BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 15 1937

VALUE OF A SPECIFIC SERUM IN THE TREATMENT OF TYPHOID FEVER

A REPORT ON SEVENTY-THREE CASES

BY

HAROLD COOKSON, M.D., B.Sc.Birm., M.R.C.P.

*Physician to the Cornelia and East Dorset Hospital, Poole; Temporary Consulting Physician to the Poole
Borough Isolation Hospital*

AND

R. V. FACEY, M.B., B.Ch.Oxon.

Bacteriologist to the Royal Victoria and West Hants Hospital, Bournemouth

In the past typhoid fever therapy has been largely confined to diet, hydrotherapy, and the treatment of symptoms; and few, if any, of the infectious fevers due to a known organism occurring in this country have been less amenable to specific measures. Anti-typhoid sera have been available for a considerable time, but these have not been subjected to potency tests by animal experiment, nor have they been standardized by titration, except for the H-antibody, which is of no value since it has neither anti-bacterial nor antitoxic effect. It is therefore not surprising that the clinical results following the use of such sera have been disappointing. Attempts at specific therapy with typhoid vaccine have also not given satisfaction, and it is doubtful if good results, if they really do occur with this method, are actually due to a specific action. In any case treatment with vaccines has a limited application, and in a severe attack of the disease, where the need is most urgent, their use is dangerous.

Within the last year or two, however, following upon the work of Felix, a serum prepared at the Lister Institute has been available the potency of which has been demonstrated in animal experiment, in which it has been shown capable of protecting against the effects of injections of live *B. typhosus* and also against the toxic action of massive doses of dead organisms (Felix and Pitt, 1934). Felix believes that virulent (Vi) strains of the organism are characterized by a special Vi antigen which renders the O antigen resistant to the O antibody; to be effective against a virulent strain the immune serum must therefore contain Vi antibody. On the other hand, as Felix and Pitt (1934) have shown in animal experiments, the Vi antibody is mainly bactericidal and has no appreciable antitoxic action. From this it is clear that therapeutic anti-typhoid serum should contain an adequate amount of O or antitoxic immune bodies in order to avoid an adverse effect produced by toxins liberated as a result of the bactericidal action of the Vi antibody. In addition to Vi antibody the Lister Institute serum contains O antibody, which is an indicator of the potency of the serum in antitoxic activity. Estimations of the Vi titre in the sera of untreated patients show this to be low until convalescence (Felix, Krikorian, and Reitler, 1935). The necessity for a balance between bactericidal and antitoxic activities will be referred to again in discussing some

favourable serum effects which appeared to be delayed. It is possible that further experience will show the desirability of using the Vi and O antibodies separately, the dosage of each being controlled by serial agglutination tests.

At the present time the results in three series of cases of typhoid fever treated with Lister Institute serum have been published. Felix (1935) reported forty-three cases together with seventeen controls who received injections of normal horse serum. At first the immune and the normal serum were given to alternate patients, the medical attendants being unaware as to which was the specific preparation. Before long, however, they became so convinced that a beneficial action followed the use of one of the sera (which was in fact the specific) that they refused to continue with the other, and no further controls were therefore obtained. The anti-typhoid serum used was unconcentrated and had maximum agglutination titres for Vi and O antibodies of 400 and 40,000 respectively; it was given chiefly by the intramuscular route, the usual dose being 50 c.cm., but this was repeated daily in severe cases to a total of three doses. Of the forty-three cases favourable effects were noted on the toxæmia in twenty-four, and on the temperature in twenty-three. Twelve patients were classed as extremely severe cases, and of these five died. C. J. McSweeney (1935) recorded the results in eight patients treated at Dublin, and Robertson and Yu (1936) in fifty-six patients treated in China; the serum used was either that obtained from the Lister Institute or, in the Chinese cases, was locally prepared by a similar method.

All these observers agreed in concluding that the serum was held to have a favourable effect on both the toxæmia and the temperature, but assessment of its value on the basis of mortality rate was impossible, since there were no controls or these were inadequate. Similarly the mortality in treated series as compared with that in other outbreaks where no serum has been used is of no value as a criterion of its efficiency because of the well-known variation in the severity of the disease from one outbreak to another. To control the results adequately it would be necessary to observe the effects in a large series of cases when serum was strictly reserved for alternate patients, all of whom should preferably be at about the

TABLE I
(IM= Intramuscularly. IV= Intravenously. (d)= Delayed.)

Case No.	Age & Sex	Serum			Effect on toxæmia	Effect on temperature	Severity	Remarks	Case No.	Age & Sex	Serum			Effect on toxæmia	Effect on temperature	Severity	Remarks
		Day given	Dose (c.cm.)	Route							Day given	Dose (c.cm.)	Route				
1	2½ M	16th	7	IM	—	—	Severe		35	16 F	12th	13	IM	—	—	Very severe	Multiple abscesses. Severe respiratory symptoms
2	4 F	13th	13	IM	+	—	Severe		36	16 M	16th	22	IM	+	—	Moderate	
3	5 M	23rd	11	IM	+	—	Moderate		37	16 F	14th	13	IM	+	+	Severe	
4	5 M	13th	10	IM	+	+	Severe				15th	7	IM	+	+		
5	5 M	34th	13	IM	—	—	Very severe		38	16 F	33rd	33	IV	+	—	Very severe	Multiple abscesses; severe hæmorrhages; two blood transfusions. Died
6	6 M	40th	11	IM	+	+	Very severe				35th	20	IM	+	—		
7	7 F	12th	10	IM	+	—	Very severe		39	17 F	22nd	33	IM	+	—	Mild	
		35th	13	IM	+	+	Very severe	Femoral thrombosis and pulmonary embolus occurred during convalescence; died			25th	33	IM	+	+		
		37th	17	IM	+	+			40	18 M	21st	13	IM	+	—	Severe	
		40th	20	IM	+	+					22nd	7	IM	+	+		
8	7 M	9th	10	IM	—	—	Very severe		41	18 F	34th	13	IM	—	—	Very severe	Septic complications; anaemia; blood transfusion. Died
		17th	20	IV	—	—					35th	33	IM	—	—		
		18th	20	IV	+	+					36th	13	IM	—	—		
9	7 F	23rd	10	IV	+	+	Severe		42	18 F	41st	33	IM	—	—		
		24th	10	IV	+	+					11th	13	IM	+	+	Very severe	
		26th	10	IV	+	+											
10	7 F	29th	15	IM	—	—	Mild	Serum given during relapse	43	19 F	26th	33	IV	+	+	Very severe	Died
		30th	20	IM	+	+(d)					31st	33	IM	+	+		
11	8 F	17th	10	IM	—	—	Mild				32nd	33	IV	+	+		
12	9 F	41st	12	IM	—	—	Moderate	Serum given in relapse	44	19 M	33rd	33	IV	+	+		
13	9 M	22nd	11	IM	+	+	Moderate		45	21 M	18th	17	IM	+	—	Moderate	
14	9 M	11th	11	IM	—	—	Severe				11th	13	IM	no toxæmia	+(d)	Mild	
		13th	13	IM	—	—					13th	17	IM				
		14th	13	IM	+	+											
15	9 M	19th	13	IM	—	—	Severe		46	23 F	37th	33	IM	+	+	Severe	Serum given during relapse
		20th	7	IM	—	—					38th	33	IM	+	+		
		27th	7	IM	—	—											
16	9 M	13th	13	IM	+	+	Severe		47	24 F	7th	33	IM	—	—	Moderate	
											10th	33	IM	—	—		
											11th	33	IM	—	—		
17	10 F	31st	13	IM	+	+	Moderate		48	25 F	18th	33	IM	+	+(d)	Severe	
		32nd	10	IM	+	+					22nd	33	IM	+	+		
18	10 F	28th	20	IM	—	—	Severe		49	26 F	16th	15	IM	+	+	Moderate	
		34th	33	IM	+	+					17th	25	IV	+	+		
19	10 M	24th	11	IM	+	+	Very severe				18th	20	IV	+	+		
20	10 F	35th	13	IM	+	+	Very severe		50	26 F	33rd	16	IM	+	+	Moderate	
		36th	13	IM	+	+											
		38th	13	IM	+	+			51	27 F	20th	20	IV	+	+	Very severe	
21	11 M	20th	11	IM	—	—	Very severe				21st	20	IV	+	+		
											22nd	17	IV	+	+		
22	11 F	26th	30	IM	+	—	Very severe	Brachial neuritis in convalescence—? serum effect	52	27 F	39th	33	IM	+	—	Severe	
		27th	33	IM	+	+					42nd	33	IM	—	+		
		28th	13	IM	+	+			53	29 F	27th	33	IM	—	—	Severe	Intestinal hæmorrhage; blood transfusion
23	12 M	31st	15	IM	+	+	Very severe	Serum given during recrudescence			28th	13	IM	—	—		
											33rd	33	IM	+	+(d)		
24	12 M	55th	13	IM	+	+	Very severe	Perforation on 31st day; serum given during relapse	54	31 F	18th	20	IV	+	—	Very severe	
											19th	20	IV	+	—		
25	12 M	20th	16	IM	—	—	Very severe		55	31 F	35th	20	IV	+	—	Severe	
		38th	13	IM	+	+			56	32 F	10th	16	IM	+	+	Mild	
		40th	13	IM	+	+											
		42nd	13	IM	+	+			57	32 F	39th	20	IM	+	+	Severe	Third dose of serum given during relapse
26	13 F	7th	20	IM	+	+	Mild				40th	33	IM	+	+		
27	14 F	11th	13	IM	+	+	Very severe				73rd	33	IM	+	+		
		13th	7	IM	+	+			58	33 F	? 4th	26	IM	—	—	Very severe	Ill three weeks before taking to bed
		14th	15	IM	+	+					? 5th	33	IM	—	—		
											? 6th	33	IM	—	—		
28	14 M	11th	13	IM	—	—	Severe		59	33 F	21st	13	IM	+	+	Very severe	
29	14 M	30th	13	IM	—	—	Severe		60	34 F	39th	13	IM	+	—	Severe	Intestinal hæmorrhage; three blood transfusions given
		35th	15	IM	+	+					40th	33	IM	+	—		
30	14 F	39th	20	IM	+	+	Severe				41st	10	IM	+	+		
											59th	10	IM	+	+		
31	14 F	25th	20	IM	—	—	Very severe	Blood transfusion	61	36 F	9th	13	IM	+	+	Severe	
32	15 M	10th	13	IM	—	—	Very severe	Died	62	37 F	2nd	33	IM	—	—	Severe	
											3rd	33	IV	—	—		
33	15 F	29th	13	IM	+	+	Severe		63	37 F	32nd	22	IM	+	—	Very severe	Anaphylactic shock after second injection
											42nd	20	IV	+	+		
34	15 M	22nd	20	IM	—	—	Severe		64	37 F	37th	33	IM	—	—	Severe	
		24th	20	IM	+	+(d)					45th	33	IM	+	—		

TABLE I—*continued*

Case No.	Age & Sex	Serum			Effect on tox- aemia	Effect on tem- perature	Severity	Remarks
		Day given	Dose (c.cm.)	Route				
65	38 F	29th 30th	20 23	IM IV	+	+	Very severe	
66	44 F	45th 47th	33 33	IM IM	—	— +(d)	Very severe	
67	46 F	6th 7th 12th	15 20 26	IM IM IM	+	— — —	Moderate	
68	49 F	29th	33	IM	no tox- aemia	—	Moderate	Intestinal haem- orrhage; blood transfusion
69	59 F	39th 40th	33 13	IM IM	— +	— +	Severe	
70	67 F	47th	15	IM	no tox- aemia	+(d)	Mild	Complicated by subacute cho- lecystitis
71	67 M	12th 15th	13 17	IM IM	— —	— —	Moderate	History of cor- onary occlusion one year pre- viously
72	70 F	25th 26th	33 20	IM IM	— —	— —	Very severe	Complicated by uraemia and thrombophle- bitis. Died
73	74 M	34th 35th	33 33	IM IM	— —	— —	Very severe	Thrombophle- bitis; convul- sion; died

same stage of the disease. This ideal has been closely approached in investigations on anti-pneumococcal serum, but up to the present it is far from being realized in clinical experiments with anti-typhoid serum, and because of the insidious onset of the fever it is hardly likely to be attained.

Results in the Present Investigation

A local outbreak in 1936, the result of a milk-borne infection which involved some 500 persons, provided an opportunity for the use of the new anti-typhoid serum. Of approximately 500 patients admitted to the local borough isolation hospitals seventy-three received serum, and with a few exceptions these were the more severe cases. Unfortunately the circumstances were not such as were likely to secure the optimum results: the majority received serum late in the course of the disease; in a considerable proportion of the cases the dosage was too low (partly because of difficulty in obtaining adequate supplies); and in a few simultaneous blood transfusion or intravenous saline infusion made it difficult to assess the results. There were no controls, the treatment being reserved largely for the more severe cases. The details are given in Table I. In all there were fifty-five classified as severe or very severe, of which twenty-seven were children aged 15 or under; the total number of children was thirty-four.

In assessing the results the stage at which treatment was started is important, since in the later stages natural improvement is more likely and might be wrongly attributed to the remedy, though this source of error will diminish in proportion to the severity of the case. During the first fourteen days of the illness twenty patients were treated (reckoning the onset from the day of taking to bed), thirteen during the third week, and forty later than this. The dosage is given in Table I; it averaged 24 c.cm. in children and 47 c.cm. in adults; in many instances it was probably too low, as the amount for adult patients recommended by the Lister Institute is three doses of 33 c.cm. of the concentrated serum. A preliminary de-

sensitizing dose of 0.5 c.cm. was given intramuscularly. The titres of the batches of serum used, estimated by agglutination, were stated to be 1 in 600–700 against strain Watson, and 1 in 60,000 against strain 0901, for Vi and O antibodies respectively.*

The results were considered in relation to effects on temperature and toxæmia separately; the latter was occasionally benefited apart from the temperature, though the reverse never occurred. Temperature, being an entirely objective observation, may be regarded as the more reliable criterion of effect, yet it is not in fact a simple matter to define exactly what is meant by a favourable effect. We have taken as an arbitrary standard the lowering of a previously high constant temperature within forty-eight hours of the injection of serum, the fall continuing for at least seven days; in many cases it reached normal and remained down permanently. Doubtful effects were classified as negative—for example, in the cases in which the temperature was falling just before the serum was given. When the result was favourable the fall in temperature was combined as a rule with an increase in the daily remission—that is, the chart showed a curve similar to that observed during the phase of spontaneous defervescence in typhoid. Effects on toxæmia, the signs of which do not require definition, were accepted only when well marked, and if evident within forty-eight hours.

Of the seventy-three cases there was a favourable action, as defined above, on toxæmia in fifty-four patients (in thirty-eight of these the effect being noted after the initial dose of serum), and on temperature in forty (in twenty-eight after the first dose). When the cases are classified according to the period of the disease at which treatment was started the results were as follows: first fourteen days, favourable effects on toxæmia in eleven and on temperature in eight of twenty treated; third week, eleven and five respectively out of thirteen; later than the third week, thirty-two and twenty-seven respectively out of forty. Three patients showed no symptoms of toxæmia (Table II).

TABLE II.—*Serum Effects Classified According to the Period of Disease Treated*

Period of disease treated	Number treated	Favourable effect on toxæmia	Favourable effect on temperature
First 14 days	20	11	8
Third week	13	11	5
Later than third week	40	32	27
Totals	73	54	40

In a further eight patients improvement was noted within two to seven days after treatment, and we have reason to think that the beneficial effects of serum may sometimes be delayed for this period. Seven of the serum-treated patients died; in two of these (Nos. 38 and 41) there was sepsis; three (Nos. 7, 72, and 73) had thrombophlebitis; two were over 70 (Nos. 72 and 73); and three were moribund when treatment was started (Nos. 38, 43, and 73). In No. 32 the dosage was wholly inadequate. Case No. 73, a man aged 74, was admitted to hospital on the thirty-fourth day of the disease, and had been about until that time.

A few cases may be mentioned individually as being of special interest.

No. 63 had a prolonged and severe illness with high temperature, delusions, and retention of urine with cystitis. On

* The serum, we understand, now supplied by the Lister Institute is of about double this strength.

the thirty-second day 22 c.cm. of serum were given intramuscularly, but this was not followed by any definite effect. Ten days later, after desensitization, 20 c.cm. of serum were given intravenously: a severe anaphylactic reaction followed, but immediately after this general improvement set in. It is possible that this favourable effect was non-specific, a result of anaphylactic shock.

Case No. 43, a girl of 19, when moribund, was given gum-saline and serum intravenously and intramuscularly to a total dosage of 132 c.cm. in a week; delirium disappeared, the patient became quiet and mentally clear, and the temperature fell; she was in an exhausted condition, however, and died six days later. Case No. 62, in which serum was given very early and in adequate doses, was fairly severe; there was no immediate effect on temperature or toxæmia, but seven days after the initial injection it began to fall and became more remittent, finally reaching normal on the nineteenth day of her illness.

Case No. 22, a girl aged 11, was severely toxic, with abdominal distension, vomiting, delirium, and lethargy, showing all the features of the typical "typhoid state," and later there was coma with incontinence of urine; the pulse was 140, being irregular and "thready." On the twenty-sixth day, when her condition appeared desperate, 30 c.cm. of serum were given intramuscularly and further doses of 33 and 13 c.cm. respectively on the following two days. Within twenty-four hours there was a marked general improvement; the patient was no longer comatose, the delirium ceased, and the temperature fell by lysis, reaching normal on the thirty-third day. Convalescence was uneventful with the exception of a brachial neuritis, which is to be mentioned later. Case No. 38, a girl, aged 16, was given 33 c.cm. of serum intravenously on the thirty-third day and 20 c.cm. intramuscularly on the thirty-fifth day; at this time toxæmia was severe and she was in a semi-conscious, delirious condition. After the injections the temperature remained high, but the restlessness and delirium cleared for forty-eight hours; a blood transfusion the day before the first dose of serum was given had had no effect on these symptoms. Unfortunately, soon after the beneficial effects were noted subcutaneous abscesses appeared and the patient died.

Serum Complications

A serum rash was observed in twenty-two of the seventy-three cases. Case No. 64, a female aged 37, who had toxic goitre, had an attack of tachycardia—pulse 160—on the day following the first injection of 33 c.cm. intramuscularly, but this soon subsided; the second injection of 33 c.cm. eight days later caused no by-effects, and the patient's general condition took a turn for the better. The observation illustrates how, in the presence of toxic goitre, a reaction to serum may be excessive, just as it is to infection or trauma. Case No. 22, a girl of 11, who had received a total of 76 c.cm. serum in three days, which is a large dose for a child, developed a brachial neuritis affecting the fifth and sixth cervical roots. Owing to the patient's exhausted condition and the absence of all subjective symptoms, the exact time of onset is uncertain, but it was first noticed about a fortnight after the serum was given. On stimulation electrically the reactions of degeneration were observed in the deltoid and inner head of the biceps. The condition is slowly improving, but after four months there is still some weakness in the affected arm. Neurological complications of serum treatment are rare; they have been reviewed by I. M. Allen (1931), who described four types: neuritic, radicular, polyneuritic, and cerebral. The radicular type, which is most common and usually affects the brachial plexus, is almost indistinguishable from the toxic brachial neuritis which occasionally follows typhoid fever. There were no other signs of serum sickness, but these are not always observed in neurological serum complications. It is, however, im-

possible to decide whether the paralysis should be regarded as a serum reaction or as a toxic effect of the disease.

A severe anaphylactic reaction was seen once only (Case No. 63). As already noted, after the reaction an improvement in this patient's condition occurred. In two children (Cases Nos. 6 and 14) a desensitizing dose of 0.5 c.cm. serum produced severe local and general reactions and further doses were withheld. Both of these children had been given serum a few days previously without reaction.

Conclusion and Summary

Previous reports on the therapeutic effect of Felix anti-typhoid serum have all been favourable, and similarly the results of the present investigation on seventy-three patients are thought to be encouraging. The serum is known to be potent in animals, and while the result of the injection of *B. typhosus* into a laboratory animal is a very different matter from the naturally occurring disease in man, the demonstration of such potency in a serum would appear desirable prior to its clinical use. Some of the difficulties in assessing the value of serum in typhoid have been mentioned, and although the present and previous reports suggest that it is a remedy of definite promise, its exact worth is to be proved only by more extended use, and, where circumstances permit, with adequate controls. An adequate control could be provided by withholding all serum from alternate patients. There appears to be no need to give the controls normal horse serum, as there is already sufficient evidence that horse serum *per se* has no beneficial effect.

In a considerable proportion (73 per cent.) of cases we noted improvement within forty-eight hours of injection of the serum. In a further 10 per cent. some benefit occurred after a few days' interval, and in these it is possible that the action of the serum was delayed. Theoretically this might occur when the antitoxic lagged behind the bactericidal action, the first effect being predominantly a destruction of organisms with liberation of toxin in amounts too great to be dealt with immediately by the available antitoxin.

The mortality in the treated patients was 9.5 per cent., which may prove to be somewhat higher than in the others (the rate for the whole epidemic is not yet available), but as the former group was selected on the basis of greater severity no comparison is possible. Of thirty-three patients treated during the first three weeks only one died; the dose of serum in this case (13 c.cm.) was inadequate.

For sporadic cases or small outbreaks, where the numbers do not admit of proper controls, we believe the evidence so far available warrants the administration of serum at the earliest possible moment, and in full doses, irrespective of the severity of the disease.

We have to acknowledge our thanks to the medical officers of health for Poole and Bournemouth, and to the honorary physicians of the Royal Victoria and West Hants Hospital, who kindly allowed us to see patients under their direct care and to make use of their case notes.

REFERENCES

- Allen, I. M. (1931). *Lancet*, 2, 1128.
- Felix, A., and Pitt, R. M. (1934). *Ibid.*, 2, 186.
- (1935). *Ibid.*, 1, 799.
- , Krikorian, K. S., and Reitler, R. (1935). *J. Hyg.*, 35, 421.
- McSweeney, C. J. (1935). *Lancet*, 1, 1095.
- Robertson, R. C., and Yu, H. (1936). *British Medical Journal*, 2, 1138.