Original Articles

CHLORAMPHENICOL IN EARLY DIAGNOSIS OF TYPHOID

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In an earlier communication the striking influence of Chloramphenicol on the course of typhoid has been shown. By now Chloramphenicol has been generally accepted as the drug of choice in the diseases of enteric group of fevers. The purpose of the present communication is to report on a series of over 250 cases of typhoid and paratyphoid, treated uniformly according to the original scheme (Woodward, 1949; Woodward, *et al.*, 1948; Treu, 1950).

In the years before the war and during the war typhoid was common enough in Calcutta, but there is a general impression that after the partition of India and the subsequent large influx of refugees the incidence of typhoid has considerably increased (enhanced virulence through mixing of populations?). Most fortunately the introduction of Chloramphenicol coincided with this increased incidence of typhoid.

Within the last three and a half years over 250 cases have been observed in private practice. There has not been a single fatality. Also the relapse-rate has been very much below the figures usually cited (Fairley, 1952). There have been four relapses only, one relapse in paratyphoid A, another in paratyphoid B, yet another in typhoid and the last in *Bacillus enteritidis* Gaertner septicemia, a relapse-rate below 2 per cent. There was, however, not one relapse in any of the cases whose treatment had begun quite early.

The vast majority of cases were treated within the first 72 hours after the commencement of fever. This may seem extraordinary as it is generally believed that typhoid cannot be diagnosed so early. Local conditions here, however, have led the practitioner to look out for typhoid within the first few days of any feverish disease, unless a different diagnosis appears obvious. A typical fact of the enteric fever-group observed here is that it very often begins with a shivering fit late in the evening or at night, while the "step-ladder"-type of beginning is less common. Sudden rises in temperature to 104° and even 105° within a few hours have been observed fairly often and such cases have been known to be treated for malaria with disastrous results.

A typical example was the case of an Anglo-Indian male, aged 28 years who consulted me on a Saturday morning about a recurrent type of headache. He had no fever then. On Monday morning he informed me that late on Saturday his temperature had risen to 104° and on Sunday night to 105°. On examination he was quite certain that he had malaria which he knew from previous experience. His blood showed no malaria parasite, Widal reaction for typhoid the same day was positive and treatment was started. This patient was gravely ill during the next three days and most of the time semi-delirious until defervescence.

He informed me later that in the house in which he lived someone else had fallen ill at the same time as he did and had been treated for malaria. When the actual cause of his disease, typhoid, had been recognized, it had been too late to save his life.

The treatment, with the exception of a few cases who were seen late and in whom the diagnosis was beyond doubt, has never been started without sufficiently suggestive positive Widal reaction. Blood-culture was positive in 75 per cent of the cases. In many cases, the positive culture-report was obtained at a time when the temperature had already become normal.

Two cases, both European females, deserve mention in this connection. Both were seen at a comparatively early stage of the disease and the clinical picture was thought to be typical of enteric fever. The Widal reaction, however, was negative for typhoid and paratyphoid and treatment was withheld. Forty-eight hours later culture showed growth of *Bact. enteritidis* Gaertner. Treatment was given as usual in typhoid-fever, with defervescence within 3 days. One case relapsed after and interval of 2 weeks.

In those few cases in whom treatment was started without having obtained laboratory confirmation first the diagnosis was confirmed later on. Amongst those cases was one, a Hindu male, who came to me from a place, 100 miles outside Calcutta, on a Saturday evening in an obvious state of typhoid-fever delirium. He was said to have been ill already for 10 or 12 days. The blood-sample, taken before starting treatment became hæmolysed, and therefore another sample had to be taken on Monday, forty hours after the beginning of treatment, while fever was still high. Blood culture was positive for *S. typhi.* though for 40 hours a high blood concentration of Chloramphenicol had already been maintained. The temperature fell to normal on the 3rd day of treatment and one day later this patient had the severest hæmorrhage from the bowels of this series. He survived without relapse.

The standard of treatment was: in adults, unless they were grossly underweight, 3G loading dose, followed day and night by .5G four-hourly as long as fever persisted. Thereafter 5 days 1.5G per day. The results of this short

course of treatment are so satisfactory that no prolongation of the treatment could be more efficacious.

Only occasionally the dose had to be increased. In one case of paratyphoid A—abrupt beginning with shivering during the night; Widal positive next afternoon; standard treatment started within 24 hours from the beginning of the fever; culture later on positive—the temperature rose to 105.8° forty-eight hours after commencement of treatment. With doubled dosage the temperature was forced to near normal within another forty-eight hours. No relapse.

There has not been a single instance in which these comparatively massive doses of Chloramphenicol have produced symptoms of collapse or shock or an increase of toxaemic symptoms. There has been no necessity for the use of analeptics because of Chloramphenicol, even in cases where the temperature fell to nomal quite rapidly.

There have been no serious by-effects of Chloramphenicol apart from occasional diarrhœa. The appearance of a red tongue has not been as frequent as is stated in the European literature. Statistical data on this point are not complete, but the impression has been throughout that in such a mixed assembly of patients, comprising Europeans of almost any nationality, Indians of most diverse origin, Anglo-Indians, Chinese etc., the European element was more predisposed to this complication. It has been a routine treatment to add Vitamin B-complex to the diet.

Under the special circumstances of Calcutta the experiences of the last few years have shaken the belief in the efficacy of typhoid immunisation very thoroughly. At least 50 per cent of the European patients had their last typhoid inoculation within a year before they fell ill. In many cases the immunisation had been done only a few weeks to a few months prior to the beginning of the disease. As a curiosity one case may be mentioned who fell ill about six hours after a TABC injection. When seen 48 hours later there was a strong suspicion that he was suffering from typhoid, confirmed by blood culture later. More than 70 people inoculated at the same time remained unaffected.

It is not intended to discuss here the immunological problems of typhoid but it has to be clearly stated that at best immunity against typhoid infection can only be relative and will be broken through if the infection is massive enough. We do not know for certain how many people remain protected and do not fall ill after being infected. However, the examples of typhoid disease, starting within a few months after a full course of inoculations, whether done here or abroad, are now so numerous that it is hard to believe that they are only the exceptions to the rule.

There is the history of a young American who consulted me with slight fever which proved next day to be typhoid. By then his temperature had risen to 103.2°, but the fever was cut short within another twenty-four hours. Nevertheless after this extremely short attack of typhoid he lost his hair, just as in former days people sometimes did after the long-lasting fever. He had acquired his typhoid by stumbling in the dark into a water-trough. He had been inoculated at home two months before falling ill.

Or the case of the boy, aged 12 years, who came from Great Britain to visit his parents, after having been duly inoculated. Within a few weeks he acquired typhoid, his mother fell ill with typhoid two days after him. The cook had been in the house eleven years, but a few months before a new house servant had been engaged. Soon, after joining the household he became ill, but was well after a few days. Some time later the cook fell ill in a similar manner. After mother and son had recovered, both cook and the other servant were found to be carriers.

A young European, whose fever was treated for nearly three weeks as malaria until typhoid at last was diagnosed, but who at least by then should have had the benefit of having been ill long enough to acquire immunity, fell ill again with fever 5 months after having recovered from the previous attack. Typhoid was proved by blood-culture. Source: the house-servant was shown to be a carrier.

Though it is true that typhoid becomes rare after the age of sixty, exceptions are not so uncommon. An Anglo-Indian patient, male, age 64 years, acquired a paratyphoid A, proved by culture, followed by a fairly stubborn relapse. The whole family was at once inoculated for typhoid and paratyphoid, but within a year his wife, also over sixty years of age, fell ill with paratyphoid A. Undoubtedly there was a carrier in this house, but his indenty could not be established.

Or the case of a young European who after inoculation in England travelled to India by sea. Within a few days of his arrival in India he fell ill with typhoid. He had not been here long enough to have acquired the disease in this country and it was probably some lemonade in Aden which caused his enteric infection only a few weeks after inoculation.

In four instances, two of paratyphoid, two of typhoid, all four confirmed by culture, it was observed that during defervescence the patients felt nauseated. For a day or so this was believed to be caused by Chloramphenicol. The real cause of the sickness became apparent when jaundice supervened. The impression was that the typhoid had activated a latent virus-infection which took the typical course of a fairly mild infective hepatitis in every case. The positive

blood-culture in these cases excludes the interpretation of the preliminary fever as the first stage of hepatitis. The diagnosis of toxic hepatitis caused by typhoid can, of course, not be excluded.

One of those paratyphoid cases with subsequent jaundice presented a contact-infection from wife to husband who had nursed her during a comparatively therapy-resistant paratyphoid B infection. When he fell ill within less than two weeks while his wife was convalescent the suspicion of paratyphoid B was confirmed without delay and treatment instituted. Both, husband and wife, had had their typhoid inoculations within a year before acquiring the disease.

In two cases, one of typhoid, the other of paratyphoid, bacteriologically proved, whose blood-count initially had been without abnormalities, the temperature did not become quite normal. High doses of Chloramphenicol were continued until after a few days both developed severe attacks of the anginose type of glandular fever. The pain and discomfort in both cases was severe, and continuation of Chloramphenicol was stopped as it was inffective. It is interesting to note that in both cases there was typical swelling of the spleen during their typhoid fever. This swelling was already considerably reduced at a time when the cervical glands became enlarged. If the only logical explanation is accepted that in those two cases the typhoid fever activated a latent infection of mononucleocusis, it also must be recognized that full doses of Chloramphenicol had not been effective in suppressing such infection or altering its course.

Discussion

The experiences of the past 3½ years have confirmed that the introduction of Chloramphenicol into the treatment of the enteric group of fevers has altered the prognosis fundamentally. The fact that in over 250 cases there was not one fatality is gratifying enough; moreover Chloramphenicol has changed the whole outlook of typhoid to such an extent that this disease, if treated early enough, can be regarded as an infection of a definitely foreseeable short duration. Many cases have lasted only 48 hours and were normal and well at the time when the result of a positive blood-culture was received. With growing experience it was felt that it was quite safe in every case to predict with assurance not only a favourable outcome but also that the patient would hardly feel seriously ill before he was on the way to recovery. In all those cases, treated within the first 72 hours there has not been one instance in which any of the complications of typhoid seen in former years could develop.

In this respect the present series differs from the publications originating from hospitals which had received their typhoid-patients at a time when the disease had lasted already a week or more and in whom Chloramphenicol could not prevent haemorrhage or perforation though it did shorten the duration of the fever. An early diagnosis of typhoid is therefore now much more important than it was previously when no specific treatment was available. Admittedly, conditions prevailing in Calcutta, where the suspicion of typhoid is always present, have been favouring an early diagnosis.

Another, very important observation must be emphasized, the complete absence of relapses in cases where treatment was begun within the first three days. Marmion (Personal communication) reports 28% relapses, and Frank *et al* (1951) postulate that Chloramphenicol may even interfere with formation of immunity and they like Marmion have adopted additional injections of typhoid-vaccine in order to reduce the number of relapses. These authors also have continued administration of Chloramphenicol rather longer than has been done in the present series. They have dealt with patients who came under treatment while in a more advanced state of the disease. The relapse-rates are, therefore, not strictly comparable, but the fact remains that Chloramphenicol, if started very early, reduces the relapse-rate to insignificance.

Since Chloramphenicol has been used extensively in the treatment of typhoid the consensus of opinion is that its specific action on the Salmonella group of bacteria is beyond doubt. Its action appears to be rather bacteriostatic than bactericidal. It is established that its effects in the carrier state are negligible and it appears that, on average 2 to 3 days are required, sometimes more, to suppress the infection sufficiently for the defence forces of the human organism to deal with the invader. If treatment is interrupted too early, and this has been observed occasionally when the supply of the antibiotic had run out, recrudescence of the fever may take place. However, if Chloramphenicol is continued for 5 days only after defervescence, the experiences reported here tend to show that within this period the body has dealt with the remaining bacteria sufficiently to prevent a relapse. That, at least, applies to those cases whose treatment was started within the first 3 days. Why did none of them relapse? Obviously, they had much less time to develop immunity than those patients whose treatment was started at a later stage and who should have developed immunity during their prolonged period of illness. But experience in typhoid has always shown that it is a disease which, after having taken its full course, will nevertheless relapse in a fairly high number of cases, and recent experience only proves that this tendency to relapse remains in those cases who have been ill for some time before being given Chloramphenicol. If there has been no relapse amongst about 200 cases treated quite early it is obvious that for the prevention of a relapse other factors than immunity must be operative, which these early cases cannot have

acquired to the same extent. It would be more logical to assume that in prolonged typhoid the bacillus often acquires a certain amount of resistance to the defensive forces of the host, while in a very short bout of fever there has not been enough time for this and that therefore the defensive mechanism of the body can eliminate the infection without possibility of relapse. Continuation of Chloramphenicol beyond 5 days after defervescence, as recommended by Lakin (1951) is therefore in all such cases not required.

The experience gained in connection with the number of patients who acquired enteric fever within weeks or months after a full course of typhoid vaccine injections allow justifiable doubt in the complete efficacy of this procedure. My own observation of renewed infection after 5 months and the observation of Frank *et al.* of 3 typhoid attacks in the same patient within one year may be interpreted as insufficient ability of certain individuals to develop immunity. But both patients lived in close contact with a carrier and their histories may indicate that there is no complete immunity in typhoid which cannot be broken through by a sufficiently virulent and massive infection.

Summary

Within the last 3½ years over 250 cases of typhoid and paratyphoid infections have been treated with Chloramphenicol without a fatality.

The relapse-rate in the whole series was below 2 per cent.

The vast majority of cases was treated within the first 72 hours of the disease. There has been no relapse amongst those cases treated so early.

There has been none of the typical typhoid complications amongst the cases treated very early, though in many it was obvious that the infection was highly virulent.

It does not appear that Chloramphenicol inhibits formation of immunity, provided treatment is begun very early.

Typhoid-immunisation as practiced to-day gives no reliable protection in cases who are exposed to virulent infection.

It has become possible to shorten the duration of typhoid to a few days. If typhoid is recognized and treated early enough with sufficient dosage of Chloramphenicol it has ceased to be even potentially a serious disease.

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. . . Editorial Note. To the questions raised by us on the futility of the inoculation and the early appearance of the agglutinins, the author has replied as follows :

The typhoid vaccine used by me and by most other physicians here was the standard vaccine made by Bathgate & Co. and also Bengal Immunity. Occasionally I have also used the vaccine prepared by the Government laboratory, Kasauli. Amongst my patients were many who had prior to coming to India inoculations abroad. The name of the makers I could not give you now.

My observations cannot leave the slightest doubt that failure of the vaccine to give satisfactory protection must be recognised. I am very well aware of the fact that these observations are greatly at variance from these made by the armies in two world wars, but it appears that lately also the British army has found good reasons to doubt in the value of typhoid immunisation. There have been far too many typhoid cases in the troops in Egypt, and I have been told that research is going on to find the reason for this failure. New methods of vaccine preparations are, as I have heard, being developed.

The very high percentage of our cases proved by positive culture in those inoculated cases cannot be disregarded. I have come to the firm belief that the protection given by the vaccines obtainable at present is not nearly as complete as I have been taught and accepted until experience has been otherwise.

It is quite true that I have also been taught that agglutinins appear not before the end of the first week of the disease. Many years ago I would hardly have thought it worth while having a Widal test done during the first days of illness. When I had learnt that a positive test can be obtained during the first 24 hours of clinical disease, and when I had this experience confirmed in many hundreds of cases, I had to change these views too. Again, the proof of the correctness of the Widal test was obtained in such high percentage of positive cultures that one has to accept the occurrance of a positive Widal in the first days of disease as a fact. Actually, I find it quite easily explained that with good technique the Widal is positive as early as that. Before the disease manifests itself clinically there has been sufficiently long

incubation time to allow the development of a positive titre. I have the feeling that all too often the positivity of the titre is in some way or other regarded as a measure of immunity. That, of course, has been accepted because we have no other means of assessing immunity against typhoid. However, I am convinced that immunity against typhoid has very little to do with a positive Widal reaction, or the presence of agglutinins. If the presence of agglutinins were to indicate immunity no typhoid case, after a disease lasting over weeks and having reached a high Widal titre, could possibly relapse. The mere fact that so many typhoid cases have relapsed in the pre-chloramphenicol-days and also relapse now, after chloramphenicol, makes one wonder what immunity in typhoid really means. Quite certainly those cases I have been able to cut short within a few days only had very much less chance to develop " immunity," but not one of them relapsed. Only those did in whom the disease had already lasted more than a few days.

Lastly: If one of my patients who has gone through an attack of typhoid, lasting 3 weeks, before I saw him at that time, could relapse after exactly 5 months only being again infected by his bearer who was than proved to be a carrier, one may justyfiably wonder what immunity in typhoid really means.

I am well aware of the fact that the observations on which I have reported in my paper do not all fit into the accepted conceptions. Never the less, the observations have been made, and if they run to some extent counter to previously accepted conceptions, I feel that those conceptions need modifications.

Opinions on these questions are invited from experts in Preventive Medicine and Bacteriology.

NUTRITIONAL PERIPHERAL NEUROPATHY RELATED TO "THE SHOULDER GIRDLE SYNDROME"* IN PERSIA AND IRAQ FORCE 1944-45

PART II†

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DIAGNOSIS

The differential diagnosis needs to be considered in three stages, the stage of onset, the developed disease and the residual lesions. Sporadic cases of course would be more difficult to differentiate but lack of familiarity with the disease had apparently been the main cause for error. In 22 cases, transferred from other hospitals or referred by various medical officers for consultation, a number of other conditions had been diagnosed such a Poliomyelitis, Progressive muscular atrophy, Leprosy, Cervical rib, Deltoid palsy, Sciatica, Sacro-iliac arthritis, Sacralisation of V lumbar vertebra, Tuberculous sacro-iliac disease, Dislocated inter-vertebral disc, Lumbar neuritis, Meralgia paræsthetica, Deformity foot, Cerebro-spinal syphilis and Fibrositis. In the first stage, the pain and numbness requires consideration of fibrositis, and the so-called 'interstitial neuritis'. Hysteria and malingering were two common pitfalls especially if the doctor did not know the patient's language. Absence of fibrositic nodules and a generalized tenderness in the whole muscle helped in excluding fibrositis. Regarding interstitial neuritis, *i.e.* 'Brachial neuritis' and 'Sciatica' the degree of wasting, localized or general, objective sensory changes and alterations in reflexes very often enabled the correct diagnosis to be made when the disease had been present for a few days. We discuss later the close resemblance in some cases to the textbook brachial neuritis. 'Sciatica' (as a result of herniation of nucleus pulposus) was suspected in a number of cases but could be excluded by lack of pain on stretching the sciatic nerve, absent reflexes outside the sciatic supply, the character and the distribution of sensory disturbances and the selective wasting of extra-sciatic muscles. In some early cases observation for a few days was necessary for a correct diagnosis. In most of our cases the error could have been avoided by a complete routine examination of the peripheral nervous system. However, we were in an advantageous position regarding this particular group of cases because we saw them usually in the stage of the established disease when the orthopædic surgeon already had excluded 'Sciatica' in the presence of some of the above features and radiological investigation.

Hysteria and malingering loomed large and it was not uncommon to come across instances of clear injustice having been meted out to some of the early cases who were forcibly kept on duty and who later proceeded to develop profound wasting. 'Great suggestibility' of Indian troops was a myth based, in our opinion, on sheer ignorance of the language and lack of 'enthusiasm' to conduct a full examination. Doubtful cases had to be referred to a psychiatrist knowing the language; his evaluation of the soldier's personality was often of material help.

The developed disease had to be distinguished mainly from poliomyelitis. Absence of fever and other constitutional symptoms at the onset, the type of onset, normal CSF, distribution of paralysis and sensory disturbances, and the course of the disease all helped in excluding

* Summary read at the Annual Conference of Association of Physicians of India at Lucknow in March 1950.

† For Part I *see* previous issue.—EDITOR, *I.M.G.*