was almost one-third as great again as that of the non-malarious children.

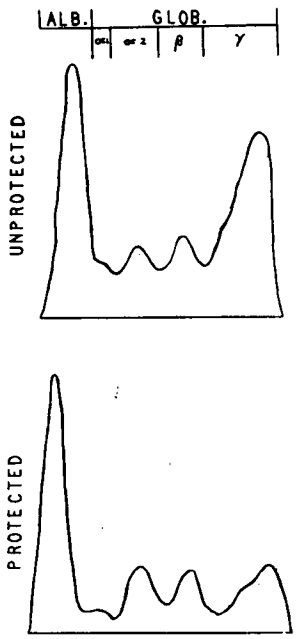

FIG. 5.—Graphs obtained from electrophoretograms of an unprotected and a protected child.

It is unfortunate that the small size of each experimental group limited the value of the statistical analysis of results. Nevertheless we have thought that such analysis would prove helpful to the reader in assessing the relative importance of the difference between protected and unprotected children. Table IX therefore summarizes these differences in mean values observed, which were greater than twice the standard error of the difference. All other differences reported in this second investigation were less than twice this value.

TABLE IX.—*Major Differences Detected Between the Protected and Unprotected Groups*

	Difference Between Mean Values or Proportions of Groups	Standard Error	Difference Divided by Standard Error
E.S.R.	19·74	3·07	6·43
Splenomegaly	93·75	18·66	5·02
Hepatomegaly	87·50	18·66	4·68
Gamma globulin (by electrophoresis)	7·78	1·88	4·14
Serum globulins (by chemical estimation)	0·56	0·14	4·0
P.C.V.	2·41	0·80	3·01
Total serum proteins (by chemical estimation)	0·46	0·16	2·87
R.B.C.	0·312	0·145	2·15
Height	1·33	0·65	2·04

Discussion

Before discussing the results observed in this investigation it must be remembered that chloroquine afforded the treated children protection only against the erythrocytic phases of the malaria parasite. It is known that the drug has no action on sporozoites or on the exo-erythrocytic phases of infection, and it must be assumed that sporozoite entry and subsequent exo-erythrocytic development occurred normally in both groups, but that in the treated children no further parasitic growth took place. It is clear, therefore, that only the erythrocytic phases can be held responsible for the production of the differences observed between treated and untreated children.

From the above results one is led to deduce that malaria exerted its maximal effects in the first 18 months of life and that by the age of 3 years the unprotected children had developed a considerable immunity to the disease, as witnessed by their ability to live asymptomatically with fairly dense parasitaemia. While the difference in the mortality rates of the two groups, which were of small size, was not statistically significant, and while the cause of death of the five unprotected children could not be ascertained, the possibility that comes to mind first, and cannot be excluded, is that the difference was related to the presence or absence of overt malaria infection.

Study of the weight curves of children of both groups indicates that acute clinical malaria tended to retard growth. This retardation did not appear to be in any way permanent, for when the malarious children had developed enough resistance to the noxious effects of the disease they rapidly regained lost ground and, despite the persistence of moderately severe parasitaemia, by the third year of life were just as heavy as their protected fellows. It should not be forgotten, however, that at this age the grossly enlarged livers and spleens of the malarious children must have contributed a disproportionate sum to the total body weight, whereas that of the protected children represented presumably normal body tissue.

These observations, coupled with the fact that no marked difference in the incidence of signs of specific nutritional deficiencies could be found between the groups at any time, suggest that in children to whom a good diet is available malaria exerts its main effect on growth not by appropriating nutrients that would otherwise be used in building body tissue but by limiting the food intake of the host through the anorexia that the clinical attack produces.

The differences observed in the mean haematological indices, of which the erythrocyte concentration and the packed cell volume alone are significantly reduced in the malarious group, appear to be entirely due to malaria. Hookworm infection cannot have contributed to these differences, for not only was the density of infection low in each group, but the incidence of ankylostomiasis was twice as high in the protected as in the unprotected children.

Wilson and Miles (1946) state that there is conflict in the evidence that malaria tends to give positive reactions in the Kahn and allied serological tests. In the present investigation no positive reaction to the tests employed was obtained in the sera of the unprotected children despite the fact that all were fairly heavily infected. These children were, however, asymptomatic, and it is possible that had they been febrile positive reactions might have been obtained.

Within recent years considerable interest has been focused upon the question of whether malaria causes substantial enlargement of the liver (Colbourne *et al.*, 1950; McGregor and Smith, 1952; Waddy, 1952; McGregor, 1954; Black, 1954, 1955). The results reported above demonstrate clearly that such is indeed the case. They also show that hepatomegaly is attributable to the erythrocytic cycle of the malaria parasite, and that the pre- and exoerythrocytic cycles within the liver do not appear to influence the overall size of that organ. In view of the good nutritional status of the members of both groups malnutrition may be discounted as an additional factor in the production of hepatomegaly in these children. From clinical examination of the children showing liver enlargement no evidence of hepatic dysfunction could be adduced. The mechanism of enlargement and the associated histological changes will be discussed in a subsequent communication.

Of particular interest are the differences observed in mean serum protein values. It will have been noted that, whereas mean albumin levels were similar in both groups, mean total protein and globulin values were much higher in the un-

protected children. Analysis of electrophoretic patterns indicated that this difference was located principally in the serum gamma-globulin fractions. The precise reason for the existence of a much higher gamma-globulin level in the serum of the malarious children is not known, but when the controlled nature of the investigation is considered it is clear that malaria must have been at least a closely related factor. Study of the literature relating to serum protein changes in malaria reveals that most communications describe observations made during the acute attack. Observers have reported a fall in serum albumin and a rise in serum globulin with an overall reduction in total serum proteins (Fulton and Maegraith, 1949). These changes are transient, and protein values revert to original levels soon after eradication of the infection. It is apparent that, hitherto, little information has been gathered on the cumulative effects on serum proteins of several years of repeated and heavy plasmodial infection.

It is possible that almost three years of continued irritation of the reticulo-endothelial systems of the unprotected children by the products of disintegration of parasitized erythrocytes may have stimulated the production of abnormally large quantities of gamma-globulin. If this is so the high values obtained in the malarious children are of no special significance, since they have their origin in a non-specific process. However, it is equally possible that these high values may be caused, at least in part, by the production of specific humoral antibodies to the erythrocytic phase of the infecting plasmodium. The observations of earlier workers justify this hypothesis. Sotiriades (1936) reported that whole blood from highly immune subjects produced beneficial results when injected into patients suffering from acute attacks of malaria, while Coggeshall and Kumm (1937) and Eaton (1938) demonstrated the presence of circulating antibodies in the sera of monkeys recently recovered from malaria. At this juncture further speculation on the mechanism of the production of the serum protein variations recorded would be valueless, and additional investigations are clearly indicated.

The difference in the mean erythrocyte sedimentation rates of the protected and unprotected children must be regarded as a sequel to erythrocyte parasitization in the latter. The high mean rate observed in the treated group, however, is puzzling. As these children were all fit and well and presented no sign of disease save for a moderate degree of intestinal helminthic infection in some cases, one wonders what part the unsuppressed hepatic phases of malaria played in raising these sedimentation rates. McGregor and Deegan (1954) observed that the mean erythrocyte sedimentation rate in a group of fit and healthy Gambian adults, who must have experienced severe repeated malarial infection in infancy and childhood, was, by European standards, abnormally high. They postulated that a possible reason for this could be that Gambian adults possessed a plasma protein pattern which differed greatly from the accepted European normal. The results of this present investigation support that view and, further, incriminate malaria as a major factor in the production of the altered pattern.

The results of urinary examination and of the evaluation of serum non-protein nitrogen levels suggest that with one possible exception the prolonged heavy malaria infections experienced by the unprotected children caused no permanent impairment of kidney function. Even in the exceptional case the relationship of quartan malaria to proteinuria is obscure, and it is possible that the two conditions were completely independent.

After more than three years of continuous chloroquine dosage no evidence of drug toxicity was found in any protected subject. Throughout this period complete suppression of the erythrocytic cycle of malaria was achieved in every subject who received regular weekly treatment.

Summary

To assess the effects of repeated heavy erythrocytic infection in African infants and young children an investigation in a hyperendemic malarial district of the Gambia began in 1951. Twenty-six infants were protected from birth by weekly doses of chloroquine base (6 mg. per kg. for the first two years and thereafter 150 mg.). A control group of equal size of unprotected infants from the same population was maintained. The established custom of infant feeding in a rural Gambian community was not modified. Members of both groups were examined regularly for three years.

The unprotected children once infected with malaria were observed to grow more slowly and to become much more anaemic than the protected children over the first two years. Mortality rates for protected and unprotected groups were 3.8% and 19.2% respectively, all deaths occurring in the first sixteen months. As increasing resistance to malaria was acquired the unprotected children made rapid growth progress.

In October–November, 1954, 16 protected and 13 unprotected children were admitted to hospital for detailed investigation and comparison. The mean weight of protected children at a mean age of 161.68 weeks was 464.50 oz. (13.167 kg.) and that of unprotected children at a mean age of 161.15 weeks was 466.15 oz. (13.214 kg.). The mean heights of protected and unprotected subjects were 35.82 in. (90.9 cm.) and 34.49 in. (87.6 cm.) respectively.

All unprotected children were found to exhibit malarial parasitaemia (plasmodial frequency being: falciparum 100%, malariae 61.5%, ovale 7.7%), but to be asymptomatic.

The nutritional status of members of both groups was assessed to be good, the incidence of deficiency signs in protected and unprotected children respectively being: skin changes 12.5% and 15.38%; bone changes 25% and 46.14%; mucosal changes 12.5% and 23.0%.

All unprotected children showed considerable hepatomegaly and splenomegaly, while 12.5% of protected children were found to have enlarged livers and 6.3% enlarged spleens.

Hookworm and ascaris ova were found in the stools of 68.8% of protected and 38.5% of unprotected children; the density of infection was greater in the unprotected group.

A marked proteinuria associated with a *P. malariae* parasitaemia was noted in a member of the unprotected group. No other gross urinary abnormality was detected in any child.

The differences detected in mean haematological indices between the protected and unprotected groups respectively were: E.S.R., 31.1 and 50.84; Hb, 11.28 and 10.88 g.%; R.B.C., 4,000,000 and 3,688,000; P.C.V., 34.37 and 31.96%; M.C.V. 86.25 and 86.92 cubic microns; M.C.H.C., 32.81 and 33.84%; W.B.C. 9,288 and 9,980; sickling trait, 12.5% and nil.

Chemical estimation of serum proteins showed the mean total serum protein (7.59 g.%) and mean globulin (3.76 g.%) values to be higher in unprotected than protected children (7.13 and 3.20 g.%). Mean albumin values were almost identical (3.92 g.% protected and 3.83 g.% unprotected), as were mean N.P.N. levels (20.85 mg. per 100 ml. protected and 19.07 mg. per 100 ml. unprotected). By filter paper electrophoresis the gamma-globulin fraction in unprotected children was found to be almost one-third greater than in protected children. The serum of only one subject, a protected child, yielded positive results in the Wassermann, cardiolipin Wassermann, Kahn, and treponemal immobilization tests.

The results are discussed and are considered to indicate that erythrocytic malaria in Gambian children exerts its main effects in the first two years of life, chiefly through the clinical illness produced by the acute attack. Malarious children, once they have acquired sufficient resistance to the noxious effects of clinical malaria, appear rapidly to make good lost ground despite the persistence of moderately dense parasitaemia. A consistent relationship between hepatomegaly and erythrocytic malaria is defined. The view is expressed that the serum protein changes observed in malarious children may in part be due to the formation of humoral antibodies.

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STUDY OF TRANSFUSED PLATELETS IN A CASE OF CONGENITAL HYPOPLASTIC THROMBOCYTOPENIA

BY

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The following case of neonatal thrombocytopenia is of interest because of the rarity of the haematological disorder, which was apparently a primary aplasia of the megakaryocytes associated with a congenital skeletal defect of the forearms, and also because it was possible to give relatively large transfusions of platelets in view of the recipient's small blood volume. In the virtual absence of platelet production in the infant, the effectiveness and survival of these transfused platelets could be readily studied.

Case History

This child, a female, was born at term of the mother's second pregnancy. Its weight was 6 lb. 2 oz. (2,780 g.). The first pregnancy had miscarried at two months. Vaginal bleeding had occurred also in this pregnancy during the twelfth week. No consanguinity existed between the parents, who were in good health.

The infant was born with a deformity of both arms, due to the absence of both radii, resulting in diminutive forearms with abducted hands, but otherwise appeared healthy. Progress was uneventful until the sixth week, when melaena occurred, immediately followed by the appearance of scattered petechiae and noticeable pallor. No drug with which blood dyscrasia could be associated had been given at any stage of the child's illness.

The infant was admitted to hospital on June 11, 1955, aged 6 weeks and weighing 7 lb. 7 oz. (3,370 g.). Nutrition and hydration were good. The child was alert and afebrile, but there was marked pallor with petechiae in the mouth and skin. The liver was palpable and enlarged. The spleen could be felt ¾ in. (2 cm.) below the costal margin. No lymphadenopathy was apparent. No other abnormality was found on physical examination. The urine was normal.

Investigations on Admission.—Hb, 5 g. per 100 ml.; white cells, 63,000 per c.mm., with a preponderance of granular cells and a marked shift to the left (for differential count, see Table I). The red cells showed frequent polychromatic forms and normoblasts. Blood group B, rhesus test positive (to anti-D), direct Coombs test negative. Platelet count

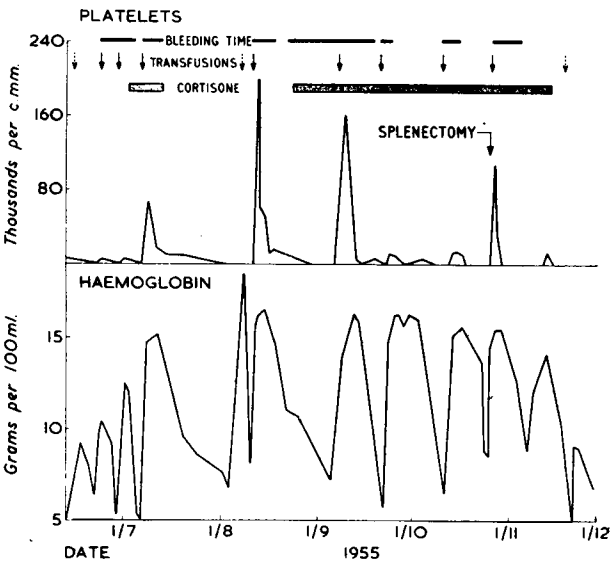

FIG. 1.—"Platelet transfusions" are indicated by arrows, and transfusions of stored blood by dotted arrows. The duration of a normal bleeding-time is shown by a continuous black line; where this is interrupted the bleeding-time was found to be longer than 10 minutes.

(Fonio's method), 3,600 per c.mm. Bleeding-time in excess of one hour. Clotting-time, clot retraction, and prothrombin times were within normal limits. Hess's test showed 15 petechiae in ½ square inch (3.2 square cm.). Serum bilirubin, 0.4 mg. per 100 ml. Tibial marrow counts (Table I) showed a normoblastic hyperplasia, active leucopoiesis, and a striking absence of platelet precursors. Prolonged search of several films from each specimen failed to show any mature or early forms of megakaryocytes. A maternal blood count was normal, with a normal platelet count. The Wassermann reaction in the mother and child was negative.

After admission a tentative diagnosis of congenital hypoplastic thrombocytopenia was made, based on the absence of platelet precursors, the haematological condition being associated with skeletal abnormalities.

On June 14 a transfusion of stored blood was given. In spite of a satisfactory rise in haemoglobin there was no appreciable effect on the bleeding-time or the platelet count, and the stools continued to be heavily blood-stained. In view of the thrombocytopenia, platelet transfusions were given (for technique, see Appendix). The improvement on each occasion was striking but transitory (Table II). Clinically, there was fading of petechiae, and the stools changed from melaenic to normal. The increased number of circulating platelets persisted for as long as five days, while the bleeding-time and the capillary fragility were found to be normal for a longer period (see Fig. 1).