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## Typhoid Fever in the African

BY

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In early days in tropical Africa, typhoid fever was said by the pioneer doctors to be rare. With the growth of cities, often in advance of water-borne sanitation, typhoid fever is now one of the commonest fevers encountered.

Whereas paratyphoid A and B are rarely encountered, *Salmonella typhi* is the usual organism responsible for enteric fever in Africa.

Although there are no essential differences in typhoid fever in the African, the disease appears unusual to doctors trained in countries where it is rare, though their fathers of some 50 years ago would be quite at home now in the typhoid wards of an African hospital during an epidemic.

### CLINICAL FEATURES

Typical, abortive, ambulant and atypical types of typhoid fever may be distinguished.

*Typical Typhoid Fever.*—The onset of the fever may appear to be abrupt, as subjective symptoms in the African are so often obscure. Some disturbance of the bowel with cough and sputum often frankly bloodstained, are usually found. More rarely, deafness may be complained of.

On examination the general appearance is that of a dull sick patient with heavily furred tongue, who dislikes examination. The pulse is relatively slow for the rise in temperature, which at the time of admission to hospital is about 101 to 102 degrees. The step-like rise in the temperature of the first week, the sustained fever of the second and the gradual fall of the third week are not as common as might be expected and irregular degrees of fever are often found, though at the onset it is not as high as during the second week. The duration of the fever can be less and often is more than the statutory three weeks; a chronic irregular intermittent fever may be encountered lasting several months which can only be diagnosed by recovering *S. typhi* from the blood.

The chest shows marked signs of bronchitis and the sputum appears purulent and not uncommonly blood-stained. The abdomen is tumid and uncomfortable, and the stool may be diagnostic, loose, peasoupy and bulky. Enlargement

of the spleen is of no help in the diagnosis of typhoid fever in the African, in whom this is frequently not enlarged; in hyperendemic malarial areas splenic enlargement is of little use in the diagnosis of any condition. A considerable albuminuria is found, and this is helpful in the differential diagnosis. Rose spots on coloured skins are commoner than is thought and should be carefully looked for on the abdomen; sometimes a quite extensive petechial rash is seen.

*Abortive Typhoid.*—Abortive attacks of typhoid are common during an epidemic, and present as a mild attack of fever with some diarrhoea lasting two or three days and are usually thought to be an attack of dysentery; the recovery of *S. typhi* from the stool brings many of these cases to light often after complete recovery has occurred.

*Ambulant Typhoid.*—There must be many cases of mild typhoid fever who never come to hospital, which accounts for the high carrier rate found in the population during an epidemic. These cases are responsible for many new infections and make control of the disease difficult at this time. They may enter hospital when an ileal ulcer perforates. It has been said that many Native races have a relative immunity to typhoid fever, but that is certainly not my experience during epidemics in Kenya, where many thousands of cases have occurred.

*Atypical Varieties.*—When cases of typhoid fever are occurring in any numbers, atypical forms are quite common. It is most important to identify these cases, as with modern treatment complete cure is obtained, whereas if left undiagnosed death is usual.

- (a) *Pneumotyphoid.*—Typhoid fever presenting as a classical lobar pneumonia with high fever, rusty sputum and lobar consolidation can be almost impossible to distinguish from classical lobar pneumonia unless the possibility of its occurrence is borne in mind. The patient is usually more toxic in pneumotyphoid, there is no response to penicillin or sulpha drugs, and the diazo reaction of the urine is invariably positive.
- (b) *Meningotyphoid.*—Meningism without changes in the cerebrospinal fluid is quite common and simulates a meningitis closely. Later a true typhoid meningitis may develop, but this is rare. Here again the diazo reaction in the urine is of great help in ward diagnosis.

(c) *Nephrotypoid*.—Fever, oedema, gross albuminuria with red cells and casts in the urine and nitrogen retention, all features closely resembling a type 2 nephritis, have been seen several times. The fever is higher than is usual with a simple nephritis and the diazo reaction of the urine is positive, typhoid bacilli being recovered from the urine. Complete recovery follows rapidly on the exhibition of chloramphenicol.

(d) *Acute Toxic Crises*.—Sudden collapse due to an acute toxic crisis is often found in undernourished people or after a loading dose of chloramphenicol has been given. The temperature becomes subnormal, the skin cold and clammy and the blood pressure falls to a low level. These features in a patient with a history of previous fever and diarrhoea may suggest typhoid fever. It is important to recognise these cases, because cortisone combined with chloramphenicol is life-saving.

*Relapses*.—There is some evidence that relapses are more frequent where chloramphenicol is given early in the fever, because of some interference with the development of immunity.

Following antibiotic treatment, relapses are often later in developing than in untreated cases and may be delayed for up to three or four weeks.

The relapse may be more severe than the primary attack and require larger doses of chloramphenicol. There are seldom more than two relapses.

#### COMPLICATIONS AND SEQUELAE

The two most important complications are haemorrhage and perforation, both occurring towards the end of the second week, the incidence of neither of which has been prevented by chloramphenicol therapy. Perforation of an ileal ulcer is the commonest and most severe complication and often goes unrecognised, especially where standards of nursing observation are lower than usual. Perforation is easily missed unless the abdomen is carefully examined daily towards the end of the second week, and any sudden change in the patient's condition must lead to a suspicion that this has occurred.

Typhoid osteitis of the spine comes on after the fever has subsided and reveals its presence as a severe backache; the previous attack of fever may have gone unnoticed, and then the

condition can be confused with a brucellosis spine or Potts' disease. X-ray changes are late in their appearance and may be absent at the time of the backache. An attack of typhoid may light up a latent pulmonary tuberculosis or a tuberculous peritonitis, which may appear as ascites during convalescence.

#### LABORATORY INVESTIGATIONS

(1) *White Cell Count*.—The white cell count helps to exclude those fevers associated with a leucocytosis. In typhoid there may or may not be a leucopenia, but the neutrophil count is relatively low. The total count varies from 8,000 down to under 4,000, but is not constant.

(2) *Blood Culture*.—Blood culture can be undertaken at any time during the illness, though a positive result is more likely during the first week. In African countries the following method of collection is useful, as it allows the specimen to be sent long distances, and a Widal reaction can be performed on the same specimen as a culture. Ten ml. of blood are withdrawn with sterile precautions and added to 0.2 ml. of 0.3 per cent. sodium poly-an-ethyl sulphionate in normal saline and rolled until well mixed, and the specimen is then despatched.

(3) *Widal Reaction*.—The Widal reaction can be of great assistance in the diagnosis of typhoid fever in Africans, as few have had any T.A.B. inoculation. It is usual to confine the test to the H and O agglutinins of *S. typhi*. One Widal may be diagnostic on the strength of the O agglutination; in other cases more than one Widal may be necessary. In children the Widal is often negative until six weeks after cessation of the fever, and I have seen a positive blood culture in the presence of a completely negative Widal which remained negative permanently.

(4) *Stool Culture*.—This examination is of use in retrospect, as typhoid bacilli are usually recovered after cessation of the fever. A useful method of preservation, allowing the stool to be sent long distances, is to put some stool in glycerine saline buffered with phosphate to about pH 8.2 in the proportion of two parts of solution to one of stool, and then despatch to the laboratory.

(5) *Ehrlich's Diazo Reaction in the Urine*.—This is a useful ward test and has been of great help in King George VI Hospital in the diagnosis of the atypical and unusual forms of typhoid. Two solutions are prepared. *Solution A*: sulphanic acid 0.5 g., conc. HCL 5.0 ml., distilled water 100 ml. *Solution B*: sodium nitrite 0.5 g.,

distilled water 100 ml. Forty parts of Solution A are added to one part of Solution B and kept in a refrigerator and made up freshly every three days. An equal quantity of this solution is then added to the urine and a few drops of 30 per cent. ammonia added and the urine shaken. A pink froth indicates a positive reaction. An orange colour must be ignored and only a true pink looked for. A positive reaction is found from the fifth to the fourteenth day of typhoid fever and in relapses and recrudescences. A positive reaction can also be found occasionally in bacillary dysentery, pneumonia and pulmonary tuberculosis. However, if the test is read carefully and interpreted intelligently, cases of pneumotyphoid, nephrotyphoid and meningotyphoid can be spotted early; it has been the practice in the surgical wards of King George VI Hospital to perform this reaction on all cases of suspected bowel perforation and to treat conservatively those in whom the reaction is positive.

#### DIFFERENTIAL DIAGNOSIS

Typhoid fever must be distinguished from most other African fevers. In malaria the onset is more sudden with rigors at onset; in the immune, a fever which persists after three days, and in the non-immune five days, with anti-malarial treatment, is not malaria. In pneumonia the temperature respiration ratio is altered and there is a leucocytosis. In typhus the onset is more abrupt, the patient is more prostrated and the eyes are injected. In meningitis the cerebro-spinal fluid is abnormal. Dysentery may be difficult to distinguish in the early stages, but there may be blood in the stool and there is often tenesmus, and the patient is not so ill.

A white cell count will differentiate those fevers which show a leucocytosis, and an eosinophilia distinguish bilharzial fever.

Pulmonary tuberculosis, tuberculous meningitis, subacute bacterial endocarditis, *B. coli* urinary infections, brucellosis and, in those areas where these diseases are found, kala azar and trypanosomiasis are all excluded by appropriate examinations. The atypical forms of typhoid have to be distinguished from lobar pneumonia, bacterial meningitis and nephritis, and typhoid osteitis of the vertebrae from brucellosis and tuberculous disease of the spine.

#### PROPHYLAXIS

*Immunisation.*—When T.A.B. vaccine was first developed, the morbidity from typhoid fever was greatly reduced. The protection afforded by T.A.B. inoculation is not, however, complete.

Marmion *et al.* (1953) have shown that protective inoculation with T.A.B. does not produce an immunity, while a previous attack of the disease confers some though not complete protection. Many failures to protect against the disease may be traced to the use of phenolised vaccine. Felix (1941) has produced an alcohol-killed alcohol-preserved vaccine which contains maximum amounts of O and Vi antigen. Endotoxoid, a formolised extract obtained from Vi strains by freezing and thawing, has been used extensively in South Africa (Grasset, 1951).

*Carrier Finding.*—The use of Vi agglutination tests to detect healthy and convalescent carriers has introduced a relatively easy method of finding carriers among a large mass of people. In some countries, which includes most of Africa, where the endemicity is high, this test may be of less use (Alcivar, 1952). Recent experience in detention camps in Kenya has shown that the Vi test is of little practical use in finding carriers in a community where the carrier rate is high.

*Identification of Organisms.*—The Vi phage typing of *S. typhi* has enabled strains of the organism to be identified so that the source of an epidemic can readily be traced. In an epidemic in Kenya five different phage types were identified and were found to correspond with organisms recovered from cases in three areas from which the detainees had come, thus illustrating that there was no single source for the epidemic.

#### CURATIVE TREATMENT

Good nursing during the febrile period and a fluid diet are just as important now as before antibiotic treatment. There is as yet no bactericidal drug against *S. typhi*, but the bacteriostatic chloramphenicol is the drug of choice. The effect of chloramphenicol is a rapid reduction in fever and toxæmia and the saving of life, but no reduction in the incidence of complications or the carrier rate (Smadel *et al.*, 1950).

*Dosage.*—The maximum dosage of chloramphenicol is 30 g. in the ordinary case (Marmion, 1952). This is best given as a continuous course with a loading dose of 3.0 g. to 4.0 g., followed by 2.0 g. daily until the fever has settled, and then 1.5 g. daily until 14 days have elapsed. The relapse rate can be reduced considerably by the daily injection of 0.02 ml. of phenolised T.A.B. vaccine for ten days. The loading dose may be unnecessary (Visani, 1951) and likely to produce an acute toxic crisis from the libera-

tion of toxins from killed typhoid bacilli. In Kenya, where at the time large supplies of chloromycetin were not available, the loading dose was omitted; 2.0 g. was given daily until the fever settled, a total dose of 8.0 g. often sufficing, without an undue increase in the relapse rate; this resulted in the treatment of three times as many cases of typhoid for the same expenditure of drug. Now it is the practice to give no loading dose, but 2.0 g. daily until the fever has settled and then 1.5 g. daily for 14 days.

Toxic effects of chloramphenicol are not infrequent and include anorexia, nausea, stomatitis, cheilosis, glossitis, skin rashes and drug fever. The routine addition of vitamin B complex, especially in undernourished people, is indicated.

#### TREATMENT OF COMPLICATIONS

(1) *Acute Toxic Crises*.—Cortisone should be used in the treatment of these cases in conjunction with chloramphenicol in doses of 200 mg. daily for two days, followed by 100 mg. daily on the third and fourth day (Gambardella and Molese, 1953). Cortisone should not be given after the tenth day in case of perforation.

(2) *Perforation*.—Perforation of an ileal ulcer is the most important and difficult complication to deal with. Laparotomy should be avoided and conservative treatment with gastric suction and intravenous infusions instituted. The mortality rate of operative treatment is high, as the small bowel is often extremely friable and a perforation difficult to find in a toxic patient. The recovery rate with gastric suction, intravenous infusions and chloramphenicol is surprisingly high.

#### OTHER ANTIBIOTICS

Aureomycin is effective in typhoid fever, but is not so good as chloramphenicol (Woodward, 1949), while terramycin has a variable effect and is only partially effective (Vakil, 1954), but may be usefully employed if a strain of *S. typhi* resistant to chloramphenicol is encountered or resistance develops during treatment (Cooke, 1955).

#### TREATMENT OF CARRIERS

Chloramphenicol does not remove typhoid bacilli from the intestine and is of no use in the treatment of convalescent or healthy carriers (Rumball, 1949). Harries (1955) has found that a combination of aureomycin and chloramphenicol in doses of 0.25 g. of each drug six-hourly to a total of 16.0 g. cures the majority.

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