

Enteric fever in young Yoruba children

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Duggan, M. B., and Beyer, L. (1975). *Archives of Disease in Childhood*, 50, 67. **Enteric fever in young Yoruba children.** Ninety-seven Nigerian children under 5 years of age had typhoid or paratyphoid fever proved by blood culture. They presented with fever, anaemia, gastrointestinal or neurological disturbances, and typhoid and paratyphoid appeared clinically indistinguishable. In this holoendemic malarial area, malaria was the most important differential diagnosis, and may have contributed to the concomitant anaemia seen in the majority of patients. Despite vigorous therapy with chloramphenicol or trimethoxazole, and blood transfusion where indicated, the mortality in both typhoid and paratyphoid was high (18% in both groups).

In Western State of Nigeria typhoid and paratyphoid are endemic and falciparum malaria is holoendemic, so that a presumptive diagnosis of malaria is likely to be made in any ill, febrile child. This may lead to delay in making a definitive diagnosis of enteric fever, and if investigations are not immediately instituted death may be incorrectly attributed to malaria. Despite the acknowledged difficulties in diagnosing enteric fever in very young children, there are some guide lines which may be followed. This paper represents 20 months' experience during which 91 children were personally studied, 57 with typhoid and 34 with paratyphoid.

Methods

Inclusion in the series was based on positive blood culture, this having been found by other workers (Wicks, Homes, and Davidson, 1971) to be the most satisfactory method of diagnosis. The one exception was a neonate with a positive stool culture.

Blood culture was by standard method, blood being subcultured after 24 hours onto MacConkey agar, and the nonlactose fermenting organisms identified by slide agglutination with commercial antisera to salmonella O and H and paratyphi BO and CO antigens, positive agglutination being taken as confirmatory.

Other routine investigations were as follows. Haemoglobin was estimated by the oxyhaemoglobin method using a photoelectric colorimeter, and sickling test was estimated by the disodium hydrogen phosphate and sodium dithionite method. Sickling was checked on all patients older than 6 months, and haemoglobin electrophoresis was done on all sickle-positive patients.

A Field stained thick blood film was examined for malaria parasites in every case, and density of infection estimated from the frequency of parasites per high power field.

Clinical investigations

Patients. All the patients were admitted from the under fives clinic where they had originally been seen by a nurse and referred to one of us. The patients included 87 Yorubas, 3 Urhobos, and one Ibo, and came largely from the town of Ilesha (56 patients) or the surrounding villages. The catchment area of Wesley Guild Hospital, which is a long established mission hospital, includes Ilesha and the surrounding countryside, making up a population of roughly 200 000. The people are mostly farmers, moving from town to farm at seasonal intervals, so that the terms 'urban' and 'rural' used here relate more to distance from hospital than to life pattern. Sex distribution was unremarkable; of the 57 typhoid patients, 29 were male and 28 female, while there were 22 female and 12 male patients in the paratyphoid group.

Seasonal incidence. Fig. 1 illustrates the seasonal incidence of typhoid and paratyphoid during one calendar year, including 36 typhoid patients and 17 paratyphoid patients, and shows a slight increase in incidence during the rainy season from May to October.

Age distribution. Fig. 2 illustrates age incidence for the typhoid and paratyphoid groups separately, and shows that while both groups contain a high proportion of very young children, over half of each group being younger than 2 years, the pattern of incidence is still somewhat different, since 18% of the paratyphoid patients were neonates compared with 4% of typhoid patients.

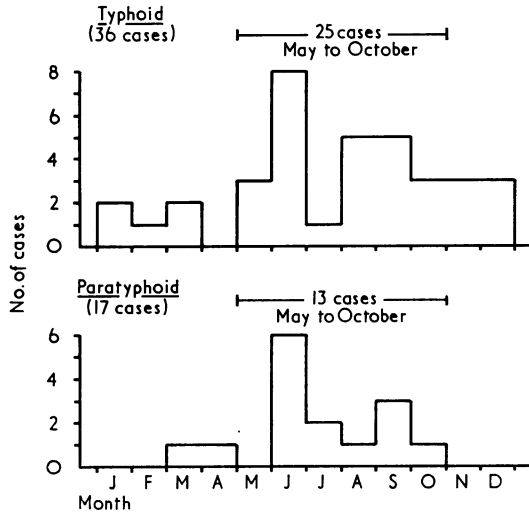


FIG. 1.—Monthly distribution of cases of typhoid and paratyphoid during the year May 1968–May 1969.

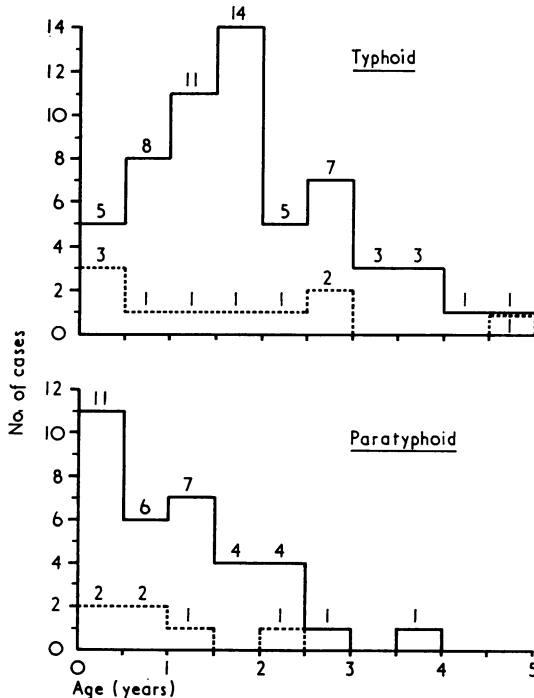


FIG. 2.—Age distribution of total number of fatal cases of typhoid and paratyphoid.

Clinical features. Typhoid and paratyphoid are discussed together, noting any differences in clinical pattern between them. The paratyphoid patients comprised 23 paratyphoid B and 7 paratyphoid C, the groups stated by Huckstep (1962) as most likely to cause generalized illness. The typing was uncertain in 4. No attempt has been made to separate the groups.

Fever. This was almost universal, the afebrile patients being neonates (discussed below) except for 2 afebrile children with kwashiorkor. Sudden onset of fever was often reported by the mothers, and 6 patients (5 typhoid, 1 paratyphoid) presented with hyperpyrexia. 6 patients who were initially afebrile and severely anaemic became febrile after transfusion and were found to have positive blood cultures. Defervescence of fever before the start of specific treatment was noted in 3 children with paratyphoid.

Haematological aspects. Anaemia was commonly seen, 52 of the patients (57%) having a haemoglobin level of less than 7.4 g/dl, and 28 patients (31%) required transfusion. The transfused patients, who were all gravely ill with a haemoglobin level of less than 4.4 g/dl, included 17 typhoid and 11 paratyphoid patients. Clinically the severely anaemic children were indistinguishable from patients with acute malarial haemolytic anaemia, being shocked, afebrile, with tachycardia and acidotic respiration. The development of fever after transfusion was a useful diagnostic pointer to the enteric fever, and prompted immediate start of specific treatment.

Possible causes of anaemia. (i) Blood loss from bowel was noted macroscopically in one typhoid patient who subsequently died. (ii) Definite malarial parasitaemia (more than three *Plasmodium falciparum* parasites per high power field) was present in only 10 patients, but malaria could not be excluded in the remainder since empirical outpatient treatment with chloroquine was routine for febrile patients. (iii) Sickle cell disease is known to be associated with salmonella infection (Lewis, 1970), and it was our practice to treat sicklers with suspicious fevers empirically with chloramphenicol without subjecting them to blood culture. They were therefore ineligible for inclusion in this series. 72 children over the age of 6 months were sickle tested, and sickle-positive bloods were subjected to haemoglobin electrophoresis. There was one patient with HbSS, one with HbSC, and 5 with genotype AS. The remainder were sickle-negative. It is thus unlikely that sickle cell disease played any part in the aetiology of the anaemia seen. (iv) Haemolysis, as evidenced by clinical jaundice was present in 8 patients, and a further 2 had frank haemoglobinuria, one before, and one after transfusion. The latter patient died with anuric renal failure. It is unfortunate that facilities did not exist to estimate G6PD function since this may well have some bearing on typhoid anaemia (Edington and Gilles, 1969). In short, no obvious causes for the anaemia could be found and though there are no 'normal' controls with whom to

compare these children, it seems clear that the prevalence of anaemia is very high in these patients. The endemicity of malaria and hookworm makes data on 'normal' children difficult to obtain.

Leucopenia. The white blood cell count was not found to be of any diagnostic help, and in the 21 patients in whom it was estimated, only 3 had a total WBC of less than 5 000/mm³. The range of WBC was 18 500 to 3 500.

Gastrointestinal presentation. Diarrhoea was a presenting feature in 34 patients (37%). It was more common in the typhoid group, occurring in 24 out of 57 patients, but was not associated with age, nutritional state, coincidental malarial parasitaemia, or prognosis. Fluid depletion was unusual. In the paratyphoid group diarrhoea was seen mainly in very young babies.

Localizing abdominal findings such as pain, distension, and a tumid abdomen, which can be important diagnostically in older children (Scragg, Rubidge, and Wallace, 1969), were seen only in 8 children over the age of 2 years. A finding of splenomegaly in children in this malarial area was of no help in diagnosis. There were no cases of gut perforation and in the case of one child, not included in the series who might have fitted this category and who died immediately after admission, necropsy showed clearly that there was perforation of an amoebic colitis.

Neurological presentation. 22 patients presented with neurological complications, 13 with convulsions and 9 with meningism. All were subjected to lumbar puncture, CSF being normal in 11, traumatically blood-stained in 4, and abnormal in the remaining 7. Abnormalities ranged from frank meningitis in 2 patients, in whom unfortunately the organism was cultured only from the blood, moderate pleocytosis of CSF in 2, and an increase in CSF protein in 3 others.

The local practice of administration or application of a tobacco and cow's urine mixture to convulsing children complicates their hospital management. Coma, partly due to nicotine intoxication, anoxia after aspiration, and possible hypoglycaemia due to an unidentified toxic agent can aggravate the clinical picture presented by the convulsing child, and in 4 of our patients it was an associated factor. Convulsions were persistent in 4 typhoid and one paratyphoid patient, and the diagnosis of typhoid encephalitis was considered but could not be proved.

Respiratory presentation. 12 children presented with either cough or clinical signs of pneumonia and there were delays in starting specific treatment in 3 cases because of an initial diagnosis of pneumonia.

Bone and joint presentation. 9 children presented with an inflammatory lesion of bone or joint, 6 with typhoid and 3 with paratyphoid. 4 suffered merely a transient swelling of the joint, *Salmonella typhi* was cultured from the knee joint in 2 patients, and *Salmonella*

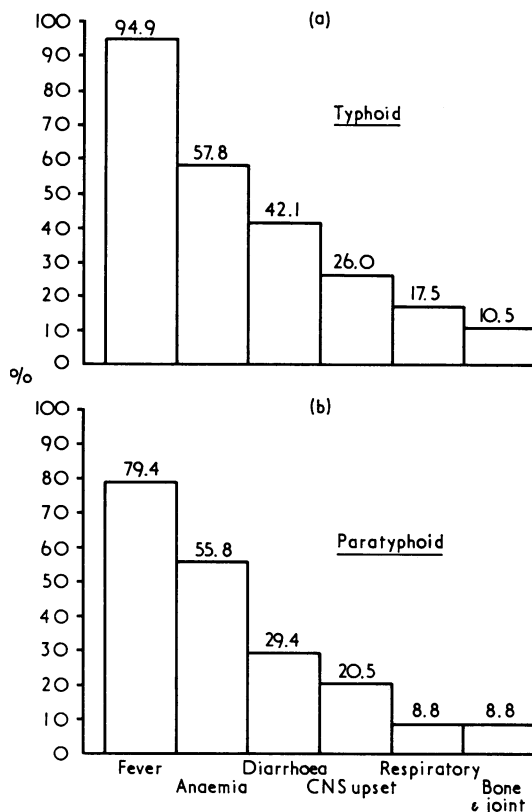


FIG. 3.—Presenting features (a) in 57 patients with typhoid, and (b) in 34 patients with paratyphoid.

paratyphi from a third. Only one child with frank osteomyelitis was a sickler.

Presentation in the neonate. The clinical pattern seen in the 8 patients under the age of one month was distinct and is therefore considered separately. 2 patients had typhoid and 6 paratyphoid. 7 were of low birthweight, and 4 were born to ill mothers. In 2 cases the mothers died at home during delivery, one mother delivered in hospital had heart failure and the other chronic nephritis. One mother of a baby with typhoid was herself a healthy typhoid carrier, but stool culture was negative in the mothers of the remaining neonates. Diarrhoea was a constant feature and 4 patients required intravenous fluids. Only one patient was febrile, the others being afebrile or hypothermic. Jaundice was present in 3 patients and severe in one fatal case. There was no associated anaemia in neonatal patients, and the 4 deaths, 2 typhoid and 2 paratyphoid, were associated with persistent diarrhoea and hypothermia.

Clinical management. The clinical impression of an ill child, though difficult to evaluate, was important in

diagnosis. Fever was sometimes absent in malnourished or collapsed anaemic children. Failure to recover after a febrile convulsion, once malaria and meningitis had been excluded, was suggestive and so-called 'cow's urine poisoning' was less frequently diagnosed.

Treatment was with chloramphenicol in most cases, though some later patients were included in a small trial of trimethoxazole. The dose of chloramphenicol used, 50 mg/kg per 24 h, was smaller than Hendrickse recommends (R. G. Hendrickse, personal communication, 1969), but we justified it on grounds of cost and availability. Dosage was doubled if there was failure to respond to treatment within 48 hours. Our impression was that death was unrelated to insufficient drug dosage. Drugs were given where possible orally, anaemia and dehydration were treated appropriately, and in patients who appeared to be acidotic, often the severely anaemic patients, an empirically calculated intravenous injection of 4.2% sodium bicarbonate was given.

Blood was given as semipacked cells and patients with clinical evidence of circulatory overload were digitalized. It is likely, however, that intravenous frusemide would have justified its cost.

Mortality. There were 16 deaths in all, a mortality of 18%, the figures being identical in typhoid and paratyphoid groups. In both groups younger babies had a higher mortality. In the typhoid patients death tended to occur early in the illness, 7 of the 10 deaths being within 3 days of hospital admission and within a week of reported onset of symptoms. There was an increased mortality among the 'rural' patients, probably relating to delay in presenting at hospital.

In the para-typhoid group the picture was slightly different. 3 of the 4 postneonatal patients had signs suggestive of embolization, with gangrene of extremities, or small patches of skin gangrene on the abdominal wall, and these died after at least 5 days of full treatment. Diarrhoea was present in 4 of the 6 fatal paratyphoid cases, though it was not associated with deaths in the typhoid group. As mentioned above, ileal perforation was not encountered.

A notable feature was the association of anaemia with poor prognosis. If the 8 neonatal patients are excluded, all the 12 fatal cases are found to fall in the anaemic group (52 patients) and 8 of them in the severely anaemic group requiring transfusion. This higher mortality among the anaemic patients was statistically significant ($P < 0.005$).

Discussion

Increased incidence of typhoid during the rainy season has been noted before in West Africa (Ikeme and Anan, 1966; Archampong, 1969; Mulligan, 1971), though the seasonal incidence elsewhere in Africa is different (Huckstep, 1962; Wicks *et al.*, 1971). The explanation usually offered is that surface drinking water supplies are probably polluted during rainy season floods (Archampong,

1969). However, the increased incidence of malaria in the rainy season is well known, and it would be interesting to postulate a relation between malaria in children and susceptibility to enteric fever. Such a relation could also explain the severe anaemia already commented upon, for which no satisfactory cause can be found. Scragg *et al.* (1969) in South Africa reported a 13.5% incidence of anaemia below 8.0 g/dl in her series of typhoid patients, but neither she nor Sood and Taneja (1961), writing from Delhi, found anaemia to be a grave clinical problem. Kaye, Merselis, and Hook (1965) have shown that mice infected with *Plasmodium berghei* show increased susceptibility to *Salmonella typhimurium* infection, and Greenwood *et al.* (1972) in Zaria have shown that in acute malaria the antibody response to salmonella O antigen is suppressed. A causative relation between acute malaria and typhoid can be at present no more than a hypothesis, but work to obtain some further evidence is being planned. It was regretted that evidence regarding the possible influence of G6PD deficiency was not available but there was no male preponderance of anaemia in the patients, and adult patients in Ilesha did not show the same severe anaemia.

With regard to other clinical aspects the presentation of typhoid and paratyphoid was similar to that described by Scragg in typhoid in South Africa, though the incidence of convulsions was higher in the present series, which consists of children at the most vulnerable age for febrile convulsions. It is also worth noting that the incidence of arthritis was higher in this series than Scragg reports, and tended to occur in a more acute phase of the disease.

The death rate of 18% was high compared with the variable reports on childhood typhoid mortality, but if one compares these figures with those for mortality in the younger children in Scragg's series they are comparable. In the South African report the overall mortality is 7%, but in infants it is 27%, and under the age of 2 years, 25%. We cannot be happy about our high mortality figures, but with deaths occurring so swiftly in the septicæmic phase of the disease there seems little more to be done except perhaps insistence on initial parenteral therapy. It is the authors' impression that typhoid in young children is very much underdiagnosed because of the rapidity of its course in these young babies, and it is their firm conviction that the disease should be considered high among the causes of fever and severe anaemia in young children in holoendemic malarial areas.

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