TREATMENT OF TYPHOID CARRIERS WITH PENICILLIN AND SULPHATHIAZOLE*

BY

R. M. FRY, M.R.C.S., L.R.C.P.

R. E. JONES, M.R.C.S., L.R.C.P., D.P.H.

B. MOORE, M.B., B.Ch.

M. T. PARKER, M.B., B.Chir.

AND

S. THOMSON, M.D., D.P.H.

(From the Public Health Laboratory Service)

Chemotherapy has hitherto yielded very disappointing results in the treatment of typhoid carriers, and radical surgical treatment is by no means regularly effective. Bigger (1944, 1946) described a synergistic action of penicillin and sulphathiazole against various organisms, including *Salmonella typhi*; and Comerford, Richmond, and Kay (1946, 1947) treated two carriers with a combination of these drugs with apparent success. It was decided to treat a larger series of known chronic typhoid carriers with the same two drugs to see if the beneficial results could be regularly expected.

Experiments were carried out at the same time to determine the sensitivity of strains of *Salm. typhi* to penicillin and sulphathiazole and to decide if penicillin is excreted in the bile in concentrations sufficient to influence the growth of *Salm. typhi*.

Sensitivity of Strains of *Salm. typhi* to Penicillin and Sulphathiazole *in vitro*

The sensitivity of the strains of *Salm. typhi* from the carriers to the separate and combined actions of penicillin and sulphathiazole was tested in nutrient broth treated according to the method described by Harper and Cawston (1945). One batch of culture medium was used throughout. Sixteen strains were tested—five of Vi-phage Type A, five of Type C, four of Type E1, and two of Type N (Craigie and Felix, 1947). Recently isolated cultures were maintained on Dorset's egg medium, and inocula for the *in-vitro* tests were prepared by two successive subcultures in broth at four-hourly intervals. Inocula varying from 5,000 to 1,000,000 organisms were subjected to the action of different concentrations of the drugs in 5 ml. of broth. The absence of turbidity after incubation for 48 hours was recorded as evidence of inhibition. A quantitative estimate of the bactericidal effect of the drugs was then made by subculturing various quantities from the original tubes into fresh medium containing an excess of penicillinase and para-aminobenzoic acid.

The results of the *in-vitro* tests may be summarized as follows.

1. Penicillin alone in a concentration of 8 units per ml. inhibited the growth for 48 hours of 11 out of 16 strains. The remaining 5 were inhibited by 16 units per ml. Complete sterilization was achieved by slightly higher concentrations, 12 strains being sterilized in 48 hours by a concentration of 16 units per ml. and 4 strains by 32 units per ml. These results were more or less independent of the size of the inoculum between 5,000 and 1,000,000 organisms and of the Vi-phage type.

2. The action of sulphathiazole alone was dependent upon the size of the inoculum. With small inocula of 5,000 to 10,000 organisms 7 strains were sterilized in 48 hours by a concentration of 1.25 mg. of sulphathiazole per 100 ml., 4 strains

required a concentration of 2.5 mg. per 100 ml., and 5 strains 5 mg. per 100 ml. An inoculum of 100,000 organisms was regularly inhibited by a concentration of 5 mg. per 100 ml., but a lethal action in 48 hours was not common. With inocula of 1,000,000 organisms a concentration of 5 mg. per 100 ml. rarely inhibited growth.

3. When the joint action of the two drugs was examined the concentration of sulphathiazole was kept constant at 5 mg. per 100 ml., the concentration of penicillin and the size of the inoculum being varied. As small inocula (5,000 to 10,000 organisms) were sterilized in 48 hours by a concentration of 5 mg. of sulphathiazole per 100 ml. no studies were made of any possible joint action of the two drugs. With large inocula (1,000,000 organisms) the presence of penicillin in small amounts together with 5 mg. of sulphathiazole per 100 ml. often inhibited growth, but a sterilizing action was seldom demonstrable. Complete sterilization of the inoculum in most cases was achieved only when the concentration of penicillin approximated to that which would bring about this effect unaided by sulphathiazole. As an approximate measure it could be stated that the presence of sulphathiazole in a concentration of 5 mg. per 100 ml. reduced to one-half the concentration of penicillin required to effect sterilization of an inoculum of 1,000,000 organisms.

Penicillin in Bile

Evidence was sought that penicillin is excreted in bile in sufficient concentration to kill *Salm. typhi* or at least to inhibit its growth. A tube was passed into the duodenum of a healthy subject who was receiving intramuscular injections of 500,000 units of penicillin every three hours. Ten minutes after the fourth injection a sample of bile aspirated after the administration of magnesium sulphate as a cholagogue contained more than 100 units of penicillin per ml. and the Oxford staphylococcus was inhibited by a 1 in 6,000 dilution of the bile in broth. The bilirubin content of this sample was 150 mg. per 100 ml. A similar examination in another person yielded a sample of bile containing more than 20 units of penicillin per ml.

A number of examinations were made of samples of bile from patients whose gall-bladders had been removed by surgical operation. In one patient a fine catheter was led into the cystic duct and left there for several days for the collection of samples of bile. After the second intramuscular injection of 500,000 units of penicillin the bile contained 25 units per ml., inhibiting the growth of the Oxford staphylococcus at a dilution of 1 in 1,280, and a concentration of 12 to 25 units was steadily maintained thereafter. A similar result was obtained in a patient whose gall-bladder was drained to relieve an empyema. Initially, this patient was given intramuscular injections of 100,000 units every three hours, and after 12 hours the fluid from the gall-bladder inhibited the growth of the Oxford staphylococcus at a dilution of 1 in 64 (approximately 1 unit), but *Salm. typhi* was not inhibited. The dose of penicillin was increased to 500,000 units every three hours, and 12 hours afterwards the concentration of penicillin in the bile was between 10 and 20 units per ml. The bile inhibited the Oxford staphylococcus at a dilution of 1 in 1,000 and *Salm. typhi* at a dilution of 1 in 8. In a third patient the contents of the gall-bladder excised one hour after a single intramuscular injection of 1,000,000 units of penicillin contained 12 units per ml.

There was thus evidence that penicillin is excreted in the bile in adequate concentrations to inhibit or destroy *Salm. typhi* if injections of the order of 500,000 units are given at intervals of three hours.

Therapeutic Trial

Seventeen faecal carriers of *Salm. typhi* were selected for treatment. There were five carriers of Vi-phage Type A, five of Type C, four of Type E1, and three of Type N.

*Based on a report to the Medical Research Council.

All were known to be regular excretors of *Salm. typhi*, as specimens of faeces had been examined in our laboratories at monthly or in some cases weekly intervals for very long periods. A single batch of yellow penicillin (Glaxo) was used for the majority of the cases, but in two who were given injections of 5 million units it was necessary to use crystalline penicillin.

Three different courses of treatment were tried; the results of these are shown in detail in the accompanying table.

Courses of Treatment for Typhoid Carriers

Course	Case No.	Known Duration of Carrier State	Vi-phage Type	Total Dosage		Result	
				Pen. (mill. units)	Sulph. (g.)		
1	1	6 years	A	30	45	Positive	11th day
	2	6 "	C	30	45	"	9th "
	3	6 "	E1	28	25	"	30th "
	4*	6 "	E1	30	45	"	14th "
	5	15 "	E1	30	40	"	8th "
	6	5 "	C	30	45	"	7th "
	7	4 "	C	30	45	"	7th "
	8	5 "	E1	30	45	"	7th "
2	9	6 "	C	48	72	"	6th "
	10	6 "	C	48	72	"	1st "
	11	3 "	A	60	70	"	119th "
	12	14 "	A	60	70	"	1st "
	13	4 "	A	60	70	"	1st "
	14	9 "	N	60	90	"	28th "
	15	7 "	N	60	90	Negative	48 weeks
	16	6 "	N	60	90	Positive	12th day
	4*	6 "	E1	60	90	Negative	36 weeks
	5	15 "	E1	65	86	Positive	6th day
	6	5 "	C	60	90	"	7th "
	14	9 "	N	60	90	Negative	36 weeks
3	13	4 "	A	120	36	Positive	1st day
	17	4 "	A	120	36	"	1st "

* Cholecystectomy two years before treatment.

Course 1. Continuous 5-Day Course.—In the continuous course of treatment 1,000,000 units of penicillin were injected intramuscularly and 1.5 g. of sulphathiazole were given orally every four hours for five days. The total course thus consisted of 30 million units of penicillin and 45 g. of sulphathiazole. Seven patients were so treated. An eighth patient received 28 million units of penicillin in doses of 500,000 units every three hours for seven days and a total of 25 g. of sulphathiazole. Seven of the eight cases were found to be excreting typhoid bacilli within two weeks of the end of treatment. The remaining case was found positive on the 30th day, but as the patient had left hospital a few days after the end of treatment no specimens were received between the 7th and 30th days.

Course 2. Intermittent 21-Day Course.—The intermittent course of treatment was designed at the suggestion of Professor J. W. Bigger. It consisted of the same four-hourly doses of penicillin and sulphathiazole in four courses each lasting two and a half days, the individual courses being separated by intervals of two to four days. The total dosage as planned was thus 60 million units of penicillin and 90 g. of sulphathiazole, but in some instances slight adjustments were necessary. The precise amounts given to the patients are shown in the table.

Eight patients received the intermittent course in the first instance. Four of these gave positive cultures within one week of the cessation of treatment, one became positive on the 28th day, and one on the 119th day. One case due to Vi-phage Type N has remained negative for 48 weeks to date and represents the only apparent success in the first 16 cases treated by a single continuous or intermittent course.

After a short interval four patients were selected for a further trial by the full intermittent course. Three of them had previously had the continuous course and one the intermittent course. Two of these four patients were positive again within a week of the termination of the second course. The other two were still negative 36 weeks after the treatment. It will be seen that two of the successes were obtained in Vi-phage Type N carriers, but a third carrier of this type (almost certainly the same strain) was not cured (Case 16). Two of the cured carriers who had harboured Vi-phage Type N showed a definite drop in their typhoid Vi-agglutinin titre. The Vi-agglutinin titre of the third

apparently cured carrier (Vi-phage Type E1) has so far remained unchanged.

Course 3. Intermittent Course with Massive Doses of Penicillin.—When the results of the above attempts were reviewed it was decided that there was little ground for optimism, and no conclusion could be reached regarding a dosage which might be expected to give encouraging results. In a final attempt two carriers were treated with injections of 5 million units of penicillin together with 1.5 g. of sulphathiazole orally every three hours for 24 hours, the total daily dosage being 40 million units of penicillin and 12 g. of sulphathiazole. The patients were so treated on three occasions, separated by rest intervals of three days. Each carrier therefore received a total of 120 million units of penicillin and 36 g. of sulphathiazole. One of these cases had been previously treated by the ordinary intermittent course of 21 days (Case 13 of the series), but the other had not previously been treated by penicillin or sulphathiazole. Both patients remained positive, and excretion of typhoid bacilli did not cease even temporarily.

In-vitro tests with the carrier strains isolated before and after treatment showed that they had not altered their resistance to penicillin and sulphathiazole.

Summary and Conclusions

Attempts were made to clear 17 chronic typhoid carriers of infection. At first eight cases were given a continuous course of treatment similar to that employed successfully by Comerford *et al.* (1946) in two cases. All eight cases resumed excreting typhoid bacilli soon after the end of the course of treatment.

When it became apparent that the continuous treatment was not as effective as had been hoped it was decided to try an intermittent course suggested by the work of Bigger (1944) as a method of eliminating "persisters." Accordingly much larger amounts of both drugs were given over a period of 21 days with rest intervals, and in eight cases there was one apparent success. Soon afterwards four of the unsuccessfully treated cases were selected for a further trial by this method, with two more apparent successes.

In order to decide if yet larger doses might succeed, two cases, one of which had been previously treated, were given 40 million units of penicillin and 12 g. of sulphathiazole a day on three occasions. Both attempts were unsuccessful.

Although the results of *in-vitro* tests suggested that typhoid carriers might be cleared of infection by some combination of penicillin and sulphathiazole the results of the therapeutic trial were not encouraging. There were only three apparent successes out of 17 cases in spite of the very large amounts of penicillin and sulphathiazole used.

We are indebted to the superintendents and medical staff of several hospitals and to several medical officers of health for their willing co-operation in making this trial. We are grateful to Dr. A. Felix, F.R.S., for much co-operation and helpful criticism of this work.

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Seven holders of United Nations Social Affairs Fellowships from Greece, India, the Philippines, and Poland arrived in London on July 19 to spend from three to six months in Britain on courses of study arranged by the British Council. Social Affairs Fellowships are awarded to those directly concerned in work of reconstruction and rehabilitation. Typical subjects of study are welfare in industry, child welfare, social aspects of tuberculosis, and juvenile delinquency. Lectures are being given on such subjects as health services, rehabilitation and resettlement of the disabled, the organization of welfare in industry, employment exchange services, the work of a borough council, the Education Act of 1944, housing management, town planning in London, administration of justice, delinquency and probation, and social security. Visits will be made to the Houses of Parliament; County Hall; St. Helier's Hospital, Carshalton; an employment exchange; the Minerva Housing Estate, Bethnal Green; and a meeting of Holborn Borough Council.