REDUCTION OF CHOLERA MORTALITY BY THE CONTROL OF BOWEL SYMPTOMS AND OTHER COMPLICATIONS*

By HEMENDRA NATH CHATTERJEE, M.D., M.S., B.A.

Infectious Diseases Ward, Chittaranjan Hospital, Calcutta

More than four decades back the pioneer work of Rogers (1913) gave to the world a new and a more or less complete treatment of cholera. His most important therapeutic contributions were: (1) Treatment of dehydration and shock by hypertonic saline transfusions; (2) treatment of uraemia and acidosis by alkaline saline transfusions; and (3) possibly a much less outstanding treatment, viz. the endeavour to control the bowel infection by means of permanganate pills.

By adopting all or some of the above lines of treatment, the previous high mortality rate of 40 to 60 per cent. of cholera has come down in the recent years to a comparatively lower figure of 20 to 30 per cent. in the hands of the Calcutta physicians (Lahiri, 1951; Chatterjee, 1953a).

This limited variability of the somewhat reduced death rate of cholera possibly depends on the various common factors like the virulence of the vibrios, the immunity of the general population, the rainfall, the subsoil water, the sufficiency of water supply, and also the economic condition of the general population. Such an unusual phenomenon as the mass migration of refugees from Pakistan, with dislocation of the hygienic set up, is expected to aggravate the mortality rate as has been the case in 1955.

Following up the pioneer work of Rogers (1913, 1921), the successive workers have tried by means of other therapeutic agents to stop the major initial symptom of cholera, viz. the copious diarrhoea. The most important of these may be mentioned as the following: Essential oils (Tomb, 1924, 1927); bacteriophage (d'Herelle and Malone, 1930; Asheshove *et al.*, 1931; Taylor *et al.*, 1930; Morrison *et al.*, 1930); sulpha drugs (Chopra *et al.*, 1941; Carruthers, 1942; Griffiths, 1942; Sadusk and Oswald, 1943; Lahiri, 1951a; Bhatnagar *et al.*, 1948); and broad spectrum antibiotics (Gauld *et al.*, 1949; Chaudhuri *et al.*, 1950;

Das *et al.*, 1951; Seal *et al.*, 1951; Roy Chaudhuri *et al.*, 1952).

However, the continued use of all the above remedies has not been able to substantiate the initial hopes entertained about these drugs. Regarding the more recent newcomers, viz. the sulphonamides and antibiotics, the general pessimistic conclusion is typified by the following statement of Konar *et al.* (1953): 'Antibiotics, like terramycin, chloramphenicol, aureomycin, and the chemo-therapeutic drugs like sulphaguanidine, formocibazol and sulphadiazine, have been tried in cholera without any significant difference in the mortality rate of treated and controlled cases.'

More recently the two major bowel symptoms of cholera, viz. vomiting and diarrhoea, appear to be controlled by somewhat newer remedies. Vomiting seems to be amenable to an anti-histaminic drug, promethazine-8-chlorotheophylline (Avomine). It is surprising to find that this preparation, which has been usually used to control the nausea and vomiting of motion sickness, can also completely check the vomiting associated with the severest bowel disease of mankind (Chatterjee, 1953b, 1955a).

Regarding choleraic diarrhoea, the writer, while working as a medical relief worker in Bengal villages in 1951, first observed that a small epidemic could be controlled by the local people by the administration of the raw leaf juice of a common plant of Bengal called pathorchur (*Coleus aromaticus*). The plant was subsequently cultivated in the garden attached to Chittaranjan Hospital, Calcutta, and the raw juice of the leaves tried during the epidemics of 1952 and 1953 with surprisingly beneficial results (Chatterjee, 1953a, 1955a), the mortality rate being 8.5 per cent. in the treated cases in contrast to the 20 per cent. mortality rate of the control cases. The dose given was 1 oz. of the raw leaf juice every hour, three times in the beginning, to be similarly repeated after eight hours if the diarrhoea continued.

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In 1954, however, there was a failure, owing to the destruction of the hospital garden due to structural constructions, and it was not possible to give the patients any *Coleus aromaticus* juice. The mortality rate of the year rose to 16 per cent.

Previously, with the help of the above product given in the form of raw juice, choleraic diarrhoea could be controlled in 92.5 per cent. of cases (Chatterjee, 1953a, 1955a) in 72 hours. Later in the epidemic of 1955 the raw leaf juice was replaced by the dried concentrated aqueous extract of the leaves given in the form of 5 gr. tablets with practically the same results as the diarrhoea could be controlled in 72 hours in 94 per cent. of cases. The tablets were allowed to disintegrate in a small quantity of water and one tablet was given hourly for three doses. The doses were repeated every eight hours if the diarrhoea continued. Altogether 200 cholera cases were treated by these tablets in 1955.

The causes of failure in the 1953 epidemic to check the diarrhoea with the help of leaf juice in the remaining 7.5 per cent. of cases have been carefully investigated by Chatterjee *et al.* (1955b). The above investigations have shown the great importance of a thorough examination of stools, which unfortunately is neglected too often and taken for granted. A most remarkable and surprising feature of the severe cases was the presence in the stools of active trophozoite forms of *entamoeba histolytica* over and above the cholera vibrio. Actual amoebic infection was present in 6.3 per cent. of our vibrio-positive cholera cases. As stated, the clinical features were very severe and the mortality rate very high (37 per cent.) (Chatterjee *et al.*, 1955a, b). The severe diarrhoea in these cases seemed to be amenable to control by the combined use of terramycin (250 mg. every four hours) and *Coleus aromaticus* juice (usual dosage). Seven cases of this double infection were given the above combined treatment. All of them recovered. As controls, eight cases were not given terramycin; three of the latter died which gives a rather high mortality figure of 37 per cent.

Terramycin, used alone, however, had not proved to be of any value in the usual cholera cases (Das *et al.*, 1951; Konar and Sen Gupta, 1951; Chatterjee *et al.*, 1955a).

In the control cholera cases treated with the orthodox saline transfusions only it has been found that diarrhoea automatically stops in only 12.5 per cent. of cases in 48 hours (Chatterjee, 1953b, 1955a). In the rest the diarrhoea continues beyond this period and leads to further prostration and prolongation of the disease.

All the cases in whom the diarrhoea continued beyond 72 hours were carefully studied. It was

found that in these cases there was an associated infection from *trichomonas intestinalis*, or *ascaris lumbricoides* with or without the *entamoeba histolytica* in some cases.

The incidence of *trichomonas* infection was 10.9 per cent., of *ascaris lumbricoides* 7 per cent., and of *entamoeba histolytica* 6.3 per cent. of the vibrio-positive patients (Chatterjee *et al.*, 1955b).

The *trichomonas* infection appear to be controlled by the use of camaquin (chloroquin), one tablet, 0.2 g., t.d.s. The flagellates usually disappeared after two days, and with the continued dose were absent up to seven days, when most of the patients had to be discharged owing to the rush.

In the *ascaris* cases santonin was given in 1 gr. dose twice daily (without calomel or purgative) in the adult on two alternate days with great relief of the subacute bowel symptoms as well as *ascaris* infection.

Either chloroquin or santonin was given only after 48 hours had passed off. As has been mentioned above, terramycin, along with *Coleus aromaticus*, was found to be very useful in the acute stages of the double infection with *entamoeba histolytica* and cholera vibrio. The diarrhoea seemed to be substantially controlled. After a free flow of urine the cases were followed up with a combined tablet of bismuth arsenillate (0.25 gr.), chloroquin (0.075 gr.), and di-iodoquinol (Neoviassept) (thrice daily) up to seven days. The stools were found to be negative both for vegetative or cystic forms of the amoeba at the end of this period.

In all cases in which the diarrhoea failed to respond in 48 hours to *Coleus* therapy (comprising 26 per cent. of cases), the time-honoured Bael fruit (*Aegle marmelos*) was given with gratifying results. It was administered in the form of a sugared decoction of the roasted semi-ripe or unripe fruit in 1 oz. doses given with the three alternate doses of *Coleus aromaticus*. This combination further increased the number of cases in whom the diarrhoea could be controlled in four days to 97 per cent. Cases with haemorrhagic stools are, however, excluded from consideration in the above group.

Haemorrhagic stools were present in 10 per cent. of cases (Chatterjee *et al.*, 1955b) and at the same time were associated with a severe symptomatology. It was observed that *Coleus aromaticus* (even with the addition of Bael) was much less efficacious in these haemorrhagic cases. But perhaps, what we have observed to be the most remarkable phenomenon in our clinical study of choleraic diarrhoea was the control of haemorrhagic stools by the fresh juice of another Indian herb named *Dudhia* (Hindi) or *Khirusi* (Bengalee)

or *Euphorbia pilulifera* (Chatterjee *et al.*, 1955a, b; Chatterjee, 1956).

It has been an almost unfailing event to have observed the dramatic relief of both diarrhoea and haemorrhage with the use of the juice of this plant given thrice daily in 1 oz. doses along with a little sugar. It is, however, rather strange that *Euphorbia pilulifera* was not found to be so efficacious in non-haemorrhagic cholera cases (Chatterjee, 1956).

It is also interesting to note that four cases also showed on culture a combined infection from the cholera vibrio (Inaba) and *Shigella flexneri* (Chatterjee *et al.*, 1955b). Although one of these was a very severe case with a fatal result, the other three were clinically of moderate severity and all recovered with the *Euphorbia pilulifera*-cum-usual saline therapy.

The pharmacology and the chemistry of these two vegetable products, viz. *Coleus aromaticus* and *Euphorbia pilulifera*, are being thoroughly worked out and will be published subsequently.

As can be expected, the control of copious diarrhoea and vomiting has greatly lessened both the necessity and the quantity of salines. Although all of our cases arrived in an advanced stage of the disease and shock, it was possible to do without intravenous and subcutaneous administration of saline in 19.5 per cent. of cases. The specific gravity of blood of all these last-mentioned cases was 1.063 or below. The other cases with a higher specific gravity of blood, who were rather late to be brought in advanced dehydration, had to be given transfusions (Chatterjee, 1955a).

The Transfusions

The majority of the cases (80.5 per cent.) had to be given intravenous transfusions. As a routine it was found very useful to give the first pint of fluid as Rogers' hypertonic saline (120 gr. of NaCl to a pint of double distilled water). Owing to the great tendency of production of pulmonary oedema in the cholera patient (Chatterjee *et al.*, 1955c) one has got to be rather careful regarding saline transfusions. From this point of view we have found that human plasma is the safest and the best thing to be given after the first pint of hypertonic saline (Chatterjee *et al.*, 1955a). In fact, the saline must be stopped immediately a patient (in an advanced stage of shock) starts showing dyspnoea and crepitations in the lungs and should be replaced with plasma, if available.

In order of efficacy and also safety, pyrrolidone solution would come second. Gelatin solution has also been found by Lihiri (1951b) to be useful, but its non-availability in proper quantity and

quality has been a great handicap for its use in the last four epidemics. We have tried dextran in four cases and have found that there was a marked retardation of the flow of urine in these few cases of cholera. Rogers' alkaline saline (sodium bicarbonate 120 gr., sodium chloride 60 gr., to a pint) is reserved for cases which show acidosis and delayed urination even after the restoration of the specific gravity of blood. In children and infants subcutaneous normal saline-cum-5 to 10 per cent. glucose solution were given along with hyaluronic acid and found to be very useful.

Our experience with blood transfusion have not been very happy, and the two patients in whom it was tried developed marked dyspnoea, from which they could be brought back with the greatest difficulty.

The quantity of fluid to be given depends on the individual case, the criterion being the specific gravity of blood, the return of pulse, the returning moist condition of the tongue and general clinical improvement with a careful watch on the respiration and pulse rate.

Complications of Cholera

Although the patients might tide over the initial stages of dehydration and shock with help of transfusions, they might be too often carried away by the various severe complications, amongst which the most important ones are:

(1) *Uraemia*. Even after the restoration of specific gravity blood with fluid and electrolytes, the kidney might still fail to work properly, leading ultimately to fatal uraemia which is responsible for about 20 per cent. of fatalities (Rogers, 1913, 1921). Following the previous work in this line (Chatterjee, 1952), the writer has found the administration of promethazine hydrochloride (Phenergan) given in the kidney region intramuscularly, along with massive intravenous doses of vitamin C (500 mg. to 1,000 mg.), of great value both as prophylactic and curative for uraemia. It has been possible to eliminate choleraic uraemia more or less completely by the help of the above line of therapy along with restoration of fluids (Chatterjee, 1952, 1955b). It should be remembered that the kidney failure in cholera is a completely reversible phenomenon, and after the cure of clinical cholera the patient never develops subacute or chronic nephritis or nephrosis (Chatterjee, 1941).

(2) *Hyperpyrexia*. This has been the great bugbear of saline treatment in cholera. For averting this danger the rectal temperature should be routinely noted before any saline transfusions are given. When the rectal temperature is above 101° F. it must be initially controlled by iced rectal saline washes by two-way tubes, and

judicious and cautious use of cryogenine (metabenzamine-semi-carbazide) (Chatterjee *et al.*, 1955c) per mouth. After the rectal temperature has come down to 101° F. or below the transfusion can be started. It has been found that each 1 gr. of cryogenine can lower the temperature by 1° F. in the cholera patient (Chatterjee *et al.*, 1955c).

(3) *Pulmonary Oedema.* This is a very common fatal complication of cholera occurring after the administration of massive doses of saline. It is evidently due to great electrolytic disturbance that occur initially in cholera as well as after the administration of massive doses of saline, including hypertonic saline, owing to the severe sodium chloride depletion that occurs in cholera (Chatterjee and Sarker, 1941). Like the vomiting of cholera, this acute pulmonary oedema may be of central origin and might be brought in by a central nervous mechanism as suggested by the experimental work of Cassein and Kistler (1954). It may be mentioned that the vomiting of cholera is amenable to antihistaminics which are believed to act centrally (Chatterjee, 1953b).

In the majority of cases the pulmonary oedema is sudden and evidently occurs without the concomitant left heart failure which is regarded to be its commonest contributory cause, particularly where pulmonary oedema is slower in onset. Consequently, any case showing dyspnoea must be treated very cautiously. Following the work of Wheatley (1952), we have used 2-benzyl imidazoline hydrochloride (Priscol) by the subcutaneous as well as intravenous route (10 mg. in 1 c.c. adult dose) in cases showing dyspnoea and have found it to be very useful in its ability to retard this complication (Chatterjee, 1955c). We have as a rule avoided atropine for its action of diminishing the secretion of urine and epinephrin, specially in the advanced stage of the disease for its well-known tendency to produce pulmonary oedema.

(4) *Inflammatory and other Complications.* The various inflammatory conditions, like phlebitis, parotitis, orchitis, pneumonia, etc., have been substantially controlled by terramycin or penicillin (Chatterjee *et al.*, 1955c).

(5) *Paralytic ileus*, which formerly occurred in 11 per cent. of cases (Chatterjee *et al.*, 1955a), has been substantially reduced by the *Coleus aromaticus* therapy. The parenteral use of pantothenic acid, after Jacques (1951), sometimes in combination with neostigmine, if necessary, has greatly relieved this dangerous complication (Chatterjee *et al.*, 1955a; Chatterjee, 1956). Gall-bladder involvement formerly occurred in about 3 per cent. of cholera cases (Chatterjee *et al.*, 1955a). It has been more or less absent in cases

treated by *Coleus aromaticus* therapy, possibly due to its ability to control diarrhoea early.

Results

Calcutta has been in the grip of a very severe epidemic of cholera in the months of April to June, 1955. Apart from the usual seasonal causes (Rogers, 1951; Rossell and Sunderarajan, 1926, 1928), there have been special contributory factors in this present year. The most important of these was the great influx of homeless refugees from Pakistan. The population of the city has increased nearly four times the pre-war figure, resulting in the failure of adequate water supply and dislocation of the public health and hygienic set up. There has also been an excessive overcrowding of the cholera hospitals, including our own. As might be well expected, the mortality rate has gone up beyond the usual range, and as far as it could be gathered from the information supplied by the Calcutta Corporation, the mortality rate has been 32 per cent. of the affected cases in the period from March to June. The treatment of cholera cases in other hospitals, as well as of the private cases, has been more or less on orthodox lines, consisting mainly on salines, sulpha drugs and kaolin. The unusual factors, briefly mentioned above, have been evidently the cause of heightened mortality rate.

Following up the therapeutic experiences gained previously during the epidemics from 1951 onwards, some of the newer drugs and methods mentioned in this paper were routinely adopted in the writer's ward during this year's epidemic.

On the other hand, some of the old remedies previously commonly used, such as atropine and adrenaline, were not used in our cases for reasons mentioned. The sulpha drugs were studiously avoided on account of their tendency to produce uraemia and increased mortality (Lahiri, 1951a). Kaolin has been discarded, being useless (Manson-Bahr, 1940).

The cholera mortality figures of the writer's ward for April and May, 1955, are compiled here, side by side with the general cholera mortality rate of the city of Calcutta as a whole, in Table I. It would be seen that the mortality figures of the former place were 7 per cent. for April, 5 per cent. for May, and 6 per cent. for both the months combined.

The corresponding figures for the over-all cholera mortality of Calcutta were 30 per cent., 32.2 per cent., and 32 per cent. for the respective periods.

The accompanying chart shows the steady declining rate of cholera mortality year by year in the former hospital after the institution of the newer methods of treatment enumerated in this

Graph (interrupted line) showing the mortality percentage curve of cholera in Chittaranjan Hospital, Calcutta, for six years, 1951-56. The mortality percentage curve of the whole of Calcutta City is also shown (continuous line), of which reliable published figures are available for the two years 1955 and 1956 only.

paper. The average of the entire 1955 epidemic (March to June) was 7 per cent. in this hospital and that of Calcutta was 32 per cent.

TABLE I.—Showing the Rate of Cholera Mortality in Chittaranjan Hospital and the General Cholera Mortality of Calcutta

Period	Cholera Cases in Chittaranjan Hospital (Writer's Ward)		Cholera Cases in whole of Calcutta	
	Number of Deaths	Mortality (%)	Number of Deaths	Mortality (%)
April ..	11	7	87	30.0
May ..	9	5	284	32.2
Two months combined	20	6	371	32.0

Appendix

This paper was compiled in June, 1955, and since it is the usual practice here to wait a year before sending an original article for final publication, the writer has had the experience of facing another severe epidemic of cholera in Calcutta during March to June, 1956, as well as of corroborating the previous experimental results.

This last particular epidemic again happened to be an extremely severe one, the total cholera mortality of Calcutta being 36.5 per cent.

In contrast to this, the total mortality rate of the writer's ward during the identical period showed a further and remarkable diminution and was only 4.7 per cent.

It is presumed that the more or less complete control of choleraic diarrhoea, of the severe shock-producing vomiting, and of the prevention

and cure of the various fatal complications such as choleraic uraemia, hyperpyrexia, etc., as well as the newer agents for intravenous transfusions such as plasma and pyrrolidones, have been the causes for this remarkable difference between the mortality rate of our own hospital and that of Calcutta, in which latter place the treatment more or less consisted of stereotyped intravenous salines.

It is unfortunate, however, that reliable cholera statistics of Calcutta are available for 1955 and 1956 only. These have been jotted down side by side with the mortality statistics of our ward from 1951 to 1956, the latter showing a progressively downward trend for the last five years until the same was less than 5 per cent. in 1956, in spite of the fact that most of our cases were admitted in an advanced degree of shock.

It may be repeated that the cholera mortality rate of Calcutta in 1956 was more than 36 per cent.

Case Note

For clinical interest regarding the details of treatment actually employed by us, the case-history of a fairly severe case is given. This will also indicate the new lines of treatment followed in our hospital.

A.B., female Hindu, aged 55. Admitted on April 13, 1955, with the following complaints: Purging, 10 times; last eight motions, rice-watery, colourless; vomiting, 12 times; anuria, seven hours.

On examination: Patient of average height, medium built, great prostration with husky voice; dry tongue; pulse imperceptible; auscultation by sphygmomanometer inaudible; specific gravity of blood, 1.070; temperature: axillary 97° F., rectal 99.8°F.; microscopic examination of stools: pus cells and epithelial cells. Culture report of stool coming after 48 hours showed agglutinable cholera vibrio (Inaba).

Treatment

First day (morning): Intravenous transfusion was started immediately. During the first six hours the patient had: Hypertonic saline, 2 pints; iso-alkaline saline, 1 pint; 5 per cent. glucose in normal saline, 1 pint.

Dissolved tablets of the extract of *Coleus aromaticus* given hourly for three doses.

First day (evening): In spite of the restoration of the specific gravity of blood to 1.058, there was no improvement in the state of collapse, pulse being still imperceptible. Transfusions were again given as follows: Human plasma solution, 1 pint; pyrrolidone solution, 2 pints.

During the first 24 hours of admission the patient had six rice-watery motions and still no urine.

Second day: Pulse could be palpated 9 a.m., but after two hours again became imperceptible. Patient was somewhat dyspnoeic, the respiration rate being 30 per minute. Few moist sounds were heard at the base.

Phenergan (2 c.c. of 2.5 per cent. solution) was given, morning and evening, in the back muscles. Stools three times, still liquid but somewhat bile-stained. No urination. Three doses of *Coleus aromaticus* as on the first day.

Blood-urea report showed 180 mg. per 100 c.c.

Third day (morning): Patient somewhat comatose; pulse feeble, 120 per minute; systolic pressure, 84 mm.; but dyspnoea was marked. Respiration 40 per minute; auscultation showed marked basal rates.

Third day (evening): Practically the same condition, dyspnoea still continuing.

Phenergan (2 c.c. of 2.5 per cent. solution) given intramuscularly in the back morning and evening. Priscol (10 mg. in 1 c.c.) intramuscularly in the morning and intravenously in the evening. No stool, no urine.

Fourth day (morning): Transfusion of 5 per cent. glucose in normal saline by drip, 2 pints, along with 500 mg. of vitamin C.

Priscol intramuscularly in the morning.

Fourth day (evening): Urination started about 78 hours after admission.

Fifth day: Patient quiet and improving. Pulse 100 per minute, regular, volume fair, B.P. 110/70. Respiration 24 per minute. Basal rates less. No stool. Urine four times.

Sixth day: General improvement continued.

7th day: Report of blood urea for the sixth day, 80 mg. per 100 c.c.

Tenth day: Report of blood urea for the ninth day, 40 mg. per 100 c.c.

Thirteenth day: Patient took voluntary discharge.

Discussion

Cholera starts primarily as a bowel disease.

The rationale of therapy should be in the first stages, to check the loss of fluid and electrolytes by way of evacuations and vomiting. This would seem to be substantially possible with the help of a vegetable product and an antihistaminic.

There is no justification in allowing the diarrhoea and vomiting to continue with idea of eliminating a hypothetical toxin or toxins.

Checking these symptoms in the earlier stage will often enable the patient to tide over without any transfusions.

In those cases where shock and dehydration has already occurred there is no other alternative but replacement.

In those cases where the evacuations have not

been checked early involvement and failure of other systems and organs, such as circulation, kidney, lungs, etc., will ensue, and each one of these complicating phenomena might be the cause of fatality. These can be checked, or substantially controlled, by various preparations available in the present day.

It will thus be observed that there is no one single drug which will be a specific for the cholera syndrome in all its stages, except perhaps when the case comes early, when the control of diarrhoea and vomiting can enable the patient to tide over.

Consequently, the therapy of cholera will depend mainly on the stage of the disease and the concomitant complications. A proper understanding of this question and the application of modern remedies can very substantially control the dosage of salines and reduce the mortality.

Summary

It has been possible to substantially reduce the mortality rate of cholera by the help of various remedies for the different signs and complications as follows:

- (1) Choleraic diarrhoea, by *Coleus aromaticus*, with or without Bael.
- (2) Haemorrhagic stools, by *Euphorbia pilulifera*.
- (3) Other associated bowel infections: (a) Acute amoebiasis, by terramycin-cum-*Coleus aromaticus*; (b) subacute amoebiasis, by bismuth arsenillate-cum-chloroquin-iodoquinol; (c) trichomoniasis, by chloroquin.
- (4) Vomiting, by promethazine-8-chlorotheophylline.
- (5) Dehydration, by human plasma, pyrrolidone and saline.
- (6) Hyperpyrexia, by iced rectal wash and metabenzamine-semi-carbazide.
- (7) Uraemia, by combined treatment with promethazine hydrochlor. (intramuscularly in the back) and vitamin C (intravenously).
- (8) Oedema of lungs, by benzyl-imidazoline-hydrochloride.
- (9) Inflammatory complications, by antibiotics.
- (10) Paralytic ileus, by pantothenic acid, with or without neostigmine.

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