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Antibiotics and the Aberdeen typhoid outbreak in 1964

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SUMMARY

This paper gives an abbreviated account of part of a research programme which followed the Aberdeen typhoid outbreak of 1964. Chloramphenicol, the main antibiotic used in treatment, was shown to have a minimum inhibitory concentration (MIC) of between 5 and 2·5 μg./ml. for the *S. typhi* phage type 34 of the outbreak. The MIC for methacycline was between 2·5 and 2 μg./ml. Whereas the deep and shallow broth techniques used gave similar results with these antibiotics, the MIC for ampicillin, and also cephaloridine, was less in the deep than in the shallow broths.

Serum assays in patients given ampicillin or cephaloridine yielded abnormally high concentrations of both antibiotics when *S. typhi* phage type 34 was the test organism whereas, with other test organisms, the concentrations were within expectation. These abnormally high values fell within expected values when the sera under investigation had first been heated to 56° C. for 30 min. before assay against the *S. typhi* of the outbreak.

The findings with ampicillin suggested that dosages given were satisfactory. With cephaloridine the concentrations found in patients' sera seemed to show that twice daily doses of 0·5 g. fell short of adequacy.

INTRODUCTION

During the Aberdeen typhoid outbreak in 1964, the main antibiotic given was chloramphenicol although limited numbers of patients were given ampicillin, cephaloridine and, occasionally, methacycline (Walker, 1965; Russell, 1965). These authors reported disappointing clinical responses except with chloramphenicol.

All four antibiotics were later investigated for activity against the *S. typhi* phage type 34 of the outbreak and also against four other phage types to assess the minimal bacteriostatic and/or bactericidal concentrations. These *in vitro* findings were useful in gauging whether or not adequate *in vivo* concentrations in the dosages used had been attained and maintained in patients.

IN VITRO ASSAY OF BACTERIOSTATIC OR BACTERICIDAL CONCENTRATIONS

Materials and methods

Bacterial strains

The *S. typhi* strains tested were the phage type 34 of the outbreak, and phage types A 1, C 1, D 1 and E 1, kindly supplied by Professor E. S. Anderson, Enteric Reference Laboratory, Colindale. Each strain was grown in Difco heart infusion broth (DHI) for 18 hr. at 37° C. and a 1/100,000 dilution in DHI was used to inoculate the tests.

Antibiotics

Standard dilutions of ampicillin, cephaloridine, chloramphenicol and methacycline were prepared weekly and stored at 4° C. Sufficient antibiotic was dissolved in 100 ml. of distilled water to give a 1000 μg./ml. solution which was sterilized by Seitz filtration and stored at 4° C. Each solution provided the standard from which working dilutions were prepared in DHI each day in a range of concentrations decreasing by 10 μg./ml. from 60 to 10 μg./ml., then by 1 μg./ml. from 10 to 5 μg./ml., by 0·5 μg./ml. from 5 to 1 μg./ml. and finally by 0·1 μg./ml. from 1 to 0·1 μg./ml., giving a total of 28 concentrations.

A solution of 5000 units/ml. of penicillinase (Parke Davis & Co.) was prepared in DHI broth and sterilized by Seitz filtration. Of this solution 1 ml. was found to be sufficient to neutralize 60 μg. of ampicillin. Oxoid blood agar base No. 2 was used to prepare 15 ml. and 10 ml. nutrient agar butts. These were sterilized by autoclaving and cooled to 45° C. before use for colony count purposes. Fresh agar butts were prepared for each set of experiments.

Previous work (Brodie, 1948; Brodie & Shepherd, 1949, 1950) had demonstrated differences in the growth behaviour of intestinal pathogens in shallow and deep-layer culture dependent upon the constituents in the media and the availability of oxygen during growth. In view of these findings, shallow and deep DHI broths were used to assess the effects of the antibiotics.

Shallow broth assays

In each experiment nine horizontal rows of sterile 1 oz. universal bottles were arranged in special racks. The rows were then numbered vertically from 1 to 8 and the 9th row 12, representing the hours at 37° C. to be given to each horizontal row.

From working solutions in DHI broth of ampicillin ranging from 60 to 0·1 μg./ml. and pre-heated to 37° C., each vertical row received 1 ml. in decreasing concentrations from left to right. The bottle in the extreme right of each row received DHI broth only and served as the control of growth. One drop of the 1/100,000 dilution of the 18 hr. culture of *S. typhi* was added to each bottle in the rack.

From each broth control bottle after inoculation and mixing, 0·5 ml. was pipetted into 10 ml. of melted agar at 45° C., mixed and poured into a sterile Petri dish. The colony counts from these provided the average number of viable *S. typhi*

added as inoculum. At the end of each incubation period, colony counts were made from the appropriate rows in medium containing 1 ml. (5000 units) of penicillinase.

Deep broth assays

The above procedures were repeated for ampicillin except that 10 ml. of the working solutions of ampicillin was added to each bottle and to the control of growth bottle. The inoculum was increased 10-fold to give, as far as possible, the closest relationship of micro-organisms per ml. in the deep and shallow experiments.

The column of broth in the deep cultures measured 2·5 cm. as against 0·25 cm. in the shallow-broth technique.

The same experimental procedures were applied when cephaloridine, chloramphenicol and methacycline were the antibiotics under test. However, since no neutralizing agents or antagonists were available for any of these, 15 ml. agar butts were used in assessing the numbers of survivors.

Results

Shortened, yet representative, examples of the experimental results have been set out in graphic form (Figs. 1–3). Each graph gives the results after shallow and deep culture. The concentrations of antibiotic used, the initial inocula per ml. and the time in hours at which subcultures were made are indicated.

Three examples of the results with ampicillin and *S. typhi* phage type 34 are set forth in Fig. 1 and showed that, in shallow broth culture, the minimal bactericidal concentration (MIC) over an 8 hr. period lay between 0·4 and 0·3 μg./ml., whereas, in deep broth culture, there was an MIC between 0·3 and 0·2 μg./ml. The results with *S. typhi* phage types A 1, C 1, D 1 and E 1 have not been reproduced since they showed the same general patterns.

Three examples of the effects of cephaloridine on *S. typhi* phage type 34 are given in Fig. 2. Again a smaller MIC of cephaloridine was required in deep culture assay than in shallow culture – 1·5 μg./ml. as against 2·5 or even 2 μg./ml. The results with phage types A 1, C 1, D 1 and E 1 followed the same pattern.

Fig. 3 shows clearly the bacteriostatic effect of chloramphenicol on *S. typhi* phage type 34. Here there was little difference between the results in shallow as against deep broth techniques. A concentration of chloramphenicol between 5 and 2·5 μg./ml. over an 8 hr. period was adequate for the maintenance of bacteriostasis. Again, the results with phage types A 1, C 1, D 1 and E 1 showed so little differences that the results have not been recorded graphically here.

Methacycline exerted a bacteriostatic influence on all the strains of *S. typhi* and, as with chloramphenicol, there was little or no difference between the results in shallow as against deep cultural conditions. A concentration of 2·0–2·5 μg./ml. was adequate to maintain bacteriostasis over an 8 hr. period.

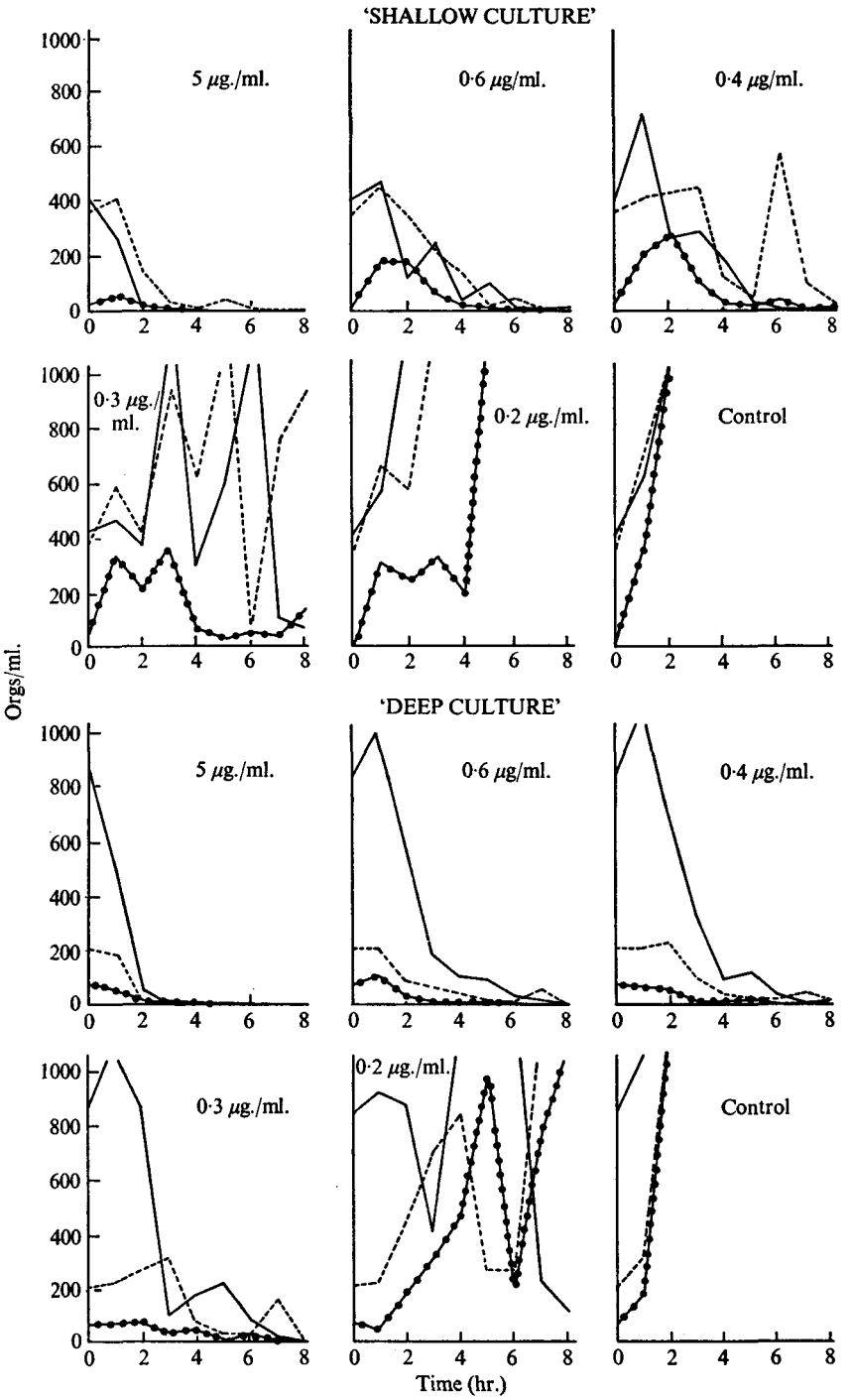

Fig. 1. Effect of ampicillin on *S. typhi* phage type 34.

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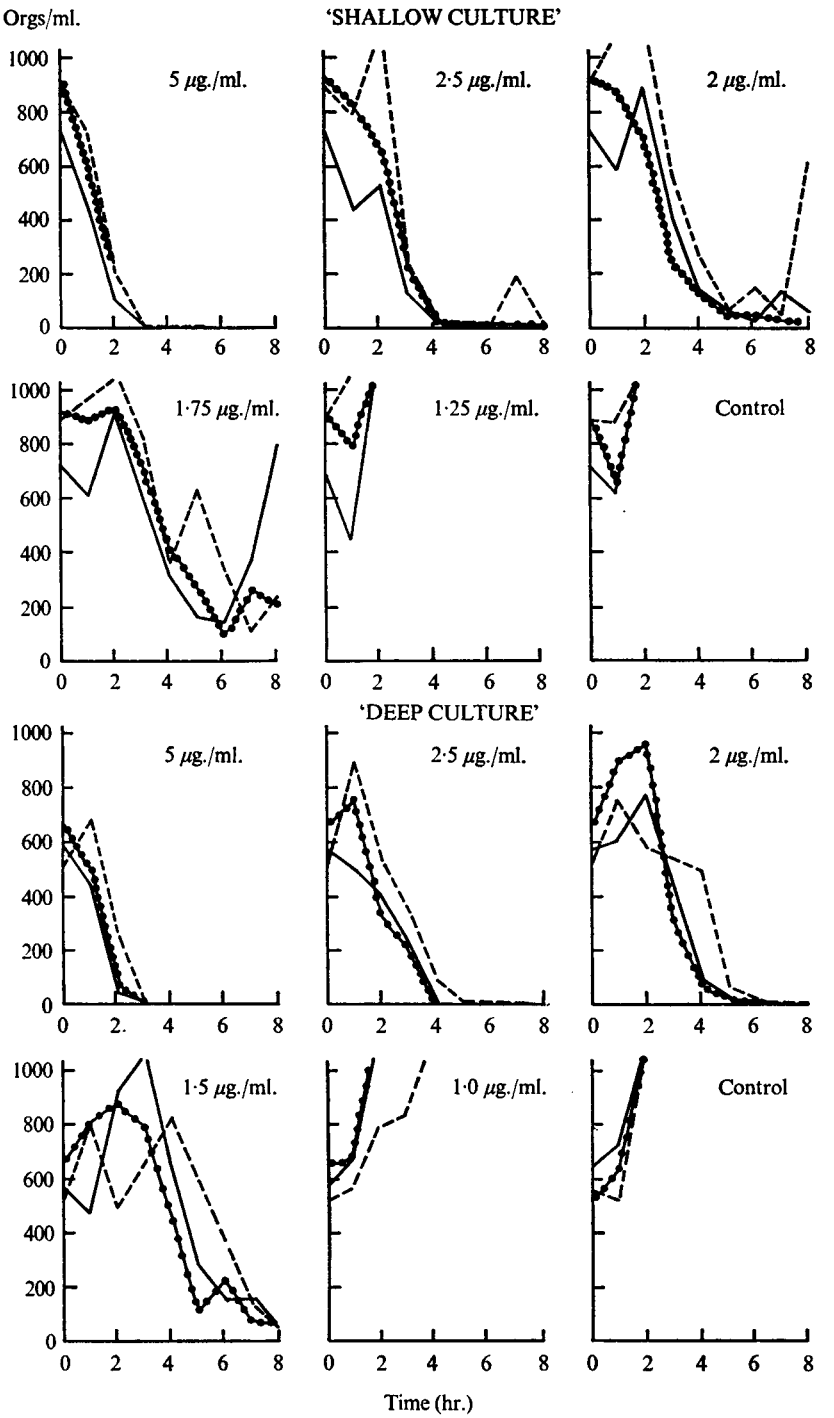

Fig. 2. Effect of cephaloridine on *S. typhi* phage type 34.

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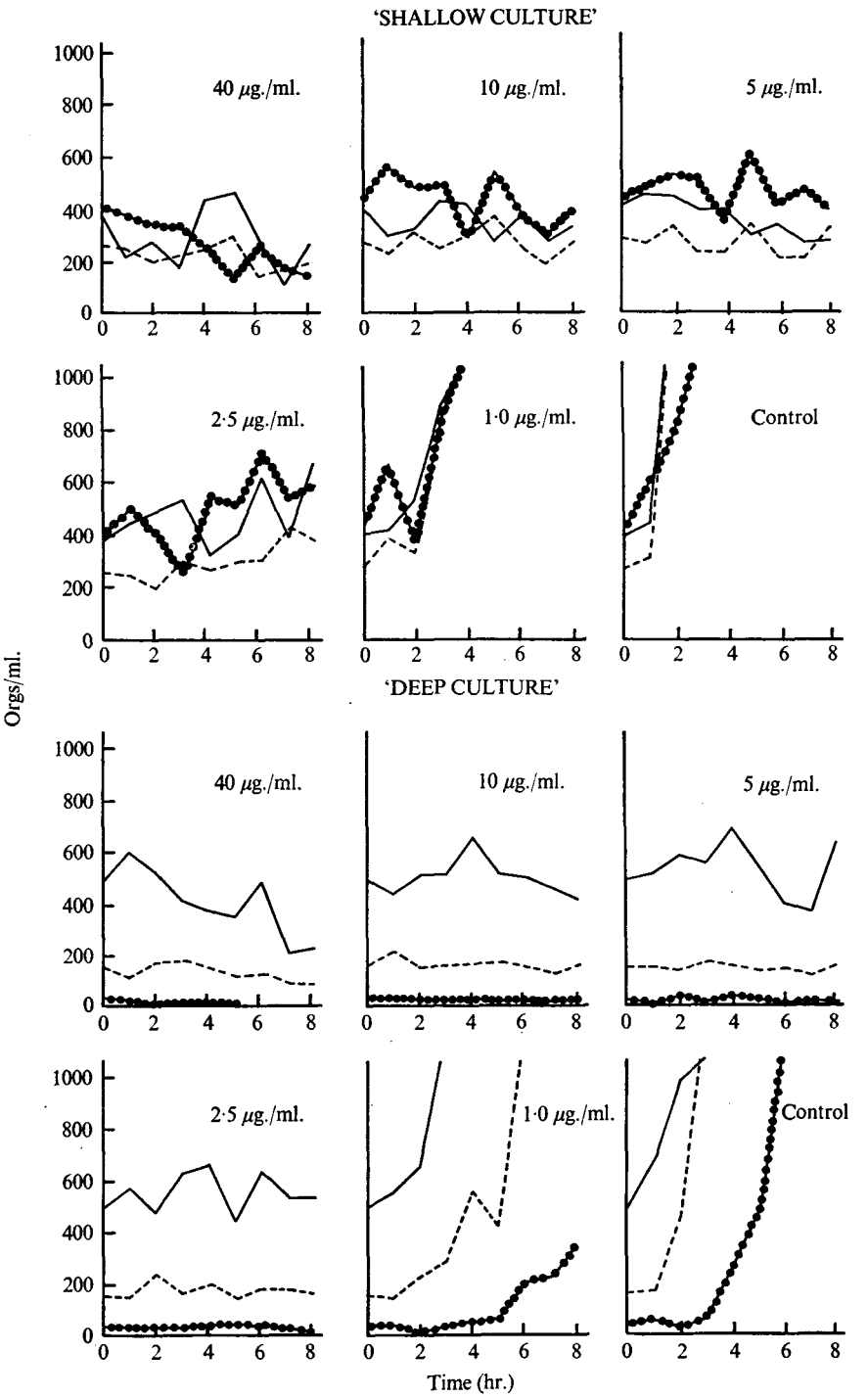

Fig. 3. Effect of chloramphenicol on *S. typhi* phage type 34.

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ANTIBIOTIC BLOOD CONCENTRATIONS IN PATIENTS RECEIVING AMPICILLIN OR CEPHALORIDINE

Materials and methods

A coagulase-positive staphylococcus, a strain of *Sarcina lutea* and the *S. typhi* phage type 34 of the outbreak were used in the assays of antibiotic concentrations in patients' sera.

The staphylococcus, and *S. typhi* were grown in DHI broth for 18 hr. at 37° C., the *Sarcina lutea* for 18 hr. at 25° C. in the same medium.

The inocula chosen, after pilot experiments, were further dilutions in DHI broth of the 18 hr. growths. The typhoid culture was diluted 1/100,000, the staphylococcus 1/10,000 and the *Sarcina* 1/100.

Standard ampicillin and cephaloridine solutions were prepared as already described. The assays were carried out according to the serial dilution tube technique described by Cruickshank (1962). The blood samples were taken over the first few days of treatment and only during laboratory working hours.

Results

Table 1 sets forth the results obtained in ampicillin treated cases. The patients are coded A to I and the times of withdrawal of the serum after giving the antibiotic, the dosage of the antibiotic, the concentrations obtained and brief clinical details of each patient are given.

It soon became evident that assessment by turbidity with *Sarcina lutea* as the test organism was at times difficult. When this occurred, the *Sarcina lutea* results so affected were not recorded. When, however, the results could be read, there was a close correlation between them and those obtained with the staphylococcus. This close correlation did not apply when *S. typhi* phage type 34 was the test organism. Comparisons of the assay results in Table 1 showed:

(1) the staphylococcus and *Sarcina lutea* gave 86 % of results similar, i.e. showing a less than fourfold difference, with 12 % higher with the staphylococcus and 2 % higher with *Sarcina lutea*;

(2) the staphylococcus and *S. typhi* gave only 35 % of results similar and 65 % higher with the *S. typhi*; and

(3) the *Sarcina* and *S. typhi* gave only 21 % of results similar and 79 % higher with the typhoid bacillus.

Table 2 gives the serum ampicillin levels in a patient with *S. paratyphi B* infection. Here, with all three test organisms, all results are closely related. This is in contrast to the results in sera from typhoid fever patients where the staphylococcus and *Sarcina* results are similar but the *S. typhi* results suggest that very high concentrations of ampicillin were present.

Table 3 shows the results of cephaloridine assays in patients' sera. Again this same pattern of discrepancy between the concentrations is evident.

A search of the available literature revealed only one reference to this phenomenon. Hermans, Martin, Needham & Nichols (1966), reporting on the laboratory and clinical evaluation of cephaloridine, state that the determination of the

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Table 1. *Serum ampicillin concentrations in typhoid patients*

Patient	Daily dosage	Time after dose (hr.)	Serum concentrations (μg./ml.) tested against *S. typhi*	Staph.	*Sarc. lutea*	Antibody titres TH	TO	TVi	BH	BO	Other data
(A) Female, aged 67	1 g. × 3 (5 days)	8	2·0	1·92	0·96	12,800	100	10	—	—	Ill for 10 days, then admitted 25. v. 1964, W positive
		2	8·0	7·68	0·96						
		8	16·0	1·92	0·48						
		2	16·0	7·68	3·84						Discharged 30. vi. 1964
		8	8·0	1·92	0·96						
		2	32·0	7·68	7·68						Relapsed 28. vii. 1964
		8	16·0	0·96	0·96						
		2	32·0	7·68	7·68						Re-admitted 5. viii. 1964, B & F positive
		8	1·0	0·96	0·96						
		2	64·0	3·84	1·92						Ampicillin started 7. viii. 1964
											Discharged 26. viii. 1964
(B) Female, aged 62	1 g. × 3 (107 days)	8	8·0	0·48	0·24						Ill for 10 days, then admitted 25. v. 1964, B positive
		2	8·0	7·68	3·84						
		8	32·0	0·48	0·96						
		2	32·0	7·68	7·68						Relapsed 16. vi. 1964, B & F positive
		8	4·0	0·48	0·48						
		2	8·0	7·68	7·68						
		8	4·0	0·96	0·96						F again positive 6. viii. 1964
		2	16·0	3·84	3·84	400	—	80	—	—	
		8	16·0	0·96	1·92						Long-term ampicillin started 8. viii. 1964
		2	4·0	3·84	0·96						
											Discharged 25. viii. 1964
											Chronic carrier
(C) Female, aged 76	1 g. × 4 (2 days)	6	8·0	7·68	—						Ill for 14 days, then admitted 30. vi. 1964, W positive
		2	8·0	15·36	3·84						
		8	8·0	0·96	0·96						
	1 g. × 3 (89 days)	2	32·0	3·84	3·84						F positive 3. vii. 1964
		8	8·0	0·24	0·24						
		2	8·0	1·92	0·96						Relapsed 30. vii. 1964
		8	4·0	0·12	0·48						
		2	1·0	0·96	0·96						F positive 2. viii. 1964
		8	4·0	0·48	0·48						
		2	4·0	1·92	—	1,600	—	40	—	—	Long term ampicillin started 4. viii. 1964
											Discharged 29. ix. 1964
(D) Male, aged 26	1 g. × 3 (39 days)	8	4·0	0·48	0·24						Ill for 5 days, then admitted 4. vi. 1964, B positive
		2	8·0	7·68	0·48						
		8	16·0	0·48	0·48						
		2	16·0	1·92	1·92						Discharged 3. vii. 1964
		8	4·0	0·48	0·48						
		2	16·0	7·68	7·68						Relapsed 24. vii. 1964
		8	4·0	0·96	0·96						
		2	8·0	1·92	1·92	1,600	—	20	—	—	Re-admitted 1. viii. 1964, B & F positive
											Ampicillin started 4. viii. 1964
											Discharged 20. viii. 1964

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Table 1 (*cont.*)

Patient	Daily dosage	Time after dose (hr.)	Serum concentrations (μg./ml.) tested against: *S. typhi*	Staph.	*Sarc. lutea*	Antibody titres: TH	TO	TVi	BH	BO	Other data
(E) Female, aged 58	1 g. × 3 (19 days)	8	16·0	0·24	0·48	12,800	—	20	—	—	Ill for 5 days, then admitted 5. vi. 1964, B, F & W positive
		8	8·0	0·24	0·48						Discharged 5. vii. 1964
		2	4·0	1·92	1·92						Relapsed 22. vii. 1964
											Re-admitted 25. vii. 1964, F positive
											Ampicillin started 29. vii. 1964
											Discharged 29. viii. 1964
(F) Female, aged 6	0·5 g. × 4 (29 days)	6	2·0	0·12	—	—	—	—	—	—	Ill for 6 days, then admitted 7. vi. 1964, B & F positive
		2	2·0	0·12	—						Relapsed 11. vii. 1964, B positive
	0·5 g. × 2 (71 days)	6	2·0	1·92	1·92						Long-term ampicillin started 20. vii. 1964
		2	16·0	3·84	—						Discharged 15. viii. 1964
(G) Male, aged 43	1 g. × 6 (16 days)	1	8·0	3·84	1·99						Ill for 7 days, then admitted 16. vi. 1964, B & F positive
		2	16·0	3·84	1·99						Discharged 18. vii. 1964
		4	16·0	1·92	1·99						Relapsed 8. x. 1964, very ill
		4	16·0	1·92	—						Re-admitted 8. x. 1964, B positive
		2	16·0	3·84	—						Ampicillin begun 12. x. 1964
		4	32·0	1·92	—						Discharged 10. xi. 1964
		2	8·0	1·92	—						
		4	8·0	3·84	—						
		2	32·0	7·68	—	800	25	160	400	—	
		4	16·0	7·68	—						
		4	4·0	3·84	—						
		2	8·0	3·84	—						
		4	8·0	3·84	—						
		1	4·0	1·92	—						
		2	8·0	3·84	—						
(H) Female, aged 46	1 g. × 3 (81 days)	8	16·0	1·92	—						Ill for 2 days, then admitted 24. vi. 1964, F & W positive
		2	32·0	3·84	—						Long-term ampicillin started 25. viii. 1964
		4	32·0	3·84	—						Discharged 11. ix. 1964
		6	32·0	1·92	—						Chronic carrier
		2	32·0	7·68	—						
		4	32·0	3·84	—	100	—	10	—	—	
		6	32·0	3·84	—						
(I) Male, aged 53	1 g. × 4 (10 days)	8	64·0	0·96	—	3,200	—	40	—	—	Ill for 8 days, then admitted 23. v. 1964, B & F positive
		2	64·0	7·68	—						Long-term ampicillin started 13. vii. 1964
	1 g. × 3 (73 days)	4	32·0	15·36	—						Discharged 29. vii. 1964
		6	64·0	1·92	—						Chronic carrier
		8	32·0	0·48	—						

B, blood culture; F, faeces culture; W, agglutination test(s).

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Table 2. *Serum ampicillin concentrations in a case of* S. paratyphi B *infection*

Patient	Daily dosage	Time after dose (hr.)	Serum concentrations (μg./ml.) tested against		
			S. typhi	Staph.	*Sarc. lutea*
Male, aged 58	1 g. × 3	8	1·0	0·12	0·24
		2	2·0	1·92	—
		8	2·0	0·24	0·48
		2	4·0	3·84	3·84
		2	4·0	1·92	1·92
		2	8·0	7·68	7·68
		8	1·0	0·96	1·92
		2	1·0	1·92	—

Table 3. *Serum cephaloridine concentrations in typhoid patients*

Patient	Daily dosage	Time after dose (hr.)	Serum concentration (μg./ml.) tested against		Antibody titres					Other data
			S. typhi	Staph.	TH	TO	TVi	BH	BO	
J	0·5 g. × 2	2	128·0	7·68	100	25	10	—	—	R.H. (male) aged 70 Chronic carrier
		4	128·0	3·84						
		6	128·0	1·92						
		9	128·0	0·48						
		12	128·0	0·06						
K	0·5 g. × 2	2	128·0	3·84	3200	—	10	—	—	L.D. (female) aged 34 Convalescent carrier
		4	64·0	1·92						
		6	128·0	0·96						
		9	128·0	0·12						
		12	128·0	0·015						
L	0·5 g. × 2	2	128·0	7·68	400	—	20	—	—	A.S. (female) aged 67 Chronic carrier
		4	64·0	3·84						
		6	256·0	1·92						
		9	256·0	0·48						
		12	256·0	0·12						

bactericidal activity of serum obtained from patients while they received cephaloridine, as tested against the micro-organisms previously isolated from the same patients, gave unusual results. Bactericidal activity was still present in dilutions of serum as high as 1/1600 in some patients. These authors went on to say that this seemed out of proportion to the expected activity when related to the concentration of the antibiotic measured by serum assay on the same samples and they stated that no explanation for this discrepancy was available at the time of reporting. Of the 25 patients treated with cephaloridine by them, only one was a case of typhoid fever, where the patient developed shock on the 8th day of treatment having been febrile for 1 month before this and while under treatment satisfactory serum bactericidal tests were obtained on a dosage schedule of 1 g. intramuscularly every 6 hr. Other infecting organisms in the remaining 24 patients ranged through staphylococci, pneumococci, streptococci, *E. coli*. *Bacteroides* sp. and one strain of *Corynebacterium xerosis*.

The present results also showed, with cephaloridine assays, the same discrepancies and to this can be added also the similar findings with ampicillin. That

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Table 4. *Ampicillin concentrations in patients' sera: effect of 'inactivation'*

Patient	Dosage	Time after dose (hr.)	Ampicillin conc. (μg./ml.) in patients' sera as below: Unheated *S. typhi*	Unheated Staph.	After 56° C. for 30 min. *S. typhi*
G	1 g. × 6 daily	1	8·0	3·84	2·0
		2	16·0	3·84	4·0
H	1 g. × 3 daily	2	32·0	3·84	4·0
		4	32·0	3·84	4·0
		6	32·0	1·92	2·0
I	1 g. × 3 daily	8	64·0	0·96	1·0
		2	64·0	7·68	16·0
		6	64·0	1·92	2·0
		8	32·0	0·48	1·0

these high concentrations were related to the use of the infecting organism in the assays was borne out in the estimations done on the paratyphoid fever patient's sera where the results with *S. typhi*, the staphylococcus and *Sarcina lutea* were in close agreement.

Were these discrepancies in the typhoid patients' sera related to the presence of typhoid antibodies? This might well be except that in patient F (Table 1) the usual antibodies – including Vi antibodies – were absent and still the high results were obtained. The effect of heating such sera to 55° C. for 30 min. seemed worth while. Sufficient sera remained from patients G, H and I to permit the assays being repeated on heated and unheated serum samples with *S. typhi* and the staphylococcus as the test organisms. Table 4 clearly shows that, after heating, the levels obtained tallied with those against the staphylococcus with the unheated serum.

DISCUSSION

Garrod, Lambert & O'Grady (1973) have indicated that the aim of systemic treatment is to attain and maintain a drug concentration in the blood and tissues of the patient sufficient to exert the effect desired until the infection has been overcome. The drug concentration between doses should exert this effect either continuously or with only short intermissions. To achieve the maximum benefit from treatment, the MIC of the therapeutic agent to kill or inhibit the invading micro-organism should be known and the dosage given should be adequate to maintain this for most of the time between one dose and the next.

For the *S. typhi* phage type 34 of the Aberdeen typhoid outbreak, the MIC of ampicillin effective over an 8 hr. exposure was found to be between 0·4 and 0·3 μg./ml. in shallow broth culture, while between 0·3 and 0·2 μg./ml. was adequate in deep cultures (Fig. 1). Which of these results should be accepted as a guide to minimal maintenance level in the patients' blood must be a matter for surmise. If, in the present context, the highest concentration of 0·4 μg./ml. is accepted and set against the patients' serum ampicillin blood concentrations given in Table 1,

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then it would appear that the doses given satisfied the purpose of the treatment, namely to attain and maintain the MIC level for most of the time between doses.

The dosage of cephaloridine, when given, was 0·5 g. twice daily by intramuscular injection. Table 3 gives the serum concentrations at specific times after injection and Fig. 2 shows that the MIC lay between 1·5 and 2·5 or even 2 μg./ml. according to whether the deep or shallow method of assay was used. To attain and maintain a reasonable MIC in the patients' bloods, the 12-hourly dosage was obviously inadequate and a 6- or 8-hourly dosage might have been more effective. However, cephaloridine only became available in 1964 – the year of the Aberdeen typhoid outbreak – and its dosage and clinical applications had not then been fully investigated and reported. Later in 1964, Muggleton, O'Callaghan & Stevens reported that an intramuscular dose of 0·5 g. in man usually yielded a blood concentration of over 12 μg./ml. at 1 hr. and still nearly 2 μg./ml. at 6 and 8 hr. The results given in Table 3 are in general agreement with the findings of these authors. The failure of cephaloridine to produce good clinical results in the few cases treated with it may be due to the apparent inadequacy of the dosage used.

No serum concentrations of chloramphenicol or methacycline were assayed. Both antibiotics exerted a bacteriostatic influence only on all the strains of *S. typhi* tested. A concentration of chloramphenicol of between 5 and 2·5 μg./ml. was adequate over an 8 hr. period *in vitro* to maintain bacteriostasis (Fig. 3). Similarly, a concentration of 2·0–2·5 μg./ml. of methacycline seemed adequate for bacteriostasis over the same period.

If only the *S. typhi* phage type 34 of the outbreak had been used in testing the concentrations of ampicillin and cephaloridine in patients' sera then high and misleading figures would have been recorded. Such findings agreed with the results of Hermans *et al.* (1966) in their studies with cephaloridine. These discrepant results in the case of ampicillin can be eliminated by heating the sera as is done to destroy complement, but whether complement or heat-labile antibodies contribute to bring about the discrepancies remains unanswered. Insufficient sera from cephaloridine treated patients remained in the present investigation to try the effect of heating in these instances. It can only be surmised that such heating would nullify the unexpected enhancements of the levels of cephaloridine in such sera.

These findings serve to stress that *in vitro* assessments of antibiotic activity in typhoid fever are not true guides to the success of the antibiotic in treatment. Furthermore, if the infecting strain of *S. typhi* is used as the test organism when assessing the concentration of ampicillin or cephaloridine in patients' sera, unduly high results can be recorded and so add to the confusion.

I am grateful to the Secretary of State for Scotland for the research grant which supported this and other work which followed on the Aberdeen typhoid outbreak of 1964. My thanks are also due to Dr Winifred McPherson and all others who assisted in any way during the investigations.

Anyone wishing to read the full report of the research should apply to the Secretary, Biomedical Research Committee, Scottish Home and Health Department, St Andrew's House, Edinburgh.

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