The Specific Treatment of Typhoid Fever

The traditional treatment of typhoid fever consists of expert nursing combined with dietetic treatment. In the last 15 years the search for more specific measures has been intensified and several claims of successes have been made. The more promising of these are:

Anti-Typhoid Serum

The elucidation of the antigenic structure of the typhoid bacillus with its H, O and Vi antigens and the chemical extraction of the O and Vi antigens made possible the production of a potent anti-typhoid serum containing both O and Vi antibody. Felix (1935) was responsible for its production and suggested that the Vi antibody prevented the multiplication of the bacillus while the O antibody dealt with its endotoxin. Numerous reports were published of its efficacy. Hodgson (1944) reported a series of 25 cases treated at this hospital and claimed that the efficacy of the serum 'appears to be prompt and very satisfactory in those states due to pure toxæmia.' His routine dose was 33 cc. intramuscularly, daily for three days. Serum is still used here in similar doses in the majority of cases but the prompt and satisfactory results of Hodgson have not been repeated. Banks (1949) states that subsequent experience has been disappointing and that 'there is certain that it rarely now produces any demonstrable effect, except when used in the first week of the disease.' Since 1946, our experience has been similar and it would appear either that the serum now available lacks some essential factor or that earlier reports were too optimistic.

Specific Bacteriophage

Knouf, et al. (1946), reported the use of bacteriophage in the treatment of typhoid fever. At first they used a stock bacteriophage but later turned to type-specific bacteriophages obtained from cultures of the patient's blood in each individual case. 1 cc. of phage was given in 500 cc. dextrose solution by slow intravenous drip and 56 patients were treated. Hyperpyrexia up to 105° or 107° F. occurred in most cases but the temperature became normal within 24 hours and remained normal in all but 10 per cent., who relapsed.

Desranlan (1948) followed Knouf's method of administration but used a mixture of types I to IV bacteriophages to obviate the delay in typing before commencing treatment. Five patients treated in the early stage showed dramatic improvement. In cases treated at a later stage of the illness, improvement was dramatic in some, but others required further courses. There were no deaths in 20 cases treated.

The results in both these series are striking and further reports are awaited with interest. Banks (1949) reports the use of phage in two carriers; in both cases alarming symptoms developed and one patient died. He regards the treatment as at present very dangerous.

Combined Penicillin—Sulphonamide Treatment

In 1946, Bigger showed that while both sulphathiazole and penicillin had some effect on typhoid bacilli in vitro, the effect of administering the drugs together was very much greater. He showed that combined concentrations of 4 units per cc. of penicillin and 10 mgm. per 100 cc. of sulphathiazole sterilized broth containing 70,000 typhoid bacilli per cc. This concentration of sulphathiazole can easily be obtained in the human body and the penicillin titre should be reached by very high dosage of 2 to 3 mega units per day. McSweeney (1946) published reports of six cases treated with the combined drugs and claimed that Bigger's laboratory results could be reproduced in patients. His régime consisted of two courses of penicillin and sulphonamide separated by a two-day interval. Each course consisted of 10,000,000 (10 mega) units given in four days by two-hourly intramuscular injections of 200,000 units, together with 1 gm. sulphathiazole three-hourly by mouth; each course was preceded by 1 gm. sodium sulphathiazole given intravenously, representing a total of 34 gm. per course. The cases were selected for severity and results were fairly convincing though limited to only six cases. Most subsequent workers have failed to reproduce his results. Bevan et al. (1948) treated 25 cases in the Aberystwyth outbreak with doses approximating
to McSweeney's but found the results very disappointing; blood cultures in some cases were positive after the treatment, and the period before negative faecal and urine cultures were obtained was not shortened.

Parsons (1948) in an analysis of cases treated in the Middle East found that results were disappointing and did not justify the added discomfort to the patient. McSweeney (1948) objects that in neither of these series was his original scheme of dosage adopted and this is a valid criticism, especially in the cases reviewed by Parsons. Comerford et al. (1947) treated two carriers and reported permanent cure after very thorough follow-up. Fry et al. (1948), however, using much larger doses than McSweeney, could report only three possible cures of 17 chronic carriers. The dosage in some of these cases totalled 48,000,000 to 65,000,000 units penicillin and 70 to 90 gm. sulphathiazole given in four courses of two and a half days with intervals of two to four days, so that although McSweeney's régime was not adhered to, it would be difficult to maintain that insufficient dosage was the cause of the failure. Possibly more relevant was the fact that the patients were chronic carriers and not acute cases.

Banks (1949) reports that with certain strains of typhoid bacilli there was dramatic response to doses of 500,000 units penicillin and 7½ gr. sulphathiazole given four-hourly for a period of six days. At Fazakerley some 27 cases have now been treated, the routine being 3,000,000 units penicillin in four doses daily for seven days and 1 gm. sulphathiazole four-hourly for five days, a total of 21,000,000 units penicillin and 31 gm. sulphathiazole. In one case, a convalescent carrier state was apparently cured but in no other case was there obvious improvement.

The essential points in this line of treatment are that the strain of bacillus should be reasonably sensitive to a combination of the drugs and that the necessary blood level of both drugs be achieved and maintained in the patient. Unless some more promising line of therapy becomes available meanwhile, it would appear desirable that further trials with laboratory control of these two points should be carried out.

Polymixin

One case, a girl of seven, was treated with intramuscular injections of polymixin (aerosporin). There was no clinical response and the child died of profound toxæmia. We had nothing to guide us in the matter of dosage and it may be our dosage was insufficient. The organism from a second case was tested but showed so little sensitivity that it was not considered worthwhile treating the case in this way.

Chloromycetin

This is a crystalline substance obtained by concentration and purification of cultures of a streptomycyes isolated from soil. It has now been synthesized but is still scarce in this country. The drug has an extremely bitter taste and is given orally in capsules; with very young children the capsules are a difficulty but we have found that if the powder is shaken from the capsule and given mixed in Nestrovite or jam, the children take it fairly readily. To infants we have given it in a mucilage suspension by nasal catheter. It has apparently no toxicity.

Chloromycetin has not yet been extensively used in typhoid fever but results so far published are striking. Woodward (1948) and his colleagues treated ten cases. They gave an initial dose of 50 mgm. per kilo body weight orally, followed two-hourly by doses of 0.25 gm. until the temperature fell and thereafter every three to four hours for five days. Improvement was noted in 24 hours and the temperature became normal in an average of 3.5 days, as contrasted with an average of 35 days in seven controls. An eighth control died on the seventeenth day. Of the ten treated patients, two had relapses with positive blood cultures which responded to a second course, one had an intestinal perforation and another a severe haemorrhage on the second and fourth days respectively of the afebrile period following treatment. In only two patients did faecal cultures remain positive after treatment and then only for a short time. It will be seen then that the relapse and complication rates remained high but the very rapid fall of temperature and return of well-being suggest that the drug has a powerful specific action in typhoid fever.
There have recently been a few brief reports of the use of chloromycetin in this country. Murga-troyd (1949) described its use in one case where there appeared to be a marked response but he did not claim that his case was sufficiently clear-cut to be convincing. Douglas (1949) described its use in one patient in whom treatment was begun on the third day of the illness; to all appearances, the illness had resolved in five days. Bradley (1949) gave a preliminary account of ten treated cases; one died soon after admission but, of the other nine, seven were apyrexial on the third day, the remaining two on the fourth and fifth day respectively. Thereafter resolution of the illness appeared complete. By contrast, although some of the inoculated male controls had short mild illnesses, others had typical attacks of typhoid fever.

At Fazakerley we have had experience of the drug only in the treatment of paratyphoid fever of which disease at the time of writing there are 50 cases in the hospital. The organism in all is of the same phage type and almost certainly all the patients have been infected from the same source. The illness is on the whole very mild and, at the request of the Ministry of Health and the suppliers of the drug, we have restricted its use, because of expense and scarcity, to the more severe cases. Up to date (July 30, 1949), eight cases have been chosen. One, a child of seven months, died after six days' treatment, the only death in the outbreak so far. The symptoms were mainly diarrhoea and slight dehydration, but correction of the dehydration by drip therapy did not improve the child's general condition, and death appeared to be due to toxaemia; no post mortem was performed. The child's condition at the outset of treatment was not worse than that of many infants suffering from gastro-enteritis who have recovered on routine treatment in this hospital, so that its death on chloromycetin treatment was very disappointing. The other seven children are doing well but they are surrounded by so many mild cases that it is difficult to demonstrate any dramatic results. One boy of six had clinical signs of pneumonia and paratyphoid bacilli were found in his sputum; within two days there was a marked improvement in his general condition and his temperature was normal within five days. A girl of nine who appeared very toxic and whose abdomen was distended and tympanitic, has been under treatment for three days; her general condition is already much improved and the temperature has settled. In the seven treated children the temperature has settled in two days in one case, three days in one case, four days in three cases and five days in two cases. This is not better than in the case of some 30 untreated children, but in a further ten untreated cases pyrexia has persisted for from nine to 15 days. Bacteriological tests of all patients are being carried out. There is some evidence that the paratyphoid bacillus concerned is more resistant to chloromycetin than a strain of typhoid bacillus isolated from another patient in hospital but it is too early to make definite statements. One's general impression at this stage is that chloromycetin has not had the dramatic effect in this outbreak that one expected, but it is fully realized that by selecting for treatment only a few severer cases from a large number of mild cases—a method dictated by economy—one is weighting the results heavily against the drug. On the other hand, apart from the one death, all the treated children are doing well and until all the patients have been seen through their illness it is too early to draw definite conclusions.

Further work is necessary before the position of the drug can be fully assessed, particularly with regard to the possibility of varying sensitivity of strains of the organisms to the drug. Clinically the assessment must await a large-scale trial in severe cases; the indications at the moment are that chloromycetin in such a test will emerge as a powerful agent in the specific treatment of typhoid fever.

I am very grateful to Dr. J. S. White, of Messrs. Parke Davis & Co., for much advice regarding the dosage and use of chloromycetin, and to Dr. Rura Mackay of this hospital for her careful clinical notes.

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BIBLIOGRAPHY

CORRESPONDENCE

CARDIOSPASM

Sir,

I thoroughly enjoyed reading Mr. Rodney Maingot's article entitled 'The Surgery of Cardiospasm', which was published in the May 1949 number of this journal.

There are one or two observations which I should like to add regarding the treatment of this condition.

In a normal person, the gastric contents are prevented from regurgitating into the oesophagus by two main mechanisms:

1. The action of the cardiac sphincter.
2. The 'pinchcock' action of the diaphragm.

Any operative procedure which is embarked upon must necessarily interfere with the first of these—but it is of the greatest importance to preserve the second, i.e. the pinchcock action of the diaphragm.

If both of these mechanisms are damaged by surgery, a patulous cardia results. This produces oesophagitis and eventually peptic ulceration of the oesophagus, which is a worse condition and is more difficult to deal with surgically than cardio-

spasm. The operation of oesophago-gastrostomy should only be mentioned in the treatment of cardiospasm to be condemned. It certainly relieves the obstruction at the cardia, but it creates a dangerous anomaly because there is nothing to prevent gastric juices regurgitating into the oesophagus. I know of at least one fatality from haemorrhage following this operation, which came from peptic digestion of the oesophageal wall.

In Leeds, a modified Heller's operation, as described by Mr. Maingot, has been performed on those cases which did not respond to dilatation with the Negus hydrostatic bag. This is a safe operation for it does not interfere with the pinchcock action, and post-operatively there has been no regurgitation into the oesophagus. It has given excellent results both symptomatically and radiologically in the 17 cases in which it has been performed. I agree with Mr. Maingot that it is the operation of choice. Other operative procedures altering the cardiac mechanism may prove to be dangerous.

Yours, etc.,

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