STREPTOMYCIN TREATMENT OF INFANTILE DIARRHOEA AND VOMITING

CONDUCT AND RESULTS OF A CONTROLLED TRIAL

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This paper gives an account of a controlled investigation into the effects of oral administration of streptomycin on infantile diarrhoea and vomiting. The work was done during 1949 at St Ann's General (formerly the North Eastern) Hospital, London, on behalf of the Medical Research Council's Antibiotics Clinical Trials (Non-Tuberculous Conditions) Committee.

Before proceeding to describe the investigation, we think it desirable to give some account of the routine working of the enteritis unit of the hospital, in so far as this affected the design and conduct of the trial.

ACCOMMODATION

Throughout 1949 the enteritis unit consisted of two wards for the treatment of infants with diarrhoea and vomiting. Each ward contained twenty-eight single cells equipped for isolation nursing. The number of infants in either ward was not allowed, normally, to exceed twenty-four at a time, and the remaining cells were available for mothers of breast-fed infants. Only one of the wards was used for the purposes of the streptomycin trial.

SOURCES AND TYPES OF CASES

Infants were sent in to the enteritis unit from domiciliary practices, from residential institutions and from other hospitals. They came from many districts, mainly in the London area. Admission to the unit was arranged at the request of the infant's medical attendant, sometimes directly, but usually through the Emergency Bed Service. The sole requirement was a medical certificate or opinion that the case was one of 'enteritis' or 'gastro-enteritis' needing admission to hospital. There were no facilities for out-patient treatment, so that an infant, once accepted, had to be admitted irrespective of the severity of illness on arrival at the hospital. Infants over one year of age were not normally accepted for admission to the unit.

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A consequence of this procedure was that infants sent to the enteritis wards were not selected by the medical staff of the hospital on any criteria other than the stated age and certified diagnosis. In this respect the practice differed from that of most children's hospitals, where mild cases can be treated as out-patients.

A further consequence of the mode of admission was that the type of case and severity of illness on arrival varied widely. The only feature common to all cases was a history of recent diarrhoea. Most of the infants, on or after arrival, were found to have diarrhoea, with varying degrees of dehydration. Many of them had signs of parenteral infection. A few had no diarrhoea after admission.

ADMISSION TO THE TRIAL

Only one of the two enteritis wards was used for the trial, and to this ward were admitted both cases for streptomycin treatment and control cases. There was no transfer of infants between the two wards. The plan was to maintain a strict alternation of admissions to each ward, in order to avoid selection of cases for the trial ward. From time to time one of the wards would be full, and it would then become necessary to admit consecutive arrivals to one ward. Twins were admitted to either ward, but each pair was sent to the same ward.

ROUTINE MANAGEMENT AND TREATMENT

Throughout the trial all cases were treated according to the established routine of the unit. This has been described by one of us in an earlier publication (Alexander, 1948). The principles may be summarized as follows:

(1) A short preliminary period of starvation.

(2) Early resumption of milk feeds.

(3) Maintenance of fluid requirements and replacement of fluid loss, by the administration of adequate quantities of fluid by the appropriate route—oral or intravenous.

The choice of the route of administration of fluids was based on a clinical assessment of the infant's general condition and of the degree of dehydration.

In mild cases the infants were given half-strength Hartmann's solution by mouth 2-hourly, for 12–18 hr., in quantities adequate for weight and age. After this period of starvation dilute milk feeds were begun, increasing in strength to a full-calorie feed on the fourth or fifth day after admission.

Moderately dehydrated infants were treated in the same way as the mild cases. If they failed to respond intravenous therapy was begun and treatment continued as for the severe cases.

Severely dehydrated infants were given fluids by the intravenous route. They were given half-strength Hartmann's solution with 5 % glucose followed by three-quarter strength human serum or plasma, in quantities calculated to replace the amount of fluid lost and to supply the total daily fluid requirements intravenously. Milk feeds were begun on the first or second day after the institution of intravenous therapy and gradually increased in strength and size. In most cases intravenous therapy was discontinued after the second day, and the infants were usually able to tolerate full-calorie feeds by the fifth or sixth day of treatment.

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CHEMOTHERAPY

Sulphadiazine was given to some of the infants in both the streptomycin-treated and control series. Originally employed for the treatment of associated parenteral infections the use of sulphadiazine in this unit had for some years been extended to the treatment of infants in whom parenteral infection was suspected, although confirmatory physical signs were not found. The drug was given by mouth in doses of 0·5 g. 4-hourly for 5 days.

Penicillin, when indicated for the treatment of parenteral infections, was given intramuscularly in doses of 250,000–500,000 units 6-hourly for 5–6 days. No other drugs were employed except iron for the treatment of anaemia. Preparations containing vitamins A, C and D were given by mouth to all infants as a routine.

ADMINISTRATION OF STREPTOMYCIN

Streptomycin was received in bottles containing the equivalent of 1·0 g. of streptomycin base. Streptomycin sulphate (Pfizer), supplied by the Medical Research Council, was used until July 1949. Streptomycin calcium chloride complex (Glaxo) was used from July onwards. Before use the powder was dissolved in sterile distilled water. Individual doses, each in 10 ml. of water, were prepared in separate containers and stored in the refrigerator until required. The period of storage was usually a few days and never exceeded 14 days. The drug was given by mouth only, the first dose immediately after admission to the ward. Three scales of dosage were employed:

1*st period* (infants admitted 3–30 January). A total of 2 g. was given over a period of 4 days—0·2 g. 6-hourly for four doses, followed by 0·2 g. 12-hourly for six doses. As this dosage failed to inhibit coliform growth from the rectal swab in the first seven treated cases it was decided to increase the dosage.

2*nd period* (infants admitted 31 January–25 August). A total of 2·8 g. was given in a period of 36 hr.—0·4 g. 6-hourly for seven doses.

3*rd period* (infants admitted 26 August–31 December). The dosage in the first 36 hr. was the same as in the second period, namely, 2·8 g., but was followed by a maintenance dose of 0·4 g. 12-hourly for a further 4 days, making a total of 6 g. in 6 days.

CONDUCT OF THE TRIAL

One ward only was used for the trial, and to this ward both cases for streptomycin treatment and control cases were admitted. When the trial was planned it was decided to give streptomycin to alternate patients admitted to the trial ward and to begin the administration of streptomycin immediately after admission. No attempt was made, therefore, to group the cases on arrival according to severity of illness, as this might be expected in some cases to have delayed the administration of streptomycin until an adequate period of observation had enabled the severity to be assessed. It was, however, decided to consider breast-fed infants as forming a special group separate from the main group of artificially fed infants. Alternate cases in each of these two groups were given streptomycin, regardless of the severity of illness on admission.

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The investigation began on 3 January 1949. From then until 31 December 1949, all infants under 1 year of age on admission to the ward were included in the trial. Cases admitted after 31 December 1949 were not included in the trial, but, in order to maintain a comparable environment for the cases remaining in the ward, administration of streptomycin to alternate new cases on admission was continued until all the infants included in the trial had been discharged.

The clinical condition of all cases was noted on admission by the admitting medical officer. Subsequent observations were made daily by the medical officer in charge of the ward, except for two periods of 3 weeks during which the infants were seen daily by another medical officer fully conversant with the methods of the unit. Detailed records of the clinical findings and progress were kept, on the basis of which the cases were ultimately classified and the response to treatment assessed.

Classification of cases

The classification of cases was made at the end of the trial. The first step was to define the type of case for inclusion in the final analysis. The number of breast-fed infants proved to be too small to warrant any comparison between streptomycin-treated and control cases in that group. Infants found to have *Salmonella* or *Shigella* infections, and those with no evidence of diarrhoea after admission, were also excluded from further consideration.

The remaining cases were all bottle-fed infants with diarrhoea from whom no recognized intestinal pathogenic organisms were isolated, and it was on the progress of these infants that the assessment of the effects of streptomycin treatment was made. The cases under consideration were classified according to the initial degree of dehydration into three severity groups:

(1) *Mild.* Cases in which there was no evidence of dehydration during the first 24 hr. after admission.

(2) *Moderate.* Cases in which signs of dehydration were present in the first 24 hr., of such degree as would normally be treated by oral administration of fluids.

(3) *Severe.* Cases with severe dehydration requiring intravenous therapy on admission or within 24 hr. of admission.

Comparability of streptomycin-treated and control series

The next step in the analysis was to compare the streptomycin-treated and control cases in each severity group in respect of factors other than dehydration that might affect the nature and course of the illness and the response to treatment. The following factors were considered:

Season of admission.

Age of infant.

Nutritional state.

Length of illness before admission.

Evidence of parenteral infection.

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Assessment of the response to treatment

The criteria used for assessment of the response to treatment were:

Degree and duration of dehydration.

Duration of diarrhoea.

Tolerance of feeds.

Dehydration was assessed on clinical signs, and the degree, duration and variation of the signs were recorded in each case. Diarrhoea was judged to have ceased when the stools had become normal in frequency, consistency and appearance. Tolerance of feeds was assessed by recording the day of treatment on which the infant's intake reached 50 calories per lb. body weight without vomiting or exacerbation of diarrhoea.

The correction of dehydration, return of stools to normal and tolerance of a full-calorie feed could be expected in most cases before the end of the first week. Subsequent recurrences of diarrhoea were regarded as separate from the initial illness and were taken into account in the final assessment. Recurrences of diarrhoea were classified as follows:

(1) *Minor upsets.* Abnormality of stools of short duration and associated with no constitutional disturbance.

(2) *Relapses.* Abnormality of stools associated with constitutional disturbance as shown by some or all of the following: pyrexia, pallor, vomiting or refusal of feeds, loss of weight or failure to gain weight, dehydration.

Relapses were further subdivided according to the degree of dehydration:

(*a*) Mild—those in which there was no evidence of dehydration.

(*b*) Moderate—those showing dehydration of such degree as would normally be treated by oral administration of fluid.

(*c*) Severe—those in which the degree of dehydration was such as to require intravenous therapy for rehydration.

CLINICAL FINDINGS

The number of infants entering the trial was 185, of whom 7 were readmitted after discharge from the ward. Infants readmitted were regarded as new cases for the purposes of this trial. The total number of cases, therefore, was 192 (Table 1).

In all, 33 cases were excluded from the final analysis. Seven were breast-fed infants and 3 were infants found to have *Salmonella* or *Shigella* infections. The remaining 23 were infants who showed no evidence of diarrhoea after admission, and, of these, 19 fell into the control series and only 4 into the streptomycin-treated series. The 159 cases shown in the analysis, therefore, included a larger number of streptomycin-treated (S.T.) than control (C.) cases. The disparity is too great to be attributed to chance alone and may indicate that in some cases streptomycin contributed to the occurrence of diarrhoea in infants who might otherwise have had no diarrhoea during the period immediately following admission. There were 57 mild cases (26 C. and 31 S.T.), 66 moderate cases (26 C. and 40 S.T.) and 36 severe cases (20 C. and 16 S.T.). The differences in numbers within

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each severity group are not too great to be attributed to chance alone and are not, therefore, considered to invalidate comparison between the streptomycin-treated and the control series.

Table 1. *Comparison of control* (C.) *and streptomycin-treated* (S.T.) *series in respect of age of infant and severity of illness on admission*

	Bottle-fed infants with diarrhoea						
	Mild		Moderate		Severe		
Age	C.	S.T.	C.	S.T.	C.	S.T.	Total C. and S.T.
0–3 weeks	—	—	1	2	—	—	3
4–7 weeks	2	1	3	8	3	2	19
8–12 weeks	5	5	9	9	2	3	33
3 months	1	2	1	5	2	—	11
4 months	7	4	2	2	2	3	20
5 months	4	3	2	2	3	3	17
6 months	1	4	4	4	4	2	19
7 months	2	5	2	2	1	1	13
8 months	2	1	—	4	2	1	10
9 months	—	3	1	—	1	—	5
10 months	2	1	—	2	—	1	6
11 months	—	2	1	—	—	—	3
Total	26	31	26	40	20	16	159

	Excluded cases						
	Breast-fed infants with diarrhoea		Specific enteritis		No diarrhoea		
Age	C.	S.T.	C.	S.T.	C.	S.T.	Total C. and S.T.
0–3 weeks	1	1	—	—	1	—	3
4–7 weeks	—	1	—	—	—	—	1
8–12 weeks	—	—	—	—	2	2	4
3 months	2	2	—	—	2	—	6
4 months	—	—	—	—	—	—	—
5 months	—	—	—	—	4	—	4
6 months	—	—	1	1	1	—	3
7 months	—	—	—	—	1	—	1
8 months	—	—	—	—	—	—	—
9 months	—	—	—	—	1	1	2
10 months	—	—	1	—	4	1	6
11 months	—	—	—	—	3	—	3
Total	3	4	2	1	19	4	33

Comparability

The trial was continued for a year to allow for possible seasonal variation in type of case but none was observed. The age distribution is shown in Table 1, from which it may be seen that there was no undue preponderance of the younger age groups in the streptomycin-treated or control series, and that cases fell into comparable groups in respect of severity of illness on admission.

Other comparability factors are set out in Table 2. In the severe groups 11 out

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of 20 control cases and 3 out of 16 streptomycin-treated cases received sulphadiazine during the first week after admission, due partly to differences in the incidence of parenteral infections. This was the most important difference between the two series. Other differences were not such as to invalidate comparison of response to treatment. The time when full-calorie feeds were first offered is included in order to show that the same routine of feeding was followed in both series.

Table 2. *Comparison of initial condition of control* (C.) *and streptomycin-treated* (S.T.) *cases in severity groups*

	Mild		Moderate		Severe	
	Control	Streptomycin-treated	Control	Streptomycin-treated	Control	Streptomycin-treated
No. of cases	26	31	26	40	20	16
Days ill before admission (mean)	6·08 ± 1·23	5·23 ± 0·52	8·23 ± 1·46	5·90 ± 0·84	4·75 ± 0·49	7·19 ± 1·22
Under weight* on admission	2	—	8	9	4	3
Parenteral infection on admission:						
(*a*) Coryza	5	12	2	8	1	—
(*b*) P.I. other than coryza	3	4	5	9	7	1
Sulphadiazine on admission or during 1st week	5	7	9	13	11	3
Full calorie feeds first offered (days) (mean)	5·84 ± 0·72	6·00 ± 0·72	4·64 ± 0·42	4·15 ± 0·15	6·65 ± 0·69	6·00 ± 0·63

* Infants were regarded as under weight if, after correction of dehydration, the weight was less than 90 % of the expected weight for birth weight and age.

Parenteral infections on admission

The parenteral infections found on admission were: broncho-pneumonia 11, bronchitis 8, suppurative otitis media 5, whooping cough 3, urinary infections 2. In addition, 28 infants, mainly in the older age groups, had signs of mild upper respiratory tract infections on admission (i.e. nasal discharge, or injection of the faucial or pharyngeal mucosa, with or without pyrexia).

Progress during first week

Table 3 presents an analysis of the clinical findings to compare the progress of cases in the streptomycin-treated and control series. No significant difference was demonstrated between the streptomycin-treated and control cases on the criteria adopted for assessment of progress during the first week of hospital stay. Taking all degrees of severity together 48 (67 %) control cases and 55 (63 %) streptomycin-treated cases were convalescent at the end of the first week of hospital stay, that is to say, dehydration had been corrected, the stools had become normal and

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Table 3. *Comparison of progress of control* (C.) *and streptomycin-treated* (S.T.) *cases in severity groups*

	Severity group						All groups			
	Mild		Moderate		Severe		C.		S.T.	
	C.	S.T.	C.	S.T.	C.	S.T.	No.	%	No.	%
No. of cases	26	31	26	40	20	16	72	100	87	100
Dehydration present in first 24 hr.	—	—	26	40	20	16	46	64	56	64
Subsequent dehydration during first 7 days	2*	2	8†	7	1‡	3	11	15	12	14
Subsequent intravenous therapy during initial illness	1	1	4	2	—	3	5	7	6	7
Cessation of diarrhoea—days after admission (mean)	4·81 ± 0·72	5·97 ± 0·90	6·85 ± 1·19	6·78 ± 0·79	6·25 ± 0·77	7·56 ± 1·40	—	5·94 ± 0·54	—	6·63 ± 0·54
Duration of initial diarrhoea more than 7 days (no. of cases)	3	5	9	11	2	6	14	19	22	25
Full-calorie feeds tolerated—days after admission (mean)	6·68 ± 0·97	6·45 ± 0·71	6·12 ± 0·69	5·93 ± 0·75	6·65 ± 0·69	8·25 ± 1·06	—	6·47 ± 0·46	—	6·54 ± 0·47
Convalescent at end of first week (in respect of 3 criteria)—no. of cases	22	23	14	23	12	9	48	67	55	63
No recurrence of diarrhoea	13	19	10	9	10	11	33	46	39	46
Minor upsets	2	2	7	7	6	4	15	21	13	15
Relapse mild	3	1	7	10	2	1	12	17	12	14
Relapse moderate	6	3	1	8	1	—	8	11	11	13
Relapse severe	2	6	1	6	1	—	4	6	12	14
Deaths	—	1	—	—	—	—	—	—	1	—

* Developing after first 24 hr. † Deteriorating after first 48 hr. ‡ Persisting after i.v. therapy.

the infants were able to tolerate full-calorie feeds. In 14 (19%) control cases and in 22 (25%) streptomycin-treated cases diarrhoea persisted after the first week in hospital.

Subsequent progress

In the mild group relapses were almost equally frequent (11 of 26 C. and 10 of 31 S.T.). In the moderate group there were relatively more relapses in the streptomycin-treated series (9 of 26 C. and 24 of 40 S.T.). In the severe group there were few relapses, and most of them occurred in the control series (4 of 20 C. and 1 of 16 S.T.).

The severity of the relapses varied. Most of the severe relapses occurred in the streptomycin-treated series (4 C. and 12 S.T.), but the difference in incidence is not statistically significant. There was one death, that of an infant aged 5 weeks who was admitted with mild enteritis and received streptomycin. She improved at first, but a severe relapse began on the 9th day, and the infant died on the 16th day.

A comparison of the progress of the streptomycin-treated cases in each of the three dosage periods showed no apparent advantage with increase of dosage. The only difference noted was that there were fewer severe relapses with the highest dosage (10 of 48 cases admitted in period II and 2 of 32 cases in period III), but no conclusion could be drawn from this, as there were no severe relapses in the control cases admitted during period III.

Tolerance of streptomycin

No difficulty was experienced in the administration of streptomycin. The drug was well tolerated and vomiting was uncommon. No difference was noted in the naked-eye appearance of the stools of streptomycin-treated and control cases.

Two infants developed transient morbilliform rashes while on streptomycin treatment. This may have been a toxic effect of the drug, as no similar rash was seen in the control series. No other toxic effects were observed. No cases of dermatitis occurred among members of the nursing staff handling the streptomycin.

BACTERIOLOGICAL INVESTIGATIONS

The primary object of the trial was to assess the effects of oral administration of streptomycin on the clinical progress of infants with diarrhoea. At the same time a bacteriological study was made, with particular reference to the effects of the treatment on certain serological types of *Bacterium coli*.

Bacteriologists during recent years have isolated from cases of infantile diarrhoea and vomiting two serological types of *Bact. coli*. The first has been known variously as *Bact. coli* var. *neapolitanum* (Bray, 1945), *Bact. coli* α (Giles & Sangster, 1948; Smith, 1949), and *Bact. coli* D433 (Taylor, Powell & Wright, 1949), and the second as *Bact. coli* β (Giles, Sangster & Smith, 1949). Kauffmann & Dupont (1950) assigned these two serological types to *Bact. coli* O group 111 and *Bact. coli* O group 55 respectively.

Throughout the present investigation rectal swabs and specimens of faeces were

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examined for *Salmonella* and *Shigella* and rectal swabs for *Bact. coli* O 111. From April 1949, examinations of rectal swabs were also made for *Bact. coli* O 55. The *Bact. coli* antisera were supplied by Dr Joan Taylor and by Dr Joyce Wright.

Method

Rectal swabs were taken from all infants, in the receiving room, immediately before admission to the ward, and were inoculated on three plates in the following order:

(1) Horse-blood nutrient digest agar (pH 7·6) containing 1 in 1000 chloral hydrate (Gillespie, 1948).

(2) MacConkey's medium.

(3) Deoxycholate-citrate medium (Hynes, 1942).

Further rectal swabs were taken daily from each infant for the first 5 days after admission and were plated on MacConkey's medium and on deoxycholate-citrate medium. After the end of the first month of the investigation daily rectal swabbing of streptomycin-treated cases was continued for 8 days after admission, or longer if there was still no coliform growth on MacConkey's medium. Rectal swabs were also taken weekly (on each Tuesday throughout 1949) from all infants in the ward and were plated on MacConkey's medium only.

All cultures, throughout the investigation, were incubated aerobically at 37° C.

Isolation of Salmonella *and* Shigella

Rectal swabs were plated on deoxycholate-citrate medium for the isolation of organisms of the *Salmonella* and *Shigella* groups. In addition, 248 specimens of faeces from 181 cases were examined. Faecal specimens were plated on deoxycholate-citrate medium and also inoculated into selenite F medium. Twenty-four-hour cultures in selenite F medium were plated on deoxycholate-citrate medium. After 18–24 hr. incubation the plates were examined for non-lactose-fermenting organisms, and, when these were found, at least four representative colonies were subcultured into liquid urea medium; those which were urease-negative after 5 hr. incubation were investigated by the appropriate biochemical and serological methods.

Isolation of Bact. coli O 111 *and* Bact. coli O 55

Coliform colonies on chloral hydrate blood agar or on MacConkey's medium were tested by the slide agglutination method with *Bact. coli* O 111 B 4 antiserum and, from April 1949, with *Bact. coli* O 55 B 5 antiserum. At least four colonies were tested before a plate was regarded as negative, and in most cases ten colonies were tested. When positive slide agglutination tests yielded presumptive evidence of the isolation of *Bact. coli* O 111 or of *Bact. coli* O 55 for the first time from any infant, either on admission or during the hospital stay, the following procedure was adopted:

(1) Colonies giving positive slide agglutination reactions were subcultured on nutrient digest agar slopes which were stored at room temperature.

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(2) The primary plates or nutrient agar slopes were sent to Miss R. E. Hilton and Dr Joan Taylor for confirmation, by tube agglutination, of the presence of *Bact. coli* of the specific serological types, and for biochemical investigation.

Streptomycin sensitivity tests

It was found by various methods that the *Bact. coli* O111 and *Bact. coli* O55 strains which were resistant to 10 units of streptomycin per ml. of medium were also resistant to 10,000 units per ml. For confirmation of sensitivity tests, the stored subcultures of *Bact. coli* O111 and *Bact. coli* O55 were tested after the conclusion of the investigation by the following standardized method:

The subcultures were plated on MacConkey's medium and incubated for 18–24 hr. One colony from each plate was picked into peptone water from which, after 5 hr. incubation, a standard loopful was inoculated into peptone water containing 10 units of streptomycin per ml. If, after 48 hr. incubation, growth was observed by naked-eye inspection, the strain was described as streptomycin-resistant. *Bact. coli* 7362, a streptomycin-sensitive strain from the National Collection of Type Cultures, was used as a control organism.

BACTERIOLOGICAL FINDINGS

Recognized intestinal pathogenic organisms were isolated from only 3 of the 192 cases admitted (*Shigella flexneri* 1 case, *Shigella sonnei* 1 case, *Salmonella adelaide* 1 case).

In all cases coliform organisms were grown from the rectal swabs taken before admission to the ward. From these admission swabs, strains identified as *Bact. coli* O111 were isolated in 35 cases (16 streptomycin-treated and 19 control); 10 of these strains (6 from streptomycin-treated cases and 4 from control cases) were resistant to streptomycin before treatment was begun. *Bact. coli* O55 was isolated from the admission swabs in 11 cases (6 streptomycin-treated and 5 control), and 2 of these strains (both from streptomycin-treated cases) were resistant to streptomycin before treatment was begun.

The infants from whom the specific *Bact. coli* types were isolated on admission were all bottle-fed and suffering from diarrhoea. Table 4 shows the correlation between the bacteriological findings and the severity of illness on admission. The streptomycin-treated and control series in each severity group were broadly comparable in respect of the number of cases *Bact. coli* O111 or *Bact. coli* O55 positive on admission. The incidence of these specific *Bact. coli* types found on admission was highest in the severely ill group. This is in accordance with the findings recorded by Holzel, Martyn & Apter (1949). Other workers (Young, Smith, Russell & McNicholl, 1951) reported α strains of *Bact. coli* to be distributed evenly among their severe and mild cases.

The remaining tables (Tables 5, 6 and 7) refer to the bacteriological findings in the 159 cases of non-specific diarrhoea that were considered in the clinical section of this paper, and the results are set out to demonstrate the inhibition, in strepto-

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Table 4. *Correlation of specific* Bact. coli *types isolated on admission with severity of initial illness*

Clinical group	Total no. of cases	*Bact. coli* O 111 positive		*Bact. coli* O 55 positive		*Bact. coli* O 111 and *Bact. coli* O 55 negative		Not tested for *Bact. coli* O 55
		No.	%*	No.	%*	No.	%*	
Control cases								
Excluded cases								
(1) No diarrhoea	19	—	—	—	—	15	100	4
(2) Specific enteritis	2	—	—	—	—	2	(100)	—
(3) Breast-fed infants with diarrhoea	3	—	—	—	—	1	(100)	2
Bottle-fed infants with diarrhoea								
(1) Mild	26	2	8	—	—	15	88	9
(2) Moderate	26	7	27	3	14	13	62	5
(3) Severe	20	10	50	2	13	7	47	5
Total controls	96	19	20	5	7	53	75	25
Streptomycin-treated cases								
Excluded cases								
(1) No diarrhoea	4	—	—	—	—	3	(100)	1
(2) Specific enteritis	1	—	—	—	—	1	(100)	—
(3) Breast-fed infants with diarrhoea	4	—	—	—	—	2	(100)	2
Bottle-fed infants with diarrhoea								
(1) Mild	31	—	—	—	—	25	100	6
(2) Moderate	40	8	20	4	14	20	69	11
(3) Severe	16	8	50	2	17	4	33	4
Total streptomycin-treated	96	16	17	6	8	55	76	24

* Based on the number actually tested for *Bact. coli* O 55 or *Bact. coli* O 111 as the case may be.

mycin-treated cases, of coliform growth from rectal swabs, and the subsequent emergence of streptomycin-resistant strains.

In 65 of the 87 streptomycin-treated cases there was no growth of coliform organisms from the rectal swab plated on MacConkey's medium, for periods varying from 1 to 11 days after the beginning of streptomycin treatment. Growth of coliform organisms from the rectal swab failed to occur in only 2 of the 72 control cases. Table 5 relates the duration of the period of 'no coliform growth' to streptomycin treatment, and other forms of chemotherapy begun during the first week of hospital stay.

The mean periods of 'no coliform growth' in the streptomycin-treated cases during the three dosage periods were (days) $0{\cdot}86 \pm 0{\cdot}55$, $1{\cdot}81 \pm 0{\cdot}28$, $3{\cdot}53 \pm 0{\cdot}55$, showing that the duration of the period of inhibition of coliform growth was on the whole longer with higher dosage.

Bact. coli O 111 strains were isolated on admission from 16 infants in the streptomycin-treated series. The strains from 6 of them were streptomycin-

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Table 5. *Duration of period of 'no coliform growth' from rectal swab in relation to chemotherapy during the first week of hospital stay*

Nature of chemotherapy		No. of days 'no coliform growth'										
During first 48 hr.	From 3rd to 7th day	0	1	2	3	4	5	6	7	8	9	10	11
Nil	Nil	46	1	.	.	.	.	.	.	.	.	.	.
Nil	Sulphadiazine only	6	.	.	.	.	.	.	.	.	.	.	.
Nil	Sulphadiazine and penicillin	1	.	.	.	.	.	.	.	.	.	.	.
Sulphadiazine only	Sulphadiazine only	11	.	.	.	.	.	.	.	.	.	.	.
Sulphadiazine only	Sulphadiazine and penicillin	2	.	.	.	.	.	.	.	.	.	.	.
Sulphadiazine and penicillin	Sulphadiazine and penicillin	4	.	.	.	1	.	.	.	.	.	.	.
Streptomycin only	Streptomycin only	18	18	8	8	7	1	.	2	2	.	.	.
Streptomycin only	Streptomycin and sulphadiazine	1	2	1	.	.	.	.	.	.	.	.	1
Streptomycin only	Streptomycin and sulphadiazine and penicillin	1	.	.	.	.	.	.	.	.	.	.	.
Streptomycin and sulphadiazine	Streptomycin and sulphadiazine	1	3	.	.	4	.	.	3	3	.	.	.
Streptomycin and sulphadiazine and penicillin	Streptomycin and sulphadiazine and penicillin	1	1	.	.	.	.	1	.	.	.	.	.

resistant, and these infants continued to excrete such streptomycin-resistant organisms for varying periods of time. The strains from the remaining 10 infants were streptomycin-sensitive. Eight of these 10 infants, after periods of 'no coliform growth' varying from 0 to 7 days, were found to be excreting streptomycin-resistant *Bact. coli* O 111 strains; one infant, after a period of 7 days' 'no coliform growth', was found to be excreting streptomycin-sensitive *Bact. coli* O 111; from the remaining infant no *Bact. coli* O 111 was isolated when the coliform growth returned. Four infants from whom streptomycin-sensitive *Bact. coli* O 55 strains were isolated on admission received streptomycin treatment. All four of these infants, after periods of 'no coliform growth' varying from 1 to 5 days, were found to be excreting streptomycin-resistant *Bact. coli* O 55 strains. From 15 control cases streptomycin-sensitive *Bact. coli* O 111 strains were isolated on admission, and streptomycin-sensitive *Bact. coli* O 55 strains from 5. No change in streptomycin sensitivity was noted in the specific *Bact. coli* strains isolated from these 20 control cases during the first 5 days after admission.

Table 6 shows the number of cases in the streptomycin-treated and in the control series from which the specific *Bact. coli* types were isolated, for the first time, after admission. Including the 11 cases shown in Table 4, from which *Bact. coli* O 55 were isolated on admission, there were 124 cases (53 control and 71 streptomycin-treated) from which no *Bact. coli* O 111 was isolated on admission. Seventy-four of these became *Bact. coli* O 111 positive after admission, 29 in the control series, and 45 in the streptomycin-treated series. *Bact. coli* O 55 was isolated, for the first time, after admission, from 34 cases, 10 control and 24 streptomycin-treated cases.

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Table 6. *Distribution of streptomycin-sensitive and streptomycin-resistant specific* Bact. coli *types isolated, for the first time, after admission*

		Bact. coli O 111 and *Bact. coli* O 55 negative on admission				*Bact. coli* O 111 positive on admission			*Bact. coli* O 55 positive on admission		
			After admission				After admission			After admission	
Group	Period of admission	No. admitted	*Bact. coli* O 111 sensitive	*Bact. coli* O 111 resistant	*Bact. coli* O 55 sensitive	*Bact. coli* O 55 resistant	No. admitted	*Bact. coli* O 55 sensitive	*Bact. coli* O 55 resistant	No. admitted	*Bact. coli* O 111 sensitive	*Bact. coli* O 111 resistant
Control cases (C.)	Jan.–Mar.	13*	7 (54)	3 (23)	Not tested for *Bact. coli* O 55		6	Not tested for *Bact. coli* O 55		—	Not tested for *Bact. coli* O 55	
	Apr.–June	8	4 (50)	2 (25)	2 (25)	—	4	—	—	1	1	—
	July–Sept.	13	—	7 (54)	2 (15)	1 (8)	6	—	—	1	—	1
	Oct.–Dec.	14	2 (14)	2 (14)	1 (7)	4 (29)	3	—	—	3	—	—
	Totals	48*	13 (27)	14 (29)	5 (14)	5 (14)	19	—	—	5	1	1
Streptomycin-treated cases (S.T.)	Jan.–Mar.	16*	2 (13)	8 (50)	Not tested for *Bact. coli* O 55		5	Not tested for *Bact. coli* O 55		—	Not tested for *Bact. coli* O 55	
	April–June	14	—	13 (93)	6 (43)	—	3	—	—	2	1	—
	July–Sept.	16	—	13 (81)	3 (19)	1 (6)	5	1	—	1	—	1
	Oct.–Dec.	19	2 (11)	5 (26)	—	12 (63)	3	—	1	3	—	—
	Totals	65*	4 (6)	39 (60)	9 (18)	13 (27)	16	1	1	6	1	1

(Figures in brackets are percentages of admission group for period stated, calculated on the number of cases tested in each period.)

* 13 C. and 16 S.T. cases, admitted during the period January–March, were not tested for *Bact. coli* O 55.

Table 7 shows the week of hospital stay in which these specific *Bact. coli* types were isolated. The *Bact. coli* O 111 strains were found on the average at an earlier period of the hospital stay in the streptomycin-treated series. Of the 45 *Bact. coli* O 111 strains isolated, for the first time, after admission from the streptomycin-treated cases, 28 (62 %) were found during the first week of hospital stay. The corresponding figures for control cases were 11 of 29 (38 %). The difference is just

Table 7. *Week of hospital stay in which specific* Bact. coli *types shown in Table* 6 *were first isolated*

Group	No. *Bact. coli* O 111 and *Bact. coli* O 55 negative on admission	*Bact. coli* types isolated after admission (not having been isolated on admission)	Week of hospital stay in which *Bact. coli* types were first isolated: 1	2	3	4 or later	Total
Control cases	48*	*Bact. coli* O 111 sensitive	7	3	2	2	14
		Bact. coli O 111 resistant	4	4	6	1	15
		Bact. coli O 55 sensitive	.	.	1	4	5
		Bact. coli O 55 resistant	.	2	2	1	5
Streptomycin-treated cases	65*	*Bact. coli* O 111 sensitive	1	1	1	2	5
		Bact. coli O 111 resistant	27	7	4	2	40
		Bact. coli O 55 sensitive	.	.	2	8	10
		Bact. coli O 55 resistant	5	3	2	4	14

* 13 C. and 16 S.T. cases not examined for *Bact. coli* O 55.

statistically significant ($P(\chi^2) < 0{\cdot}05$). In the streptomycin-treated series, 40 of 45 (89 %) of the *Bact. coli* O 111 strains isolated, for the first time, after admission, were streptomycin-resistant, a higher proportion than in the control series in which 15 of 29 (52 %) were streptomycin-resistant. This difference is statistically significant ($P(\chi^2) < 0{\cdot}01$). Similar tendencies were apparent in respect of *Bact. coli* O 55 strains isolated, for the first time, after admission, but the numbers are smaller and the statistical evidence correspondingly weaker.

DISCUSSION

Previous workers have used streptomycin in the treatment of infantile diarrhoea and vomiting, and some have claimed encouraging results (Pulaski & Amspacher, 1946; Leisti, 1947; Goettsch, Cobley & Mulloy, 1948; James, Kramer & Armitage, 1948; Diwany, Abdin & Omar, 1950). On the other hand, the results of controlled trials reported by Holzel *et al.* (1949), Lowdon & McNeill (1951) and Young *et al.* (1951) indicate that streptomycin has no therapeutic advantage over accepted forms of treatment. These divergent views may be explained partly by differences in the types of case in which the drug has been tried, and partly by a lack of general agreement on criteria for classification and assessment of progress.

The aetiology of infantile diarrhoea and vomiting remains obscure. It is recognized that dietetic, nutritional and infective factors may contribute to the illness of a particular infant, but their relative importance is often difficult to determine. Infants described as having dietetic diarrhoea are said to respond to

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adjustments in the nature, strength or quantity of the feeds offered; but this is true also of many mildly or moderately ill infants whose diarrhoea is judged, either on clinical or epidemiological grounds, to be of infective origin. Furthermore, the presence of signs of parenteral infection in an infant does not necessarily indicate that the causation of the infant's diarrhoea is different from that of another infant in whom signs of parenteral infection are not found.

In the classification of cases for purposes of treatment, recognition of the degree of dehydration is of the first importance, irrespective of the possible causation of the dehydrating illness. In practice, the severity of dehydration on admission is the guide to the type of treatment the infant initially receives. The cases under consideration in the present series, therefore, have been classified according to the degree of dehydration observed clinically at the time of admission or within 24 hr. of admission. Signs of parenteral infection were noted, but were not used for purposes of classification. The importance of the more severe parenteral infections was held to lie in their possible influence on the progress of the case.

The progress of an infant with diarrhoea is affected profoundly by treatment. In particular, the nature and quantity of fluid and food administered, and the route of administration, may largely determine recovery. In most units established in Great Britain excellent results have been obtained solely by the adequate administration of fluid. The additional benefit to be derived from a chemotherapeutic agent may therefore be difficult to assess. The drug is being tested, not on the natural disease, but on an illness the course of which has been modified by measures directed to the replacement of fluid loss. A routine treatment of all cases of similar degree of severity is a necessary preliminary, therefore, to the study of the effects of any particular therapeutic agent. Such a routine was in existence in this unit before the present trial began. It was verified, by subsequent analysis, that the streptomycin-treated and control series had in fact been of similar severity and had received similar treatment apart from the giving of the trial drug.

Infantile diarrhoea and vomiting is a syndrome of variable severity and duration, and it is not easy to formulate satisfactory criteria for assessment and comparison of progress. As there was only one death among the 192 cases in the trial, case fatality rates could not be used for comparative purposes. Weight changes in the early stages of an infant's stay in hospital are dependent on a number of factors, among the most important of which are the nature and quantity of the food and fluid intake. In infants with diarrhoea, the degree and duration of dehydration and the measures taken for its correction increase the difficulty in the interpretation of weight changes. Weight measurements were not used, therefore, for assessment of progress in this trial. The criteria which were adopted, namely, degree and duration of dehydration, duration of diarrhoea and tolerance of feeds, as defined in the text, appeared to us to be applicable in all cases and to be the most relevant indications of recovery.

During the stage of convalescence relapses of diarrhoea occurred in a number of our cases. Relapses of varying degree of severity are by no means uncommon in infants recovering from diarrhoea and vomiting, and several workers have considered that some relapses may be due to cross-infections occurring in spite of

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the usual barrier-nursing precautions (Alexander, 1948; Taylor *et al.* 1949; Young *et al.* 1951). The fact that in our series the severe relapses occurred mainly in cases only mildly or moderately ill on admission would seem to support this hypothesis. It was for this reason that it was thought desirable in the analysis to separate clear-cut relapses from the initial illness. The final assessment was based, therefore, partly on the initial illness, with particular reference to the progress during the first week of hospital stay, and partly on subsequent relapses.

Interpretation of continued diarrhoea may present difficulty. There is evidence that cross-infection may occur early in the hospital stay, even during the first week (Roden & Wright, 1952). A secondary illness may then overlap the primary and appear clinically as a continuation of the initial illness. It is possible, therefore, that persistence of diarrhoea after the first week of hospital stay, may, in some of our cases, have been the result of early cross-infection. The bacteriological findings in this investigation lend support to the cross-infection hypothesis and are in general agreement with those recorded by Holzel *et al.* (1949). It must be stressed, however, in the interpretation of the findings, that the specific serological types of *Bact. coli* were used only as 'indicator organisms', and it is not suggested that they should, at this stage of our knowledge, be regarded as pathogens. The relation of cross-infection with specific *Bact. coli* strains to clinical relapses has not been analysed further in this paper as, at the time of the investigation, a more detailed cross-infection study was already in progress in the other ward of the unit.

In an enteritis unit consideration of the individual case cannot be separated from consideration of the group as a whole. The possibility of transfer of infection from one case to another is always present, but the risk may vary from time to time, depending on the nature of the cases and the conditions in the ward. The introduction of a drug which is effective against the infecting agent may limit the spread of that agent in the ward. Should the infecting agent be responsible for relapses of diarrhoea and vomiting, administration of the drug to alternate cases admitted to the ward would affect the cross-infection rate and, therefore, the relapse rate in both trial and control groups. The indirect effects of a chemotherapeutic agent on the clinical course of all the cases in a trial ward may not as yet have received sufficient consideration in the planning of chemotherapeutic trials.

A further complicating factor arises when administration of the drug under trial is followed by the emergence of infective agents resistant to its action. In the present investigation there was no clinical evidence that streptomycin was effective in the treatment of diarrhoea, but the bacteriological findings are of interest as illustrating the manner in which an effective drug might lose its therapeutic action owing to the spread of resistant organisms. It was found, that, early in the trial, streptomycin-resistant strains of the specific serological types of *Bact. coli* emerged in individual cases and spread in the ward community, either from these cases or from cases admitted with resistant strains. The isolation of streptomycin-resistant strains of *Bact. coli* following the administration of streptomycin has been recorded also by other workers (Holzel *et al.* 1949; Lowdon & McNeill, 1951). Should these organisms cause infantile diarrhoea and vomiting, resistant forms spreading in

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a ward community could give rise to cases against which the trial drug would be ineffective. A trial of the same drug in circumstances more unfavourable to the spread of resistant organisms, for example, in domiciliary practice, might well give a different result.

No attempt will be made here to discuss the significance of the association of specific serological types of *Bact. coli* with infantile diarrhoea and vomiting, but one reason advanced by other workers for the therapeutic use of streptomycin was its effect on the coliform flora of the intestine. According to this hypothesis the inhibition of coliform growth in the gut should contribute to clinical improvement. In the present trial the dosage of streptomycin was shown to be adequate in most cases (65 out of 87) to inhibit coliform growth from the rectal swab, for periods varying from 1 to 11 days. In spite of this it would seem from the clinical findings that streptomycin treatment, although begun at the earliest possible opportunity after admission to hospital, had no beneficial action on the cases in the trial series. It is a matter for conjecture whether this negative result is in any way associated with the spread of streptomycin-resistant coliform strains, or whether the clinical course of infantile diarrhoea and vomiting is unaffected by a drug acting on the coliform flora of the intestine.

SUMMARY

1. An account is given of the design and conduct of a controlled trial of streptomycin by mouth in the treatment of infantile diarrhoea and vomiting.

2. The classification of cases is described. The streptomycin-treated and control series are shown to be comparable in respect of severity of illness on admission and in respect of other factors likely to affect progress.

3. The criteria adopted for assessment of progress are defined, viz. degree and duration of dehydration, duration of diarrhoea and tolerance of feeds.

4. Comparison of streptomycin-treated and control cases was based partly on progress during the first week of hospital stay and partly on subsequent progress.

5. No significant difference was shown between the streptomycin-treated and the control series in respect of progress during the first week. Severe relapses of diarrhoea were proportionately higher in the streptomycin-treated series, but the difference was not statistically significant.

6. The bacteriological investigations are described. *Bact. coli* O group 111 and *Bact. coli* O group 55 were used as 'indicator organisms' in studying the immediate and delayed effects of streptomycin on the coliform flora of the intestine. The results show the inhibition, in streptomycin-treated cases, of coliform growth from the rectal swab, and the subsequent emergence of streptomycin-resistant strains.

7. Evidence of cross-infection with the 'indicator organisms' is given. Problems of cross-infection and relapses of diarrhoea are discussed in relation to the assessment of the effects of a chemotherapeutic agent.

8. The difficulty of defining criteria for classification of cases and assessment of progress is discussed.

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REFERENCES

ALEXANDER, M. B. (1948). *Brit. med. J.* **2**, 973.
BRAY, J. (1945). *J. Path. Bact.* **57**, 239.
DIWANY, M., ABDIN, Z. N. & OMAR, A. (1950). *J. R. Egypt. med. Ass.* **33**, 593.
GILES, C. & SANGSTER, G. (1948). *J. Hyg., Camb.*, **46**, 1.
GILES, C., SANGSTER, G. & SMITH, J. (1949). *Arch. Dis. Childh.* **24**, 45.
GILLESPIE, E. H. (1948). *J. clin. Path.* **1**, 99.
GOETTSCH, E., COBLEY, G. & MULLOY, M. (1948). *Paediatrics*, **2**, 1.
HOLZEL, A., MARTYN, G. & APTER, L. (1949). *Brit. med. J.* **2**, 454.
HYNES, M. (1942). *J. Path. Bact.* **54**, 193.
JAMES, U., KRAMER, I. R. H. & ARMITAGE, P. (1948). *Lancet*, **2**, 555.
KAUFFMANN, F. & DUPONT, A. (1950). *Acta path. microbiol. scand.* **27**, 552.
LEISTI, P. (1947). *Ann. Med. intern. Fenn.* **36**, 575.
LOWDON, G. M. & MCNEILL, M. M. (1951). *Brit. med. J.* **2**, 767.
PULASKI, E. J. & AMSPACHER, W. H. (1946). *Bull. U. S. Army Med. Dep.* **6**, 750.
RODEN, A. T. & WRIGHT, J. (1952). In preparation.
SMITH, J. (1949). *J. Hyg., Camb.*, **47**, 221.
TAYLOR, J., POWELL, B. W. & WRIGHT, J. (1949). *Brit. med. J.* **2**, 117.
YOUNG, W. F., SMITH, G., RUSSELL, A. & MCNICHOLL, B. (1951). *Brit. med. J.* **2**, 770.

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