The Role of Malaria in Nutritional Anemias

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Anemia is one of the most common manifestations of malaria. The causative mechanisms are multifactorial, and the severity of the anemia varies in relation to the level of malaria transmission in a population. The anemia of acute malaria in non-immune individuals is usually normocytic and presents no special morphologic features; however, in malaria endemic areas subjects frequently have multiple pathology including iron and possibly folate deficiency. Interactions between nutritional factors and malaria infection in the causation of anemia are complex (1). In addition, the stability of malaria in an area influences the risk of developing anemia. In unstable malaria areas anemia occurs at all ages, whereas in stable areas anemia is most evident in young children and pregnant women. Where transmission is seasonal, marked changes in the prevalence of anemia may occur, especially in children (2).

THE EPIDEMIOLOGY OF ANEMIA IN MALARIA ENDEMIC AREAS

In order to appreciate the role and complexity of malaria in relation to nutritional anemia, it is important to understand the magnitude of the effect of parasitemia on hemoglobin concentration and how this alters in children and adults, especially pregnant women.

Children

Table 1 summarizes studies which estimate the improvement in hemoglobin in children when malaria is controlled. Overall this amounts to a 10% to 20% increase in the hemoglobin concentration. The increase is most evident in younger children (who are less immune) and is likely to be greatest when acute malaria infections are more frequent (9). None of these studies provide sufficient background information about iron or folate status to permit an interpretation of how these changes might be influenced by the child’s nutritional status. It is known that malarial anemia may remit spontaneously without treatment, although this appears to be dependent on the presence or absence of chronic splenomegaly (10). In villages in The Gambia
**TABLE 1. Magnitude of the effect of malaria on hemoglobin concentration in children**

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of study</th>
<th>Age group</th>
<th>Difference in hemoglobin value* (g/dl)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanzania</td>
<td>Vector control</td>
<td>3 months to 9 years (978)</td>
<td>(+1.3)–(+2.3)</td>
<td>Draper (3)</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>Vector control</td>
<td>3–15 years (1391)</td>
<td>(+1.3)–(+2.1)</td>
<td>Crane and Kelly (4)</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>Vector control</td>
<td>1–10 years (374)</td>
<td>(+0.3)–(+2.7)</td>
<td>Schofield <em>et al.</em> (5)</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>Presence or absence of current parasitemia</td>
<td>0–1 years (103)</td>
<td>+2.0</td>
<td>Spencer (6)</td>
</tr>
<tr>
<td>Gambia</td>
<td>Presence or absence of current parasitemia</td>
<td>2–4 years (221)</td>
<td>+1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–9 years (130)</td>
<td>+0.3</td>
<td></td>
</tr>
<tr>
<td>Gambia</td>
<td>Controlled trial of chemoprophylaxis</td>
<td>3–36 months (33)</td>
<td>(+1.2)–(+2.1)</td>
<td>McGregor <em>et al.</em> (2)</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Controlled trial of chemoprophylaxis</td>
<td>3 months to 2 years (152)</td>
<td>+1.1</td>
<td>Bradley-Moore <em>et al.</em> (8)</td>
</tr>
</tbody>
</table>

*The range of improvement of the hemoglobin concentration is given for different age classes which have been combined.

where malaria is highly endemic and childhood splenomegaly is almost universal, anemia relapses are frequent, whereas in other villages where splenomegaly rates are lower, many anemias remit without relapse (11). In determining nutritional interactions it is therefore important to obtain additional information on such factors as splenomegaly and reticulocytosis as indicators of malaria experience.

In infancy, marked changes in hemoglobin values occur in healthy children in the first months of life. This pattern of change alters in malarious areas as shown in Fig. 1. The lower hemoglobin values in malaria-exposed infants are related to the high incidence of malaria infection from the first months of life (14). Clearly if malaria has a role in influencing the onset of nutritional anemia or conversely if iron or folate status alters host susceptibility to malaria, then the onset of these interactions must occur in early infancy. Although it has been suggested that young babies are protected from malaria infection, there is good evidence that they are normally susceptible to malaria although they develop less clinical disease (14).

**Pregnant and Nonpregnant Women**

Table 2 shows the mean hematological values in pregnant and nonpregnant women from coastal Papua New Guinea in relation to the presence or absence of parasitemia. Malaria reduces the mean hemoglobin by 0.3 g/dl, which is less than the effect on hemoglobin of malaria in children. The difference in hemoglobin values is greatest in primigravidae (0.7 g/dl) (15), who are more susceptible to *Plasmodium falciparum* malaria than are multigravidae (16). Comparable differences in hemoglobin values associated with malaria in pregnancy have been reported from The Gambia (17).
It is frequently stated that multigravidae are at greatest risk of developing anemia in tropical countries because of the cumulative demands on iron stores of successive pregnancies. In malarious areas anemia is generally seen more commonly in primigravidae and in mid-pregnancy (Fig. 2) (16). Hypersplenism makes a major contribution in about 25% and immune hemolysis in about 5% of severe anemias (18).

### TABLE 2. Mean hematological values (± SD) in pregnant and nonpregnant women with and without malaria parasitemia (Madang Province, Papua New Guinea)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonpregnant</th>
<th></th>
<th>Pregnant</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malaria-</td>
<td>Malaria-</td>
<td>Malaria-</td>
<td>Malaria-</td>
</tr>
<tr>
<td></td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.6 ± 1.3</td>
<td>9.9 ± 1.3</td>
<td>8.5 ± 1.3</td>
<td>8.8 ± 1.6</td>
</tr>
<tr>
<td>(n = 17)</td>
<td>(n = 38)</td>
<td></td>
<td>(n = 92)</td>
<td>(n = 191)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>32.1 ± 4.4</td>
<td>33.1 ± 3.5</td>
<td>28.5 ± 4.1</td>
<td>29.4 ± 4.9</td>
</tr>
<tr>
<td>(n = 17)</td>
<td>(n = 39)</td>
<td></td>
<td>(n = 86)</td>
<td>(n = 175)</td>
</tr>
<tr>
<td>FEP (µg/dl)</td>
<td>42.4 ± 25.5</td>
<td>39.1 ± 17.9</td>
<td>34.9 ± 14.6</td>
<td>34.3 ± 16.0</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 37)</td>
<td></td>
<td>(n = 87)</td>
<td>(n = 181)</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>30.1 ± 3.0</td>
<td>30.1 ± 3.7</td>
<td>30.1 ± 3.2</td>
<td>30.1 ± 3.6</td>
</tr>
<tr>
<td>(n = 17)</td>
<td>(n = 38)</td>
<td></td>
<td>(n = 85)</td>
<td>(n = 173)</td>
</tr>
<tr>
<td>Red cell folacin (nmol/l)</td>
<td>1558 ± 469</td>
<td>1396 ± 629</td>
<td>1635 ± 928</td>
<td>1943 ± 960</td>
</tr>
<tr>
<td>(n = 17)</td>
<td>(n = 39)</td>
<td></td>
<td>(n = 49)</td>
<td>(n = 98)</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>3.3 ± 2.7</td>
<td>1.6 ± 1.7</td>
<td>1.5 ± 1.5</td>
<td>2.3 ± 2.4</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 22)</td>
<td></td>
<td>(n = 32)</td>
<td>(n = 80)</td>
</tr>
</tbody>
</table>
ROLE OF MALARIA IN NUTRITIONAL ANEMIAS

Because iron and folate deficiency commonly occur in these populations, several levels for nutritional interactions are possible.

CYCLE OF INTERACTION OF MALARIA AND NUTRITIONAL ANEMIA

In young children and pregnant women living in endemic areas, malaria-associated anemia may present with features compatible with iron deficiency and folate deficiency states (3). To what extent does malaria cause nutritional anemia, and does iron and folate deficiency subsequently influence the host's susceptibility to malaria? There is some evidence that persistent or recurrent parasitemia induces iron deficiency, although the mechanisms are uncertain. These include the following:

1. There is reduced absorption of iron during the acute period of the illness (19).
2. Low haptoglobin levels, which result from intravascular hemolysis, will reduce the formation of haptoglobin/hemoglobin complexes which are removed from the circulation by the liver, reducing iron availability (20). Once this happens the iron in any additional free hemoglobin will be lost to the body either acutely (as hemoglobinuria) or, more commonly, as haemosiderinuria over a longer period (13).
3. There is immobilization of iron in hemazoin complexes (malaria pigment) (21,22).

The magnitude of such mechanisms in subjects experiencing chronic recurrent parasitemia is unknown. For example, in some individuals it may take up to 200 days before parasitemia is suppressed and under holoendemic conditions subjects may experience one or two infected mosquito bites each week. It is difficult to assess the contribution to malabsorption under such conditions of high transmission.

Comparison of the prevalence of iron deficiency in malarious and nonmalarious
areas is affected by differences attributable to diet or other confounding factors. Nevertheless, it is of interest that iron deficiency is a widespread cause of anemia in coastal Papua New Guinea, where malaria is endemic (13), but in the New Guinea highlands, where it is not endemic, there is evidence that iron deficiency is a much less frequent cause of anemia (23,24). Where iron status is already marginal, or latent iron deficiency is already present, the additional losses produced by malaria may be sufficient to tip the scales towards overt iron deficiency. In Liberia, significantly lower HbA2 levels were observed in children from malarious compared to the non-malarious areas; in addition, malaria prophylaxis led to an increase in the HbA2 levels, to values comparable with those from children in nonmalarious areas (25). The authors suggested that these findings may be attributable to iron deficiency caused by malaria.

Carefully conducted clinical studies in The Gambia by Abdalla (21) have not implicated malaria directly as a cause of the high prevalence of iron deficiency observed. Iron deficiency could not be attributed as the sole cause of dyserythropoiesis in patients with chronic malarial anemia. An earlier detailed study by Abdalla et al. (26) also showed that the pathophysiological mechanisms responsible for the dyserythropoiesis of *P. falciparum* malaria are different at different stages of illness.

Hemolysis from malaria stimulates erythropoiesis and increases the requirements for folate (27). This conclusion is based mainly on evidence from a clinical trial reported by Fleming et al. (28) of antimalarial chemoprophylaxis in pregnant women in northern Nigeria. Serum folate activity fell more rapidly in pregnant women not protected from malaria by chemoprophylaxis. In this same population, protection from malaria has also been shown to prevent severe anemia and megaloblastosis in pregnancy even without the addition of a folate supplement (29).

Megaloblastic anemia in infants and children other than the severely malnourished has been reported infrequently from tropical countries (30). This is surprising in view of the expected high prevalence of folate deficiency secondary to malarial hemolysis. Infants and young children experience high attack rates from malaria and show much higher parasite densities than do adults (14), and there is no adequate explanation of why folate deficiency anemia is not more frequent if malaria is a significant contributory factor. Megaloblasts have been reported in the bone marrow in a selected group of anemic children in Zaria, northern Nigeria, in whom it was estimated that 40% had presumed folate deficiency. Malaria was diagnosed in 74% of those with megaloblastic erythropoiesis (31). However, a proportion of these children had sickle cell disease and it was not clear what percentage had dyserythropoiesis, as described by Abdalla and Weatherall (26) in anemic children with malaria. In a small group of hospitalized children with anemia of unknown origin, Hendrickse and King (32) described peripheral blood monocytosis and megaloblasts in bone marrow samples.

Other studies in Nigeria indicate that iron deficiency is of greater importance in children than folate deficiency, which was not considered a major cause of anemia (33). In north Transvaal, South Africa, 25% of 3- to 5-year-old children had red cell folate activities below normal and none had high folate values, but malaria is not endemic in this area (34).

Figure 3 represents schematically a proposed pattern of interaction between ma-
Hypochromic anaemia
- Reduced iron stores
- Altered recovery from malaria
- Increased risk of iron and folate deficiency

Megaloblastic anaemia
- Abnormal ontogeny of immune system

**FIG. 3.** Postulated cycle of interaction of malaria and nutritional anemia. **Hypothesis:** The variation in the incidence of hypochromic and megaloblastic anemia in children relates to the interactions of malaria and diet in the mother, such that her anemia status is related to the immunological response to malaria in children, which in turn influences the severity of anemia in them (62).
Malaria and nutritional anemia. It is drawn to represent a cycle of events which may influence both maternal and fetal health. The potential influence of folate deficiency on the ontogeny of the immune system in the fetus has been little investigated, although there is evidence that its role may be significant (35). Iron deficiency impairs host-cell-mediated immunity (36–38) and phagocytosis (39). In the model shown in Fig. 3 the sequence of events begins with the infection and anemia status of the mother. Research is required to investigate the associations between maternal malaria and iron status and neonatal and infant anemia.

THE INFLUENCE OF IRON AND FOLATE STATUS ON MALARIA RISK

Iron Status

A number of reports in the 1970s indicated that hyperferremia following iron administration may exacerbate subclinical malaria infection (40–42). These studies concerned case reports in malnourished adults and hospital patients receiving oral and parenteral iron therapy. If iron is an important requirement for parasite multiplication, malaria would be suppressed in iron-deficient subjects. McGregor (9) considers that in view of the widespread frequency of iron deficiency and asymptomatic malaria infection in highly endemic areas, it is surprising that so few reports describe reactivation of malaria following iron therapy. In his experience in treating children with parasitemia and with iron deficiency in The Gambia, clinical recrudescence did not occur.

Two controlled trials investigating iron therapy and risk of malaria infection in children have been undertaken in Madang Province, Papua New Guinea. Oppenheimer et al. (43) reported an increase in the prevalence and effects of parasitemia in infants 6 to 12 months old who had received an intramuscular injection of iron at 2 months of age. Conversely, Harvey et al. (44) in the same area found no increased risk of malaria or splenomegaly during a 3-month follow-up period in anemic school children receiving a daily oral iron supplement. These results are not contradictory but would indicate that if immunity to malaria is low (as in infancy), iron supplementation enhances parasitemia, whereas in older children who have developed a degree of acquired immunity to malaria, host immunity overrides any direct effect of iron supplementation on parasite growth. In The Gambia a controlled trial with oral iron in anemic children 6 months to 5 years of age showed a significantly increased risk of severe malaria parasitemia, but not low-density parasitemia, in the iron-treated group (45). In a different study in older, less anemic children (5–14 years) in The Gambia, an iron and vitamin supplement did not significantly increase the risk of parasitemia, although there was a trend toward higher parasite counts in those receiving the supplement (46). Once again these results would indicate that in older children (who have better immunity), iron treatment is less likely to result in malaria recrudescence.

A single prospective study in semi-immune pregnant women given iron dextran (Imferon) injections did not show increased parasite prevalence in the treated compared to the control group (47). During a longitudinal study of malaria in pregnancy
in Madang, Papua New Guinea, there was no increased risk of malaria recrudescence following intramuscular Imferon in women receiving antenatal chloroquine prophylaxis despite a high prevalence of chloroquine-resistant malaria in the area (B. Brabin, *unpublished observations*). In a retrospective study at Madang Hospital a higher malaria prevalence at delivery was observed in women who had received antenatal Imferon (48). However, because anemic women are more likely to be parasitemic, this evidence is inconclusive. Further investigations are required on the influence of iron supplementation of anemic women on infection risk in pregnancy.

**Folate Status**

Maternal folate deficiency has been reported to affect infant growth and increase the risk of delivery of small-for-date babies (49–51). Growth-retarded babies have an increased susceptibility to infection (52). For these reasons, clinical and epidemiological data are required to determine if folate supplementation in infants and children alters their susceptibility to malaria. A single study from The Gambia of folate supplementation in children aged 3 months to 5 years showed no significant difference in malaria parasite rates between children who received a folate supplement and those who did not (53). In this study there was a trend toward higher mean red cell folate in those exposed to malaria. If folate deficiency is uncommon in children in the tropics, then supplementation is unlikely to alter malaria risk.

Other studies have reported high red cell folate concentrations in children experiencing malaria infection. These are summarized in Table 3. The mean value in some of these studies is above the upper value for the normal assay range (8,21,54).

The explanation for these raised values is uncertain. Explanations proposed include the following:

1. *De novo* synthesis in the parasite, with a shift to oligoglutamates or other breakdown products which might be utilized by the parasite (8,21,54). This is unlikely

<table>
<thead>
<tr>
<th>Country</th>
<th>Age</th>
<th>Malaria-positive</th>
<th>Malaria-negative</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papua New Guinea</td>
<td>2 months</td>
<td>1530 (<em>n = 10</em>)</td>
<td>1060 (<em>n = 288</em>)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>1464 (<em>n = 31</em>)</td>
<td>1237 (<em>n = 177</em>)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months*</td>
<td>1650 (<em>n = 56</em>)</td>
<td>1108 (<em>n = 187</em>)</td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>1 year</td>
<td>1520 (<em>n = 7</em>)</td>
<td>893 (<em>n = 12</em>)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1031 (<em>n = 23</em>)</td>
<td>650 (<em>n = 13</em>)</td>
<td></td>
</tr>
<tr>
<td>Gambia</td>
<td>6 months to 7 years</td>
<td>1409 (<em>n = 77</em>)</td>
<td>—</td>
<td>21</td>
</tr>
</tbody>
</table>

* Significant difference between mean values.
to explain the large differences seen in total red cell folate because it would require uninfected red cells to acquire parasite folate during erythropoiesis.

2. Folate trapping within the immature metabolically active red cell (55). Again uninfected red cells would need to be affected.

3. Preexisting high red cell folate favoring parasite growth (54). This is improbable because it would indicate whole populations have a very good folate status.

4. Reticulocytosis, associated with hemolysis, increases the immature red cell population, which have higher mean red cell folate concentrations (56).

A significant association between the reticulocyte count and red cell folate values was found in nonpregnant women in Madang, Papua New Guinea (Fig. 4) (B. Brabin, unpublished observations), although in pregnant women from the same area this association was not observed. Other correlation coefficients between hematological variables in pregnant or nonpregnant women from this study population are shown in Table 4. The highly significant associations between hemoglobin values and MCHC and FEP values indicate that iron deficiency is an important cause of anemia in this population. In pregnant women, hemoglobin is negatively correlated with red cell folate and reticulocyte count. This situation is paradoxical and indicates that red cell folate is a poor indicator of folate status under malaria endemic conditions. In The Gambia, seasonal increases in red cell folate corresponded with the rainy season, a period when food folates were less readily available (57). Although not discussed by the authors, these changes are most likely to be due to the effects of seasonal malaria.

It is uncertain whether the raised blood folate levels can be wholly attributed to reticulocytosis. In Papua New Guinea, exceptionally high values occurred in some subjects with low reticulocyte counts, whereas a significant correlation between folate levels and reticulocyte counts was not observed in pregnant women (see Table 4). This raises the question of how such a situation can occur in pregnant women.
women, who are likely to be folate-deficient and at high risk of megaloblastic anemia. It should be noted that serum folate levels are not raised in these populations.

It is improbable that the high concentrations of folate would influence nutritional status, since quantitatively these concentrations represent only a small percentage of daily folate requirement. However, high concentrations in placental intervillous spaces could influence folate transfer to the fetus. Table 5 shows the mean red cell folate activities in paired maternal and cord blood samples from a holoendemic area of western Kenya (Nangina) and from a rural health center in Coastal Papua New Guinea (Alexishafen). Cord values are high especially in Papua New Guinea, and the significant association with maternal levels would suggest that the high maternal concentrations have nutritional implications for the fetus. The infant: maternal folate ratio is lower in these studies than that reported in temperate climates (58), which could indicate that with high maternal concentrations a threshold for placental transfer has been reached.

**TABLE 5.** Red cell folate activity (± SD) in paired maternal-cord samples from holoendemic malaria areas

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of patients</th>
<th>Red cell folate (nmol/l)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cord</td>
<td>Maternal</td>
</tr>
<tr>
<td>Western Kenya</td>
<td>11</td>
<td>1140 ± 511</td>
<td>791 ± 452</td>
</tr>
<tr>
<td>(Nangina)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papua New Guinea*</td>
<td>40</td>
<td>2030 ± 523</td>
<td>1620 ± 515</td>
</tr>
<tr>
<td>(Alexishafen)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Correlation maternal-cord pairs = +0.34 (p < 0.05). (B. Brabin, unpublished data.)
TREATMENT SCHEDULES FOR NUTRITIONAL ANEMIA IN MALARIA ENDEMIC AREAS

In view of the frequent association of iron deficiency with malaria, iron therapy has been recommended for treating anemia associated with malaria (21,59). Abdalla (21) has suggested that it must be given after treatment of malaria in view of the possibility that administration of iron may lead to malaria recrudescence. Although there is little evidence for this in older semi-immune children, in younger children or those who have severe malnutrition, malaria should be treated first to avoid the risk of recrudescence with refeeding.

Fleming and Werblinska (31) and Topley (60) have recommended the routine use of folate supplements in children with malaria. Abdalla (21,61) does not recommend their use because he believes that the morphological changes in the bone marrow (dyserythropoiesis) relate to malaria but not to hematinic deficiency. There is certainly at present no evidence that giving folate increases risk of malaria and recrudescence (53). In pregnancy, iron and folate supplements should be given routinely with antimalarials during the antenatal period because there is no evidence that this alters malaria risk.

ACKNOWLEDGMENT

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REFERENCES

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**DISCUSSION**

Dr. Adelekan: I cannot agree that by itself malaria causes folate deficiency in pregnant women. As I pointed out earlier, pregnancy represents a changed physiological state in which the hormonal changes and the demands of the fetus are sufficient to precipitate folate deficiency even in the woman who does not have malaria.

With regard to your data on red cell folate, how do you explain the increased values found in both pregnant and nonpregnant women? If the red cell folate values were raised only in
the pregnant women, I could have said that in the pregnant state red cell folate may be useful for transfer to the developing fetus. Since the same phenomenon is reported in nonpregnant women as well I cannot explain it. What were the serum folate values?

There is clearly a different mechanism for malaria-associated folate deficiency in children and pregnant women. In Abdalla’s study in The Gambia, which you cited, neither folate deficiency nor iron deficiency was reported in the children. Of the Nigerian studies, one was carried out in the north and one in the south. There are different climatic conditions and malaria prevalences in the two regions. The south is a rain forest area where malaria is endemic and transmission stable; the north is mostly savannah where malaria transmission is unstable. Folate deficiency reported from the north may be related to the unstable nature of the malaria, whereas in the south folate deficiency has not been reported in malaria-infected children. Except in very severely malnourished children we do not usually see folate deficiency.

**Dr. Brabin:** With regard to the first point, I would suggest that malaria infection in pregnancy enhances the risk of folate deficiency already present. I am not suggesting that the megaloblastosis only relates to the malaria. Clearly these women can be at risk of folate deficiency for dietary reasons as well as because of increased fetal requirements. But the convincing clinical evidence from northern Nigeria, reported by Fleming, indicates that malaria increases the risk of megaloblastic anemia during pregnancy.

In relation to red cell and serum folate values, we showed in western Kenya that serum folate levels were low while red cell levels were high. Examination of the neutrophils showed no evidence of increased hypersegmentation to suggest megaloblastosis. Our studies in pregnant women in western Kenya were done in the early 1980s, and at that time we felt that the high red cell folate values were incompatible with the view that these pregnant women, who were living under malaria endemic conditions, were at risk of developing megaloblastic anemia. Since then all the evidence from other investigators, working with populations who should be folate-deficient, has confirmed this phenomenon. I have to say that it is an enigma at the moment how subjects who are probably folate-deficient can have high red cell folate concentrations. In the pregnant women we studied in Kenya, the red cell folate values fell in those receiving malaria chemoprophylaxis—more evidence for a link with malaria.

I agree we have to be very careful about comparing findings in different malarial regions. We do not know when the children studied by Abdalla acquired their infection. When they were admitted to the Unit in The Gambia they may only recently have become infected, perhaps at the end of the dry season, and would have experienced only a short duration of parasitemia. They would therefore not be at risk of megaloblastosis at this stage. On the other hand, the cases studied by Fleming had experienced chronic parasitemia during pregnancy.

One of the intriguing findings in severe malnutrition in relation to malaria is that children with kwashiorkor rarely develop malaria and there has never been a case of cerebral malaria described in association with kwashiorkor.

**Dr. Cooper:** I don’t understand the red cell folate data. The folate in erythrocytes is the pentaglutamyl form of 5-methyl tetrahydrofolate, which is retained in the cell because it binds in the DPG pocket of reduced hemoglobin. Without such binding it would leak out of the erythrocytes. No folate is incorporated into mature erythrocytes, and very little is taken into reticulocytes. The folate in erythrocytes therefore reflects the folate incorporated from the plasma into the maturing erythroid cells in the bone marrow. These cells incorporate folate to 50 or more times the concentration in the plasma. When we tried to increase erythrocyte folate, it required 100 mg of folic acid per day to achieve an erythrocyte folate concentration.
of 10 µmol/l. When bone marrow erythroblasts mature they may lose 20% or so of their folate. The folate content of reticulocytes is only higher than that of mature erythrocytes after treatment of cobalamin deficiency, in which the deficiency of cobalamin blocks the storage of intracellular folate.

Your data show subjects with plasma folate values of about 8 nM developing very high erythrocyte folate concentrations. From where did the erythrocytes obtain the folate? If the malaria parasites modified the folate in the erythrocytes to produce excessive values in the assay, the same paradox of low serum–high erythrocyte folate should not have been seen in the control group which was not infected with malaria. I find the data mysterious.

Dr. Brabin: I cannot explain it. However, the phenomenon has been shown in three separate studies in different areas by different investigators, so it appears to be genuine.

Dr. Viteri: Have you looked at folate levels in other tissues and are they similarly high? The reason for my question is that the polyglutamates in red cells are not the same as in other tissues. Have you looked at autopsy material in the malarial population?

Dr. Brabin: This is an important point. Autopsy material is difficult to acquire and we have no data as yet, but this is something that should be investigated.

Dr. Adelekan: In view of the persistence of the doubt about whether to give iron to individuals with certain infections, is it wise to treat malarial children with iron as well as with folate and antimalarial drugs?

Dr. Brabin: I take the same view as that expressed earlier: There are very few indications not to give iron to children who have an iron-deficiency anemia. What often happens is that iron is given to older children, once the anemia has become severe, while the process of developing iron deficiency actually began much earlier. We need to give iron at the earliest appropriate time to children living under these conditions. MacGregor’s 30-year experience in The Gambia of giving iron to children showed no apparent increased risk of recrudescence of malaria.

Dr. Azubuike: We carried out a study in Enugu on anemic children who received a trial of iron therapy for 76 weeks. They responded very well. In spite of the malaria which is endemic in southern Nigeria, we do use iron in malaria-infected children.

Dr. Hallberg: Is it not true that malaria parasites are more prone to invade young red cells such as the reticulocytes? If this is the case, iron therapy will be a confounder because when you give iron you increase the numbers of reticulocytes and thus the probability of being infected.

Dr. Brabin: You are correct. It has been shown that immature red cells are more susceptible to invasion by P. falciparum and you would expect on that basis that if there was a marked erythrocytosis there could be a recrudescence of parasitemia.

Dr. Siimes: I don’t understand why children with malaria have iron deficiency. What is the connection?

Dr. Brabin: First there is the general epidemiological point (which does not answer your question) that wherever you find malaria you also find iron deficiency. On the theoretical level we know that malaria pigment, hemazoin, contains substantial amounts of iron and it is probable that this pigment is unavailable to the body stores, remaining deposited in the liver, bone marrow, and cells for long periods of time. It is in theory possible that where significant amounts of this pigment are formed the iron supply may be reduced in subjects on marginal diets. Haptoglobin concentrations may also influence the risk of developing a reduced supply of iron. With hemolysis, haptoglobin levels will be low and the formation of hemoglobin complexes will be reduced, so the iron in those complexes will not be available.
to the parasites. Hemoglobinuria also occurs with malaria, and that is another source of iron loss.

Dr. Hershko: The proceedings of this symposium will have an important impact on what people are going to do in the coming years. I think it is important that there should be some statement reflecting the view of the majority on the issue of treating iron deficiency anemia in tropical countries. We keep mentioning kwashiorkor, and now we have begun speculating about reticulocytosis. However, the basic fact is that there is no good randomized study which shows that oral iron supplementation or the prevention of iron deficiency anemia involves a significant risk of aggravating malaria or any other infection. This is a topic of controversy and will continue to be so, and I am afraid that this book will be quoted to support whatever preconceived ideas people have. However, I do have the feeling that a large number of people are suffering from iron deficiency who may not get treated because of some minor issues which do not reflect the views of the majority of this forum.

Dr. Fomon: Perhaps Drs. Brabin, Adelekan, and Viteri would comment on this statement. It is important to see whether there is general agreement on this point.

Dr. Adelekan: I would agree that the overwhelming evidence is that the administration of oral iron has no effect on infection, though the use of parenteral iron to treat iron deficiency should be discouraged.

Dr. Brabin: I agree with these comments of Dr. Adelekan.

Dr. Viteri: I agree too.