to the bites of infected mosquitoes under these conditions has recently been discussed by Macdonald (1950), who points out that the only reasonable explanation of the discrepancy between observed and calculated figures is that the number of infective bites to which the infants are exposed must be less than that estimated.

In the great malaria epidemic of Ceylon in 1934–5 one of the most difficult features to explain was the explosive nature of the outbreak. During the early stages of the epidemic, outbreaks of sickness were mainly confined to adults, there being a remarkable absence of mortality among infants during the first four weeks at least. Gill (1938) has pointed out that if we attribute this outbreak to new infections rather than to a wave of relapses, it would be necessary to assume that at the beginning of the epidemic the main biting activities of *A. culicifacies* were directed towards adults. In the light of the observations described above this explanation now seems much more feasible.

Before these speculations about conditions in other countries carry us into deep water it will obviously be necessary to repeat these observations on their particular vector *Anopheles*. The possibility that this biting factor may also enter into problems of other insect-borne diseases can hardly be overlooked. Culicine mosquitoes appear to bite infants rather more readily than anophelines do, but no systematic observations have yet been done on them, and there should be many interesting possibilities in following up this line of inquiry.

Summary

Observations on the biting habits of *A. albimanus* on family groups in Jamaica have shown that babies are bitten much less frequently than older children or adults. Similar behaviour has been seen in *A. aquasalis* and *A. bellator* in Trinidad. This uneven distribution of bites and feeds has been discussed in relation to general problems of malaria transmission and epidemiology.

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Research on "agenized" flour is carried a step further by a note from a Nottingham group of research workers (*Nature*, May 12, p. 773) which describes how they were at first unable to produce convulsions in rabbits and traced this to the presence in the animal's diet of greenstuff, which seemed to protect against convulsive doses of the toxic substance. It will be recalled that flour is improved in keeping and baking quality by treatment with "agene" (nitrogen trichloride), and some time ago it was shown that flour treated in this way and fed to dogs and rabbits gave them fits. Medical Research Council workers were unable to produce any abnormal symptoms or signs in human beings given large amounts of the treated flour. The toxic substance was identified by chemists as a derivative of methionine, an amino-acid occurring naturally in the protein of the flour, and as little as 2 mg. would cause convulsions in a normal rabbit. A rabbit getting 150 g. of fresh greens a day, however, would be protected, or almost completely so. The reason for this is so far unknown. The toxic substance has been studied in the laboratory for its inhibitory effect on the growth of the bacterium *Leuconostoc mesenteroides*, an effect abolished by glutamine. Fresh greenstuff is often rich in glutamine, and it may be this which protects the rabbit.

BLACKWATER FEVER IN AFRICAN CHILDREN

BY

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The rarity of blackwater fever among indigenous African adults is well recognized (Fairley, 1946; Joyeux and Sicé, 1950; etc.). Sporadic cases do, however, occur, and larger numbers have been reported under special circumstances, as, for example, when adult Africans have migrated from non-malarial hill country to an endemic malarial area. This has been recorded in the Cameroons (Strong, 1944). Again, blackwater fever cases have been observed among groups of Africans who have been using either antimalarial suppressive drugs or mosquito-nets. Thus, Findlay (1949) noted a definite increase in cases among West African soldiers, who were taking no quinine, but who were being partially protected by mosquito-nets and mosquito control.

In addition, there would seem to be some unexplained geographical factor to be considered. Gelfand (1944) records that he has never seen a case of blackwater fever in an African, presumably referring to experience in S.E. Africa, and more particularly Southern Rhodesia. Shelley (1931), in a review of cases seen in Nyasaland between 1921 and 1930, makes no reference to the disease having occurred in Africans during this period. In contrast to this, cases occurring sporadically are noted occasionally in West African adults.

In normal circumstances blackwater fever is extremely unusual amongst indigenous African children, despite the fact that, during childhood and more especially infancy, severe attacks of subtertian malaria occur frequently, at least in Nigeria. However, as is mentioned by several authorities (Manson-Bahr, 1945; Maegraith, 1948), if the development of malarial immunity ("premunition") is interfered with—as, for example, by the repeated inadequate quinine treatment of malaria in childhood—blackwater fever can occur. Thus, Chesterman (1935) observed a case of blackwater fever in an African child aged 2½ years. There was a past history of occasional dosage with quinine for attacks of fever. The blood film showed *Plasmodium falciparum*. The illness was precipitated by the taking of quinine, and consisted of a single mild bout of haemoglobinuria, lasting only a day. Mackey (1928) recorded a case in Nigeria. This occurred in an Ibo child aged 2½ years. Again there was the same background of occasional treatment with quinine over a number of years. The blood film showed *P. falciparum* to be present. In this case a severe bout of haemolysis, with typical urine changes, was followed by increasing jaundice, unconsciousness, and death.

In contrast to these two reports, Jackson (1935) has described a case in an infant of 16 months in the Plateau Province of Northern Nigeria. The blood film showed *P. falciparum*. The onset of the illness was associated with the taking of quinine, but there was no definite history of previous quinine therapy.

Case 1

A Yoruba boy aged about 2 years was admitted to hospital at 6 p.m. on February 8, 1949. His mother, an ex-nurse of a fairly low standard of training, gave the following history. The child had always been delicate and had had fever frequently, sometimes as often as monthly. This had always been treated by the mother with a tablespoonful of quinine mixture, given for one or two doses on each occasion. About a week before admission a further attack of fever occurred, for which the mother gave a tablespoonful of quinine mixture. After this the child seemed improved until the actual day of admission, when the pyrexia recurred, together with a shivering attack, general malaise, and vomiting. A further tablespoonful of quinine mixture was given at about 10 a.m. At 4 p.m. the mother noticed that the child had passed about 8 oz. (230 ml.) of dark reddish-black urine.

On examination the child was obviously ill, with a temperature of 101° F. (38.3° C.) and a pulse of 104. The liver was enlarged one fingerbreadth, and the spleen was just palpable. Laboratory investigations:—(1) Urine: dark blackish-brown in colour, similar in appearance to strong Turkish coffee, and faintly acid; chemical tests for blood strongly positive; albumin +++; microscopical examination showed granular casts and debris ++; no red blood corpuscles seen. (2) Blood film: scanty ring forms of *P. falciparum* were present.

Treatment was begun with phenobarbitone, ¼ gr. (16 mg.) twice daily for three days, and proguanil, 100 mg. twice daily for 10 days. Haemolysis continued for just over 36 hours, the urine changing gradually from a Madeira-wine colour to a dark yellow. The child developed bronchopneumonia on the fourth day after admission; this responded rapidly to a seven-day course of procaine penicillin (1 ml. intramuscularly daily). On discharge on February 20 the patient seemed to have made a complete recovery, although the haemoglobin was only 75%. An oral iron mixture was prescribed and the mother was advised to keep the infant on permanent proguanil prophylaxis.

Case 2

A Yoruba boy aged about 2½ years was admitted to hospital on December 19, 1949. His mother, the wife of a schoolmaster, gave the following history. For the previous 15 days the child had been ill with fever and a slight cough. Treatment with various non-specific remedies had been tried by the parents. On the day before admission the child had been given two tablespoonfuls of quinine mixture on two occasions. (The patient, who had had frequent attacks of "fever" in earlier infancy, had often been treated with short courses of quinine for a day or two.) At 9 a.m. on the day of admission the mother noticed that the child was passing urine "like blood."

On examination the child did not seem to be seriously ill. There was a slight anaemia. The liver and spleen were not palpable. The temperature was 100.6° F. (38.1° C.) and the pulse 120. Laboratory examinations:—(1) Urine: reddish-brown in colour, similar in appearance to angostura bitters; chemical tests for blood strongly positive; albumin +++; microscopical examination showed deposit of mainly unidentifiable debris; no red blood corpuscles observed. (2) Blood film: very occasional ring forms of *P. falciparum* seen. (3) Haemoglobin 60%.

Haemolysis stopped after about 24 hours, and the urine cleared rapidly. Treatment with phenobarbitone, ⅛ gr. (8 mg.) four times daily for three days, and mepacrine, 0.05 g. twice daily for seven days, was started on admission. The temperature returned to normal after two days. Convalescence was uninterrupted. Treatment with oral iron was given for the anaemia. The mother was advised to begin permanent proguanil prophylaxis.

Case 3

A 6-year-old Yoruba boy was admitted to hospital on April 3, 1950. He gave a history of having had fever for three days. There was no history of his having taken native medicine or having been bitten by a snake. On the morning of the day of admission he had noticed that his urine was dark. He gave a history of having had a similar type of illness some two years before.

Examination showed an anaemic child with a temperature of 104° F. (40° C.) and a pulse of 114. The liver was enlarged two fingerbreadths and the spleen three fingerbreadths. Laboratory investigation:—(1) Urine: port-wine colour; slightly alkaline; chemical tests for blood strongly positive; albumin +++; microscopical examination showed cellular debris in abundance; no red blood cells; granular casts ++. (2) Blood films (on three occasions): no malarial parasites present. (3) Haemoglobin, on April 4, 55%. (4) Examination for sickling showed no evidence of this after 24 hours.

Treatment was begun with mepacrine, 0.1 g. twice daily, and oral iron. Haemoglobinuria continued for about two days, the urine clearing rapidly after this. The boy was discharged on April 13.

Case 4

A 5-year-old Yoruba boy was admitted to hospital on April 27, 1950. The father, a clerk, gave the following history. The patient had had numerous attacks of fever during earlier childhood; these had often been treated with short courses of quinine. The present illness began four days before admission with a further bout of fever, for which the father gave a dose of about 1 oz. (28 ml.) of quinine mixture. In the evening of the day before admission the child had been passing dark-coloured urine, which had continued up to the time of admission. He had vomited once.

On examination the patient showed a definite icterus and anaemia. The liver was not palpable. The spleen could just be felt. The temperature was 99.8° F. (37.7° C.) and the pulse 110. Laboratory investigations:—(1) Urine: dark brownish black in colour; chemical tests for blood strongly positive; albumin +++; microscopical examination showed no red blood cells; granular casts +; unidentifiable debris +. (2) Blood film: scanty rings of *P. falciparum*. (3) Haemoglobin 60%.

Treatment was started with proguanil, 100 mg. thrice daily for seven days, and phenobarbitone, ¼ gr. (16 mg.) thrice daily for five days.

Haemoglobinuria continued on the morning of April 28. The child had become delirious, and was obviously severely anaemic and markedly icteric. The pulse was 130. A blood transfusion was refused by the parents. At 6 p.m. the haemoglobinuria had stopped, but the child had become comatose, with a feeble thready pulse (about 150 a minute). He died in the early hours of April 29.

Discussion

It will be noticed that in three of these cases there was a definite history of occasional dosage with quinine during earlier childhood, the actual haemolytic crises following the last doses of quinine. The parents were all of an educated type—that is, ex-nurse, schoolteacher, clerk. The incidence of blackwater fever in Europeans in Nigeria has dramatically fallen in the last few decades. This is indicated by the fact that in 1948 only two cases were recorded, both of which recovered (Nigeria, 1950). In addition, it must be remembered that this fall has occurred despite a very great increase in the European population. The most probable main explanation of this decline is that regular prophylaxis

with antimalarial drugs is now carried out almost automatically by most of the European population.

In contrast to this it seems not unlikely that blackwater fever may in the near future occur with increasing frequency amongst the educated African population, especially the children. Antimalarial drugs are increasingly easy to obtain, and skilful advertising in the cinema, press, and shops will certainly make new African converts to malaria chemotherapy. The danger lies in the likelihood that in many cases chemoprophylaxis will not be continuous—either because the desirability of this may not have been appreciated or for financial reasons. If this is so, the African child in a hyperendemic zone will neither be adequately protected from malaria nor be able to build up immunity to it. A similar situation may be produced by the repeated casual treatment of all fevers in African infants with inadequate doses of antimalarial drugs. This may be overstating the case, as the most likely offender —quinine—is being to a certain extent ousted by the synthetic antimalarials mepacrine and proguanil. However, quinine is still sold very widely, and blackwater fever has been described after mepacrine. Blackwater fever after proguanil does not seem to have been recorded. It must be mentioned, however, that proguanil has been in use for only a few years, and then during the period when the importance of the regularity of prophylactic dosage has been very widely accepted and put into practice.

In the paediatric out-patient department in Ibadan only intelligent educated mothers who can afford it are advised to give their children malarial chemoprophylaxis in the form of proguanil. In addition, it is stressed to them that this must be an uninterrupted process and, indeed, should continue throughout life, as otherwise there is a definite danger that the pernicious manifestations of subtertian malaria—that is, cerebral malaria, etc.—may occur in adult life. It is realized that not all authorities would agree with this advice, as they feel that the "normal" process of repeated infection with subtertian malaria that occurs in almost all African children in a hyperendemic zone is inevitable and not such a serious matter as is usually suggested. This has been stressed by the work of Garnham (1949) in the Luo tribe of Kenya and by Swellengrebel (1950) in the African population (Cimarons) of a village in the interior of Surinam. Both authors note that, despite an almost universal infection with *P. falciparum* during infancy and childhood, only a very small mortality, or even morbidity, is attributable to malaria in these areas. It seems unlikely, though admittedly statistically unproved, that similar conditions pertain in Nigeria, where severe and often fatal pernicious attacks of subtertian malaria are seen comparatively frequently in young children and appear to represent the price paid for the development of malarial immunity in the surviving majority.

Summary

The rarity of blackwater fever in Africans, especially in childhood, is discussed. Four cases occurring in Nigerian children are recorded.

The fall in incidence of blackwater fever in the European population of Nigeria is noted.

The possibility of an increase in the number of cases of blackwater fever in the children of educated Africans, following the wider casual use of antimalarial drugs in the home, is considered.

In view of this danger it is advised that only intelligent educated mothers should be advised to give their children chemoprophylaxis—in the form of proguanil. The desirability of continuing this into adult life is mentioned.

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LABORATORY DIAGNOSIS OF URINARY-TRACT INFECTIONS

WITH SPECIAL REFERENCE TO LACTOSE-FERMENTING COLIFORM STRAINS

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The common infecting agents in disease of the urinary tract are organisms of the coliform group. This is a group of immense complexity, and a prolonged bacteriological analysis is necessary before any one member can be accurately described. It is therefore common routine practice to disregard these minor differences and describe them by some all-embracing term such as *Bact. coli* (Ainsworth-Davies, 1950) or simply as "coliform bacilli." It is the purpose of this paper to show that the subdivision of the group into true *Bact. coli* and *Bact. aerogenes* species, and a group containing all other lactose-fermenting Gram-negative bacteria to be called "atypical strains of the coliform group," may be of practical importance. A simple means of achieving this is described, utilizing only information obtainable in 24 hours. The results obtained by this method have been compared with those from one of the standard longer techniques. The data have also been analysed to see if they show any correlation between the nature of the infecting strains and the pathology of the lesions.

The incidence of a variable proportion of *Bact. aerogenes* strains in these infections has many times been reported, and recently attention has also been drawn to the sulphonamide insensitivity and penicillin sensitivity of large numbers of coliform organisms. The fact that nearly all are sensitive to streptomycin and to some of the newer antibiotics (Frank *et al.*, 1950) in no