CHLORAMPHENICOL IN TYPHOID FEVER

A PRELIMINARY REPORT OF CLINICAL TRIAL IN 6 CASES

BY

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Chloramphenicol (chloromycetin) is a new antibiotic derived from a soil streptomycetes known as *Streptomyces venezuelae*. It was first isolated for therapeutic purposes by Ehrlich and his associates in 1947.

The first report of the beneficial effect of this antibiotic in typhoid fever came from Woodward and his co-workers in Malaya in 1948. Since then the drug has been given a trial by many workers in different parts of the world. Murgatroyd (1949) has tried it in one case in London. A controlled trial is in progress in the United Kingdom as a result of the recent Berkshire outbreak (Bradley, 1949). In India the drug has been tried in typhoid fever by Shah (1949) and by Vakil (1949).

The diagnosis of typhoid fever may be open to doubt in many of the cases of these two Indian authors. Shah's series of 33 cases contains only eight with positive blood cultures, and Vakil does not mention the number of cases in which blood culture was positive in his series of 14. Neither of these authors mentions previous T.A.B. inoculation in their cases.

Method

We have tried the drug in the clinical investigation ward of the King Edward Memorial Hospital in six cases—three males and three females, all being adults. Details of these cases are given in the Table. In all of them blood culture

case (also compare the phage types, see above). None of the cases had previously been inoculated with T.A.B. vaccine. Five cases were severely toxic before the treatment was started and one was moderately toxic. Two of the cases (Nos. 2 and 5) had received previous type-specific parenteral phage therapy without any demonstrable benefit.

All the six cases were observed in the investigation ward meant for treatment of typhoid cases alone. Hence all the patients received the same general nursing and dietetic treatment (Patel *et al.*, 1947), the administration of the drug being the only controlled variable.

Chloramphenicol was started in the second week in one case, in the third week in three cases, in the fourth week in one case, and in the fifth week in one case. In the last two cases the drug was tried during a clinical relapse. The dosage schedule was uniform in all cases: 1 g. initially followed by 1 g. one hour later and 0.25 g. two-hourly day and night until temperature was normal for 48 hours. Then 0.25 g. three-hourly for the next 48 hours, and finally 0.25 g. four-hourly till a total dosage of 18 g. was given. However, only one case (No. 2) could be given the full 18 g. The response was dramatic, the temperature touching normal in 36 hours and remaining normal.

Owing to short supply the other two cases that recovered (Nos. 5 and 6) received 12 g. and 16 g. respectively. Both of them responded very well, the temperature coming down to normal in 24 and 48 hours respectively, but the former case relapsed after an afebrile period of 12 days. This might probably indicate that 12 g. was an inadequate dose. During this relapse *Salmonella typhi* were again isolated from the blood. As chloramphenicol was unobtainable the relapse could not be treated with it.

The other three patients died. They received chloramphenicol orally for 48, 26, and 40 hours respectively, the amount of drug given being 8, 5.5, and 6 g. respectively.

Case 1 received 8 g. of chloramphenicol in 48 hours. This patient should have at least started responding (cf. Bradley, 1949: in nine treated patients the signs of resolution were obvious within 48 hours—i.e., after the administration of

Table Giving Various Data of Six Cases

Case No.	Age and Sex	Vi Phage Type	Previous Specific Treatment	Initial Toxicity	Day of Disease on which Treatment Started	Duration of Treatment	Total Dosage	Temperature Normal in Hours	Toxic Reactions	Result	Comment
1	25 F	A	Nil	Severe	28th	48 hours	8 g.	—	—	Died	Case of clinical relapse with bacteraemia
2	23 M	?	Parenteral phage therapy	„	35th	6½ days	18 g.	36	—	Cured	„ „
3	38 M	?	Nil	„	11th	26 hours	5.5 g.	—	—	Died	Probably chloramphenicol did not get a chance to act
4	24 F	E ₁	Nil	„	17th	40 „	6 g.	—	Rigor	„	Patient went into hyperpyrexia and peripheral vascular failure
5	20 F	A	Parenteral type-specific phage therapy	Moderate	19th	70 „	12 g.	24	—	Cured	Dramatic response in a phage failure case. Relapse after an afebrile period of 12 days
6	25 M	A	Nil	Severe	15th	6½ days	16 g.	48	Erythema-papular rash	„	Rash disappeared in 3 days

was positive, the Vi phage types of *Salmonella typhi* isolated being "A" in three cases, "E₁" in one case, and ? (untypable) in two cases. These six cases were encountered during a period extending from the latter half of May to July, 1949. Typhoid fever being endemic in Bombay, it was not possible to collect all the cases from the same outbreak. The cases came from widely scattered parts of the city and from different walks of life: two were peons, one a hotel worker, one a nurse, and two were performing domestic duties. None gave a history of contact. In all probability the source of infection was different in each

8 g. of the drug), but she rapidly developed peripheral vascular failure and died. Owing to her early death No. 3 apparently received inadequate dosage. In Case 4 the patient developed a rigor about 24 hours after starting the treatment. She went into hyperpyrexia and died 16 hours later.

Results

In all the three cases that recovered the temperature fell by crisis or rapid lysis in 24–48 hours. This is the usual experience of other workers in most of their cases. In all these three cases the constitutional improvement was

striking and was seen earlier (within the first 24 hours) than the fall in temperature. Woodward *et al.* (1948) had a similar experience. Shah (1949), however, finds just the reverse thing. In his opinion the effect on the toxic state is slower than the effect on fever. The fall in temperature occurs in two stages (Murgatroyd, 1949; Vakil, 1949). An initial fall is followed by a rise, the temperature then subsiding gradually. This was seen in two of our cases.

Toxic Reactions.—Chloramphenicol seems to be non-toxic for all practical purposes (Murgatroyd, 1949; Shah, 1949; Vakil, 1949). One of our cases developed a transitory erythemo-papular rash, mainly on the trunk. A similar finding has been noted by Shah in one case. The rigor that occurred 24 hours after the beginning of treatment in Case 4 may not have been a symptom of drug toxicity. It could well have been a hyperpyrexial reaction during the course of the disease, or it may have been due to rapid lysis of a large number of organisms. It is only tentatively included here, because it has not been observed by other workers. Shah found signs of cerebral irritation in seven cases. We did not come across any other toxic reactions, neither did Woodward *et al.* However, Shah and Vakil attribute nausea, anorexia, diarrhoea, circulatory failure, oliguria, and retention of urine in some cases to chloramphenicol. The cause of death in Case 1 in the present series was circulatory failure, but whether this was due to the drug or the disease it is difficult to say. Vakil describes a tendency to leucopenia.

Relapse.—One of our cases (No. 5) relapsed after chloramphenicol therapy and after an afebrile period of 12 days. The blood culture became positive during the relapse.

Vakil has noticed relapse following chloramphenicol therapy in two cases, and Shah found one relapse in his blood-culture-positive cases and four cases of relapse if his whole series of 33 cases is considered. In three of Shah's cases the relapse occurred during maintenance therapy and in one case after an afebrile period of nine days. Woodward *et al.* found that in the doses used chloramphenicol did not prevent relapses. He came across relapses with bacteraemia in two cases after an afebrile period of 10 and 16 days. Both responded to a second course of the antibiotic. The organisms isolated during these recurrences were as sensitive to chloramphenicol as before. Shah's cases, too, responded to further chloramphenicol therapy.

Complications.—It has been shown by Woodward *et al.* that chloramphenicol does not prevent intestinal perforation and haemorrhage even in the afebrile period of the disease. After treatment with it one of his cases developed intestinal perforation on the second day of normal temperature, and another case had massive intestinal haemorrhage on the fourth day of normal temperature. Such complications were also encountered by Vakil. In our small series we have not come across these complications.

Duration of Fever After Institution of Chloramphenicol Therapy.—The average duration was 3.5 days with Woodward *et al.* and 1.5 days in our cases. The average duration of the afebrile course of the disease was approximately 12.5 days, whereas in Woodward's control group it was 35 days.

Urine Cultures.—The urine cultures, before, during, and after chloramphenicol treatment have been found to be consistently negative by Woodward *et al.* The urine cultures were not done in the present series.

Stool Cultures.—Positive stool cultures after chloramphenicol therapy are well known (Woodward *et al.*, 1948; Murgatroyd, 1949; Rumball and Moore, 1949). Murga-

troyd's case had a stool culture positive for *Salm. typhi* after the course of chloramphenicol. Woodward *et al.* found positive stool cultures in two cases; later these became negative. Rumball and Moore treated a 9-year-old chronic faecal typhoid carrier with 30 mg. chloramphenicol per kg. of body weight (i.e., three times the therapeutic dose) for seven days, and the boy still continued to pass typhoid bacilli in the stools. This was surprising in view of the fact that *Salm. typhi* are inhibited *in vitro* by 0.25 µg. of chloramphenicol per ml., while in the usual therapeutic dose the blood level attained is 40–80 µg. per ml. (Woodward *et al.*, 1948).

Blood Culture.—With chloramphenicol therapy the blood cultures become sterile, but turn positive during a relapse. This is what we observed in Case 5.

Comment

Our series is too small for any statistical evaluation of the drug; neither is the series ideal for such a purpose, because in none of the cases was the treatment started in the first week. We agree with Bradley (1949) that the advantages of chloramphenicol cannot be fully explained or exploited until the effect on cases in the first week of the disease is measured. It may be mentioned that Shah has tried chloramphenicol in six blood-culture-positive cases (out of his series of 17 cases). In four of these the treatment was started in the first week. All these cases have recovered dramatically and without any complications following on it. Chloramphenicol is more effective in typhoid fever than aureomycin, and that, too, in a smaller dose per kg. of body weight (Patel *et al.*, 1949). We believe that the drug is the most effective therapeutic agent available at present against typhoid fever.

Summary

Six culture-positive typhoid cases treated with chloramphenicol are reported.

It is plain that chloramphenicol strikingly alters the course of typhoid fever by exerting a specific therapeutic action. However, an extensive controlled trial is necessary to determine the optimal dose.

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The Cerebral Palsy Unit at Queen Mary's Hospital for Children, Carshalton, Surrey, was opened in January, 1943, and was the first of its kind in Great Britain. There has since been set up an "advice clinic" at the Lambeth Hospital, where cases of cerebral palsy are assessed from the point of view of suitability for treatment and where parents and relatives are given advice about the management of cerebral palsied children. A booklet has now been produced presenting advice to parents and others on daily treatment, schooling, rest, speech, and other points. The booklet, which is well produced, contains a number of black-and-white sketches and gives useful information in the form of question and answer. Copies may be obtained from the hospital at Carshalton (price 1s.).