

# Observations on Cholera Treated Orally and Intravenously with Antibiotics

With Particular Reference to the Number of Vibrios Excreted in the Stool

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*In order to determine the effect of antibiotics on the course of cholera, precise observations of clinical symptoms and quantitative examination of vibrios in the stool were carried out on 17 patients with cholera El Tor from the Philippines. Seven patients were treated orally with kanamycin, tetracycline, chloramphenicol or erythromycin, 7 intravenously with chloramphenicol or tetracycline, and 3 were not given any antibiotic.*

*Both the oral and the intravenous routes of administration of the antibiotics were suitable for shortening the period of diarrhoea and reducing the excretion of vibrios in the stool.*

*The number of vibrios in 1 ml of watery stool during the first day of illness was about 10<sup>8</sup> in every case. There was marked reduction in the number within 1 hour, and complete disappearance of vibrios within 10 hours, of the start of treatment in most cases. However, vibrios reappeared later in some cases.*

*Kanamycin, a non-absorbable antibiotic, was found to be less effective than absorbable antibiotics such as chloramphenicol and tetracycline.*

About 15 years ago, the prevailing opinion was that the use of antibiotics could not affect the prognosis of cholera. Since 1963, however, the favourable effect of antibiotics as a supplementary therapy for cholera has gained recognition (Carpenter et al., 1964; Greenough et al., 1964; Kobari, 1965; Wallace et al., 1965).

It has been known that any antibiotic or antimicrobial chemical agent can shorten the duration of diarrhoea and the excretion of vibrios in the stool and can diminish the amount of fluid required for the treatment. However, the following questions have yet to be answered:

- (1) How fast do vibrios disappear in the stool?
- (2) How long does it take to stop the diarrhoea?
- (3) What is the best route of drug administration?

In addition, much remains to be known about the pathogenesis of cholera and the mechanism of the action of antibiotics on the clinical symptoms.

A preliminary investigation to clarify these problems was carried out in 1964, the results of which are reported elsewhere (Kobari et al., 1967).<sup>5</sup>

In 1965, a more detailed study was undertaken to clarify the effects of various kinds of antibiotics on the signs of collapse, on diarrhoea, and on the number of vibrios in the stools, through continuous observation of clinical symptoms and quantitative examination of vibrios in stools collected at frequent intervals. The results of this study are reported in the present paper.

## MATERIALS AND METHODS

For this investigation El Tor patients were selected from those admitted to San Lazaro Hospital, Manila, between June and November 1965. These

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TABLE 1  
PARTICULARS OF PATIENTS AND TREATMENT

Case No.	Age (years)	Sex	Antibiotic used	Route	Interval between administrations (hours)	Period of administration (days)
1	15	M	None (Control)			
2	19	M	None (Control)			
3	31	F	Chloramphenicol	Intravenous	8	3
4	29	F	Tetracycline	Intravenous	6	1
5	22	F	Chloramphenicol	Oral	6	3
6	40	M	Erythromycin	Oral	6	3
7	45	F	Tetracycline	Oral	6	3
8	52	F	Kanamycin	Oral	4	3
9	26	M	Chloramphenicol	Intravenous	6	3
10	24	M	Chloramphenicol	Intravenous	6	1
11	25	M	Kanamycin	Oral	6	1
12	24	F	Kanamycin	Oral	6	3
13	29	M	Control			
14	23	F	Kanamycin	Oral	6	3
15	35	F	Tetracycline	Intravenous	6	3
16	25	F	Chloramphenicol	Intravenous	6	3
17	20	F	Chloramphenicol	Intravenous	6	3

were typical cholera patients, passing 2 litres of stools or more within 8 hours after admission.

The age and sex of the patients, the kind of antibiotic used for the treatment and its route of administration are indicated in Table 1.

The patients were observed continuously until they were hydrated and revived from collapse. The blood pressure and body temperature were measured every hour until these became normal. The specific gravity of whole blood and/or plasma was examined on admission, and the examination was repeated every 8 hours until the normal level was reached.

The stool was collected directly from the rectum by a rubber catheter every 1 or 2 hours within the first 8 hours after admission, and every 3 hours for the following 15 hours.

The quantitative examination of vibrios was carried out on the collected stool specimens. Tenfold serial dilution was done from  $10^1$  to  $10^8$ , and 0.1 ml of each dilution was streaked on TCBS agar. After overnight incubation, the number of colonies was

counted. If the stool was not watery, 1 g of stool was dissolved in 10 ml of saline solution and the number of vibrios was counted by tenfold serial dilution.

When it was not possible to collect stool directly, rectal swabs were used for culture by the direct and enrichment methods.

#### CASE REPORTS

##### Case No. 1 (Table 2, Fig. 1)

*Clinical details.* A. O., 15 years old, male, was admitted on 22 June 1965 at 09.10 hours because of vomiting and continuous diarrhoea of 10 hours' duration. Vomitus was moderate in amount and consisted of food previously taken in. Stool was voluminous, rice-watery, with a fishy odour. No medication had been given except a leaf concoction given by the patient's mother. On admission, the patient was markedly dehydrated, conscious and coherent with cold, clammy perspiration, washer-

TABLE 2  
OBSERVATIONS ON CASE No. 1 (CONTROL)

Date	Hour	No. of colonies of vibrio on TCBS agar culture of tenfold serial dilution <sup>a</sup>							No. of vibrios in 1 ml stool	Amount of stool (ml)	Colour of stool
		10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-8</sup>	10 <sup>-9</sup>			
22 June	10	U	U	U	83	8	2	0	8.3 × 10 <sup>8</sup>	70	rice-watery
	12	U	U	154	20	4	0	0	1.5 × 10 <sup>8</sup>	760	rice-watery
	14	U	U	61	4	0	0	0	6.1 × 10 <sup>7</sup>	740	rice-watery
	16	U	U	155	24	2	0	0	1.5 × 10 <sup>8</sup>	430	rice-watery
	18	U	U	66	6	0	0	0	6.6 × 10 <sup>7</sup>	700	light yellowish
	20	U	U	138	32	1	0	0	3.2 × 10 <sup>8</sup>	570	light yellowish
	22	U	U	69	6	?	0	0	6.9 × 10 <sup>7</sup>	610	yellow-brown
	24	U	U	52	?	?	0	0	5.2 × 10 <sup>7</sup>	220	yellow-brown
23 June	2	U	U	50	?	?	0	0	5.0 × 10 <sup>7</sup>	100	yellow-brown
	4	U	U	9	?	0	0	0	1.1 × 10 <sup>7</sup>	470	yellow-brown
	6	U	U	37	?	?	0	0	3.7 × 10 <sup>7</sup>	180	dark green
	8	U	U	71	6	0	0	0	7.1 × 10 <sup>7</sup>	240	dark green
24 June	11	U	449	30	2			3.0 × 10 <sup>7</sup>	—	yellow (mucus)	
25 June	11	U	590	62	11			6.2 × 10 <sup>7</sup>	—	yellow (mucus)	
26 June				60	6			6.0 × 10 <sup>7</sup>	—	yellow (mucus)	
27 June								d(+) e(+) <sup>b</sup>	diarrhoea stopped		
28 June								d(-) e(-) <sup>b</sup>			
29 June								d(-) e(-) <sup>b</sup>			

<sup>a</sup> U = confluent growth; ? = uncertain.

<sup>b</sup> Since diarrhoea had stopped, rectal-swab cultures were made; "d" indicates direct culture, and "e" enriched culture; + and - indicate the presence and absence of growth, respectively.

woman's hands and sunken eyeballs. Blood pressure was 20/0, body temperature 36.5°C. Blood and plasma specific gravity were 1.067 and 1.032, respectively. Fluid therapy was started on admission. One tablet of placebo was given orally 2 hours later; thereafter, every 6 hours for 3 days. All the collapse signs and symptoms disappeared after initial hydration. The blood and plasma specific gravity fell to 1.052 and 1.026, respectively. Fluid therapy was discontinued when the plasma specific gravity became normal and the stool output became negligible.

The stool, measured every 2 hours during the first 24 hours, amounted to a total of 5090 ml. The daily output had decreased to about 600 ml (more urine than stool) by the sixth hospital day. The colour changed from rice-watery to light yellow 8 hours after hydration treatment (18 hours after onset), and then to brownish, and finally to dark greenish 20 hours after admission.

The clinical course was uneventful. The patient was ambulatory and asymptomatic on the sixth hospital day. He was discharged on the tenth hospital day as clinically improved and bacteriologically negative for El Tor vibrios on 3 consecutive occasions.

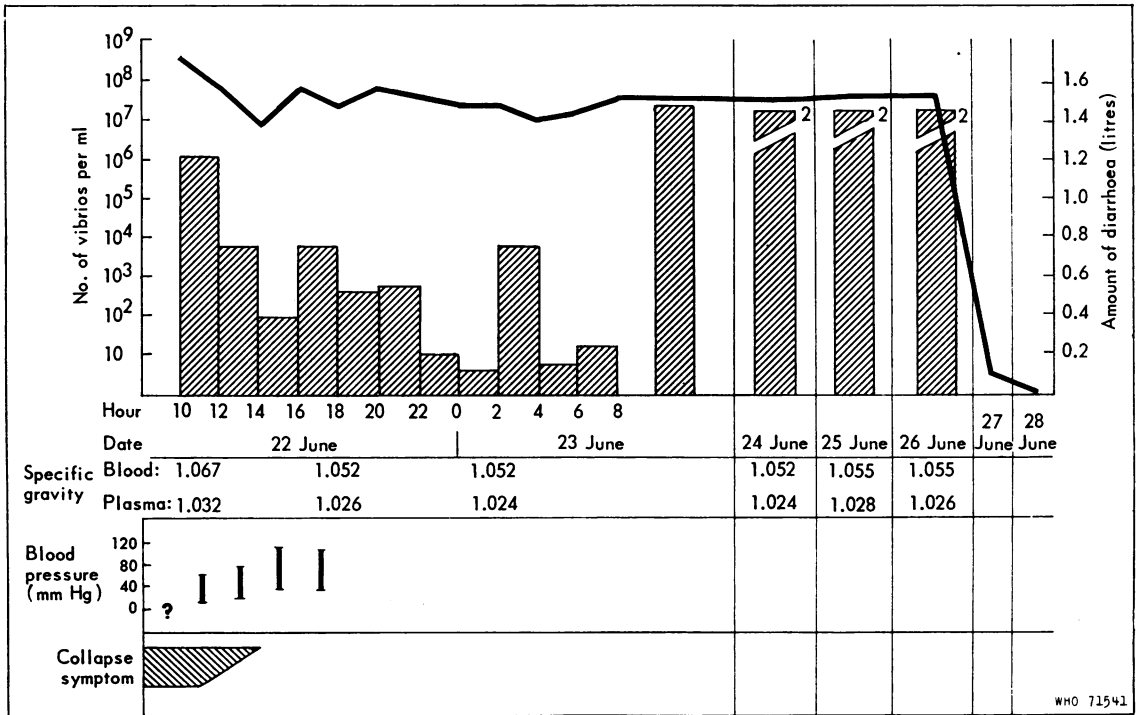
*Bacteriological results.* The number of vibrios in 0.1 ml of serially diluted stool, the amount of stools and certain clinical details are indicated in Fig. 1.

About 10 hours after admission, the number of vibrios was almost 10<sup>8</sup> per ml of stool, and for the following 4 days, the number was about 10<sup>7</sup> per ml; watery diarrhoea continued during this period.

*Case No. 3* (Table 3, Fig. 2)

*Clinical details.* V. L., 31 years old, female, was admitted on 10 July 1965 at 06.15 hours because of vomiting of yellowish, watery material, profuse frequent diarrhoea, abdominal cramps and aphonia of 4 hours' duration. Stool was copious and

FIG. 1  
PARTICULARS OF CASE NO. 1 (CONTROL)



WHO 71541



Amount of diarrhoea.



No. of vibrios per ml of stool.

haemorrhagic, and its colour was reddish-pink like meat infusion. On admission, the patient presented signs and symptoms of marked dehydration and acidosis such as sunken eyeballs, washerwoman's hands, deep, rapid respiration, cold, clammy perspiration, aphonia and abdominal cramps. Blood pressure could not be measured, body temperature was 36°C. The plasma specific gravity was 1.038. Fluid therapy was started on admission. Five hours after admission, chloramphenicol (500 mg) was given by intravenous injection; thereafter, 4 doses were given at intervals of 6 hours. By the tenth hour, all the signs and symptoms of severe dehydration had disappeared. Blood pressure was 120/50. Body temperature was 37.5°C. Plasma specific gravity was 1.032. At the nineteenth hour, the patient had carpo-pedal spasms relieved by 10 ml of 10% calcium gluconate. Except for the diarrhoea, the patient had

no other complaints until the fifty-sixth hour; fluid therapy was then discontinued, with the plasma specific gravity at 1.025 and the stool output negligible in amount.

The stool output measured at 6-hour intervals showed a variable decrease from 3700 ml in the first 6 hours to 3600 ml, 2600 ml and 1600 ml in succeeding 6-hour periods. During the next day the total output was 3000 ml; after that no more watery stool was seen. The peculiar bloody colour of the stool had disappeared almost completely by 5 hours after admission; the stool became rice-watery and soon after the colour changed to yellowish.

The patient was ambulatory and symptom-free after the fifty-sixth hour. She was discharged as clinically improved, and bacteriologically negative for vibrios on 3 consecutive occasions, on the tenth hospital day.

TABLE 3  
OBSERVATIONS ON CASE No. 3 (TREATED INTRAVENOUSLY WITH CHLORAMPHENICOL)

Date and hour	No. of colonies of vibrio on TCBS agar culture of tenfold serial dilution <sup>a</sup>									No. of vibrios in 1 ml stool	Amount (ml) and colour of stool	Admin-istration of antibiotic (chloramphenicol)	
	10 <sup>0</sup>	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-8</sup>				
10 July													
10.30				U	U	205	24	2	0	2.0 × 10 <sup>8</sup>	} 3 700 bloody	+	
11.00				U	U	151	17	2	0	1.5 × 10 <sup>8</sup>			
11.30				U	346	17	0	0	0	1.7 × 10 <sup>7</sup>			
12.00				U	61	15	0	0	0	6.1 × 10 <sup>6</sup>	} 3 600 rice-watery	+	
13.00				75	26	?	0	0	0	2.6 × 10 <sup>6</sup>			
15.00	U	U	84	6	0	0	0	0	0	8.4 × 10 <sup>4</sup>			
17.00	U	U	22	0	0	0	0	0	0	2.2 × 10 <sup>4</sup>	} 2 600 light yellow	+	
20.00	3	4	1	0	0	0	0	0	0	4.0 × 10 <sup>2</sup>			
23.00	0	0	0	0	0	0							
11 July											} 1 600 yellow-green	+	
2.00	0	0	0	0	0	0							
5.00	0	0	0	0	0	0							
8.00	0	0	0	0	0	0							
11.00	0	0	0	0	0	0						+	
12 July	0	0	0	0	0	0							
13 July										d(-) e(+) <sup>b</sup>			
14 July										d(-) e(+)			
15 July										d(-) e(-)			
										d(-) e(-)			

<sup>a</sup> U = confluent growth; ? = uncertain.

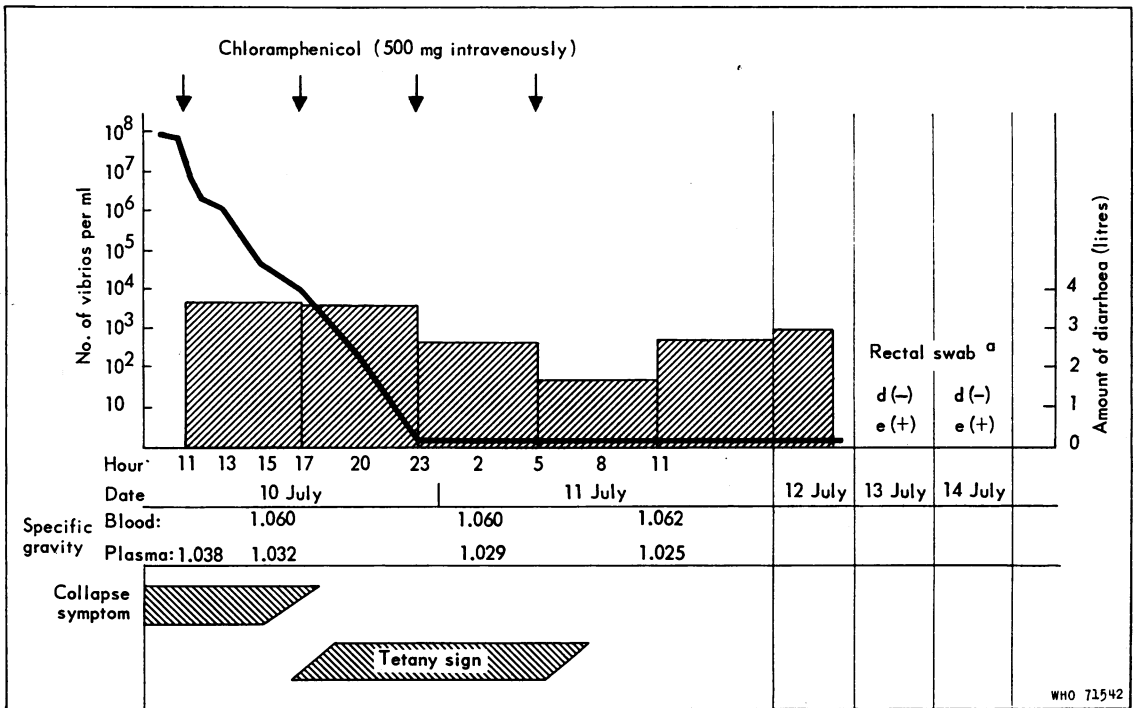
<sup>b</sup> Since diarrhoea had stopped, rectal-swab cultures were made; "d" indicates direct culture, and "e" enriched culture; + and - indicate the presence and absence of growth, respectively.

**Bacteriological results.** The results of the quantitation of vibrios in 1 ml of stool are shown in Table 3. Before treatment, 2 examinations showed the number of vibrios in 1 ml of stool to be  $2.0 \times 10^8$  and  $1.5 \times 10^8$ . Thirty minutes after intravenous chloramphenicol the number per ml was reduced to  $1.7 \times 10^7$ , after 1 hour to  $6.1 \times 10^6$ , after 2 hours to  $2.6 \times 10^6$ , after 4 hours to  $8.4 \times 10^4$ , and after 6 hours to  $2.2 \times 10^4$ . Three hours after the second injection the number of vibrios per ml was reduced to  $4.0 \times 10^2$ . Finally, vibrios disappeared completely 12 hours after the first injection and 6 hours after the second. After that, despite continued quantitation, no vibrio was detected in the watery stools; however, on the second and third days after the intravenous treatment was stopped, a very few vibrios were detected by the enrichment procedure.

**Case No. 7 (Table 4, Fig. 3)**

**Clinical details.** R. S., 45 years old, female, was admitted on 23 August 1965 at 10.55 hours because of frequent diarrhoea and vomiting of 2 days' duration, and cramps of the upper and lower extremities. Vomitus consisted of previously ingested food. Stool was moderate in amount, rice-watery, with a fishy odour. The patient took 2 tablets of sulfaguanadine and sulfathiazole before seeking consultation. On admission, the patient was moderately dehydrated, conscious and coherent with husky voice, washerwoman's hands and cramps of the lower extremities. Blood pressure was 60/40, body temperature 36.8°C. Specific gravity of the plasma was 1.036. Fluid therapy was started on admission. Tetracycline (500 mg) was given orally 2 hours later; thereafter, every 6 hours for 3 days. After

FIG. 2  
PARTICULARS OF CASE NO. 3 (TREATED INTRAVENOUSLY WITH CHLORAMPHENICOL)



WHO 71542



Amount of diarrhoea.



No. of vibrios per ml of stool.

<sup>a</sup> d = direct culture; e = enriched culture; + = growth present; - = growth absent.

the initial hydration, the signs and symptoms of dehydration disappeared. Blood pressure became 78/68; body temperature rose to 37.4°C. The plasma specific gravity decreased from an initial 1.036 to 1.031 after hydration; subsequently reaching 1.028, 1.030, 1.025 and finally 1.024 at the forty-eighth hour.

The stool output, measured at 6-hour intervals, decreased from 2500 ml in the first 6 hours to 1200 ml, 2200 ml, and 1400 ml in successive 6-hour periods; thereafter, 1200 ml, 1300 ml, and finally 1000 ml at the forty-eighth hour. The stool colour changed from rice-watery in the first 6 hours to yellowish; however, at the twelfth hour, the colour was bloody, becoming greenish-yellow at the sixteenth hour. The colour then changed gradually to green, and finally to brown at the forty-eighth hour.

The clinical course was uneventful. The patient was ambulatory at the fiftieth hour. She was discharged on the sixth hospital day as clinically improved, and bacteriologically negative for vibrios on several occasions.

**Bacteriological results.** The number of vibrios in 1 ml of stool was  $1.4 \times 10^8$  on admission and  $4.3 \times 10^8$  just before administration of the antibiotic, 1 hour after which the number was  $2.7 \times 10^7$ , declining to  $7 \times 10^4$  after 2 hours. The results of 8 quantitative examinations made more than 3 hours after admission were completely negative; 3 cultures also remained negative after enrichment.

*Case No. 8* (Table 5, Fig. 4)

**Clinical details.** E. L., 52 years old, female, was admitted on 23 September 1965 at 07.20 hours

TABLE 4  
OBSERVATIONS ON CASE No. 7 (TREATED ORALLY WITH CHLORTETRACYCLINE)

Date and hour	No. of colonies of vibrio on TCBS agar culture of tenfold serial dilution <sup>a</sup>									No. of vibrios in 1 ml stool	Amount (ml) and colour of stool	Admin-istration of antibiotic (chlortetra-cycline)	
	10 <sup>0</sup>	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-8</sup>				
23 Aug.													
11				U	U	147	13	1	0	1.4 × 10 <sup>8</sup>	} 2 500 rice-watery	+	
12				U	U	U	43	1	0	4.3 × 10 <sup>8</sup>			
13				U	276	13	1	0	0	2.8 × 10 <sup>7</sup>			
14			?	7	0	0	0			7 × 10 <sup>4</sup>			
15			?	0	0	0				0			
18	0	0	0	0	0	0				0	} 1 200 yellowish	+	
21	0	0	0	0	0	0				0			
24	0	0	0	0	0	0				0			
24 Aug.													
3	0	0	0	0	0					0	} 2 200 bloody, then greenish-yellow	+	
6	0	0	0	0	0					0			
9	0	0	0	0	0					0	} 1 400 green	+	
12	0	0	0	0	0					0			
25 Aug.										d(-) e(-) <sup>b</sup>			
26 Aug.										d(-) e(-)			
27 Aug.										d(-) e(-)			

<sup>a</sup> U = confluent growth; ? = uncertain.

<sup>b</sup> Since diarrhoea had stopped, rectal-swab cultures were made; "d" denotes direct culture, and "e" enriched culture; + and - indicate the presence and absence of growth, respectively.

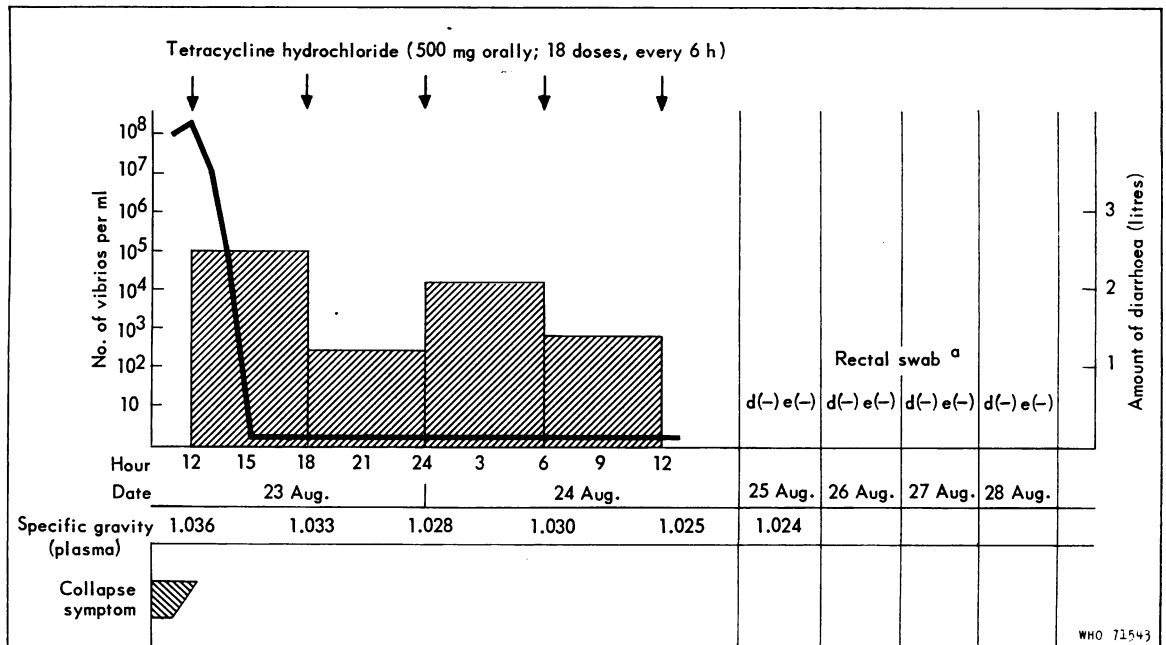
because of vomiting and frequent, profuse diarrhoea of 10 hours' duration. Vomitus was watery and moderate in amount. Stool was copious, rice-watery. On admission, the patient was severely dehydrated, conscious, with cold perspiration, washerwoman's hands, sunken eyes, and deep, rapid respiration. Blood pressure was 80/40, body temperature 36°C. Blood and plasma specific gravities were 1.054 and 1.030, respectively. Rapid infusion with normal saline solution was started on admission, but the patient soon developed chills; the venoclysis was therefore slowed down and a warm compress was applied to the extremities. Kanamycin (500 mg) was given orally 2 hours after admission and subsequently every 4 hours for 3 days. The patient continued to vomit until the eleventh hour after admission, when the second litre of 2% sodium bicarbonate solution was infused. Moreover, the patient had tetany at the eleventh hour for which

10 ml of 10% calcium gluconate was given intravenously. The tetany disappeared at the seventeenth hour. The signs of dehydration gradually disappeared. Plasma specific gravity showed a relatively slow fall from an initial 1.030 to 1.026 at the forty-eighth hour. Fluid therapy was discontinued on the seventh hospital day, when the diarrhoea ceased and the plasma specific gravity was 1.026.

The stool output was measured every 4 hours during the first 24 hours; the total for this period was 11 900 ml plus 800 ml of vomitus. On succeeding days, the total daily output was 5700 ml, 3500 ml, 5000 ml, 5800 ml, 2200 ml and finally 500 ml on the seventh hospital day. The stool colour changed from rice-watery on admission to yellowish-brown at the twenty-fourth hour, and thereafter to yellowish-green, greenish, greenish-brown and yellowish-brown.

The patient was ambulatory and symptom-free

FIG. 3  
PARTICULARS OF CASE NO. 7 (TREATED ORALLY WITH TETRACYCLINE)



Amount of diarrhoea.



No. of vibrios per ml of stool.

<sup>a</sup> d = direct culture; e = enriched culture; + = growth present; - = growth absent.

after the seventh hospital day. On the twelfth hospital day, she was discharged as clinically improved, and bacteriologically negative for vibrios on 3 consecutive occasions.

**Bacteriological results.** The number of vibrios in 1 ml of stool was  $1.8 \times 10^7$  on admission and  $5.0 \times 10^6$  just before the oral administration of the first dose of kanamycin, and it did not decline appreciably until just before the third administration of the drug. Thereafter the 2-hourly counts gave  $4.4 \times 10^2$ ;  $2.3 \times 10^3$ ,  $6.4 \times 10^2$  and  $1.2 \times 10^4$  per ml.

#### Summary

**Clinical symptoms.** The symptoms of collapse were not affected by the use of antibiotics. The low blood pressure and weak pulse improved and other symptoms of collapse subsided within a few hours after the start of rehydration treatment. The speed of recovery from these symptoms did not seem to be

different in the cases treated with antibiotics and in the control group.

It is clear that the duration of diarrhoea could be shortened by the use of antibiotics. However, hourly observations showed almost no difference between the antibiotic group and the control group with regard to the amount of diarrhoea in the first and the second 6-hour periods after the antibiotic treatment. After this time lag, the number and volume of stools were markedly reduced in the antibiotic-treated group. These improvements seemed to appear rather suddenly.

It can be seen from Table 6 that in the majority of the cases treated, diarrhoea stopped within 1-3 days after treatment, while in the control group it continued for about 4 days. However, in 2 cases treatment with oral kanamycin failed to stop diarrhoea, which continued for 3 days in one of the cases and for 7 days in the other. The duration of diar-



TABLE 5  
OBSERVATIONS ON CASE No. 8 (TREATED ORALLY WITH KANAMYCIN)

Date and hour	No. of colonies of vibrio on TCBS agar culture of tenfold serial dilution <sup>a</sup>									No. of vibrios in 1 ml stool	Amount (ml) and colour of stool	Administration of antibiotic (Kanamycin)		
	10 <sup>0</sup>	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-8</sup>					
23 Sept.														
9			U	U	181	17	1	0	0	1.8 × 10 <sup>7</sup>	} 3 700 rice-water	+		
10			U	U	80	6	0	0	0	8.0 × 10 <sup>6</sup>				
11	U	U	U	U	53	16	0	0	0	5.3 × 10 <sup>6</sup>				
12	U	U	U	U	U	54	11	1	0	5.4 × 10 <sup>7</sup>				
13	U	U	U	U	U	46	6	0	0	4.6 × 10 <sup>7</sup>				
14	U	U	U	U	71	7	1	0	0	7.1 × 10 <sup>6</sup>				
16	U	U	U	U	147	19	0	0	0	1.4 × 10 <sup>7</sup>	} 2 600 rice-water	+		
18	44	16	1	0	0	0	0	0	0	4.4 × 10 <sup>2</sup>				
20	50	23	2	0	0	0	0	0	0	2.3 × 10 <sup>3</sup>	} 1 500 rice-water	+		
22	64	16	1	0	0	0	0	0	0	6.4 × 10 <sup>2</sup>				
24	U	121	6	0	0	0	0	0	0	1.2 × 10 <sup>4</sup>	} 1000 rice-water	+		
24 Sept.														
2	0	0	0	0	0	0	0	0	0	0				
4	0	0	0	0	0	0	0	0	0	0			} 2 000 light yellow	+
6	0	0	0	0	0	0	0	0	0	0				
8	0	0	0	0	0	0	0	0	0	0			} 1 100 green-yellow	.
10	0	0	0	0	0	0	0	0	0	0				
15	0	0	0	0	0	0	0	0	0	0				
25 Sept.	U	U	U	U	173	?	?	?		1.7 × 10 <sup>7</sup>				
26 Sept.	4	0	0	0						4 × 10 <sup>1</sup>				
27 Sept.	U	18	0	0						1.8 × 10 <sup>3</sup>				
28 Sept.	U	U	U	U	344	50	?	?		5.0 × 10 <sup>7</sup>				
29 Sept.	U	U	U	U	U	67	10	0		6.7 × 10 <sup>7</sup>				
30 Sept.	U	U	200	21	1	0	0	0		2.1 × 10 <sup>5</sup>				

rhoea was shortened in all the cases treated orally with chloramphenicol, tetracycline and erythromycin.

The group treated for only 1 day, as compared to the group treated for 3 days, showed no distinct difference as far as duration of diarrhoea was concerned.

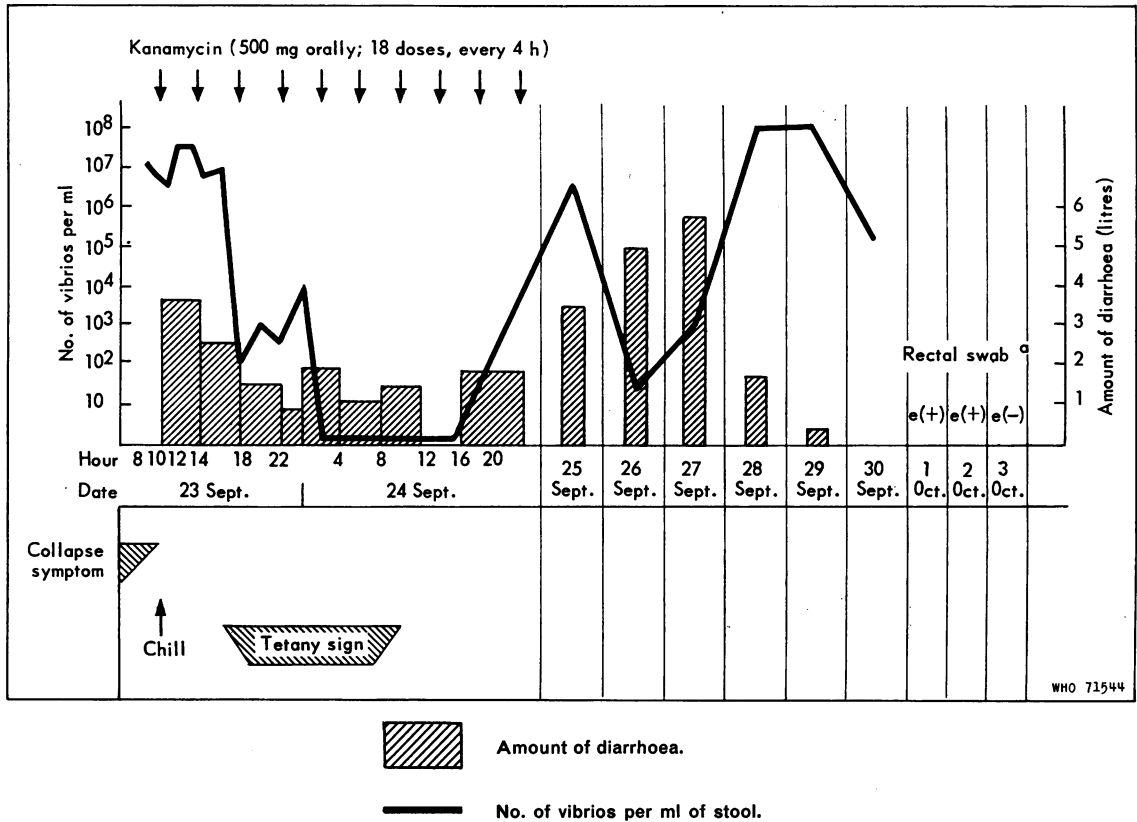
*Bacteriological results.* During the first day of illness the number of vibrios in 1 ml of watery stool was about 10<sup>8</sup> in every case.

In the control group, while diarrhoea continued, the number of vibrios did not show any marked variation; almost the same number of vibrios (about 10<sup>8</sup> ml) was excreted until the diarrhoea stopped.

On the other hand, in cases treated with antibiotics, the number of vibrios was greatly and suddenly reduced from 10<sup>8</sup> to less than 10<sup>3</sup> or 10<sup>2</sup> only 1 hour after the start of the treatment. As indicated in Table 6, no vibrio could be found in 0.1 ml of stool within 10 hours of the start of the treatment in the majority of cases treated with antibiotics. In some cases, the vibrios disappeared in 4–6 hours. In 2 cases treated with kanamycin and in 1 case treated with intravenous chloramphenicol, the stool became negative for vibrios in about 20 hours.

Vibrios reappeared in the stool in 5 cases among the treated group after a negative period of from 12 to 24 hours. Of these 5 cases, 3 were treated intra-

FIG. 4  
PARTICULARS OF CASE NO. 8 (TREATED ORALLY WITH KANAMYCIN)



<sup>a</sup> e = enriched culture; + = growth present; - = growth absent.

venously with chloramphenicol and 2 were treated orally with kanamycin. One of the kanamycin-treated patients had diarrhoea for 7 days and was positive for vibrios for 8 days. Vibrios reappeared in the stool in 3 cases treated for 1 day and in 2 cases treated for 3 days.

Antibiotics given intravenously, such as chloramphenicol and tetracycline, seemed to be about as effective as those given orally, as far as antibacterial activity is concerned.

Among the oral antibiotics, kanamycin seemed to be inferior to others in its effect on the vibrios.

#### DISCUSSION

The experiences recorded by several authors (Carpenter et al., 1964; Greenough et al., 1964) and the results of our preliminary trial (Kobari, 1965) on

the treatment of cholera confirm that the use of antibiotics shortens the period of diarrhoea and the excretion of vibrios in the stool, although it has little beneficial effect on the symptoms of collapse.

Hourly observation showed that the amount of diarrhoea did not decrease for about 10 hours after antibiotic treatment. After 12 hours, however, the frequency of passage of stools was markedly reduced, and the amount of stool decreased considerably. On the other hand, the vibrios in the stool disappeared by 6 hours after treatment. Diarrhoea persisted for some hours after the vibrios had disappeared from the stool.

In the absence of sufficient knowledge of the pathogenesis of cholera, it is difficult to explain the persistence of diarrhoea after the disappearance of the vibrios from the intestines. There are 2 possibilities: it may be due to the time required by the intestines to recover from the functional disturbance

TABLE 6  
SURVEY OF TREATMENT DETAILS AND RESULTS

Case No.	Antibiotic (route; and period of administration in days)	Amount of stool (ml) in first 24 hours after admission	Duration of diarrhoea	Duration of positive cultures after start of treatment	Reappearance of vibrio (day of treatment)
1	Control	5 130	4 days	5 days <sup>b</sup>	
2 <sup>a</sup>	Control	8 400	4 days	2 days <sup>b</sup>	
3	Chloramphenicol (i.v.; 1)	11 500	48 hours	10 hours	3rd
4	Tetracycline (i.v.; 1)	9 200	48 hours	6 hours	
5	Chloramphenicol (oral; 3)	7 400	24 hours	12 hours	
6	Erythromycin (oral; 3)	14 000	24 hours	4 hours	
7	Tetracycline (oral; 3)	7 300	24 hours	4 hours	
8	Kanamycin (oral; 3)	10 800	7 days	13 hours	2nd-9th
9	Chloramphenicol (i.v.; 3)	10 740	36 hours	2 (?) hours <sup>c</sup>	3rd
10	Chloramphenicol (i.v.; 1)	13 600	36 hours	17 hours	3rd-5th
11	Kanamycin (oral; 1)	12 300	3 days	18 hours	2nd, 3rd
12	Kanamycin (oral; 3)	5 250	30 hours	6 hours	
13	Control	12 100	4 days	4 days	
14	Kanamycin (oral; 3)	13 700	30 hours	21 hours	
15	Tetracycline (i.v.; 3)	8 100	36 hours	8 hours	
16	Chloramphenicol (i.v.; 1)	6 000	30 hours	4 hours	
17	Chloramphenicol (i.v.; 1)	4 400	24 hours	6 hours	

<sup>a</sup> Admitted on the third day of illness, all others on the first day.

<sup>b</sup> After day of hospitalization.

<sup>c</sup> Quantitation tests on dilutions more than  $10^{-3}$  not examined.

caused by the vibrios; or, if the diarrhoea is assumed to be caused by some toxic substances produced by the vibrios, it is not difficult to visualize the continuation of diarrhoea after eradication of vibrios. The former presumption seems more probable, although there has been no distinct evidence.

All cases had practically the same number of vibrios in their stools on the first day of illness. It may be presumed, therefore, that the number of vibrios in the intestines reaches its maximum on this day and no more multiplication is possible. It is interesting to note that in the control group, which did not receive antibiotics, the vibrios continued to multiply as long as the diarrhoea continued.

Regarding the value of different types of antibiotics in the treatment of cholera, it might have been presumed that non-absorbable antibiotics would be more effective than others because vibrios are limited to the intestines. Our observations, however, have

shown otherwise. Kanamycin, a non-absorbable antibiotic, was less effective than the easily absorbable drugs in shortening both the duration of diarrhoea and excretion of vibrios. This drug, even when given every 4 hours instead of at 6-hour intervals, failed to show better results.

It has been shown experimentally that an orally given dye takes only 90 minutes to be excreted from the anus in a severe case of cholera. It may be assumed, therefore, that non-absorbable antibiotics given orally come in contact with each square centimetre of the intestines for only a few seconds. Based on this assumption, the use of non-absorbable antibiotics in the treatment of cholera cases with severe diarrhoea cannot be recommended.

On the other hand, not only the easily absorbable antibiotics but also the ones given intravenously were very effective in shortening the periods of diarrhoea and excretion of vibrios. A drug given

intravenously usually attains a very low concentration in the intestines under normal conditions. However, the condition of the intestines in a case of cholera is probably different from that in a normal person or in other diseases, as a large amount of body fluid is being poured into the intestines. It may be presumed, therefore, that the distribution of a drug given intravenously to a cholera patient is such that it passes into the lumen of the bowel in a higher concentration than is possible under normal conditions. The superior effect of the intravenous route in the administration of antibiotics for the treatment of cholera can thus be explained.

It is remarkable that the number of vibrios was reduced so drastically within an hour of administration of antibiotic. The earlier the antibiotic is given, the sooner the number of vibrios in the intestines is decreased. The period of multiplication of vibrios, and consequently the number of vibrios in the intestine of the cases treated with antibiotics, differ significantly from those in the control group.

Reappearance of vibrios in the stool after a series of negative cultures is an important problem, particularly from the public health standpoint. After 2 or 3 doses of antibiotics, the stool culture sometimes became positive after having been nega-

tive for 12–24 hours. Of course, there is still the possibility that a small number of vibrios survived somewhere in the intestines even after antibiotic treatment, since most antibiotics have a bacteriostatic and not a bacteriocidal action. Besides, it would be impossible even for a bacteriocidal drug to kill the entire population of vibrios in the intestines. However, it would be very difficult (and not necessarily important from a public health viewpoint) to detect vibrios, if any, remaining in the intestines by ordinary examination of stool cultures. They would probably disappear naturally from the intestines in due time.

If an ordinary examination of the stool reveals the presence of vibrios again, it may be presumed that multiplication of vibrios in the intestines has been re-activated by an unknown cause. This may be described as "bacterial relapse" and its frequency may be closely correlated to the number of vibrios that survived and the period of survival after antibiotic treatment. So far, it has been established that 1 day's treatment with antibiotics is not sufficient to inhibit completely the multiplication of vibrios in the intestines. Most of the cases treated for 1 day only showed reappearance of vibrios 1 or 2 days after the cessation of treatment (see Table 6).

## RÉSUMÉ

En vue de déterminer l'effet des antibiotiques sur l'évolution du choléra, on a fait sur 17 sujets atteints de choléra El Tor, venant des Philippines, des observations précises des symptômes cliniques et une recherche quantitative des vibrions dans les selles. Sept malades ont été traités par voie orale à la kanamycine, à la chlortétracycline, au chloramphénicol ou à l'érythromycine, 7 par voie intraveineuse au chloramphénicol ou à la tétracycline, et 3 n'ont pas reçu d'antibiotique. On a aussi administré à tous les malades un traitement réhydratant classique pour remplacer l'eau et les électrolytes perdus dans les selles et les vomissements.

On a constaté que les antibiotiques administrés par voie orale comme par voie intraveineuse raccourcissaient

efficacement la période de diarrhée et réduisaient l'excrétion de vibrions dans les selles. Le nombre de vibrions par millilitre de selles liquides pendant le premier jour de maladie était de  $10^8$  environ dans tous les cas. Dès le début du traitement, il y a eu une réduction marquée de ce nombre en une heure, et disparition complète des vibrions en 10 heures, dans la plupart des cas. Mais les vibrions sont réapparus plus tard dans certains cas. Les antibiotiques n'ont pas eu d'effet sensible sur les signes de collapsus circulatoire, que le traitement réhydratant, en revanche, faisait disparaître.

La kanamycine, antibiotique non absorbable, s'est révélée moins efficace que des antibiotiques absorbables tels que le chloramphénicol et la tétracycline.

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