# Replacement of Water and Electrolyte Losses in Cholera by an Oral Glucose–Electrolyte Solution

NATHANIEL F. PIERCE, M.D., R. BRADLEY SACK, M.D., RUPAK C. MITRA, M.B.B.S., JOHN G. BANWELL, D.M., KENNETH L. BRIGHAM, M.D., DAVID S. FEDSON, M.D., and ARABINDO MONDAL, M.B., CH.B.

*Calcutta, India*

**SUMMARY** **The efficacy of an orally administered glucose-electrolyte solution in replacing stool losses of water and electrolytes in severe cholera was evaluated. After initial intravenous rehydration intravenous fluids were discontinued, and subsequent water and electrolyte losses were replaced by the oral solution administered via nasogastric tube. In 9 of 10 patients so treated, water, electrolyte, and acid-base balances were adequately maintained by this method until diarrhea ended. One patient with very severe diarrhea required small amounts of additional intravenous fluids to maintain water balance. Patients receiving the oral solution had a small but significant increase in stool output during oral fluid administration when compared with the 10 patients in the control group who received only intravenous replacement of stool losses. Calculated absorption of the oral fluid was 87%. Duration of diarrhea and of *Vibrio cholerae* excretion were not prolonged by the oral solution administration. The role of glucose in the absorption of water and sodium by the small bowel is discussed. The study suggests a useful role for such an orally administered glucose-electrolyte solution in the management of cholera.**

THE PRESENT METHOD of treatment of cholera, which depends upon the replacement of water and electrolyte losses entirely by the intravenous route, has been proved highly effective (1, 2). However, adequate supplies of appropriate pyrogen-free intravenous fluids and of persons skilled in their administration are often unavailable in cholera-affected areas. This is especially true when cholera occurs in impoverished rural areas. For this reason we have pursued studies evaluating the possible usefulness of orally administered glucose-electroylte solutions in the replacement of water and electrolyte losses in cholera. Previous studies have indicated that there is significant absorption of water and electrolytes from glucose-electrolyte solutions administered by mouth to cholera patients (3–6). A study comparing an oral glucose-electrolyte solution with a standard intravenous regimen (7) as means of replacing water and electrolyte losses in severe cholera is reported. The results indicate that after a brief period of initial intravenous hydration, adequate water, electrolyte, and acid-base balance can be maintained in most patients solely by the replacement of stool losses with an oral glucose-electrolyte solution.

## METHODS

All studies were conducted between May and July 1968 at the Infectious Diseases Hospital, Calcutta. Only adult men over

Received December 18, 1968; revision accepted February 20, 1969.

From the Johns Hopkins University Center for Medical Research and Training, the Infectious Diseases Hospital, and the School of Tropical Medicine, Calcutta, India.

This study was supported in part by research grants AI-07628-01 and SR07TW00141-07CIC, U. S. Public Health Service, Washington, D. C.; and by funding under Public Law 480, Section 104 (c), Agreement 5x4317.

Requests for reprints should be addressed to Nathaniel F. Pierce, M.D., Department of Medicine, the Johns Hopkins Hospital, Baltimore, Md. 21205

TABLE 1. Composition of Orogastric Glucose-Electrolyte Solution

| Sodium | Potassium | Chloride | Bicarbonate | Glucose | Osmolarity |
|---|---|---|---|---|---|
| | ←—mEq/liter—→ | | | mmoles/liter | mOsm/liter |
| 100 | 10 | 70 | 40 | 120 | 327 |

the age of 20 years with clinically severe cholera were studied.

Most patients studied had the onset of copious "rice water" diarrhea less than 18 hr before admission, had a systolic blood pressure less than 80 mm/Hg, were dehydrated at admission, and passed more than 800 ml of stool during the first 6 hr after admission. None had received antibiotics or intravenous fluids before entering the hospital. In all patients *Vibrio cholerae*, biotype El Tor, was isolated in large numbers from stool obtained at admission.

During the first 6 hr after admission all patients received the same treatment. This consisted of rapid correction of dehydration and base-deficit acidosis with an intravenous solution containing sodium (154 mEq/liter), chloride (103 mEq/liter), and lactate (51 mEq/liter). Rehydration was completed within 60 to 90 min after admission. Thereafter, intravenous fluid was given to replace measured stool losses on a volume-for-volume basis. Patients were studied on metabolic beds permitting separate collection of stool and urine, the former being passed through a hole in the bed into a calibrated container. Stool and urine output were determined by weight to the nearest gram. Patients received nothing by mouth during the first 6 hr except tetracycline (7, 8), which was initiated 3 hr after admission in a dosage of 500 mg every 6 hr for 48 hr.

At the end of 6 hr patients were randomly assigned to one of two treatment groups. The first was a *control group* that continued to receive intravenous replacement of stool losses, as described above, until diarrhea ceased. Patients in this group also received small amounts of water by mouth, if they wished—the volume not exceeding 250 ml each 6 hr. Food was not given until diarrhea ended. This method of treatment represents a slight modification of the routine treatment of cholera in adults presently recommended by this laboratory (7). In the second group (*orogastric group*) treatment was modified in an attempt to maintain adequate water, electrolyte, and acid-base balance during continuing severe diarrhea solely by the intragastric administration of a glucose-electrolyte solution (Table 1). A freshly prepared glucose-electrolyte solution was given via nasogastric tube at a rate adjusted to exceed stool output by 100 ml each hour. The nasogastric route of administration was used to eliminate error in intake measurement and because it permitted patients to sleep if they desired. Hourly rates of administration were determined by the stool output of the preceding hour and the cumulative balance up to that point—the balance representing the orogastric intake less stool output. The excess of 100 ml each hour was given to replace urinary and insensible water losses. Patients in this group received neither food nor water by mouth until diarrhea ceased. Orogastric replacement was continued until liquid stool output ceased. After selection to this group, no further intravenous fluids were given unless significant dehydration occurred as indicated by plasma specific gravity exceeding 1.030.

In all patients outputs of stool, urine, and vomitus, if any, were recorded hourly throughout the study, as were intravenous and orogastric fluid intake. In calculating the net volume of orogastric fluid intake the volume of any vomitus was subtracted. Heparinized blood from the femoral or brachial artery was obtained at admission and at 6, 18, and 30 hr thereafter, unless diarrhea had ended before this, for determination of plasma specific gravity, pH, $P_{CO_2}$, bicarbonate, sodium, potassium, chloride, and glucose. Samples of liquid stool were obtained via sterile rectal catheter at the same intervals. An aliquot of the total stool output for the first 6 hr and for each of the next two 12-hr periods was also obtained. Sodium, potassium, and chloride content were determined on aliquots of each stool sample. In addition, total carbon dioxide content, glucose, and osmolarity were determined on samples obtained by rectal catheter.

Sodium and potassium determinations were by a Patwin flame photometer with internal lithium standard. Chloride was determined by a Cotlove chloridometer. The pH, $P_{CO_2}$, and bicarbonate concentration were determined by a Radiometer pH meter-27 with capillary electrode and Astrup microtonometer. Some bicarbonate determinations were made in a Van Slyke volumetric gas apparatus. Glucose was determined by a glucose oxidase method on samples frozen promptly after collection. Osmolarity was determined by a Fiske osmometer within 24 hr of collection on specimens stored at 4 C

TABLE 2. Comparison of Groups at Admission

| Characteristic | Control Group (10 Patients) | Orogastric Group (10 Patients) |
|---|---|---|
| Age, *years* | 46 (28–66)* | 38 (20–65) |
| Weight, *kg* | 39 (34–45) | 41 (33–48) |
| Duration of illness before entry, *hr* | 13 (5–26) | 9 (3–15) |
| Systolic blood pressure, *mm Hg* | 25 (0–70) | 40 (0–80) |
| Pulse, *min* | 123 (88–160) | 133 (100–180) |
| Temperature (rectal), *F* | 99.8 (98.0–102.6) | 100.2 (97.2–103.5) |
| Respiration,/*min* | 35 (26–44) | 38 (28–64) |
| Arterial pH | 7.19 (7.09–7.33) | 7.21 (7.12–7.29) |
| Plasma bicarbonate, *mEq/liter* | 9 (3–13) | 12 (8–15) |
| Plasma specific gravity | 1.040 (1.033–1.045) | 1.041 (1.035–1.046) |

* Mean, range indicated in parentheses.

but not frozen. Plasma specific gravity was determined in an automatically compensated refractometer (American Optical Co.). All biochemical determinations were performed in duplicate.

Liquid stool for culture was obtained via a sterile rectal catheter at admission. Thereafter, rectal swabs were obtained daily until discharge. All specimens were plated promptly on bile-salt agar, thiosulfate citrate bile salts medium, deoxycholate agar, and *Salmonella-Shigella* agar. Specimens were also plated on the first two media after 6- to 8-hr enrichment in pH 9.2 peptone water. Suspicious colonies were identified by oblique light and confirmed as *V. cholerae* by standard agglutination and biochemical techniques.

## RESULTS

Twenty patients were studied, 10 in each group. Comparison of the groups at the time of admission and in the first 6 hr after admission is summarized in Table 2. Groups did not differ significantly in regard to age, weight, duration of illness before admission, vital signs obtained at admission, arterial pH, plasma bicarbonate, or plasma specific gravity at admission.

Intravenous and orogastric fluid replacement are summarized in Figure 1 and Table 3. Total fluid given from admission to termination of diarrhea and intravenous fluid given during the initial 6 hr are both greater in the orogastric treatment group, but these differences are not statistically significant. It should be noted that the average total fluid given to the control group does not include water given by mouth after the initial 6 hr. This did not exceed 250 ml during any 6-hr period in any patient. The duration of requirement of fluid replacement was comparable in each group. Only one patient in the orogastric group required additional intravenous fluids after initiation of orogastric fluids. This patient had diarrhea that was distinctly more severe than any other patient in either group. His stool output was 1,015 ml/hr in the first 6 hr, and he was given 29.7 liters of glucose-electrolyte solution during the period of orogastric infusion. Except in this patient, the average hourly rate of orogastric fluid infusion during any

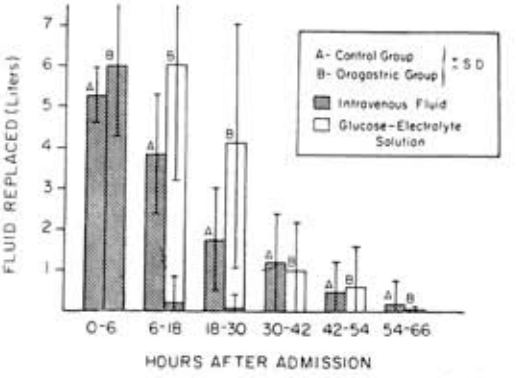


FIGURE 1. Comparison of fluid replacement during intravenous and orogastric maintenance. Means for each group ± SD are presented. Patients in control group drank up to 500 ml of water during each 12-hr period (not presented). Only one patient in the orogastric group required intravenous fluids after the initial 6 hr.

TABLE 3. Summary of Fluid Replacement

| | Control Group* | Orogastric Group* | Statistical Significance† |
|---|---|---|---|
| Total fluid administered, *liters* | 12.8 ± 3.5 | 17.8 ± 8.5 | Not significant |
| Intravenous fluid, *liters* | | | |
| 0–6 hr | 5.3 ± 0.7 | 6.0 ± 1.7 | Not significant |
| Beyond 6 hr | 7.4 ± 3.2 | 0.3 ± 0.9 | $P < 0.001$ |
| Orogastric glucose-electrolyte solution, *liters* | 0‡ | 11.6 ± 6.6 | — |

* Values indicate mean ± SD.
† Statistical evaluation was by Student's *t* test, not significant indicating $P > 0.05$.
‡ The control group was given small amounts of water by mouth, not exceeding 250 ml each 6 hr.

12-hr period did not exceed 570 ml/hr, a rate well tolerated by all patients studied. Only the patient described above had significant emesis during orogastric infusion. He vomited a total of 2.2 liters during orogastric infusion, which was given at rates as high as 1,158 ml/hr.

Figure 2 summarizes the average stool output for each group during consecutive 6-hr periods. During the initial 6-hr observation period stool output was slightly although not significantly greater in the orogastric group. During the next four 6-hr periods average stool output by the orogastric group exceeded that of the control group in each period, but the difference was significant only during the period 18 to 24 hr after admission ($P < 0.05$). In each group average stool output between 6 and 48 hr after admission decreased in a manner that could be reasonably represented by a straight line fitted by the method of least squares. Total stool volume, duration of diarrhea, and duration of detectable vibrio excretion (Table 4) did not differ significantly between groups.

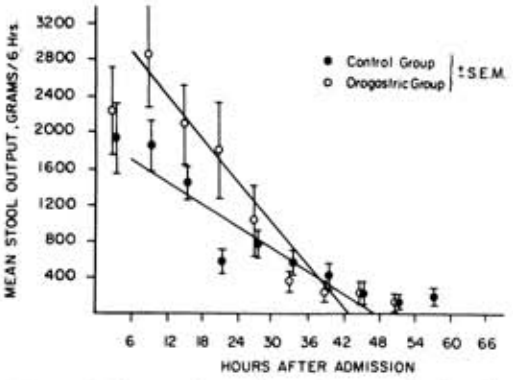


FIGURE 2. Comparison of stool output during intravenous and orogastric maintenance. Mean stool outputs ± SEM for each group during consecutive 6-hr periods are presented. During the initial 6 hr both groups received only intravenous fluid replacement. Stool output by the orogastric group was greater than the control group during the period 18 to 24 hr after admission ($P < 0.05$). Straight lines representing the average rate of decrease in stool output have been fitted for each group for the period from 6 to 48 hr by the method of least squares. The coefficient of correlation of these lines are as follows: control group, $r = 0.91$; orogastric group, $r = 0.97$.

Stool composition for each group at admission and 6, 18, and 30 hr thereafter is summarized in Figure 3. There was a definite increase in carbon dioxide content while osmolarity, chloride, and potassium tended to decrease during the course of the illness. These patterns were observed in both groups of patients. Significant differences between groups were observed, however, in chloride content at 18 hr ($P < 0.01$) and 30 hr ($P < 0.05$) and in osmolarity at 18 hr ($P < 0.02$) and 30 hr ($P < 0.01$). Glucose was occasionally detectable in stool of patients receiving the orogastric infusion but in no instance exceeded 5 mg/100 ml. Glucose was not detected in stool of patients in the control group.

Arterial blood and plasma determinations are summarized in Table 5. All patients showed evidence of marked isotonic dehydration with base-deficit acidosis at ad-

TABLE 4. Comparison of Course of Illness*

| | Control Group | Orogastric Group |
|---|---|---|
| Total stool volume, *liters* | 8.2 ± 2.6† | 11.0 ± 7.8 |
| Duration of diarrhea, *hr* | 44 ± 15 | 37 ± 12 |
| Duration of vibrio excretion, *days* | 1.1 ± 0.4 | 1.4 ± 0.5 |

* There was no significant difference between groups.
† Mean ± SD.

mission. These abnormalities were uniformly corrected by 6 hr in both groups. At this time some patients in both groups were moderately hypokalemic and mildly hyperglycemic. Mean values of arterial electrolytes, pH, $P_{CO_2}$, bicarbonate, glucose, and plasma specific gravity did not differ significantly between groups at either 18 or 30 hr after admission. All determinations at 18 and 30 hr remained essentially normal except for occasional moderate hypokalemia in each group and a single patient

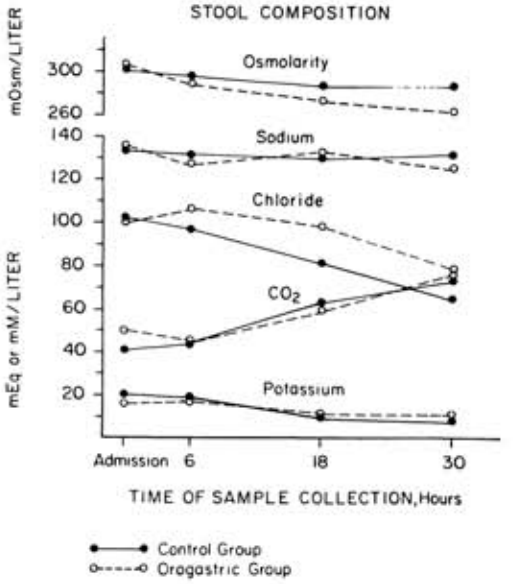


FIGURE 3. Comparison of stool composition during intravenous and orogastric maintenance. Each point represents the mean for the 10 members of the groups. Values that differed significantly between groups were carbon dioxide content at admission ($P < 0.05$), chloride content at 18 hr ($P < 0.01$) and 30 hr ($P < 0.05$), and osmolarity at 18 hr ($P < 0.02$) and 30 hr ($P < 0.01$).

TABLE 5. Summary of Arterial Values

| Determination | Group | Value at: Admission | 6 hr | 18 hr | 30 hr |
|---|---|---|---|---|---|
| pH | Control | 7.19 ± 0.08* | 7.43 ± 0.09 | 7.46 ± 0.06 | 7.43 ± 0.07 |
| | Orogastric | 7.21 ± 0.05 | 7.45 ± 0.02 | 7.44 ± 0.03 | 7.43 ± 0.05 |
| $P_{CO_2}$ | Control | 23 ± 7 | 34 ± 8 | 37 ± 4 | 38 ± 5 |
| | Orogastric | 31 ± 6 | 35 ± 5 | 39 ± 5 | 36 ± 5 |
| Bicarbonate | Control | 9 ± 3 | 21 ± 3 | 25 ± 2 | 24 ± 3 |
| | Orogastric | 12 ± 2 | 24 ± 3 | 26 ± 3 | 24 ± 3 |
| Sodium | Control | 141 ± 4 | 142 ± 5 | 142 ± 5 | 140 ± 5 |
| | Orogastric | 138 ± 3 | 140 ± 4 | 139 ± 3 | 139 ± 5 |
| Potassium | Control | 4.5 ± 0.9 | 3.6 ± 0.3 | 3.5 ± 0.3 | 3.6 ± 0.5 |
| | Orogastric | 4.5 ± 0.8 | 3.6 ± 0.4 | 3.8 ± 0.6 | 4.0 ± 0.5 |
| Chloride | Control | 107 ± 3 | 106 ± 6 | 103 ± 4 | 104 ± 4 |
| | Orogastric | 103 ± 6 | 107 ± 5 | 103 ± 9 | 103 ± 9 |
| Plasma specific gravity | Control | 1.040 ± 0.004 | 1.027 ± 0.002 | 1.025 ± 0.002 | 1.025 ± 0.003 |
| | Orogastric | 1.041 ± 0.004 | 1.026 ± 0.002 | 1.027 ± 0.002 | 1.026 ± 0.003 |
| Glucose | Control | 180 ± 26 | 129 ± 29 | 104 ± 17 | 94 ± 16 |
| | Orogastric | 169 ± 49 | 133 ± 21 | 137 ± 49 | 115 ± 28 |

* Mean ± SD.

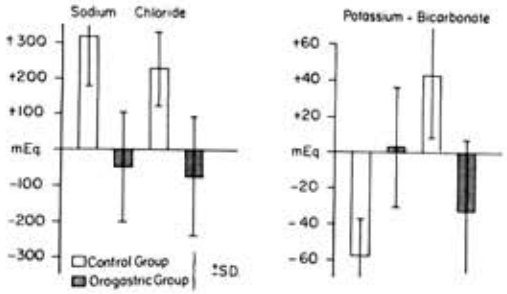


FIGURE 4. Net electrolyte balances during the period 6 to 30 hr after admission. Net balance for each electrolyte was calculated as the total orogastric or intravenous intake, or both, less total stool output for the period 6 to 30 hr after admission.

in the orogastric group with plasma specific gravity exceeding 1.030 at 18 hr. Patients in the orogastric group remained mildly hyperglycemic during this period.

The net balances in milliequivalents (orogastric or intravenous intake less stool output) of sodium, potassium, bicarbonate, and chloride for each group in the period from 6 to 30 hr after admission are summarized in Figure 4. The control group showed definitely positive net balances of sodium and chloride, a slightly positive net balance of bicarbonate, and a moderately negative net potassium balance. In the orogastric group net balances were only slightly negative for sodium, chloride, and bicarbonate, and balance was essentially zero for potassium. In general, electrolyte balances in the orogastric group deviated less from zero than did those in the control group.

The percent of the orogastric solution retained by the patient during the period of orogastric maintenance was determined by the following equation:

$$R = (1 - \frac{S}{G}) \times 100\%$$

in which $R$ = percent of orogastric solution retained during the period of orogastric maintenance, $G$ = the amount of orogastric fluid during this period, and $S$ = the increase in measured stool output above what would have been expected if the group had been maintained intravenously. The expected stool output on intravenous maintenance was that observed in the control group proportionally corrected for the slightly greater initial 6-hr stool output in the orogastric group. Determined by this method, average total stool output during orogastric replacement exceeded the expected output in this period by 21%. The percent of orogastric fluid retained by the patient was 87%.

There was no unusual morbidity in either treatment group. There was no mortality.

## DISCUSSION

Despite the development of highly effective methods for the treatment of cholera (1, 2) case fatality rates still exceed 30% in many cholera-affected areas of the world (9). Such areas are usually rural, impoverished, and ill-equipped medically. Given such conditions, simplification of treatment methods is essential if effective treatment is to reach the patient. Further simplification of therapeutic technique should assist in reducing cholera deaths in these areas (9).

It is well documented that active glucose absorption enhances sodium and water absorption in the normal human small bowel (10). Furthermore, in human cholera (3, 5, 6) and experimental animal models of cholera (11, 12) active small-bowel glucose absorption and the associated passive absorption of sodium and water from an intestinal perfusion fluid remain intact during active diarrhea. By way of contrast, in human cholera, water, sodium, and chloride are not retained during oral administration of an isotonic electrolyte solution that does not contain glucose (13). Previous studies by this unit have shown that with the use of orally administered glucose-containing electrolyte solutions it has been possible to maintain satisfactory water, electrolyte, and acid-balance in most patients with

severe cholera during stool output of up to 800 ml/hr for a period of 12 hr by replacing stool losses only with such a solution (5, 6). The present study has extended these latter observations in an effort to further evaluate the possible therapeutic role of an appropriately composed orally administered glucose-electrolyte solution in the management of severe cholera.

The study was a controlled therapeutic trial of a single, oral glucose-electrolyte solution, the composition of which was chosen on the basis of previous studies by this unit (6). The results indicate that after a brief initial period of intravenous rehydration, it is not difficult to maintain satisfactory water, electrolyte, and acid-base balance in most patients by such an oral solution for the remainder of the duration of diarrhea. In 9 of 10 patients so treated no further intravenous fluids were required despite continuing severe diarrhea. There was no prolongation of the duration of diarrhea or of detectable *V. cholerae* excretion when such an oral solution was used. One patient, with the highest rate of stool output among the 20 patients studied, did require additional intravenous supplementation. This suggests that continued intravenous supplementation in small amounts may be required by a few patients with unusually severe disease during the time that stool output exceeds approximately 800 ml/hr. These data also indicate that there is a small but probably significant increase in stool output (approximately 21%) associated with administration of the oral glucose-electrolyte solution used in this study. However, the calculated portion of water absorbed from the glucose-electrolyte solution used (approximately 87% absorbed) is greater than that achieved in prior studies in which 37 to 72% of orally administered water was retained by the patient (6). The prior studies evaluated two solutions with higher glucose content (160 and 220 mmoles/liter) and greater osmolarity (380 and 421 mOsm/liter) than in the present study and one isotonic solution with much lower glucose content (40 mmoles/liter). It is clear from these previous studies that raising both glucose content and total osmolarity will not achieve greater absorption of the glucose-electrolyte solution than observed in the present study. It is probable that both the total osmolarity and the glucose-to-sodium ratio in the glucose-electrolyte solution are determinants of net absorption in the small bowel during infusion of the solution. The glucose-electroylte solution used in the present study was slightly hypertonic, being 37 mOsm above average cholera stool osmolarity. Previous studies of the separate influences of glucose and osmolarity upon small-bowel water absorption in rats have shown a significant decrease in net water absorption when total osmolarity of the intestinal perfusion fluid was increased above isotonicity by as little as 43 mOsm/liter, glucose concentration being held constant (14). It seems likely that further alterations in composition of the glucose-electrolyte solution, including the use of a strictly isotonic solution, might permit complete absorption of the fluid and its constituents. For use in a simplified therapeutic regimen it is highly desirable that the oral solution be completely absorbed, thus avoiding any increase in stool output due to treatment. Studies evaluating a solution incorporating these changes are being planned.

Adequate maintenance of water, electrolyte, and acid-base balance during orogastric glucose-electrolyte infusion was confirmed in this study by satisfactory arterial values of sodium, bicarbonate, chloride, pH, $Pco_2$, and, with the exception discussed above, plasma specific gravity. These values did not differ significantly from similar observations in the control group. Some patients in each group had moderate hypokalemia that was asymptomatic. Absorption of the oral glucose load was essentially complete in all patients studied. Only

very small amounts of glucose were detectable in some stool specimens.

The oral glucose-electrolyte solution used contained less sodium and chloride than found in adult cholera stool. However, net balances, oral intake less stool output, during the period of orogastric replacement for sodium, potassium, chloride, and bicarbonate were closer to zero than were those in the control group during the same period. Two factors influence this observation. First, the orogastric infusion rate purposely exceeded stool output by 100 ml/hr so that adequate water for urinary and insensible losses would be provided. In so doing additional electrolyte was also given which largely compensated for the lower sodium and chloride concentration in the glucose-electrolyte solution. Secondly, the intravenous solution used in the control group contained more sodium and chloride than the average concentration of these electrolytes in stool over the course of the disease. This accounts for the positive balance of these electrolytes in the control group. It is clear that replacement of stool electrolyte losses was provided as adequately in the orogastric group as in the control group. In both groups the deviations of net balance figures from zero were within limits well tolerated by the patients.

This study demonstrates a means of replacing water and electrolyte losses in cholera that reduces the dependence upon intravenous fluids. It is not likely, however, that the need for intravenous fluids can be eliminated because no other means of fluid replacement would be satisfactory at the time of initial treatment when very rapid fluid replacement is necessary to correct the life-threatening hypovolemia and base-deficit acidosis. It is also apparent that individuals with unusually rapid diarrhea may require continued intravenous supplementation until the rate of stool output diminishes. Likewise, persons with previous gastric or intestinal surgery with resultant alterations in the gastric or intestinal emptying time may not tolerate the rate of oral fluid administration required in severe cholera.

In this study the glucose-electrolyte solution was administered by nasogastric tube for reasons of convenience. In a group of patients subsequently studied the oral solution has been given by mouth in comparable volumes with equal ease. Oral replacement was withheld during the first 6 hr after admission to establish meaningful and comparable rates of stool output in all patients before initiation of oral replacement. It is quite possible, however, that oral replacement might be commenced earlier without difficulty after initial correction of hypovolemia by the rapid administration of only 2 or 3 liters of intravenous fluid to an adult patient (4). If so, this would reduce the intravenous fluid requirement to about 20% of that needed when all fluid is given intravenously. Such a reduction could be of great importance in areas in which supplies of sterile pyrogen-free intravenous fluids of appropriate composition are inadequate to meet the needs of a cholera epidemic. Such conditions often prevail when cholera occurs outside of major metropolitan areas or in areas in which it is not anticipated. The use of such an oral solution would have the additional advantage of low cost, ease of preparation, and the ability to store safely the required ingredients for prolonged periods. These are all factors of practical importance in areas in which cholera is prevalent. It should be stressed, however, that this regimen would require at least equally close supervision of the patient as the established method of treatment which depends entirely upon intravenous fluids. Regardless of the route of fluid replacement, it is essential that fluid losses be replaced accurately if mortality is to be prevented.

Further studies are necessary before an optimal regimen involving the oral replacement of water and electrolytes in cholera can be evolved. In addition to those men-

tioned above, the possible role of oral water and electrolyte replacement in children and infants with cholera should be evaluated. This is important because during cholera epidemics children and infants usually suffer higher case fatality rates than do adults. This is due, at least in part, to the greater technical difficulties encountered in parenteral water and electrolyte replacement in small children. The efficacy of such oral solutions in persons with acute dehydrating diarrhea not due to *V. cholerae* should also be evaluated. This disorder frequently occurs during cholera epidemics, and it is usually impossible to differentiate these patients from those with cholera at the time of initiating therapy (15).

## Acknowledgments

The authors would like to thank Dr. P. M. Manji, Superintendent, Infectious Diseases Hospital, and Dr. J. B. Chatterjea, Director, School of Tropical Medicine, Calcutta, for their support in the performance of this work.

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## Question of the Month

## (Gastroenterology)

407. The "benign" jaundice that occasionally occurs in the third trimester of pregnancy is probably most closely related to

(A) High progesterone level
(B) A specific defect in glucuronide conjugation
(C) Autoimmune process
(D) High estrogen level
(E) The common use of diuretics in this stage of pregnancy

[*This* Question of the Month *is from the* Medical Knowledge Self-Assessment Program *of the ACP. The answer and a reference are given on p. 1218 of this issue*—Ed.]