Summary

The clinical features of thrush napkin rashes are described; yeasts were isolated from 42 out of 47 cases so diagnosed in one year.

The condition is common. Of the babies born in an obstetric hospital, 3% were known to have been affected by the age of 6 months. Thrush infection should always be considered in the differential diagnosis of napkin rashes.

Treatment is described and some aetiological factors are considered.

It is emphasized that oral thrush was present in less than one-third of the cases.

There was a significantly increased incidence of vaginal thrush in the mothers of babies with thrush napkin rashes.

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SICKLING AND MALARIA IN THE GOLD COAST*

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In 1946 Beut suggested that the sickle-cell trait might protect the bearer from the effects of malaria in hyperendemic malarial areas, thus accounting for the high incidence of the trait in certain parts of Africa. Allison (1954) and Raper (1955), in East Africa, reported statistically significant differences in the incidence of malarial parasites in sicklers and non-sicklers. Moore *et al.* (1954), in East Africa, and Archibald and Bruce-Chwatt (1955), in Nigeria, could not confirm this difference.

The present paper records the results of sickling tests carried out during routine malaria surveys in the Gold Coast during 1954-5, and is a continuation of investigations already reported which suggested that sickling protected the bearer from malarial infestation (Edington, 1954; Colbourne and Edington, 1954b) but in which, owing probably to the small number of individuals examined, the accepted level of statistical significance was not reached. Two groups have been studied—Frafra in the Northern Territories of the Gold Coast, and inhabitants of Accra (mainly Ga) situated in the extreme south. The results have been conflicting and may explain the lack of uniformity noted by the authors quoted above.

The present investigation leaves a number of questions unanswered, but it is felt that the findings should be published, as they raise a number of interesting points.

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Method of Investigation.—We investigated 680 Frafra inhabiting the small village of Yorugu, in the Northern Territories of the Gold Coast, and 1,015 inhabitants of Accra, a large town situated in the extreme south of the country. In Accra the examinations were carried out in homes, schools, day-nurseries, workshops, and infant welfare clinics attended by healthy children. No hospital patients were examined. In addition, 52 infants from the suburbs of Accra were observed from birth to the age of 6 months and the effect of malarial suppression on 68 schoolchildren was assessed.

Technical Procedures

The rapid metabisulphite method was used to detect the presence of the sickle-cell trait. Malarial parasites were detected by staining thick blood films with Giemsa stain diluted to 4% in water buffered to pH 7.2. When necessary, species determination was confirmed by examination of a thin blood film. Parasite densities were calculated in thick films, assuming the leucocyte count to be 8,000 per c.mm., a figure probably within the normal limits in the Southern Gold Coast (Colbourne *et al.*, 1950). 400 white cells were counted and the number of parasites seen in these fields was noted. The groups into which the densities were classified (see Table II) are very broad, and it would require more than 100% error in the parasite count for the density to be wrong by more than one group. The sickling tests were performed and the parasite rates and densities estimated by independent observers.

An interesting point arose in the examination of the thick films. A number had a dense blue background in which could be seen the ghosts of many red cells, some containing a reticulin network. When the corresponding thin films were examined numerous target cells, poikilocytes, and polychromatic cells were seen. In the investigation in Accra four such films were seen and examination of the children revealed that they were suffering from sickle-cell anaemia. Two mechanisms were probably involved in the abnormal appearance of the thick films: the increase in target cells, which are more resistant to hypotonic solutions, and an increased number of reticulocytes. It is therefore possible by the examination of thick films in a malaria survey to detect likely cases of sickle-cell anaemia. This appearance in the thick film is not diagnostic, as it has also been noted in children recovering from an acute attack of malaria when a reticulocyte crisis occurs.

Malaria and Sickling in the Newborn

The blood of 52 babies, of whom 13 were found to have the sickle-cell trait, was examined weekly up to the age of 6 months. During the course of the investigation only 40 attended regularly, but 46 were examined at the end of six months. The results of the investigation are shown in Table I.

From this table it will be seen that at the end of six months 6 of the 11 sickling and 22 of the 35 non-sickling infants had suffered from malaria. All infections were by *P. falciparum*, apart from one mixed infection with *P. malariae* and *P. falciparum* in a non-sickler. The parasite densities were greater in the non-sicklers, the average

TABLE I.—Malaria and Sickling in Infants in Accra

Age	Sickling Under Observation		Non-sickling Under Observation	
	No. Under Observation	"Positive"	No. Under Observation	"Positive"
0-1 month	12	—	36	—
2-3 months	12	1	34	3
4-5 months	11	1	34	4
6-7 months	9	2	34	13
8-9 months	9	5	31	18
10-11 months*	11	6 (54%)	35	22 (63%)

*"Positive" means that the infant had a positive blood film at some time during the period under observation.

*Including 6 defaulters traced between fifth and sixth months.

densities at first infection being 1,125 and 150 parasites per c.mm. Too much emphasis should not be placed on these densities, however, in view of the small numbers involved. One non-sickler had a density of well over 50,000 parasites per c.mm. and, although the densities are recorded on a geometric scale, with such small numbers this one heavy infestation weights the figures in favour of the sicklers.

In these 52 infants, one child who became infected with malaria was proved to be suffering from sickle-cell-haemoglobin-C disease. He appeared to be fat and healthy, the spleen was not palpable, and the peripheral blood showed evidence of a very mild haemolysis.

It was confirmed that the percentage of cells sickling was low at birth and increased with age. The majority of the cells assumed the sickle-cell shape at the age of 3 months.

Target cells in excess of 4% were seen in the peripheral blood films of 80% of these babies. The reason for this phenomenon is not understood, and further work requires to be done.

Accra and Yorugu Surveys

The results obtained in Accra are shown in Table II, and those of Yorugu in Table III.

It will be seen that in Accra there was a lower parasite rate in the sicklers at all ages, while in Yorugu there was a difference only in the infants, and this may have been due to the small number surveyed.

Amalgamation of the groups appears to give a more pronounced protective effect in childhood, decreasing with advancing years, but this is probably due to the difference

TABLE II.—*Sickling and P. falciparum Infections in Accra*

Age Group	Total	Sickling Positive				Sickling Negative			
		No.	P.f. +	Rate	Density	No.	P.f. +	Rate	Density
Under 1 year ..	106	20	6	30%	1.7	86	31	36%	2.8
1-4 years ..	265	43	9	21%	1.6	222	52	23%	2.6
5-10 " ..	302	48	19	40%	2.2	254	127	50%	2.7
11+ " ..	342	62	8	13%	1.1	280	60	21%	1.5
Total ..	1,015	173	42	24.3%	1.8	842	270	36.4%	2.4

$$\chi^2 = 4.76.$$

The density of parasites per c.mm. is measured according to the following arbitrary units: 1=1-100; 2=101-500; 3=501-1,000; 4=1,001-2,000; 5=2,001-5,000; 6=5,001-10,000; 7=10,001-20,000; 8=20,001-50,000; 9=over 50,000.

TABLE III.—*Sickling and P. falciparum Infections in Yorugu*

Age Group	Total	Sickling Positive				Sickling Negative			
		No.	P.f. +	Rate	Density	No.	P.f. +	Rate	Density
Under 1 year ..	58	7	3	43%	4.3	51	45	88%	3.8
1-4 years ..	134	8	8	100%	3.5	126	120	96%	3.5
5-10 " ..	135	13	13	100%	2.1	122	116	95%	2.1
11+ " ..	353	38	23	60%	1.3	315	175	56%	1.4
Total	680	66	47	71%	2.8	614	456	74%	2.7

TABLE IV.—*Parasite Densities Over 1,000 per c.mm. in Accra and Yorugu*

Age Group	Accra				Yorugu			
	Sickling Positive		Sickling Negative		Sickling Positive		Sickling Negative	
	P.f. +	Density over 1,000 per c.mm.	P.f. +	Density over 1,000 per c.mm.	P.f. +	Density over 1,000 per c.mm.	P.f. +	Density over 1,000 per c.mm.
Under 1 year	6	0	31	5 (16%)	3	2 (67%)	45	24 (48%)
1-4 yrs.	9	0	52	13 (25%)	8	3 (38%)	120	51 (43%)
5-10 "	19	3 (16%)	127	35 (28%)	13	2 (15%)	116	18 (16%)
11+ "	8	0	60	4 (7%)	23	1 (4%)	175	7 (4%)
Total	42	3 (7%)	270	57 (21%)	47	8 (17%)	456	100 (22%)

χ^2 for difference in rates in Accra = 4.56. $P < 0.05$. χ^2 for difference in rates in Yorugu = 0.61. $P > 0.30$.

in the age composition of the two groups. These two groups from different localities show very different results.

The densities of parasites are shown in Tables II to IV. It will be seen that they follow the pattern of the parasite rate—a significant difference in favour of the sicklers in Accra, and practically no difference in Yorugu.

P. malariae and the Sickle-cell Trait

The infection rate with *P. malariae* in sicklers and non-sicklers under the age of 11 years in Accra and Yorugu is shown in Table V. As with *P. falciparum*, the rate of infection is much higher in Yorugu than in Accra. If both areas are taken together the *P. malariae* infection rate is 14%.

TABLE V.—*P. malariae and Sickling in Children Under 11 Years Old in Accra and Yorugu*

	Sicklers			Non-sicklers			χ^2
	Examined	<i>P. malariae</i> Positive	Rate	Examined	<i>P. malariae</i> Positive	Rate	
Yorugu	28	11	39%	299	126	42%	2.2
Accra	111	9	8%	562	26	5%	
Total	139	20	14%	861	152	18%	0.9 P=0.3

of the 139 sicklers and 18% of the 861 non-sicklers under the age of 11 years. Over the age of 11 *P. malariae* was much less common. The difference is so small that one cannot postulate that the trait gives any protection. In Accra *P. malariae* was actually more common in sicklers. A possible explanation of this difference between the species of parasite is their different behaviour in the host. Developing forms of *P. falciparum* are thought to occur only in the erythrocytes in the internal organs, with no late exoerythrocytic forms in the liver cells. In the case of *P. malariae*, however, in addition to schizogony occurring in the blood, exoerythrocytic schizogony in the liver cells is considered to be a continuous process. This difference would explain the lack of protection afforded by the trait against *P. malariae* infestation when compared with *P. falciparum*, as *P. malariae* can maintain itself in the host's liver cells independently of the red blood cell and consequently independently of the type of haemoglobin therein.

Suppression of Malaria in Schoolchildren

In Accra 68 schoolchildren, of whom 14 sickled, were kept free from malarial parasites for a year by suppressive drugs; during the subsequent year suppressive drugs were withdrawn. Seven of the 14 sicklers (50%) and 19 of the 54 non-sicklers (35%) became infected during this year. The average density of infection in the sicklers was about 1,000 and in the non-sicklers about 500 parasites per c.mm.

A control group of 74 schoolchildren, of whom 15 sickled, were also observed for a year. During this period 10 never suffered from parasitaemia; three of these were sicklers (20% of the group) and seven non-sicklers (12% of the group). Eighteen were absent from school with a sickness which on clinical and parasitological grounds was diagnosed as malaria. Five were sicklers (33% of the group) and 13 non-sicklers (22% of the group).

These results suggest that, in this age group, although it has been shown that sickling partially protects against malarial parasitaemia, it has little protective action against the milder clinical effects of the disease. In this age group, however, malaria is not a cause of mortality, and the important age group in Accra, 6 months to 5 years, remains to be investigated.

The findings would accord with the theory of one of us (G. M. E.) that malaria is a potent factor in initiating the crises of the abnormal haemoglobin diseases seen in the Gold Coast.

Discussion

This attempt to confirm or refute the protective action of sickling against *P. falciparum* malaria in the Gold Coast

has led to the unexpected result that there appears to be a protective influence in the south but not in the north.

A striking difference between the areas is the intensity of malarial transmission (Colbourne and Wright, 1955a, 1955b). In the parts of Accra from which these figures were collected the number of infected mosquito bites per person per year varies from about one-half to three, and the parasite rate does not rise above 50% at any age in childhood; in Yorugu the transmission is much more intense—about 30 infected bites a year—and the parasite rate approaches 100% in children. The parasite rate quoted by Raper (1955) suggests that the malaria transmission in the area where he was working was similar to Accra. Archibald and Bruce-Chwatt's (1955) figures from Nigeria suggest a higher rate of transmission, similar to that found at Yorugu.

It has been shown that in endemic areas the age at which children die from malaria depends on the intensity of infection (Colbourne and Edington, 1954a). In the less malarious parts of Accra about 5% of children died from malaria before they were 5 years old and the deaths were fairly evenly spread over the first five years of life; in the more malarious suburban areas there were many more deaths from malaria in the first two years of life. Transmission in Yorugu is more intense than in any part of Accra, so that the critical period is probably the first year of life. Our results have shown a difference in favour of the sicklers in this group, but the number of sickling infants is too small for any firm conclusions to be drawn.

Therefore in areas where malaria transmission is intense it will be necessary to examine large numbers of children under the age of 1 year to discover whether sickling has any protective action. In these areas the parasite rate between the ages of 1 and 5 years is of the order of 100% in sicklers and non-sicklers, so that no difference in rates is possible (Table III).

In Accra there appears to be a significant difference in the rates at all ages; this may protect the younger children from death from malaria; it seems to have had little effect on morbidity from malaria in older children.

In Accra also there is a greater density of parasites in the infected non-sicklers; it might be expected that if in Yorugu the intensity of infection had obscured a difference in the rates a difference of density would have been apparent. This is not so, and we must conclude that these results give little support to a protective action at Yorugu unless immunity is acquired so rapidly in the first year of life that no differences in parasite densities can be found over the age of 1 year.

Apart from the differences in the intensity of malaria transmission in these two areas, however, there may also be a marked difference in the incidence of haemoglobin C. In Accra, the incidence of haemoglobin S is in the region of 18% and of C 12%. In the Moshie, ethnologically related to the Frafras, the incidence of S is 5% and of C 21% (Edington and Lehmann, 1956, unpublished data). It is therefore possible that haemoglobin C interferes with the results obtained in Yorugu; but as the parasite rate in the 1–10 years group approaches 100% it cannot affect the rate in this age group.

Although it would appear that in Accra the trait partially protects against the parasite of *P. falciparum* malaria there is little information available on the amount of protection which the trait would require to give or to the number of deaths from malaria which would be necessary in the non-sicklers to maintain a high incidence of the S gene in a given population. Neel (1955) has calculated that, in a community in which the incidence of this gene is 40%, 16% of the total population, all without the sickle-cell trait, would have to die from malaria to maintain a constant incidence of the gene in the population, if all S homozygotes die before reaching adult life. The comparable mortality rate from malaria in Accra in non-sicklers would have to be approximately 11%. In Accra, where the incidence of

sickling is in the region of 18% and of haemoglobin C 12%, the S gene is eliminated from the population not only by the loss of S homozygotes but also by the mortality caused by sickle-cell-haemoglobin-C disease, a not uncommon cause of death in pregnancy (Edington, 1955, unpublished observations).

It has been calculated that in this district approximately 5% of children under the age of 5 years die from malaria. deaths in the older age groups being negligible (Colbourne and Edington, 1954a); this figure is much lower than the calculated mortality required to maintain a high incidence of the trait in the population if all the S homozygotes die before the age of procreation. It is most probable that very few S homozygotes survive to adult life (J. and C. Lambotte-Legrand, 1951; Vandepitte, 1955). Edington and Lehmann (1955a) described from the Gold Coast the cases of two relatively healthy male adults whose haemoglobins on electrophoretic analyses and solubility studies were indistinguishable from the haemoglobin described in sickle-cell anaemia. Family studies have, however, since shown that these patients were not SS homozygotes but had inherited a combination of the sickle-cell and a thalassaemia-like trait (Edington and Lehmann, 1955b). Vandepitte *et al.* (1955) have shown that mutation, although the rate may be relatively high, does not alone explain the high incidence of the sickle-cell gene (25%) in Leopoldville. It may, however, be a contributory factor. It must therefore be presumed that the protection afforded the sickler against *P. falciparum* malaria in Africa cannot be the only mechanism responsible for the high incidence of this gene in many populations unless the mortality from malaria in non-sicklers is very much higher than the literature would lead one to suppose.

Summary

Malarial parasite rates and densities of 1,015 inhabitants of Accra and 680 Frafras living in a village in the Northern Territories of the Gold Coast have been determined and correlated with the presence or absence of the sickle-cell trait in the blood.

In Accra the sickle-cell trait appeared partially to protect the bearer against *P. falciparum* infection in all age groups, whereas no protection over the age of 1 year was noted in sicklers in the North.

The possibility of variations in the intensity of malaria transmission and the incidence of haemoglobin C being responsible for these findings is discussed.

The sickle-cell trait was not found to give protection against *P. malariae* infection in either district.

A group of Accra schoolchildren was also observed, and it was found that malaria was responsible for morbidity in both sicklers and non-sicklers. The possibility of malarial infection thus initiating crises in the sickling group of abnormal haemoglobin diseases is pointed out.

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