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PRITECH

Technologies for Primary Health Care

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CONTROL OF CHOLERA IN BELIZE

A Report Prepared By PRITECH Consultant:
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INTRODUCTION AND ACKNOWLEDGEMENTS

The Ministry of Health in Belize requested the USAID mission in Belize to provide a consultant to review the nation's cholera control plan (Information Paper No 12 of 1991, Ministry of Health Response to outbreak of cholera in South America) and offer suggestions on the plan. The request was forwarded through USAID to the Pritech Project who identified Dr. David Sack from Johns Hopkins to carry out the review. When the request was made, epidemics of cholera had occurred in South America, primarily in Peru, but during the week of the review, cases of cholera were also reported in the State of Mexico, immediately to the north of Belize; hence, the review assumed increased urgency.

Because of cholera's appearance in Latin America, the government had already formed a cholera committee, called the "National Committee for the Prevention and Control of Epidemics" (NCPCE) indicating that the committee's role could be expanded beyond cholera in the future. The committee was given the responsibility "to study, analyze and develop an action plan to prevent a possible outbreak of cholera in Belize." The committee developed such a plan and included a multidisciplinary group representing the various ministries responsible for different aspects of disease control. These included individuals from water and sanitation, health education, clinicians and nurses, microbiology, epidemiology, logistics, etc. The committee formed subcommittees to carry out much of the work of the group, though, so far, the committee has acted primarily as a whole body, and has not yet received reports from the subcommittees. The subcommittees include committees on a) water, b) food, c) health education, d) waste disposal, e) surveillance and epidemiology.

I would like to acknowledge the generous cooperation of Mr. Linares, head of the NCPCE who was the primary contact for my review. I also appreciated the encouragement and assistance of Ms. Barbara Sandoval, USAID mission representative to Belize and of Mr. Patrick McDuffie, USAID project development officer, who provided additional guidance and assistance.

EXECUTIVE SUMMARY

The committee had drawn up an admirable plan for preventing cholera's introduction into the country. In general the plan attempted to follow WHO guidelines, and this consultant found little to criticize about the plan. However, several issues arise from the plan; especially 1) the relative priorities of the various aspects of the plan, and 2) need to "flesh out" some of the components of the plan.

A third issue related to #1 is a suggestion to change somewhat the primary mandate of the committee from **preventing** a possible outbreak of cholera in Belize to "**limiting** the morbidity and mortality if (or when) cholera comes to Belize." This goal can be expanded to include the following specific objectives: 1) to prevent cholera deaths, 2) to prevent cholera complications, 3) to limit spread of cholera within the nation, 4) to limit spread of cholera within families, 5) to monitor effectiveness of the cholera control program.

Prevention of the introduction of cholera into Belize may not be possible in view of the multiple ways it can spread, and the likelihood that cholera will continue to threaten the region for months and years to come. Changing the emphasis toward control of the adverse consequences of a cholera epidemic results in a shift in priorities of the components of the plan. Highly important is 1) the provision of highly accessible and effective case management, 2) sensitive case detection with epidemiologic surveillance to identify modes of spread, 3) vigilance and improvement of safe water supplies, 4) education of the population regarding personal hygiene, sanitation, and food preparation, and 5) improvement of sanitation facilities. Though vigilance at borders might prevent the introduction of some cases, early detection of imported cases may be more important so as to limit spread of the disease within the country.

In preparing the plan one recognizes that cholera is geographically close and that outbreaks of disease could occur at any time. If an epidemic were to occur, a large number of patients might need treatment immediately and the Ministry of Health would face a major and sudden medical emergency. In preparing for the immediate threat, one must also realize that the cholera problem will likely be with Belize for many years to come. Even if Belize were to avoid cholera this year, the threat of cholera will continue as long as the disease exists in the region. Hence, the plan must consider needs for both the immediate crisis as well as the longer term control of cholera. Furthermore, the inputs into cholera control will benefit the entire diarrheal disease control program.

With a disease like cholera which carries the threat of epidemics and death, there are significant economic implications for the country since cholera could severely damage tourism; this has already happened in Peru. Thus, when considering potential expenditures for cholera control, one must weigh these expenditures against the loss of revenue if cholera is not controlled. A rapid and effective response to the problem could effectively reassure the tourist industry.

Following are the specific recommendations.

RECOMMENDATIONS

1. ESTABLISH DEFINITIONS AND RATES FOR MONITORING CHOLERA IN BELIZE.

2. PREPARE TO TREAT LARGE NUMBERS OF CHOLERA PATIENTS

a. Insure that all cholera patients receive effective treatment through training of medical personnel.

b. Prepare clear directives for case management in Belize.

c. Clearly identify sites for cholera treatment in Belize, especially in Belize City.

d. Utilize rapid epidemiologic assessment teams (see below -- 3b) to provide and teach case

management of cholera during epidemics in more remote areas.

e. Prepare and stockpile supplies for an outbreak.

f. Use first cases as teaching cases for the medical community.

g. Form subcommittee for case management as one of the subcommittees of the NCPCE.

3. ESTABLISH CASE DETECTION METHODS FOR THE COUNTRY AND MAINTAIN ACCURATE RECORDING OF CASES.

a. Train medical community to detect and report cases of cholera.

b. Establish rapid epidemiologic assessment teams to carry out epidemiologic surveillance and to carry out case control studies of risk factors.

c. Coordinate plans for reporting cases to the press to prevent misunderstandings and conflicting information.

4. INITIATE PLANS FOR IMPROVING WATER SUPPLY AND SANITATION.

a. Carry out environmental sampling of environmental water and sewage.

b. Vigilance with chlorine levels in municipal water systems.

c. Microbiology surveillance of water and sewage sources.

d. Food microbiology in the event of outbreak.

e. Prepare and intensify long term plans for increasing potable water coverage to households.

f. Prepare and intensify long term plans for increasing acceptable sewage coverage.

5. STRENGTHEN IEC ACTIVITIES

a. Focus messages to address specific groups at high risk.

b. Limit messages to those which are of proven importance to cholera control -- not too many messages at once.

c. Stress the role of personal hygiene, especially 1) handwashing with soap, and 2) use of safe

water.

d. Evaluate IEC messages.

e. Target messages to non-English speakers

6. ATTEMPT TO LIMIT CHOLERA'S IMPORTATION.

a. Routine monitoring at airports with stress on reporting any cases.

b. Do not require cholera immunization certificates at borders.

7. MAINTAIN COMMITTEE COORDINATION, AND INTEGRATE CHOLERA CONTROL EFFORTS INTO OVERALL DIARRHEA CONTROL EFFORTS.

8. EVALUATE EFFECTIVENESS OF THE CHOLERA CONTROL EFFORT.

a. Maintain indicators of cholera in Belize and indicators of the success of the control program.

b. Carry out case-control studies of any cholera deaths or complications to learn factors which can be improved.

c. Carry out KAP surveys to understand perceptions and practices about cholera before during and after cholera comes to Belize. This can include random samples of populations groups as well as the medical community.

ESTIMATING THE MAGNITUDE AND NATURE OF THE EPIDEMIC

There is no way to accurately predict the magnitude of a cholera epidemic since so many variables effect this. With a population of 191,000 a very severe epidemic might effect 1% of the population (1910 hospital cases). With water and sanitation measures already being strengthened, it would seem an epidemic of this magnitude is unlikely and that a more likely scenario is the occurrence of pockets of cholera affecting groups of high risk individuals. The groups with the highest rates are nearly always those with low socio-economic status and those who have very poor water and sanitation conditions. We expect however that the extent of cholera in Belize can be decreased by a rapid and effective control program.

INDICATORS OF CHOLERA EPIDEMICS. Several "outcome events" can be used when expressing the magnitude of the cholera problem. The usual outcome event is the number of cases of cholera, and can be expressed as the number of cases per 1000 population (incidence). If a few cases occur, a cholera case is defined as a patient who has diarrhea and from whom *V. cholerae* is isolated. In a large scale epidemic with many cases, a "working case definition" will be needed using clinical symptoms and signs alone. At the same time, fecal samples should be obtained from a sample (every fifth patient for example) in order to provide an estimate the number of cholera cases (number of cases meeting clinical case definitions multiplied by the percent positive).

A second outcome is the number of cholera deaths and is expressed as case fatality rate (number of cholera deaths per 100 cases of cholera treated). A third measure is the number of complicated cases (e.g. acute renal failure, pulmonary edema, etc.) and is expressed as complications per 100 cases of cholera treated. These indicators are related both the success of case management and the accessibility of treatment facilities.

Other indicators of the success of the cholera control program are more difficult to estimate. For example, one would like to prevent secondary spread from infected individuals. When sanitation is excellent, there is no spread to other persons and all cases are the result of food, either imported or contaminated in the natural environment. This is the presentation in the U.S. On the other hand, when sanitation is poor, many cases result from fecal-oral spread through contaminated water and food. The first situation is characterized by individual isolated cases while the second is characterized by massive outbreaks in families and communities. So far, however, there is no accepted index with which to quantitate the degree of secondary spread.

IMMEDIATE NEEDS TO CONTROL THE EPIDEMIC

With the immediate threat of an epidemic, several steps need to be instituted immediately to insure that the first cases of cholera will be treated appropriately, that the case fatality and complication rates will be low and that the initial outbreaks will be limited in scope. These steps include the following:

1) Insuring that any and <u>all cholera patients receive effective treatment</u> with adequate rehydration and antibiotics. This will require rapid training of all physicians on case management of severe diarrhea. This can probably be accomplished with workshops for physicians to be held in the very near future.

2) <u>Preparing clear directives for case management in Belize.</u> While WHO documents serve as the guide for case management, these recommendations leave a few options up to the individual situation. I recommend that the committee prepare specific recommendations for case management for Belize with specific antibiotic dosages, etc. These can be presented at the workshops and can be distributed to the private physicians.

3) Clearly identifying sites for cholera treatment. These have been identified as the district hospitals (in the districts) but plans for Belize City are still somewhat indefinite. Apparently, the Public Health Bureau offices were identified for Belize City, but I would suggest that Belize City Hospital would be preferable in view of the relatively low number of cases which would be seen at one time. The desire to avoid treating cholera at the City Hospital may have been somewhat out of fear of cholera. However, the facilities and supplies available at the Hospital would suggest that this is a more logical location for cholera treatment. Also, it would be more sustainable.

With a population of 50,000 persons in Belize district, one could expect up to 500 cases over a years time, with most(80%) occurring during a 2 month period. With an average hospital stay of 2 days, this would be 800 patient days during 2 months -- less than 10 per day, and hardly enough to justify setting up a separate field hospital. If separate facilities are needed, a tent could be set up in (or near) the hospital grounds.

4) Establishment of rapid epidemiologic assessment teams. When the first cases are identified, teams should be prepared to go to the sites, to confirm the cases, to carry out case control studies, to collect specimens, and to assist with training of local medical officers. These teams should be assembled now and should go through practice "mock outbreaks" so that they will know exactly what to do when the first cases appear. The teams should be mobilized if a) cases of bacteriologically confirmed cholera occur anywhere in the country, or b) if 2 or more cases of adult watery diarrhea report for treatment (even without bacteriologic confirmation), or c) if there is any adult diarrhea death.

Questionnaires are needed to identify cases and family contacts and the current enteric investigation appears to be suitable for initial recording (see appendix). In addition however,

a case-control questionnaire needs to be developed and a strategy for selecting controls described so that suspected vehicles of transmission can be quickly identified. If specific foods are implicated, samples should be returned to the lab in Belize City. A visit to the central stores at Belize City Hospital suggested that some of the supplies needed for cholera case management were not in stock.

5) Prepare supplies for an outbreak. This will include rehydration solutions (Ringer's lactate and ORS packets), I.V. infusion sets and needles, cholera cots, antibiotics, disinfectants. I suggest that these be prepared now in a quantity to manage 50 patients and kept in readiness. Some of the supplies needed may not be as available as they should be and the collection of this cholera supply kit will insure that the Ministry is able to respond immediately. I understand that some of the supplies (cholera cots, for example) may be manufactured from materials from the British or Belize military. If this is so, prototype models should be constructed now to be sure resources and skills are available when needed.

CHOLERA CASE MANAGEMENT

Case management is the key to preventing deaths from cholera and this is an item of first priority. Experience with other epidemics suggest that the initial cases have a much higher risk of death, but that after medical personnel are familiar with case-management, case fatality rates decrease to less than 1%. If preparations are made, the early high case fatality rates can be avoided. Effective case management will depend on training of medical personnel, 2) clear treatment plans, and 3) availability of supplies and medicines.

Treatment should stress rapid rehydration with ORS and I.V. therapy (with Ringers lactate)

as needed and antibiotics. I suggest that the committee carefully consider a single regimen of antibiotics and weigh the costs and benefits of single dose doxycycline versus multiple dose tetracycline. Though doxycycline is more expensive (per capsule), the treatment course of single dose doxycycline may be more cost-effective and logistically simpler. Whichever is chosen, I recommend that it be standardized for Belize.

I do not recommend antibiotic treatment for family contacts, however, if the committee decides to do this, I recommend single dose doxycycline to simplify treatment and to avoid over-treatment of the population. WHO documents leave the issue of antibiotic treatment of contacts somewhat vague, though clearly they would like to discourage it.

When the first cases occur, these cases should be used as teaching cases for the medical community.

CASE DETECTION

If cholera does occur, mechanisms must be established so that they are identified as quickly as possible. This will require training of medical staff including community health workers and nurses to report any suspected cases. To be specific, they should report any cases of 2 or more adult diarrhea, or any adult diarrhea deaths. If cases are suspected, fecal specimens should be sent to the laboratory in Belize City and the rapid assessment teams should be notified.

Cholera "normally" appears first in coastal port communities; hence, Belize City would normally be the first area to expect cholera. Since cholera follows the routes of people, remote areas might become the first locations for cholera if the organism is carried by illegal travelers from South America; hence, remote areas must also be on the alert for cholera.

The committee should establish a central log of all suspected and confirmed cases and they (the committee) should maintain the central source of information for the country. The MOH should then base its announcements on this data base. In other words, plans are needed to assure high quality data and to avoid multiple sources of information which could contradict the official reports of numbers and locations of cholera.

IMPROVING WATER AND SANITATION

Environmental monitoring. The goals of environmental monitoring will be 1) to insure high quality potable water for municipalities and for users of wells, and 2) to detect the presence of cholera in sewage as an indicator or cholera activity.

For the first goal, ministry officials have already increased vigilance to assure adequate concentration of residual chlorine in municipal water supplies of Belize City. This should be extended to other municipalities as well.

For the second goal, a few selected points should be sampled periodically. The points to be sampled will need to be worked out by discussions between the epidemiologists and the microbiologists; however, it would seem that points in the sewage lagoon and the open sewer in Belize City would be logical sites.

Environmental bacteriology for cholera is not normally recommended for cholera control programs; hence, this recommendation is optional. The reason for suggesting it for Belize is the relatively small size of Belize and possibility to actually carry out the surveillance which would not be possible for a country such as Peru or Brazil. When carrying out environmental sampling, the

data will need to be interpreted with care so as not to confuse non-O1 *V. cholerae* or non-toxigenic O1 *V. cholerae* with the epidemic *V. cholerae*.

Food microbiology may be appropriate in the context of cholera cases, but routine microbiological surveillance would not seem to be indicated.

Prepare and intensify long term plans for increasing potable water coverage to households. Mr Linares and I spent one day observing the various water systems in Belize including two styles of hand pump wells, open ring wells, rain water collection systems, community water systems from drilled wells and the municipal water system for Belize City. In addition, I understand that some families still obtain water from other surface water sources. The water from drilled water is unlikely to be a source for cholera transmission but open wells and water stored in open containers can become contaminated. Municipal water systems are especially a concern simply because they serve so many people; however, Belizean officials have correctly stressed the importance of chlorination to limit cholera's spread.

Of interest was the strong preference for rainwater as a source for washing and drinking. Large investments have already gone into collection devices for rainwater from roofs. To my knowledge, rainwater has not been a vehicle for transmission of cholera, since birds and other small animals which might contaminate the rainwater do not carry cholera. A microbiological survey of a sample of rainwater reservoirs might be indicated to determine the coliform counts of this type of water which is so highly prized in Belize.

Water storage is also an issue in Belze since even though water is often provided through municipal systems, water still must be collected in containers and taken to the home. Water in containers can thus become contaminated even though it was safe when taken from the tap. In this regard, water containers with small opennings which prevent hands from going into the water have

been found useful to limit cholera's spread in Calcutta. In Belize a gourd wiht a very small opening is often used (a water cooler) for storing small amounts of drinking water. Assuming the water is clean, this should be an excellent water storage vessel.

Prepare and intensify long term plans for increasing acceptable sewage coverage. A recent survey carried out by CARE suggested that acceptable sanitation lagged far behind water services in Belize. The CARE survey however included pit latrines among the unacceptable types. Though VIP latrines are preferable, an ordinary latrine will prevent the spread of cholera well, as long as the drilled well used for drinking water is sufficiently distant. Discussions in Belize suggested that most persons used some type of latrine or other more acceptable sanitation facility; however, this is an area which needs further study. The open sewers in Belize City are a major concern however, because these sewers flow directly into the sea and can contaminate the sea environment readily. For the purposes of cholera control, the use of improved sanitation facilities and the avoidance of using facilities which directly empty into the open sewers should be stressed.

INFORMATION, HEALTH EDUCATION AND COMMUNICATIONS

The Ministry is already carrying out considerable efforts to increase awareness of cholera in Belize. If cholera occurs in Belize, these efforts will have to be intensified to provide more specific messages and will need to be targeted to specific groups. For example one series of messages could inform persons where to seek treatment if they have symptoms of cholera. Another could stress the importance of the use of latrines and of hand washing. Specific messages should be planned to discourage raw fish consumption. Another should target persons who use surface waters to stress the importance of boiling. Avoid too many messages in one announcement, since people will not remember all of the messages. The current announcements appear to be raising awareness of the problem, but behavior is more difficult to change.

Integration of IEC activities into primary health care activities (e.g. through the community health promoters and clinics), into school lessons, water and sanitation health education activities, and public service announcements are excellent. These various vehicles for information complement each other and the Ministry has done a good job of insuring the messages are consistent.

A program of IEC evaluation will be important to develop in order to understand what messages are being "received by the consumer" of the information. An informal survey of lay persons suggested that they were aware of the approaching problem, but had a very poor understanding of what cholera was, how one could prevent it, or what one should do if they developed symptoms.

The IEC program will need to target messages to the high risk groups. The "average" Belizean may be at low risk, and in general the high risk persons are on the fringe of society and therefore more difficult to reach with IEC messages. Tribal groups and refugees may be especially vulnerable; therefore, special activities may be needed in languages other than English.

PREVENTION OF INTRODUCTION OF CHOLERA INTO THE COUNTRY

Much effort has gone into monitoring national borders, and health checks may be appropriate. However, past experience has shown that absolute prevention of cholera into the country is not possible and attempting to completely control travelers may result in misunderstanding and other adverse outcomes for Belize. For the international airports I support the policy that persons coming from cholera areas be given a card instructing them to report to a given treatment facility in the event that they develop symptoms of diarrhea. It should be clear, however, that <u>a vaccination certificate should not be required for entry into the country</u> since this does not effectively exclude cholera's entry.

Monitoring travelers going overland across borders are more difficult but again should stress the importance of seeking treatment for diarrheal disease. Excessive restrictions will limit case detection, and the disease may spread before authorities realize that the outbreak is occurring. Thus, while vigilance is appropriate and persons who are symptomatic should be treated effectively, the emphasis should be on early case detection of any cases so that its spread can be limited within the country.

Illegal drug traffic may pose a unique risk since there is no control over these travelers and they will be coming from cholera areas of South America. Advice related to controlling these travelers is outside my area of expertise, except to raise the possibility that cholera could begin in remote areas of the country rather than starting in the coastal areas as is normally the case. Thus, one may want to stress surveillance in areas of known drug traffic.

MAINTAIN COMMITTEE COORDINATION, AND INTEGRATE CHOLERA CONTROL EFFORTS INTO OVERALL DIARRHEA CONTROL EFFORTS.

The committee is carrying out an extremely important role in preparing for a cholera epidemic and for a potential long-term problem with cholera. The various disciplines, and ministries involved in the committee are all crucial for cholera's control. Thus the continued functioning of the committee will greatly facilitate efficient communications of the various activities for cholera control. No one activity can manage the problem alone and all components are needed.

While focusing on cholera, the efforts to detect and treat cholera will benefit the entire diarrheal disease control effort in Belize, and these benefits may far exceed the benefits in controlling cholera itself. Even during major cholera epidemics, more children die from other types of diarrhea, but these deaths have not, in the past, stimulated the types of effective public health responses needed

to truly deal with the problems. Thus the cholera control program should support and facilitate the other diarrheal disease control activities already going on in Belize.

EVALUATE EFFECTIVENESS OF THE CHOLERA CONTROL EFFORT.

Evaluation of control programs like the cholera control program is critical for its success. Since this is a new problem for Central America, outside "experts" do not necessarily have all knowledge needed to carry out an effective and cost effective program. Thus, it is crucial for Belizean scientists and officials to critically appraise their own activities and to determine which were more or less effective.

DOCUMENTS AND APPENDICES TO BE INCLUDED

Appendix A: Daily schedule of visit

Appendix B: Point-by-point response to National Plan

Appendix C: Publications related to use of doxycycline and tetracycline

Appendix D: Enteric evaluation form (from MOH, Belize)

Appendix E: Preprint of a chapter on cholera treatment from a new textbook on cholera.

Appendix A

SCHEDULE FOR VISIT TO BELIZE

25 June

11:30	arrive
1:30	Briefing at USAID
3:00	Meeting at Public Health Bureau with Mr. Linares
5:00	Return to hotel
6:00	Informal meeting with Mr. McDuffie (USAID) at hotel

26 June

8:30	Briefing with Mr. Fred Smith, Permanent Secretary, Ministry of Health; Dr. Lopez, epidemiologist; Ms. Shirley Johnson, principle nursing officer.
9:30	Meeting at Public Health Bureau with technical group
11:00	Review of laboratories
1:00	Visit to Maskall (rural area to see clinic and rural water systems). Return by way of municipal water plant.
5:45	return to hotel

27 June

8:00	Meeting at WASA depot to review health education program of water and sanitation projects
10:00	Meeting with Dr. Gregorio Pott, Director of Health Services. Also reviewed central stores and visited Belize City Hospital
11:00	Meeting at PAHO (UNICEF not available)
1:00	Preparation of report
3:00	Debriefing and meeting with NCPCE (cholera committee)
5:00	Return to hotel and prepare report

28 June

8:30	Debriefing at USAID with Ms. Sandoval (AID Representative) and Mr. McDuffie. Handed in draft report.
10:15	Gave draft report to Mr. Linares
10:30	to airport to return to US

Appendix B

POINT BY POINT REVIEW OF INFORMATION PAPER NO 12.

FORMATION OF COMMITTEE

Terms of reference. I have suggested in my review about changing the terms of reference of the committee. It may not be possible to totally prevent cholera in Belize; however, it should be possible to minimize its spread and prevent death or complications from cholera.

The health education efforts have been remarkable in terms of raising the awareness toward cholera.

PROBLEMS IDENTIFIED

1. Safe water supply. Safe water supply is a priority in Belize and the committee will need to be able to receive reports efficiently to assure that the municipal water remains safe.

2. Disposal of feces. This is a major problem and much effort is needed to 1) provide health education regarding personal hygiene and 2) increase coverage of municipal sewage systems. For the short term, the education is critical; for the long term, the capital expenditure is needed.

3. Sanitary handling of food. 1) IEC programs are needed to target street vendors concerning proper handling of food and personal hygiene. 2) Monitoring of imported food has proven to be very difficult. Suspect food should be well cooked. This especially applies to seafood, whether imported or not.

4. Health education. This is an area of great importance. This needs to be described in more detail with focused and targeted messages developed and tested. The permanent secretary showed much interest in developing this area more fully and I agree with him on its importance.

5. Surveillance and epidemiology. This is another area which needs further development in terms of developing specific plans for monitoring and field evaluation when cases are detected. This is discussed more fully in the review.

MANAGEMENT OF CHOLERA

1. The Public Health Bureau was identified as the site for cholera treatment in Belize City. I suggest re-evaluating this. The Bureau is far from the hospital and a new treatment facility would have to be created. I would rather see the Belize City Hospital treat the patients since they have the facilities for managing patients and have the infrastructure already in place.

2. Sixty beds are planned for the treatment facility. I don't expect that this number will be needed with a population of about 50,000 persons in Belize City. Ten to 20 beds should be sufficient at the peak of a major epidemic.

3. I arrived at somewhat different estimates for the number of cases of cholera as illustrated here:

Population	191,000
Incidence in major epidemic (hospital)	1%
Number of cases needing hospital	1,910

The number of persons who become infected or have mild cholera (not requiring hospitalization) may be far greater; however, they would not stress the system as the cases do which require hospital treatment.

VACCINATION

I agree that there is no need to consider vaccination. Also it should be clarified to quarantine officials that vaccination certificates are not needed for incoming travelers from abroad.

I did mention that new oral cholera vaccines are being tested which may offer some assistance in the years to come; however, they are not available yet and, in any case, would not change the need for the types of public health activities described in these planning documents.

DISTRICT MANAGEMENT

This appears to be excellent. IEC activities should clarify where persons should go from treatment. A few designated places should be well established to treat all cases.

COORDINATION

Coordination is critical to the success of the program and the MOH has done an excellent job in insuring that all programs are involved in the cholera control efforts. This needs to be continually stressed. NGO's also need to become involved but I was not able to review coordination efforts with the NGO's.

APPENDIX C1

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Single-Dose Doxycycline for Cholera

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To determine the efficacy of single-dose doxycycline in the treatment of cholera, we carried out a randomized prospective trial in 65 patients. Treatment consisted of either a single dose of 200 mg of doxycycline (or 4 mg/kg in patients less than 15 years old) or multiple doses of doxycycline, 500 mg over 4 days (or 10 mg/kg in patients less than 15 years old). There were no differences between the groups in the volumes of intravenous fluid required, volumes of diarrheal stool, or durations of diarrhea. The mean duration of positive stool cultures for *Vibrio cholerae* was similar for the two groups, although in both groups several patients continued to excrete Vibrios in the stool for more than 3 days. Blood levels of antibiotic demonstrated that the doxycycline was absorbed in spite of the rapid transit time associated with severe diarrhea. These results suggest that although tetracycline remains the drug of choice for cholera, doxycycline is a reasonable alternative, and that a single dose of 200 mg (4 mg/kg in children) is effective clinically.

The treatment of cholera has been improved and simplified in recent years. These improvements include the use of standardized intravenous and/or oral solutions for rehydration and hydration maintenance, coupled with antibiotics which decrease the volume and duration of diarrhea. These measures allow health workers to treat cholera inexpensively and with virtually complete success. Tetracycline is the antibiotic of choice (4, 7). Doxycycline, a long-acting tetracycline, has, however, been shown to be equally effective when given for 4 days (6). More recently, shorter courses of doxycycline have been used successfully for cholera, including a single dose of 200 or 300 mg given on the first day of illness (2). A single-dose therapy has many advantages, one of which would be to eliminate problems of patient compliance. It would also simplify logistics in treating hospitalized patients during an epidemic, since no further antibiotic would need to be given after the initial dose.

Since doxycycline may cause a dose-related side effect of nausea and vomiting, we felt that 200 mg in a single dose was the maximal dose that would be tolerated by all patients with severe diarrhea, many of whom are vomiting already. The present study was designed to compare the effectiveness of a single 200-mg dose of doxycycline with a 4-day multiple dose course of the same drug, using a regiment that has previously been shown to be equally effective with tetracycline (6) in a group of actively purging patients with cholera.

MATERIALS AND METHODS

Male patients, aged 5 to 50 years, who visited the Cholera Research Hospital, Dacca, Bangladesh with a clinical history of acute watery diarrhea, evidence of ≥5% dehydration, and a stool dark-field examination positive for *Vibrio cholerae*, and who continued to purge following admission, were eligible for the study. Patients who had taken antibiotics within 1 week of hospitalization were excluded from the study, as were patients who had dual infections with two or more bacterial pathogens. The study was explained to all patients, and informed written consent was obtained from the patient, or from the parents in the case of children.

All patients were weighed, placed on cholera cots, and clinically examined, noting especially the signs of dehydration. A catheterized stool specimen was obtained for microscopic examination and for culture. The patients were rehydrated within 2 to 4 h using standard intravenous therapy (1) and were maintained on intravenous maintenance hydration. Food and water were allowed as soon as the patient tolerated this.

Patients were assigned to either a single-dose or multiple-dose doxycycline regimen according to a predetermined list of random numbers. Patients receiving a single dose were given 200 mg of doxycycline (or 4 mg/kg if aged less than 15 years) after rehydration, within 2 to 4 h of admission and after some food had been taken. Patients receiving multiple-dose therapy received 100 mg of doxycycline (or 2 mg/kg if less than 15 years of age) in a similar manner; this same dose was then repeated after 12 h, and then daily for 3 days.

Fluid intake and output measurements were recorded every 8 h. Rectal swab cultures were obtained daily for the duration of the hospitalization. Patients remained in the hospital until their diarrhea had ceased for at least 24 h and their fecal culture was

negative for 2 consecutive days. Diarrheal stool was defined as loose or watery stool which could be poured from the bucket for measuring.

All fecal cultures were plated immediately onto MacConkey, *Salmonella-Shigella*, and Monsur agar plates and were also inoculated in taurocholate tellurite peptone water for 6 h for subsequent plating onto a second Monsur agar plate (5). Bacteria from colonies typical of *V. Cholerae* were tested for agglutination with polyvalent O group 1 and specific antisera and were tested for hemagglutinating activity with chicken erythrocytes.

Serum was obtained from 24 patients for the measurement of doxycycline serum levels. These were obtained 2 h after the first dose in both treatment groups, and 18 to 24 h after the first dose in the single-dose group. Five patients who received a single dose and whose level was measured on the day of admission were again given 200 mg on day 5 (the day of discharge for these patients) after their diarrhea had ceased; blood was again obtained 2 h after taking the drug. Serum levels were determined by the microbiology laboratory at Pfizer Laboratory.

RESULTS

Seventy-four patients were initially admitted into the study. Nine were eliminated for one of the following reasons: stool culture revealed *Shigella* in addition to *V. cholerae* (two), stool culture failed to confirm diagnosis of cholera (three), patient absconded (two), error in dosage of doxycycline (two). Of the 65 patients with bacteriologically confirmed cholera (El Tor) who completed the study, 36 received single-dose doxycycline and 29 received multiple doses of doxycycline. The two groups were similar in regard to mean age, dehydration, duration of diarrhea prior to hospitalization, and admission white blood count as shown in Table 1.

Patients were able to take the doxycycline without difficulty soon after initial hydration and after some food was taken. Three patients who were given the drug before taking food vomited the medication, and in these cases the doxycycline was administered again.

Patients in the two groups required similar mean volumes of intravenous fluid and purged similar mean volumes of stool, as shown in Table 2. In both groups most of the total diarrheal stool was passed during the first 24 h, and in both groups more than 90% of the intravenous fluid was given during the first 24 h.

The results of stool cultures are also shown in Table 2. Although the mean duration of *Vibrio*-positive stool culture was approximately 2 days in both groups, 9 of 36 (25%) patients in the single-dose group and 4 of 29 (14%) in the multiple-dose group continued to have *V. cholerae* isolated from stool specimens for more than 3 days. Those patients with a positive culture on day 4 were treated with tetracycline, 4 g over 2 days, and discharged.

Doxycycline was absorbed during active purging, as indicated by blood levels of the drug. All of 12 patients in the single-dose group and 10 of 12 patients in the multiple-dose group had detectable levels of doxycycline in the serum 2 h after the first dose of antibiotic, with a mean level of 1.9 μg/ml (range 0.8 to 3.5) and 0.78

TABLE 1. *Comparison of patients receiving either single-dose or multiple-dose doxycycline*

Dose	Parameters[a]			
	Age (years)	Duration of diarrhea prior to admission (h)	Weight gain during hospitalization (%)	Admission white blood count
Single	22 ± 3	12 ± 2	8.2 ± 0.4	20,300 ± 1,200
Multiple	25 ± 3	13 ± 2	8.0 ± 0.5	16,600 ± 900

[a] Mean ± standard error.

TABLE 2. *Intravenous fluid requirements, stool volumes, and stool culture results in patients with cholera receiving either single-dose or multiple-dose doxycycline*

Dose	Intravenous fluid requirements (ml/kg)[a]			Mean duration of therapy (h)
	Total	During first 24 h	Total maintenance	
Single	210 ± 22	190 ± 15	130 ± 22	26
Multiple	230 ± 22	210 ± 10	154 ± 22	26

Dose	Diarrheal stool (mg/kg)[a]		Duration of diarrhea (h)		Mean duration of positive stool culture for *V. cholerae* (days)
	Total	During first 24 h	After hospitalization	Of output >1 mg/kg per h	
Single	130 ± 20	100 ± 8	33	26	2.3
Multiple	140 ± 19	130 ± 15	33	26	2.0

[a] Mean ± standard error.

μg/ml (range 0.2 to 1.9), respectively. The level at 18 to 24 h in the single-dose group was unchanged with a mean of 1.9 μg/ml (range 0.1 to 4.7). Five of the patients who received single-dose therapy during active cholera were again given 200 mg of doxycycline on day 5 after diarrhea had stopped. The mean 2-h blood level of these five patients during diarrhea had been 2.1 μg/ml (range 1.0 to 3.5 μg/ml), and on day 5 it was 3.2 μg/ml (range 2.2 to 4.0 μg/ml) ($P > 0.1$ by paired t test).

DISCUSSION

Tetracycline remains the drug of choice in the treatment of cholera since it shortens the duration of diarrhea and eliminates the *Vibrio* from the stool within 1 to 2 days. Doxycycline is equally effective clinically in lessening the diarrhea; the duration of excretion of the *Vibrio*, however, is not as effectively shortened as with tetracycline therapy. Whether these asymptomatic culture-positive patients represent a significant public health risk to the community is not clear, especially since the hospitalized and treated cholera patients may represent only a small fraction of the total number of people infected with and excreting *V. cholerae* during a cholera epidemic (8). Nevertheless, it would seem reasonable to use a drug that was maximally effective both clinically and bacteriologically under optimal treatment conditions.

There are situations, however, where doxycycline may be appropriate, especially where supervision of patients, by necessity, is minimal, such as in outpatient clinics and rehydration centers. When using a single dose of doxycycline, the practitioner can ensure that the patient has taken his full course of therapy, and does not have to rely on patient compliance to complete the therapy. Doxycycline is also indicated in patients in whom renal failure is a potential complication and in whom toxic levels of antibiotic might accumulate if tetracycline were used.

This study has shown that doxycycline is well absorbed in spite of active watery diarrhea with the associated rapid transit time. Serum levels 2 h after a 200-mg oral dose in normal subjects average 3 μg/ml, which is comparable to the levels seen in our patients with cholera (3).

Although antibiotics shorten the diarrhea, maintenance of hydration with intravenous and/or oral fluid therapy remains the primary mode of therapy, and no antibiotics can replace the need for careful attention to the status of hydration in patients with severe watery diarrhea.

Since single-dose doxycycline is effective in the treatment of cholera, it might also be expected to be useful in treating other watery diarrheal diseases such as those due to enterotoxigenic *Escherichia coli*. Future studies will be necessary to establish its efficacy in the treatment of this disease.

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APPENDIX C2

Randomised double blind trial of single dose doxycycline for treating cholera in adults

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Abstract

Objective—To compare the efficacy of a single dose of doxycycline (200 or 300 mg) with the standard mutiple doses of tetracycline in patients with cholera.

Design—Randomised double blind controlled trial. Patients were given a single 200 mg dose of doxycycline, a single 300 mg dose of doxycycline, or multiple doses of tetracycline (500 mg, six hourly intervals).

Setting—Hospital in Bangladesh treating diarrhoea.

Patients—261 Patients aged over 15 admitted to the hospital with severe dehydration due to acute watery diarrhoea associated with *Vibrio cholerae*. All vibrios isolated from the stools and rectal swabs of patients, including those patients with prolonged excretion of vibrios, were sensitive to tetracycline. The stools of all patients at admission were negative for shigella and salmonella.

Interventions—All patients received rapid intravenous acetate solution for the first four hours after admission to hospital. They were then entered in the study and randomised. Oral rehydration was started immediately after the intravenous treatment. If signs of severe dehydration reappeared during oral treatment patients were given rapid intravenous acetate solution until dehydration was fully corrected.

Main outcome measures—Stool output in first 24 hours and till diarrhoea stopped, total intake of oral rehydration fluid, duration of diarrhoea, and excretion of vibrio after receiving antibiotic treatment.

Results—The median stool outputs during the first 24 hours (275 ml/kg body weight) and till diarrhoea stopped (296 ml/kg body weight) were significantly higher in patients receiving 200 mg doxycycline as a single dose than in patients receiving either standard tetracycline (242 ml/kg body weight and 254 ml/kg body weight) or 300 mg doxycycline (226 ml/kg body weight and 255 ml/kg body weight). Similarly, median consumption of oral rehydration solution (18·45 l) was significantly higher in patients receiving 200 mg doxycycline than in patients receiving either 300 mg doxycycline (16·10 l) or standard tetracycline (14·80 l). Almost equal numbers of patients in each group required unscheduled intravenous acetate solution to correct dehydration during antibiotic treatment. Patients treated with doxycycline (low or high dose), however, had more prolonged excretion of bacteria.

Conclusions—A single 300 mg dose of doxycycline is as effective as the standard multiple dose tetracycline treatment for cholera in terms of stool output, duration of diarrhoea, vomiting, and requirement for oral rehydration solution.

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Introduction

Patients with cholera are effectively treated with intravenous and oral rehydration fluids. Simultaneous administration of antibiotics, however, considerably reduces the stool volume, duration of diarrhoea, and excretion of vibrio in the stool, thereby decreasing the need for intravenous fluids and nursing care. Various doses of tetracycline are effective in the treatment of cholera.[1-3] Doxycycline, a long acting tetracycline, is effective clinically when given as a single dose of 200 mg or 300 mg[4-6] or over four days.[7] Multiple doses of tetracycline, however, have been found to be better than single doses of tetracycline or doxycycline, particularly in shortening the duration of excretion of vibrio in the stool.[4-6] For inpatients effective single dose treatment would save nursing time and reduce the cost of hospital treatment. In outpatient clinics or in the community during an epidemic multiple dose treatment is difficult to supervise and a single dose would, if effective, be preferable.

Doxycycline seems to be an excellent antibiotic for cholera (except in the unusual case of *Vibrio cholerae* resistant to tetracycline). Its intestinal absorption is not impaired by the presence of food, and nearly all of a dose is absorbed. As it has a half life of 15-20 hours therapeutic plasma concentrations persist much longer than with tetracycline. For infections that are normally treated with doses of tetracycline every six hours doxycycline can be given once daily. Doxycycline is excreted through the kidneys and liver, but it is also excreted directly across the small intestinal mucosa, placing the antibiotic where it can be most effective. Because of the multiple excretion mechanisms toxic concentrations do not usually accumulate, even in patients with renal or hepatic failure. One disadvantage of doxycycline is its association with nausea and vomiting if given orally. This side effect is dose related (being more common with a daily dose of 300 mg than 200 mg) and can be lessened by giving the drug with or after food. Treatment with doxycycline is now cheaper than that with tetracycline.

Recently, the World Health Organisation has been revising its recommendations on the use of doxycycline in cholera with special reference to situations where single dose treatment would be especially appropriate, including rural treatment centres, refugee camps, and other settings where supervision of treatment is minimal. Although several studies have shown the efficacy of both single and multiple doses of doxycycline, no single study has directly compared the antibiotic treatment options or evaluated the degree to which nausea and vomiting might interfere with treatment with higher doses (300 mg) of doxycycline. We therefore undertook this study.

Patients and methods

Two hundred and sixty one patients aged over 15 with a clinical history of acute watery diarrhoea of less than 24 hours' duration and whose stools were found to contain *V cholerae* by dark field microscopy were eligible for the study. These patients reported to this centre from Dhaka and its suburbs from June 1986 to December 1987. Patients were excluded if they had taken antibiotics within one week of admission to hospital, were pregnant, or had other systemic illnesses or if cultures of their stools or rectal swabs, or both, were negative for *V cholerae*. The study protocol was approved by the human ethical review and research

review committees of the centre and WHO. Written consent was obtained from each patient before selection for the study.

Three previous studies of similar patients given antibiotics showed mean total stool outputs of 250 ml/kg body weight with a standard deviation of 100 ml/kg body weight.[1-4] Based on these studies a sample size of 82 per group was estimated to be necessary to detect a significant difference between mean purging rates ≥50 ml/kg body weight (at 5% significance level and power of 80%). Another 15 patients were recruited to each group to account for deviated course or drop outs.

On admission to the observation ward patients were weighed and their clinical signs recorded to permit correct assessment of dehydration. During the first four hour observation period they were rehydrated with isotonic intravenous Dhaka solution (containing sodium 133 mmol/l, potassium 13 mmol/l, bicarbonate equivalent 48 mmol/l, and chloride 99 mmol/l) to replace the fluid deficit. Consenting patients whose purging rate exceeded 20 ml/kg body weight during the four hour basal period were then admitted to the study and were maintained with a glucose oral rehydration solution to match the stool output. They were then assigned to one of three treatment regimens: group 1 received mutiple doses of tetracycline (500 mg every six hours; eight doses), group 2 single doses of doxycycline (300 mg), and group 3 single doses of doxycycline (200 mg).

Preparations of the drugs were provided by Pfizer, Bangladesh, as identical capsules for all three groups. The drugs were labelled separately, and eight capsules were put into numbered identical envelopes; patients randomised to single doses of doxycycline received the active drug in the first dose and a starch placebo in subsequent doses. Randomisation was incorporated into the serial number of the envelopes containing medicine. These numbers corresponded to the order of patients entering the trial so that the first patient received capsules from envelope number one. The code for the drugs was kept at the headquarters of WHO in Geneva, and a sealed copy of the code was also sent to the director of the centre to be kept in a locked cabinet.

The first capsules were given to patients within four to six hours of their admission to the ward after they were adequately hydrated and had taken some simple foods (rice, vegetables, fish, lentils, bread, banana, etc). All patients were carefully monitored daily for any side effects. Intake of rehydration fluid, stool output, and vital signs were recorded every eight hours. The number of episodes and volume of vomiting after admission to the study ward were carefully determined.

A stool specimen was obtained on admission for examination by dark field microscopy and for culture of *V cholerae*, salmonella, and shigella. *Campylobacter jejuni* was not sought in the culture. A catheter specimen of the stool or rectal swab was obtained each morning for culture of *V cholerae*. The specimens for dark field microscopy were examined immediately and after four hours' incubation (37°C) in alkaline peptone water. A presumptive report of *V cholerae* was made if the examination showed organisms with typical motility and if this motility was inhibited by *V cholerae* antiserum.

For culture of *V cholerae* inoculation was made in tellurite taurocholate gelatin agar both directly and after six hours' incubation in alkaline peptone water. *V cholerae* was reported if typical colonies were observed (positive reactions to gelatinase and tellurite and appeared translucent) that agglutinated in *V cholerae* 01 antiserum. The isolates were further characterised by agglutination with specific antiserum and chicken red cells and by sensitivity to polymixin B.

All patients were observed closely until their diarrhoea had stopped for at least 24 hours and their faecal cultures had been negative for *V cholerae* for two consecutive days. Bacteriological relapse was defined as the isolation of *V cholerae* from the stool or rectal swab of a patient who had had negative cultures on two preceding days. Bacteriological failure was considered to have occurred in patients in whom vibrio excretion in the stool was prolonged and continued throughout the study. Diarrhoea was defined as ended when a patient had not passed a watery stool for eight hours. Therapeutic failure was considered to have occurred in patients in whom signs of dehydration reappeared and intravenous fluid treatment had to be restarted.

Finger prick samples of blood were obtained from each patient to estimate packed cell volume and plasma specific gravity (TS meter, American Optical) on admission and two days later to determine the degree of dehydration.

Statistical analyses were done by Wilcoxon's rank sum test, Kruskal-Wallis one way analysis of variance, and χ^2 test, with statistical package for the social sciences (SPSS PC+).

TABLE I—*Characteristics of patients on admission to hospital with cholera*

	Treatment group		
	Tetracycline (n=84)	Doxycycline (300 mg) (n=80)	Doxycycline (200 mg) (n=82)
Age (years):			
Median	25	25	25
Range	15-55	15-60	12-55
Sex (M/F)	52/32	48/32	48/34
Weight at admission (kg):			
Median	40	40	39
Range	25-70	27-60	28-58
Duration of diarrhoea before admission (h):			
Median	14	14	13
Range	4-30	3-30	4-30
No of stools passed since onset:			
Median	16	20	20
Range	5-40	4-60	5-50
No of vomits since onset:			
Median	6	6	7
Range	1-25	1-30	1-30
Dehydration on admission to the study:			
Mild	1		
Moderate	12	13	10
Severe	71	67	72

Results

Two hundred and sixty one patients were initially recruited to the study. Fifteen were excluded because their faecal cultures were negative for *V cholerae*. The characteristics of the three groups of study patients at admission were comparable (table I). Of the 246 patients, 217 were treated successfully, but therapeutic or bacteriological failure, or both, occurred in 29.

The primary objective of the study was to compare the reference group receiving multiple dose tetracycline with the two groups receiving doxycycline. The results of Kruskal-Wallis one way analysis of variance for stool output in the first 24 hours ($p=0{\cdot}016$), total stool output till diarrhoea stopped ($p=0{\cdot}041$), and total intake of oral rehydration solution ($p=0{\cdot}020$) were significant. Pairwise treatment comparisons were then made with Wilcoxon's rank sum test between the tetracycline group and the two doxycycline groups.

Table II shows the clinical characteristics of the patients after intervention. No significant difference was observed between patients receiving conventional tetracycline (group 1) and high dose doxycycline (group 2) for stool output during the first 24 hours, total stool output till diarrhoea stopped, total intake of oral rehydration solution till diarrhoea stopped, duration of diarrhoea, or number of patients who vomited. Patients receiving low dose doxycycline had a significantly larger stool output till diarrhoea stopped

TABLE II—*Clinical course of illness, stool output, duration of diarrhoea, and [illegible] oral rehydration solution in patients with cholera during treatment. Figures are median (quartile) values except where stated otherwise*

	Treatment group			95% Confidence interval for difference between medians		p Value for	
	Tetracycline (n=84)	Doxycycline (300 mg) (n=80)	Doxycycline (200 mg) (n=82)	Tetracycline v doxycycline (300 mg)*	Tetracycline v doxycycline (200 mg)	Tetracycline v doxycycline 300 mg	Tetracycline v doxycycline 200 mg
No of patients who vomited*	18	24	32				
Stool output in first 24 h (ml/kg body weight)	242 (149, 323)	226 (159, 310)	275 (201, 357)	−29·3 to 49·3	−76·6 to −4·3	0·66	0·032
Total stool output till diarrhoea stopped (ml/kg body weight)	254 (159, 377)	255 (175, 349)	296 (219, 420)	−36·4 to 57·1	−93·1 to −0·4	0·72	0·052
Duration of diarrhoea (h)	32 (24, 48)	32 (24, 47)	40 (24, 48)	−5·0 to 5·0	−8·0 to 0·0	0·97	0·170
Total intake of oral rehydration solution (l)	14·8 (10, 22)	16·1 (10, 22)	18·45 (15, 23)	−3·5 to 2·0	−6·0 to −1·0	0·54	0·007
Weight at discharge (kg)	43 (38, 47)	44 (40, 48)		42 (38, 47)		0·36	0·69
No of patients receiving unscheduled intravenous fluids	10	8		9			

*Difference between tetracycline group and doxycycline (300 mg) and doxycycline (200 mg) groups were significant, p=0·047 (χ^2=3·94).

TABLE III—*Number of patients with excretion of V cholerae in stool for four consecutive days*

Day	Treatment group			p Value for	
	Tetracycline	Doxycycline (300 mg)	Doxycycline (200 mg)	Tetracycline v doxycycline (300 mg)	Tetracycline v doxycycline (200 mg)*
1	35	49	50	0·01	0·01
2	6	15	18	0·03	0·007
3	2	8	5	0·04	NS
4	1	7	3	0·02	NS

*Difference between two doxycycline groups was not significant for any of the four days.

and during the first 24 hours and higher consumption of oral rehydration solution during treatment than patients receiving standard tetracycline. The proportion of patients who vomited was higher in the doxycycline groups combined than in the tetracycline group (χ^2=3·94, p=0·047). Almost equal numbers of patients in each group required unscheduled intravenous rehydration during antibiotic treatment.

Of the 246 study patients, 138 had classical *V cholerae* and 108 had the El tor biotype isolated in their stools. Excretion of *V cholerae* in the stool was prolonged in both groups of patients receiving doxycycline (table III). Patients treated with doxycycline also had a higher incidence of bacteriological relapse and failure than those treated with tetracycline. The proportion of patients in whom bacteriological relapse and failure occurred was higher in both doxycycline groups compared with the tetracycline group (χ^2=3·20, p=0·07 with 200 mg doxycycline and χ^2=7·38, p=0·006 with 300 mg doxycycline). Plasma specific gravity and packed cell volume were similar in the three treatment groups.

Discussion

The study showed that 300 mg doxycycline is as effective as standard tetracycline treatment in terms of stool output and need for oral rehydration solution. No significant difference in duration of diarrhoea was observed among the groups. Treatment with intravenous fluid had to be restarted in some patients in each group during maintenance with glucose oral rehydration solution, although all had initial intravenous rehydration. This is not unusual for patients with cholera with severe purging.[7-10] The duration of excretion of vibrio after doxycycline treatment was longer than that with tetracycline treatment. It is not clear, however, if these patients with prolonged excretion represent an important public health risk to the community.

The primary mode of treatment in acutely dehydrating cholera remains early rehydration and maintenance with intravenous or oral fluid treatment, or both. A single dose of 300 mg of doxycycline was an acceptable alternative to standard treatment with tetracycline despite a somewhat longer duration of excretion of vibrio. This regimen would help reduce problems of patient compliance and simplify logistics in treating patients with cholera, especially in the community and during epidemics.

In Bangladesh the total cost of a course of tetracycline is 49 cents whereas a single 200 mg dose of doxycycline would cost 12 cents and a 300 mg dose 17 cents. In a busy hospital like this centre, which treats 14 148 patients with cholera annually, the cost of antibiotics for these patients could be reduced from $6862 to $2467 by changing to single dose doxycycline.

The present study was conducted only in adults with proved cholera. Although tetracycline is not recommended for use in children, because of the life-threatening nature of cholera and the effectiveness of tetracycline and doxycycline further study with single dose doxycycline in children should be considered.

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APPENDIX D

Ministry of Health Belize,

ENTERIC DISEASE INVESTIGATION

Form Completed By: ..... (Print Name) Disease Diagnosis .....

Patient's Name ..... Age: ..... Sex: ..... Name of Parent (if child) .....

Address: ..... District: ..... City: ..... Rural Location: .....

Physician Seen? Yes ☐ No ☐ If Yes, Name and Location: .....

Hospitalized? Yes ☐ No ☐ If Yes, Where? ..... Admission Date ..... Discharge Date .....

Occupation ..... Secondary Occupation ..... Employer .....

Symptoms (Check)

Fever	☐	**Headache**	☐	**Diarrhea**	☐	Constipation	☐
Chills	☐	**Loss of Appetite**	☐	**Vomiting**	☐	Bloody Stools	☐
Malaise (*weakness*)	☐	**ABD Pain** (*cramps*)	☐	**Nausea**	☐		

First Symptom .....

Date of Onset .....

Duration of Major Symptoms (*e.g.* Diarrhea, Fever etc .....

Recent Contact with Enteric Cases? Yes ☐ No ☐ Not Sure ☐

Association with Common Meal? Yes ☐ No ☐ Not Sure ☐ If Yes, Where? .....

Water Source .....
(*specify quality and whether tap, stand pipe, stream, etc.*)

When .....

With Who .....

What Foods were Eaten .....

For Children under 2 Years Old; is Child being Breast Fed (Nursed) without Supplemental Drink or Feedings?

Yes ☐ No ☐ Not Sure ☐

Lab. Work(Type, Date, Result)

Remarks .....

(See Over)

FAMILY MEMBERS

	Name	Relation	Age	Sex	Occupation	* Ill	Date of Onset	STOOL Date	STOOL Laboratory	STOOL Result	Remarks
1											
2											
3											
4											
5											
6											
7											
8											
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*If a family member is ill with an enteric disease, fill out a full Enteric Disease Investigation form on the ill family member.

CHOLERA: Chapter 11 Clinical Management of Cholera

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11.0 CLINICAL MANAGEMENT OF CHOLERA

11.1 INTRODUCTION

Cholera patients who receive adequate treatment will almost always recover fully and rapidly. For a disease capable of spreading in epidemic fashion and causing case fatality rates of 50% or more, the development of successful, simple and inexpensive therapy constitutes one of the most dramatic success stories of modern medical research and its application to a major public health scourge. Using rapid rehydration, a seriously ill patient in profound shock with no detectable pulse or blood pressure is able to sit, talk and eat within a few hours and can return to work within two to three days. Furthermore, this life saving and dramatic treatment can be rendered at a very low cost.

This chapter describes the development of the strategies for clinical management, the basis of optimum therapy and a treatment plan for cholera patients. Since cholera affects largely underprivileged populations in developing countries, the management plan recommended attempts to be simple yet scientifically appropriate. Because treatment of cholera patients in remote areas presents special challenges, a description of the treatment of patients in the home or in "makeshift" rehydration centers is also included.

Manifestations of severe cholera are due almost entirely to the loss of salts and water in the stool and in the vomit although other complications of cholera may occur if effective rehydration is not accomplished. Objectives of treatment are: 1) rapid replacement of water and salts already lost; 2) maintenance of normal hydration until diarrhea ceases by replacing further fluid losses as they occur; 3) reduction of the magnitude and duration of diarrhea with suitable antibiotics; and 3) prompt introduction of a normal diet to minimize the adverse nutritional effects from the illness.

11.2 DEVELOPMENT OF CHOLERA TREATMENT

The history of cholera and its treatment has been described in chapter ( ). Some of the landmarks in the development of appropriate fluid replacement of cholera are given in Table 11-1. Historically mortality from cholera among inpatients declined steadily as the therapy employed the type of fluid replacement which more closely met the actual needs with respect to volume, rate of delivery, and electrolyte content. The most recent landmark in cholera therapy was the development of oral rehydration therapy (ORT) using solution containing glucose and appropriate salts. According to a Lancet editorial, the discovery that glucose facilitated the intestinal transport of sodium and water may have been the most important medical discovery of the century.[1] This discovery and its application to public health has led to the development of a practical, simple, safe, available, inexpensive and effective means of treating dehydration from cholera and other dehydrating diarrheal diseases. Being a powerful tool, ORT (along with appropriate feeding) has emerged as one of the foundations for diarrheal diseases control programs world wide.

Through the ages, many can claim to have used oral rehydration therapy, beginning at least as far back as Hippocrates. Certainly many cultures of the world have given various types of fluids to their children during bouts of diarrhea. These fluids have ranged from apple juice to yoghurt (we could not identify a fluid beginning with "Z"). While these traditional fluids were undoubtedly helpful in many cases, the basic understanding of the mechanisms of absorption, the need for rehydration, and the appropriate types of fluids to be used was lacking. Consequently they could not be used effectively in cholera patients nor in those with other forms of severe diarrhea in whom rehydration was critical. After the fluid and electrolyte requirements were known for cholera and a highly effective treatment regime based on intravenous therapy was developed, attention could be turned towards more cost effective ways of delivering these rehydration fluids.

11.2.1 Glucose Facilitated Absorption of Salts and Water

Physiologists have long studied the relationship between glucose and sodium absorption from the small intestine. Some examples of these research efforts relevant to the development of

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ORT include the following: 1) In 1902 Waymouth Reid, a Scottish physiologist, demonstrated enhanced sodium absorption in the presence of glucose by the mammalian small intestine using dog intestinal loops;[2] 2) Barany and Sperber in 1939 confirmed these findings using rabbit small intestine[3]; 3) Riklis and Quastel showed in 1958 that sodium ion was linked to glucose absorption;[4] 4) Schedl and Clifton in 1963, using intestinal intubation techniques in human volunteers, demonstrated a dramatic improvement in sodium chloride and water absorption from Ringer's solution in both the jejunum and ileum with the addition of 1 gram percent glucose;[5] 5) Subsequently, in vivo studies in normal human small intestine defined the quantitative relationships of glucose with enhanced sodium and water absorption.[6,7,8]

More recently it was hypothesized that this intestinal glucose facilitated absorption of sodium and water from the small intestinal lumen remained largely intact during cholera. Phillips first validated this approach in a few profusely purging adult cholera patients.[9,10] In contrast to earlier studies[11] in which an oral electrolyte solution, but without glucose, did not lead to absorption of the fluid, the glucose containing electrolyte solution was absorbed from the small intestine and led to a positive fluid and sodium balance. Deaths occurred during these early trials of oral therapy; however, and Phillips did not believe that a practical form of therapy had been discovered. Nevertheless, this demonstration may be regarded as the beginning of the scientific development of oral rehydration therapy.

Subsequently, Pierce[12,13] in Calcutta and Hirschhorn[114] in Dhaka evaluated isotonic oral rehydration salt solutions containing glucose and sodium in approximately equal concentrations and dramatically demonstrated the substantial decrease in the requirement for intravenous fluids indicating that absorption was taking place across the small intestine. Studies in animal models[15] showing that glucose mediated absorption took place in the intestines of dogs challenged with cholera toxin helped to confirm these findings.

To be useful as a public health tool, this physiologic observation had to be extended to larger numbers of patients with both cholera and non-cholera diarrhea. This was carried out in Dhaka by Cash and Nalin[16] and later in refugee camps in India[17]. During the war of independence of Bangladesh, refugees fled across the border into India. In these conditions of poor sanitation and scarce medical resources, oral rehydration therapy was used as a matter of necessity and it performed extremely well. Case fatality rates of about 3% were not as low and they would have been with adequate intravenous supplies; still, ORT saved most of the patients and proved that oral rehydration was a powerful tool for controlling epidemics. This helped to convince the health planners and public health workers of its obviously important role as a public health weapon.

Soon to follow were independent studies from Calcutta and Dhaka which provided additional evidence for the usefulness of ORT in cholera patients.[18,19,20,21] Demonstration of the success of ORT in adult cholera patients was then followed by a series of clinical trials in children with cholera,[22] in infants and small children with diarrhea due to rotavirus[23] enterotoxigenic E.coli and other etiologic agents.[24]

Another demonstration of the power and versatility of oral rehydration in a practical setting was the decrease in diarrhea mortality following the introduction of an ORT program in a village in southern Bangladesh.[25] Here, ORT was provided by a packet distribution program in which depot holder families maintained a supply of ORS packets and were trained how to make the solution for their neighbors. Furthermore the village members knew where to obtain the fluids in their own village and were taught the value of rehydration. Thus rehydration could begin at an early stage in the illness.

With such clinical and public health demonstrations as those cited above, ORT emerged as a major therapeutic tool with the ability to correct dehydration and maintain hydration in acute diarrhea in all but the most severe cases and in all ages irrespective of etiologic agents.

11.2.2 Composition of Oral Rehydration Solutions

Early trials of ORS in cholera used solutions containing sodium 90-120 mmol, potassium 10-25 mmol, sodium bicarbonate 30-48 mmol, and glucose 110-120 mmol per litre of solution.[24] In 1971 the World Health Organization began recommending an ORS containing 90 mmol of sodium, 20 mmol of potassium, 80 mmol of chloride, 30 mmol of bicarbonate, and 111 mmol of glucose per litre of water. This ORS (now modified with citrate, see below) has been successfully adapted and extensively tested both under controlled hospital conditions as well as in the field. It meets the varying needs of rehydration therapy in all ages suffering from acute diarrheas due to many etiologic agents including cholera.

Several factors were considered in devising the appropriate formulation. It was known that the cholera patient looses bicarbonate and potassium in addition to sodium and water in the isosmotic stool. Thus, the replacement solution should replace these losses with a solution of similar concentration of electrolytes to correct the acidosis and potassium deficiency. Furthermore sodium and glucose absorption is coupled and are thus absorbed on an equimolar basis. Therefore, it was appropriate to have similar concentrations of glucose and sodium. Finally the solution should not be excessively hypertonic since an excessive osmotic load is associated with a lessened absorption and increased diarrhea. Two grams of glucose appeared to be optimal for absorption;[14] higher concentrations increase the osmolality excessively and are counterproductive.

11.2.2.1 ORS formulations containing trisodium citrate.

A base is needed in the ORS to replace the bicarbonate lost in the cholera stool and correct the resulting metabolic acidosis. Sodium bicarbonate was originally selected for ORS;[24] however, ORS packets with sodium bicarbonate has a short shelf life (a few months), especially in hot and humid tropical climates. It therefore seemed appropriate to select a different base for ORS. Laboratory studies demonstrated that ORS containing 2.9 grams of trisodium citrate dihydrate in place of 2.5 grams of sodium bicarbonate was the most stable of the candidate formulations evaluated, and it seemed likely that citrate would perform as well as bicarbonate in the solution.[26] Subsequently clinical trials were undertaken to compare the efficacy of an ORS containing citrate with ORS containing bicarbonate.[27,28,29,30] Among those studies undertaken in adults and older children with cholera with dehydration and acidosis, the acidosis of those receiving the citrate ORS was corrected at a rate equal to that of those patients receiving bicarbonate ORS. In one of the studies in adults with cholera, diarrhea stool output was significantly decreased in the group receiving citrate ORS and in two other studies there was a similar trend. Among studies undertaken in infants and children below two years of age with moderate to severe dehydration from non-cholera diarrhea, citrate ORS was found to be uniformly as effective as bicarbonate ORS in correcting acidosis and dehydration. However, no reduction in diarrhea stool output was observed in these children. In conclusion ORS with citrate was found to be at least as effective as ORS with bicarbonate but to have a significant advantage in its improved shelf life. However, one should not hesitate to use ORS with bicarbonate when the situation requires it since this is also highly effective in the treatment of dehydration. Presently all centrally produced and distributed ORS packets by UNICEF, WHO and other agencies are citrate based.

The currently recommended composition of ORS with citrate is shown on Table 11-2.

11.2.2.2 Sucrose as a substitute for glucose in ORS formulation.

Since glucose is not locally manufactured in many countries and is not available in many households, studies were conducted to evaluate sucrose (table sugar) as a possible alternative to glucose. Sucrose is broken down by the intestinal brush border enzymes into glucose and fructose, and it was expected that glucose should be available to participate in the absorptive process. It was possible, however, that sucrase activity would be insufficient during diarrhea, and that this would result in a sucrose malabsorption and a worsening of the diarrhea. Also it was known that fructose, which is much less efficient than glucose in its absorption might create an osmotic load leading to increased diarrhea. Hence the studies showing the effectiveness of sucrose as an alternative were reassuring.[23,31,32]

Although the studies comparing sucrose with glucose show them to be nearly equivalent,

all studies have suggested a slight trend in favor of glucose. Also occasional patients have been documented to have a sucrose malabsorption and these patients will need a glucose solution for severe diarrhea. In spite of these relative deficiencies, the availability of sucrose in most homes, its local production and economy, and its efficacy for the vast majority of patients make it an acceptable alternative to glucose for ORS. However, when preparing packets for mass distribution, the slight advantage of glucose suggests that glucose is preferred since, in this situation glucose can generally be obtained at a price similar to that for sucrose. If sucrose is used, one should use 40 grams/liter in order to obtain a yield of 20 grams of glucose.

11.2.2.3 Starches and Cereals in ORS

As an extension of the desire to make ORT available and acceptable to the people who use it, the use of cereals, especially rice, has been evaluated as the substrate in place of glucose. Rice has many attributes which make it attractive for ORT in addition to its cultural familiarity. Starches and proteins in cereals, when broken down by the digestive processes in the intestinal tract, release glucose, amino acids and short chain peptides, all of which are organic solutes which may enhance the absorption of sodium and water. In addition cereals may also be used in larger quantities, thus providing some additional calories with little or no osmotic penalty.

Molla, using retrospective controls, demonstrated that rice powder ORS (30 grams per litre) was as effective as sucrose based ORS (40 grams sucrose per litre) in adults and older children with cholera.[33] Subsequently Patra demonstrated in a controlled clinical trial in children with cholera and non-cholera diarrhea that rice powder containing ORS (50 grams precooked rice powder per litre) could reduce the volume and the duration of diarrhea.[34] A follow up clinical trial by Molla in adults and older children, predominantly with cholera, confirmed that a rice powder (80 grams rice powder per litre) ORS (in comparison to standard ORS) could reduce diarrhea stool volumes and ORS requirement.[35] In a more recent clinical trial in children with cholera and non-cholera diarrhea, Patra used a combination of cooked rice powder (50 grams per litre packet) and glycine (111 mmols per litre) in ORS and showed that adding glycine to rice did not further improve its efficiency.[36]

In studies conducted so far, rice-based ORS has proved to be at least as efficacious as glucose in rehydrating patients with cholera and other diarrheal diseases. Additionally the use of rice rather than a sugar as the carbohydrate source may be associated with a reduction in the total diarrheal stool output.[33,34,37]

Starches other than rice may also be used, as demonstrated by Alam and colleagues who found that a well hydrolyzed wheat based oral rehydration solution also significantly reduced the diarrhea stool output in children with cholera.[39] The wheat product used, which contained 11.5 grams % protein and 87 grams % carbohydrate (60% maltose, 15% maltotriose and 10% maltodextrins), was completely soluble in water and did not require cooking. Finally, preliminary analysis of trials with ORS based on other cereals such as wheat and maize have shown that these may also be used as substrates to promote absorption (unpublished data from studies at ICDDR,B).

Practical constraints of the currently used rice based ORS formulations include the need for cooking prior to use and a short shelf life of the prepared solutions particularly in hot and humid conditions (6 to 12 hours). Although the need for cooking makes rice and other cereal based ORS less suitable as a prepackaged product (unless a precooked stable cereal based ORS can be produced), the results of studies with cereal based solutions should also be very useful proxy indicators for the efficacy of cereal based home fluids for early home therapy.

In summary, cereal based ORS formulations tested so far are highly encouraging. Based on these results and the acceptability of a rice based formula in Bangladesh, the ICDDR,B currently uses a rice based ORS (50 grams per liter of rice powder) as its routine rehydration solution at its treatment centers. Rice based ORT is not seen as competing with the glucose formulation; rather, both are acceptable and either can be used depending on local circumstances.

If a packet formulation can be prepared with an economical and stable rice powder which does not require cooking, the rice based formula will likely become much more popular.

11.2.2.4 Improved ORS formulations (super ORS)

Oral rehydration therapy with the present ORS formulation is intended to rehydrate the patient but, with the possible exception of cereal based ORS, does not reduce the volume, frequency or duration of diarrhea. This raises the practical problem of its acceptance by patients and by parents of ill children who would like to see a dramatic improvement in the severity of the diarrheal symptoms. This desire leads to a continuing demand for anti-diarrheal medication.

It has been postulated that a super ORS formulation could be developed which could utilize a combination of pathways of absorption which in turn would lead to a net decrease in diarrhea volume[37]. Such a super ORS could theoretically induce reabsorption of the endogenous secretion in addition to facilitating the absorption of the fluids administered, and thus it would become an antidiarrheal medication as well as a form of rehydration.

The mechanisms which could be utilized in a super ORS include the following. a) organic nutrient linked absorption, b) the use of glucose polymers rather than glucose, c) weak organic acid linked absorption, and d) colonic salvage of salts and water by short chain fatty acids.

Glucose is one organic nutrient which is linked to absorption; however, other d-hexoses and certain amino acids, e.g. glycine and l-alanine, also can be utilized. Early studies in adults and older children with cholera and non-cholera diarrhea indicated that an ORS prepared with a combination of glucose and glycine (110 mmols per litre) could substantially reduce the stool volume and duration of diarrhea.[40] Subsequently a double-blind controlled clinical trial of glucose and glycine (111 mmols of each per litre) based ORS in children with cholera and non-cholera diarrhea showed that the stool volume, duration of diarrhea and volume of ORS requirement were reduced compared with controls receiving the standard glucose ORS formula[41]. A recent double-blind clinical trial in Indonesia confirmed that a glucose and glycine containing ORS formulation reduced diarrhea stool output in actively purging adult cholera patients (Moechtar et al, unpublished data). Finally preliminary results from a similar clinical trial of ORS with l-alanine in older children and adults with cholera showed a marked reduction in stool output and duration of diarrhea among patients receiving the l-alanine ORS compared to the standard ORS controls. (Patra et al, unpublished data).

When glucose is administered in a free form, the upper limit of its effective concentration is about 2 grams per 100 ml; higher concentrations are associated with an increase in the diarrhea. One way to effectively increase the concentration of glucose while minimizing the risk for the osmotic penalty is to use a suitable polymer(s) of glucose which releases glucose on digestion at a rate favorable for its absorption. These glucose polymers include the maltodextrins of various grades as well as natural foods containing starch and protein.

The suggestion that weak acids might increase fluid absorption was alluded to when discussing citrate ORS above. Weak organic acids e.g. acetate, n-butyrate, and propionate are rapidly absorbed from both the small and large intestine. These weak acids are exchanged for bicarbonate; and sodium and potassium are absorbed in the process. Sodium citrate has also been shown in a rabbit model to stimulate absorption of sodium and potassium.[42]

Whether these physiologic improvements in ORT will result in a substantially better oral rehydration formulation is not yet known. If additional substrates are to be added to the standard ORS packet, its formulation will depend on a clinically significant improvement in efficacy while not adding appreciably to the cost of the solution. At present the cereal based formulae come the closest to meeting these requirements.

11.2.2.5 Incomplete Oral Rehydration Solutions

The practical considerations which led to the development of sucrose ORS has also been extended further to consider simple "sugar-salt" rehydration solutions which contains neither potassium nor added base and thus can be prepared from ingredients normally found in the home. Since these solutions do not have a base or potassium, patients who receive only this solution have an increased risk for both continued acidosis and hypokalemia.[43] For the more common non-cholera diarrheal illnesses which tend to be less severe and are generally the focus of community health programs, the incomplete simple solutions can be used effectively.[44] However, they should be used with a diet supplemented with potassium rich foods during and after diarrheal episodes to compensate for the potassium loss.

For heavily purging cholera patients, however, the incomplete formula is not sufficient and should be used only as a temporary measure until an appropriate complete solution can be obtained. Diarrhea treatment centers, clinics, and hospitals should always prepare a complete solution including a base and potassium since patients receiving assistance from these sources tend to be more ill and require the complete solution.

11.3. Use of Intravenous fluids.

The alternative appropriate intravenous rehydration solutions are described briefly in Table 11-3 and their compositions are shown on Table 11-4. The issues which had to be addressed in the development of the I.V. solutions were similar to those described for ORT, namely replacement fluids were needed which replaced diarrheal losses of water and electrolytes during cholera. Although many of the basic concepts were learned in the early 1800's, they were not widely held until this century and were not utilized until mid century.

In spite of the importance and success of ORT, intravenous rehydration still plays a critical role in the treatment of cholera. For cholera patients who present with severe dehydration and shock, rapid infusion of appropriate I.V. fluid is life saving. For diarrheal diseases other than cholera, patients with such profound and rapid dehydration are unusual, but for cholera, especially during epidemics, it occurs frequently. Since cholera usually occurs in geographic areas with few medical resources, ORT conserves the limited I.V. supplies which are available.

The composition of a standard I.V. solution for cholera patients is based on the concept that the fluid given should replace the losses of the cholera stool which, in a severely purging cholera patient contains sodium (100-140 mmol per litre), bicarbonate (30-50 mmol per litre), and potassium (15-30 mmol per litre) with an osmolality close to that of plasma. A suitable polyelectrolyte solution for intravenous use should therefore contain (per litre) sodium (110 to 140 mmol), potassium (10-15 mmol), a base (30-50 mmol), and chloride (70-100 mmol). Lactated Ringer's (Hartmann's fluid) is one of the recommended fluids because it is the one commercially available I.V. solution with a suitable composition. In cholera endemic areas special polyelectrolyte fluids may be prepared especially for diarrhea treatment, e.g. the "Dhaka Solution"[45] or "DTS"[46] (diarrhea treatment solution), or others.[47] Fluids such as normal saline or normal saline containing glucose should only be used if a more suitable polyelectrolyte solution is not available and if the I.V. fluids are critical to treat a patient in shock. If this less desireable solution is used, complete ORS should be instituted as early as possible to replace the base and potassium not included in saline. 5% dextrose in water (D5W) is not suitable for a patient with cholera.

Treatment with intravenous fluids is recommended only for patients with severe dehydration and signs of hypovolemia. For these patients intravenous fluids are given to completely rehydrate the patient, and this can generally be accomplished within 2 to 4 hours. After this complete initial rehydration most patients can be maintained with oral rehydration therapy, although about 10-15% of hospitalized patients may need an additional short course(s) of intravenous therapy due to high purging rate and recurrence of signs of dehydration. Generally these patients who again become dehydrated while on oral rehydration therapy will be those whose purging rate is in excess of 10 ml/Kg/hour.[32]

Extensive experience indicates that a single intravenous solution may be used for all age

groups with cholera as well as with non-cholera diarrhea who require such I.V. rehydration. Except for the rare case of a complicated patient in which electrolyte balance has been compromised by inappropriate fluids already given, it is not necessary to tailor-make a solution for the individual patient. This saves a great deal of effort in not having to prepare separate solutions for individual patients and it allows para-medics and nurses (rather than physicians) to largely manage patients.

11.4. Antibiotics

11.4.1 Antibiotic therapy of patients.

The purpose of giving antibiotics to cholera patients is to decrease the volume and duration of purging.[48,49] Antibiotics are not "life-saving" for cholera patients as they are for many other severe infections. In cholera the use of tetracycline will a) reduce the duration of diarrhea by about 50% to an average of about 2 days; b) reduce the volume of diarrhea after initiation of treatment by about 60%, c) reduce the duration of Vibrio excretion to an average of one day and a maximum of 48 hours. Thus, the use of appropriate antibiotics lessens the expense and duration of treatment which in turn allows for the treatment of more patients when supplies and personnel are limited. It also increases the success rate with oral rehydration therapy since such therapy need not be so prolonged.

Antibiotics are given orally and are usually started after completing initial rehydration, i.e. about 4 to 6 hours after starting therapy in a dehydrated patient. It is neither urgent nor of additional benefit to use injectable antibiotics.

Tetracycline is the antibiotic of choice. The dose for adults is 500 mg every 6 hours for 48 to 72 hours (some use 250 mg every six hours for three days) while the dose for children is 50 mg/kg/day in four divided doses for 48 to 72 hours. Doxycycline, a long acting tetracycline, can also be used in a single dose of 300 mg for adults and 4 to 6 mg per kg of body weight for children below 15 years of age.[50,51,52] Doxycycline may cause nausea but this is lessened considerably if patients eat some food before taking the drug.

If tetracycline cannot be used, one may use furazolidone, 100 mg every six hours (for children, 5 mg/kg/day in four divided doses) for 72 hours; erythromycin, 250 mg every six hours (for children, 30 mg/kg/day in three divided doses) for 72 hours; or trimethoprim-sulfamethoxazole (8 mg of trimethoprim and 40 mg of sulfamethoxazole per kg per day, in two divided doses for 72 hours). For young children tetracycline syrup may not be available in some countries, in which case liquid preparations of furazolidone, erythromycin or trimethoprim-sulfamethoxazole can be used. Sulfadoxine (fanasil) has been used in one dose for the treatment of cholera. However, resistance to it has been found in a few countries in Africa and potentially serious adverse reactions (e.g. Stevens-Johnson syndrome) can occur following a single dose. Chloramphenicol is also effective and can be given in the same dosage as tetracycline but it has no advantage over tetracycline and may have serious side effects.

Though not an antibiotic, the use of cholera phage as a treatment for cholera should be mentioned.[53] Orally administered cholera phage have been tested as a way to eliminate the V. cholerae from the intestine of patients. Although the phage were safe and had an anti-Vibrio biolological effect, tetracycline was much more effective clinically, as well as being more practical.

11.4.2 Prophylactic Antibiotics

When cholera epidemics occur there is sometimes pressure to provide prophylactic antibiotics to family contacts of cholera patients and even to whole communities. Tetracycline or doxycycline, when given to family contacts, can prevent secondary cases from occurring.[54] The difficulty in giving prophylactic antibiotics, however, is in developing and implementing a policy of providing antibiotics to high risk individuals selectively without giving massive amounts of antibiotics to whole communities. Prophylactic antibiotics for cholera can create enormous antibiotic pressure in the community leading to the emergence of antibiotic resistant strains. While

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family contacts are at higher risk for developing cholera; during an epidemic, treatment of family members would represent only a small fraction of those who will become infected. Also the risk of cholera for those living in cholera endemic area extends over a prolonged time period and this also makes prophylactic antibiotics impractical. Considering the cost of such a program, it becomes even more impractical. Hence, the use of prophylactic antibiotics is not recommended.

11.4.3. V. cholerae Resistant to Multiple Antibiotics.

Resistance of V. cholerae to tetracycline and other antibiotics has been reported from East Africa[55] and Bangladesh.[56] In these two geographic areas resistance was mediated by conjugative plasmids bearing resistance to multiple antibiotics; however, the resistance patterns of the strains from the two areas were different from each other. With time the epidemic stains seemed to disappear to be replaced once again by sensitive ones. In Africa there had been excessive use of prophylactic tetracycline for cholera and it was postulated that this encouraged the emergence of the resistant strain.

Clinically the presence of resistant strains may be suspected by an inadequate clinical response after administration of the antibiotic. Thus, it may be important to determine the antibiotic susceptibility of representative strains periodically and to be aware of the resistance pattern of the organism in adjacent geographical areas. Since V. cholerae which are resistant to one antibiotic are frequently multiply resistant, it is necessary to define the sensitivity pattern of the local strains to determine which of the effective antibiotics should be used.

11.5. Antidiarrheal and Antisecretory Agents

Kaolin, pectin, activated charcoal, bismuth sub-salicylate have not been shown to be of value in the treatment of cholera. In one study charcoal interfered with the beneficial effect of tetracycline[57]. In another, a charcoal-gm1 ganglioside preparation which was documented to have bound lumenal cholera toxin was used in an attempt to block absorption of the toxin to the mucosa. This therapy lead to a moderate reduction in the rate of purging in cholera patients, but only for a short period early in the illness[58]. Opiates and opiate-like compounds and other inhibitors of intestinal motility are useless and may be harmful in cholera.

There has been considerable enthusiasm for the development of antisecretory drugs which would, through an understanding of the cellular mechanisms of the secretory processes, turn off intestinal secretion in cholera patients. Such an effective antisecretory agent might simplify the treatment of the cholera patients since it would further shorten the duration of the illness and decrease the course of rehydration needed.

Several drugs have been shown to have an antisecretory effect in experimental animal studies, and some of these have been tested in patients. Chlorpromazine, a phenothiazine with antisecretory properties in animal models, also proved to significantly reduce the stool volume of cholera patients if they were rehydrated with and maintained on intravenous fluids and were not given antibiotics.[59,60] A follow-up study was carried out to determine if this physiologic observation could be confirmed using a study design in which chlorpromazine was added to a routine treatment regimen, including antibiotics and ORT. In this follow-up study there was no overall difference between treatment groups; though, there was a suggestion that chlorpromazine did have some antisecretory effect in severely purging children.[61] Unfortunately children taking chlorpromazine also developed somnolence which interfered with the administration of oral rehydration fluid; hence, chlorpromazine is not recommended. If another phenothiazine could be identified which retains the antisecretory activity of chlorpromazine without producing somnolence, it might still be useful.

Berberine, an alkaloid used extensively as a traditional remedy in Asia for diarrhea, has also been shown to have an antisecretory affect in animal studies.[62] However controlled clinical trials testing the effectiveness of the drug in patients with cholera have not been definitive. In two studies among adults with cholera or cholera like diarrhea it had either no effect upon the rate of stool output or reduced the rate minimally.[63,64] In another trial involving patients with

enterotoxigenic E. coli diarrhea, it had a more marked beneficial effect.[65] So far it has had no side effects which would limit its usefulness. Additional studies, perhaps using other dose schedules, are needed to determine if it has a clinical use in secretory diarrhea.

Other drugs which have been tested in patients include nicotinic acid,[66] aspirin,[67] indomethacin,[68] chloroquine,[69] and somatostatin.[70] Nicotinic acid showed a possible but marginal effect, but the others showed no benefit.

In summary although antisecretory drugs could potentially assist in the treatment of cholera patients, none so far have proved to be of use in routine clinical management.

11.6. Feeding during cholera.

Over the last 20 years a large number of studies have introduced early feeding as part of the standard treatment. Subsequently a series of studies vindicated this clinical wisdom. This conclusion is based on the observation that food does not interfere with recovery from cholera, that it can be absorbed even during an episode of cholera, and that food may provide substrate for ORT.

Molla showed that children with cholera are able to eat and that the mean caloric intake during the acute phase was 75 calories per kg per 24 hours. This increased to 111 calories per kg per 24 hours two weeks later.[70] Further, he showed that macronutrients can be absorbed by children during cholera. 70% of the fat intake, 47% of the protein intake, 88% of the carbohydrate intake, and 81% of the calories (mean values) was absorbed during the acute phase of the illness. This increased two weeks later to 90%, 73%, 93% and 91% respectively.[71] Additionally, trypsin and amylase activities in adult cholera patients during a basal period and after a stimulation by Lund's test meal is well preserved during the acute phase of the disease.[72]

In a group of young children (1-2 years) with cholera, a nitrogen balance study during the acute phase showed that a positive nitrogen balance could be promptly achieved with liberal milk feeding even before diarrhea was controlled even in clinically severe cases.[73] Finally in a controlled clinical trial Dr. Khin Muang U in Burma compared a group of severely dehydrated children with cholera served with rice meals along with appropriate fluid therapy (initial I.V. followed by ORT) to a control group who received no food for 24 hours.[74] The group receiving rice meals showed a significant increase in the diarrhea stool output but demonstrated a better weight gain compared to the controls. Recovery was uneventful.

In conclusion early liberal feeding of cholera patients assists nutritional recovery and is compatible with a rapid and uneventful recovery. The concept of early feeding appropriate for age is complimentary with that of the improved ORS. In both situations, additional substrates are provided early in the illness. In one case they are provided for their nutritive value; in the other, they are provided to increase absorption of electrolytes and water. It may be that the introduction of appropriate food with the variety of nutrients thereby provided, may in fact, convert the standard ORS into an improved ORS.

11.7. CLINICAL MANAGEMENT

11.7.1. Diagnosis and Assessment of Patients at a Treatment Center.

The diagnosis of patients with severe cholera (cholera gravis) is usually not difficult because of the sudden and dramatic signs and symptoms. Patients usually come for treatment after only a few hours with diarrhea, vomiting, and weakness. The onset is sudden and the diarrhea is generally described as painless, in contrast to shigellosis in which defecation is associated with many cramps. The diarrhea stool is at first loose, then it becomes more watery and takes on the appearance of "rice water." Likewise the vomit has the same appearance. As the disease worsens and the dehydration becomes more severe, the patient's voice becomes weak, his mentation fades, and he is too weak to hold himself upright. The breathing is noticeably labored. The patient may complain of a dry mouth, and urine flow stops.

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On examination the cholera patient appears extremely weak with poor mentation and evidence of dehydration, e.g. decreased skin turgor, sunken eyes, dry mucous membranes, and a weak or undetectable radial pulse. Kussmaul respirations may be evident. The dramatic aspect of the disease is the rapidity with which a healthy person can become so sick. The appearance is sometimes described as cadaveric.

The case described above is typical of cholera, but much less severe episodes of cholera also occur, and the mild cases cannot be distinguished clinically from other acute watery diarrheal diseases. Also a few other etiologic agents can also cause a cholera gravis syndrome, most notably the enterotoxigenic E. coli. For management of the individual patient however, it is not necessary to know with certainty whether the acute diarrheal syndrome was due to a Vibrio cholerae or another agent. The rehydration therapy is the same.

The assessment of the patient with the acute dehydrating diarrhea syndrome consists of evaluating him for signs of dehydration, estimating the severity of the dehydration and then estimating the fluid requirements. This must be accomplished rapidly since the severely dehydrated patient may literally be within minutes of death unless hydration is instituted immediately. One estimates the degree of dehydration through a clinical assessment of the signs of dehydration. Laboratory tests (hematocrit, plasma specific gravity, or serum proteins) are useful in research studies for comparing groups of patients, but the clinician must formulate a treatment plan for the individual patient based on the clinical examination.

As a guide, the severity of dehydration is categorized into four categories: none, mild, moderate, and severe. Patients with no objective signs of dehydration are categorized as "none" while realizing that at least 5% of the body weight must be lost before signs of dehydration develops. Patients with some evidence of dehydration, mildly decreased skin turgor for example, will be categorized as having mild dehydration and their fluid deficit will be estimated at 5%. Moderately dehydrated patients whose deficit is estimated at 7.5% have obvious signs of dehydration with dry mucous membranes, somewhat sunken eyes, and poor skin turgor. The radial pulse of these patients will be diminished and rapid but will be palpable. Severely dehydrated patients whose deficit is estimated at 10% are extremely weak with poor mentation, very poor skin turgor, very sunken eyes and a barely perceptible or absent pulse. Although no one sign should be used to the exclusion of others, among the various signs of dehydration, many experienced clinicians find palpation of the radial pulse to be the most helpful in differentiating between moderate and severe dehydration. Skin turgor must be interpreted with caution in elderly patients or malnourished children since the skin may have lost its elasticity from the underlying condition.

To guide rehydration therapy and assist in the clinical follow up, each patient should be weighed on admission. This need take only a minute and is extremely helpful in calculating the patient's net fluid balance.

9.2.1 Rehydration.

Rehydration is the first form of treatment for a patient with cholera or with acute diarrheal dehydration of any etiology. For mild to moderate degrees of dehydration this can generally be accomplished with oral rehydration, but patients with severe dehydration (i.e. with evidence of shock) need intravenous rehydration therapy. As a first step to therapy, one calculates the estimated volume needed to rehydrate the patient. A practical method to determine this volume is to first determine the patient's weight in kilograms and then estimate the percent dehydration. By multiplying the percent dehydrated by the body weight, one arrives at the volume of fluid required for rehydration. For example, a severely dehydrated adult weighing 40 Kg will require four liters of rehydration fluid to correct dehydration (10% of 40 Kg = 4 kg = 4 liters). Similarly a mildly dehydrated child weighing 10 kg will require 500 ml of rehydration fluid for initial rehydration.

When intravenous fluids are needed they should be given rapidly to cholera patients in order to quickly restore circulating volume. As an approximate guide half the estimated volume of fluid requirement in a severely dehydrated patient should be given over the first one hour, initially as fast as possible until radial pulse is palpable; such a patient should be fully hydrated in two to four hours time at which time the I.V. line can be removed. Sometimes it may be necessary to start an I.V. line at several sites simultaneously to restore circulation quickly. The composition of the appropriate I.V fluids was discussed in section 11.3. As soon as the patient can tolerate oral fluids, administration of ORT can begin since usually the cholera patient will continue to pass watery stool and this loss must be replaced as soon as possible with oral solution. ORS is then used to continue to replace the ongoing stool losses as they occur until the diarrhea is over.

Oral rehydration rather than intravenous can be given both for initial rehydration as well as for replacement of ongoing fecal losses for most patients with mild or moderate dehydration. The composition of the oral rehydration salt solution was discussed in section 11.2.2 and is shown in on Table 11-2.

Early in the treatment patients may continue to vomit and this may be a constraint to ORS administration. However, with persistence and with small, frequent feedings, most patients will retain enough fluid to become rehydrated. Small children may prefer teaspoon amounts at a time while older patients can drink from cups. Usually family members (especially mothers) are the best providers of oral therapy solution and nurses should primarily provide supervision, encouragement and guidance to the family in the treatment of a patient rather than giving it themselves.

The adequacy of fluid replacement should be assessed by the following simple bedside methods: 1) return of pulse to normal strength and rate; the pulse rate will be below 90 per minute in adults; 2) return of normal skin turgor; if skin turgor has returned to normal but pulse remains rapid, other causes of shock such as sepsis, cardiac infarction should be sought; 3) the return of a feeling of comfort to the patient with the disappearance of cyanosis, muscular cramps, nausea and vomiting; children who are drowsy or in stupor may not become fully alert for twelve to eighteen hours despite adequate rehydration; 4) return of normal fullness to the neck veins; 5) weight gain; a severely dehydrated patient should gain 8-10% in body weight after rehydration; this is a specially useful guide in small children; 6) return of urine output; this usually occurs in twelve to twenty hours of initial rehydration.

11.7.3 Maintenance therapy

After the initial fluid and electrolyte deficit has been corrected (i.e., the signs of dehydration have disappeared), it is important to replace ongoing abnormal losses of fluids and electrolytes that are associated with continuing diarrhea--this is maintenance therapy. For severely dehydrated patients who receive I.V. fluids for rehydration, ORT should begin as soon as the patient can begin taking fluids. The principle is to provide oral rehydration solution in a volume to match the volume of fluid lost by diarrheal stools and vomiting, and in addition, to provide hypotonic fluids for the body's normal daily fluid requirements For older children and adults fluids normally consumed (e.g. water) can be given as desired in addition to the required ORS solution. For infants and young children breast feeding should be continued, and in non-breast fed babies other fluids should be offered at regular intervals.

Patients are most easily treated while lying on a cholera cot (see figure 1) since this allows collection and measurement of stool most efficiently. A calibrated bucket beneath the central hole in the cot into which the stool collects allows sufficiently accurate measurement of stool output to guide the subsequent administration of maintenance hydration. One simply measures the volume of the stool output periodically (e.g. every four hours) and assures that an equivalent amount of oral rehydration solution is taken by the patient and that the rate of intake approximately matches the output. The patients should be given bedside urinals and instructed to pass urine separately from the stool. Children's beds can be similar to the adult cholera cots

although separation of urine from stool in children is more difficult but will need to be estimated. A simple input output chart at bedside (as shown in Table 11-5) should be maintained showing amounts of intravenous and oral solutions and the volume of stool output. In a few of the hospitalized cholera patients, signs of dehydration may recur while on oral maintenance therapy. If this occurs, additional intravenous fluids are needed, following which oral maintenance should be resumed.

Antibiotics should be started within 3-6 hours of starting fluid therapy as indicated earlier. Use of antibiotics conserves intravenous fluids and maximizes the use of the hospital beds which are available and substantially reduces demand on trained manpower.

11.7.4 Diet

Cholera patients should be offered food appropriate for age during maintenance therapy with the choice of food guided by the patient's appetite. Food should not be withheld from cholera patients; there is no benefit in "resting the bowel."

A summary of treatment for cholera patients is shown on Table 11-6.

11.8. Complications of Cholera

Complications of cholera are rare if correct treatment is rapidly provided, since most complications result from delay in therapy or provision of inappropriate fluids. Case fatality rates for cholera patients at the ICDDR,B is less than one half of one percent and these low rates are reproduced in other simple treatment centers. The few cholera patients who die are those who arrive at the treatment center after death has already occurred or are those whose death was due to another underlying condition or disease, e.g. malnutrition or pneumonia.

Complications that may be seen include the following:

1) Persistence or recurrence of signs of dehydration and hypovolemic shock. This may occur due to inadequate volume replacement. In a cholera patient the cause is almost always inadequate fluid replacement although other causes of a shock should be kept in mind. Occasional cholera patients will pass only small volumes of stool while accumulating intestinal secretions in their gut lumen. These patients with "cholera sicca" may develop signs of shock sometimes with a swollen abdomen suggestive of an acute peritonitis. These patients require rehydration with I.V. fluids to restore the circulating volume while waiting for stool to pass. A rectal tube may be helpful.

2) Persistence of vomiting. Vomiting is part of the cholera syndrome and can interfere with ORT. If it continues more than a few hours, it is likely due to the persistence of acidosis and/or hypovolemia. Usually ORS can be given in small amounts frequently to maintain a positive balance, but if this is not possible, I.V. fluids should be used.

3) Acute renal failure.[75] Mildly elevated blood urea is seen commonly in cholera patients due to the dehydration (pre-renal azotemia), but acute renal failure is much less common than it was formerly because the usual treatment practice now includes rapid rehydration. When acute renal failure occurs it is usually seen in those who have had repeated or prolonged episodes of hypotension as a result of inadequate fluid replacement. This may happen for example, when there is a shortage of I.V. fluids or when the trip to the treatment center takes several hours and the patient receives just enough fluids on the way to keep him alive but not enough to restore circulating volume. When acute renal failure develops the patient should be treated for acute tubular necrosis by managing fluids and electrolytes. Dialysis may be required in a few patients. When the diuretic phase of the renal failure occurs, care must be given to insure adequate fluid intake to match urinary output. Unless the urine flow rate becomes excessively large, the hydration of these patients can be maintained with oral rehydration solution, though the electrolyte content of this solution will have to be adjusted to balance the urinary losses. Two percent glucose in the solution should still be used to facilitate absorption.

4) Hypokalemia. Hypokalemia may occur if the potassium losses of a heavily purging patient are not replaced by potassium in the rehydration fluids. Although rarely symptomatic in adults, it can cause severe symptoms in children, e.g. abdominal distension, paralytic ileus, urinary retention, muscular weakness, cardiac arrhythmias and even death.

5) Overhydration. This results from excessive intravenous (or less commonly oral) fluid replacement and is manifested by swelling of the eye lids, full neck veins, slow full pulse. Excessive I.V. fluids can even lead to frank cardiac failure, but this has not occurred with ORT.

6) Acute pulmonary edema. Pulmonary edema can occur due to over-replacement of intravenous electrolyte solutions as mentioned above, but has been reported especially when the metabolic acidosis was left uncorrected (e.g. overuse of normal saline I.V. rather than an I.V. fluid with a base).[76]

7) Hypoglycemia. Normally patients with cholera have a fall in their blood sugar during treatment for cholera. This is likely a nonspecific response to the correction of the stress. Severe hypoglycemia on the other hand occurs rarely, nearly always in children and is usually manifested as the sudden onset of seizures. The mechanism of this complication is not understood, but it does not seem related necessarily to malnutrition. If seizures should occur, a blood sample should be obtained for glucose determination and an intravenous bolus of glucose should be given immediately (without waiting for the glucose results). If hypoglycemia is confirmed, the patient should continue on intravenous fluids with glucose, and follow-up blood samples should be obtained to document that blood glucose levels are in a normal range.

8) Abortion. Women in the third trimester of pregnancy may abort if they become severely dehydrated. The treatment principles of pregnant women are the same as for other patients.
9) Fevers. Fevers occurring early in therapy may be due the administration of incorrectly prepared fluids or the repeated use of I.V. administration sets. This can be avoided by using pyrogen free fluids and disposable administration sets.

10) Incorrect Diagnosis. During cholera epidemics other serious illnesses associated with diarrhea may be diagnosed clinically as cholera. Such illnesses may include meningitis, septic shock, myocardial infarction, and typhoid fever.

11.9. Cholera in Remote Areas.

11.9.1. Rural or Community Diarrhea Treatment Centers.

Treatment of severe diarrheal disease and cholera can be provided at relatively modest treatment centers. Examples of such treatment centers exist in several countries and may be but do not have to be associated with other hospitals. Oral therapy can be provided in the home for patients with no or mild dehydration; however, there is no question that moderately dehydrated patients will receive more effective care in a treatment center where treatment can be supervised. In one example of a treatment center assisted by the ICDDR,B, a community provides a small house and trained volunteers (paid a subsistence salary) and these volunteers care for the patients. The ICDDR,B provides training to the volunteers and some logistic support, but the treatment center itself is nearly self supporting from a small fee it receives from its patients. Another example of a treatment center is one operated as a unit of a hospital. Here under physician's overall supervision, paramedics treat the patients who visit. In both situations case fatality rates for cholera have been the same as it is when physicians provide the care. The success of these treatment centers has depended on the training received by the paramedics and on continued logistic support (provision of rehydration supplies, antibiotics, and periodic in-service training) from physicians and other institutes, but the treatment provided can be extremely cost-effective.

11.9.1. Recognition of an Epidemic.

Since cholera occurs most often in remote areas, and since surveillance systems for

diarrheal disease is usually non-existent in these area, many outbreaks of cholera go undetected. Where surveillance systems have been established through clinic or hospital records for diarrhea, seasonal changes are noted frequently. Where such records are not kept, an outbreak is often detected when a cluster (2 or 3) adults die of acute watery diarrhea. (In developing countries diarrhea associated deaths in young children are all too common; hence, childhood diarrhea deaths often do not lead to outbreak investigations.) Other simple but more sensitive mechanisms are needed to identify cholera in remote areas and to transmit this information to central health authorities. Once identified, management of outbreaks can be relatively inexpensive and can prevent many unnecessary deaths.

11.9.2. Management of a Cholera Outbreak.

Principles of clinical management of individual patients during outbreaks of cholera are the same as already described. If treatment centers are already established, efforts may have to be made to increase the inventory of rehydration supplies and to reorganize the medical staff to handle an increased load. If a treatment center is not available within a reasonable distance, an assessment will need to be made as to the advisability of establishing a temporary treatment center. For this readers are referred to "Guidelines for cholera control, WHO/CDD/SER/80.4 REV.1(1986)" available from the World Health Organization.

If an outbreak is detected, a team should be formed to organize the available resources and provide treatment to the people. A plan for this organization may already be a part of a national diarrhea control program or it may have to be formulated by the health or community authorities. The team will have several functions. 1) to quickly assess the nature and severity of the problem; 2) to obtain the needed resources for establishing a treatment center if this is appropriate; 3) to work with the community leaders to assist with the cholera control plans; 4) to provide training to persons (usually local physicians and/or village volunteers) who will be providing care; 5) to insure that the surrounding people know of the availability of treatment; 6) to continue to assist the community by "trouble shooting." Records should be kept on these outbreaks to help in the monitoring of cholera and in assisting future teams with managing such situations.

Often times the arrival of a team experienced in the treatment of cholera will help to allay the panic which understandably accompanies a cholera epidemic. The team will need to bring hydration supplies (I.V. and ORS packets) and antibiotics, and these can often be obtained through the Health Ministry. Most of the other resources are likely to be available in the community and one of the challenges for outbreak teams is to help the community to mobilize their own resources. Establishment of a treatment center can occur in nearly any facility. School buildings, community centers, huts or houses can be used, and in some climates, no buildings are needed at all. A list of supplies for establishing a treatment center is shown in Table 11-7.

Prophylactic antibiotics are not indicated during such outbreaks although persons should be taught to drink safe water if possible. Boiled water is the safest water for drinking, though this may not always be practical. Immunization with the current injectable cholera vaccine is not a cost effective way to control a cholera outbreak and such a program may divert effort from more effective actions.

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Table 11-1: LANDMARKS IN THE TREATMENT OF CHOLERA

1. Hermann (1830) observed hemoconcentration in cholera patients and proposed the idea of injecting fluid into their veins.

2. O'Saughnessy (1831-32) accurately described "deficient saline matters" after carefully examining blood from cholera patients.

3. Latta (1832) treated 15 moribund cholera patients and 5 survived; Lancet considered the treatment to be life saving.

4. Rogers (1908-9) treats cholera patients with sufficient volumes of intravenous hypertonic saline using aseptic precautions; mortality dropped from 70% to 30%.

5. Sellards (1910) described acidosis in cholera and used alkali; Rogers adds alkali to regimen and mortality drops to 20%.

6. Phillips, Watten, Carpenter, Gordon (1958-1964) measured exact loss of water and electrolytes in cholera; developed details of I.V. clinical management using isotonic saline and alkali plus oral water; mortality dropped to less than 1%.

7. Phillips, Pierce, Hirschhorn (1964-1968) established that cholera patients can absorb electrolytes and water if glucose is included in the oral solution, thus establishing the scientific basis for oral rehydration therapy.

Table 11-2: **ORS SOLUTION**

The formula for Oral Rehydration Salts (ORS) recommended by WHO, and first used in 1971, is shown in table A. The quantities shown under A are for the preparation of one litre of ORS Solution and the concentrations of the components of this solution are shown under B.

A. Composition by weight of oral rehydration salts (ORS)

(quantities shown for preparation of one litre of ORS Solution)

Ingredient	Grams
1. Sodium chloride	3.5
2. Trisodium citrate, dihydrate	2.9
or.	
Sodium hydrogen carbonate (sodium bicarbonate)	2.5
3. Potassium chloride	1.5
4. Glucose, anhydrous*+	20.0

*Or Glucose, monohydrate 22.0 g, or Sucrose 40.0 g.

+ 50 g rice powder can replace 20 g glucose. To prepare a rice powder solution: put 50 g rice powder (i.e. rice flour) in 1100 ml of water and bring it to boil. Continue boiling for approximately 7 minutes when the mixture becomes opalescent. Allow it to cool, add and mix the three salts. Serve the solution warm. After 8 hours discard and prepare a fresh batch.

(Continuation of Table 11-2)

B. Molar concentration of components of ORS Solution

Component	mmol/litre of water	
	citrate containing solution	Bicarbonate containing solution
Sodium	90	90
Potassium	20	20
Chloride	80	80
Citrate	10	-
Bicarbonate	-	30
Glucose	111	111

Table 11-3: SOLUTIONS FOR INTRAVENOUS INFUSION

Ringers Lactate: This is the best commercially available solution. Lactate yields bicarbonate for correction of the acidosis. Although its potassium concentration is low, prompt introduction of ORT during maintenance provides adequate amount of potassium.

Special solutions (e.g. Dhaka Solution or DTS): Dhaka solution is produced in Bangladesh and is in routine use for all patients with diarrhea and dehydration. Acetate is the preferred base because it is more stable during storage than lactate. This and similar other special diarrhea treatment solutions are not available commercially. Some national diarrheal diseases control programmes are producing similar special solutions suitable to treat diarrheal dehydration in all age groups.[45,46]

Normal saline: Also called physiological or isotonic saline, this solution is often readily available. It will not correct acidosis and will not replace potassium. This is a poor choice but may be used if it is the only solution available. Normal saline in 5% dextrose is also often available. The same comments apply for this as for normal saline.

5% Dextrose in Water: Do not use for the treatment of dehydrating diarrheal diseases.

TABLE 11-4: IONIC COMPOSITION OF INTRAVENOUS INFUSION SOLUTIONS

Intravenous solutions	mmol/Litre				
	$+$ NA	$+$ K	$+$ Ca	Cl	lactate or acetate
1. Ringer's Lactate	130	4	3	109	28
2. Dhaka Solution[45]	133	13	0	98	48
3. Diarrhea Treatment Solution[46]	118	13	0	83	48
4. 2 Saline : 1 lactate[47] (when combined!)	158	0	0	103	56
5. Normal saline	154	0	0	154	0
6. 5% Dextrose in Water (do not use)	0	0	0	0	0

Table 11-5: BEDSIDE INTAKE-OUTPUT CHART (sample)

Patient's Name:_____ Number:_____

Date of Admission:_____ Time of Admission:_____

Age:_____ Sex:_____ Body weight:_____Kg (Initial)

Initial Fluid Deficit (in percent)_____% Rehydration volume_____ml

Date	Time	Intake			Output			Net Balance
		I.V.	ORS	Other	Stool	Vomit	urine passed (Y/N)	

Table 11-6: SUMMARY OF CLINICAL MANAGEMENT OF CHOLERA PATIENTS

1) Rehydrate: Estimate degree of dehydration and rapidly replace water and electrolytes already lost with appropriate oral or I.V. solution, depending on severity.

2) Maintain hydration: Replace ongoing abnormal stool losses with ORT and provide water for normal evaporative and urinary losses.

3) Antibiotics: Give to shorten the severity and duration of diarrhea.

4) Nutrition: Do provide food appropriate for age as soon as a patient is able to take it. Do not wait for the diarrhea to stop.

TABLE 11-7: EQUIPMENT AND SUPPLIES FOR A MAKESHIFT

DIARRHEA TREATMENT CENTER

I. REHYDRATION SUPPLIES:

a) 240 liters I.V. polyelectrolyte solution (e.g. lactated Ringer's solution (480 bags of 0.5 liters each) with giving sets

b) 10 disposable syringes (5 or 10 ml)

c) 10 needles (18 g) for adults

d) 20 needles (21-23 g) for children

e) 10 scalp vein sets

f) 10 naso-gastric tubes (adult size 16 fr. 20 inch long, child size 8 fr. 15 inches long)

g) 1300 packets ORS (for one litre each)

II. ANTIBIOTICS:

a) For Adults and older children: 3200 capsules tetracycline, 250 mgm (16 caps per case) **or** 600 caps doxycycline, 100 mg (3 caps per case) **and** furazolidone tablets (for pregnant women)

b) For younger children: doxycycline syrup or furazolidone syrup

TABLE 11-6 (continued): A MAKESHIFT DIARRHEA TREATMENT CENTER

III OTHER SUPPLIES: a) Two large water dispensers with tap, (marked at 5, 8, 10 litre intervals) for making ORS solution in bulk;

b) 20 bottles (1 litre) for ORS solution (e.g. I.V. bottles);

c) 20 bottles (0.5 litre),

d) 40 tumblers, 200 ml;

e) 3 kidney dishes,

f) 5 spirit lamps.

g) flashlights (2), (or hurricane lantern)

h) cotton (5 kg)

i) alcohol (250 ml),

j) adhesive tape (3 reels).

k) soap

l) disinfectant

m) bleaching powder

IF POSSIBLE:

a) Cholera cots (adults)

b) Cholera cots (infant)

c) Plastic drain sheets

d) Plastic buckets

e) Patient scales

These suggestions are based on approximately 200 cases (typical for an outbreak in a total population 100000) assuming that 40 cases will require initial intravenous fluid followed by ORT and the remaining 160 cases can be managed exclusively with ORT.

LEGENDS FOR FIGURES

Figure 11-1: Rehydration of a patient with cholera. The girl shown in this series of photographs has many of the features of cholera. Note the sunken eyes and poor skin turgor in photograph A. The hand shown above the abdomen had just released a fold of skin and the skin remains tented. The same patient is seen a few hours later in photograph B. C and D show the same girl on the second and third day following rehydration therapy.

Figure 11-2: The photograph shows a simple scale for weighing babys immediately before rehydration begins. The weight gain during therapy is an excellent way to assess rehydration status.

Figure 11-3: Oral rehydration therapy should involve the family.

Figure 11-4: Oral rehydration therapy is a component of primary health care and should be taught to mothers everywhere. Shown here is a community health worker teaching a group of mothers in Bangladesh how to make ORS.

Figure 11-5: The best time to teach oral rehydration therapy is when it is needed. Here a community health worker assists a mother in preparing and administering a rice based, homemade solution and gives it to her child with diarrhea.

LEGENDS FOR FIGURES (continued)

Figure 11-6: Feeding is an important part of the treatment of diarrhea patients. Usually patients can begin eating within a few hours of beginning treatment.

Figure 11-7: Maintenance of intake and output records as well as nursing care are simplified with a cholera cot. The cot in the foreground has the plastic sheet removed to show the simple construction. In the background are cots with the plastic sheets. A sleeve in the plastic sheet guides the diarrhea stool into a plastic bucket underneath the cot so that its volume can be measured periodically. Patients can be covered with a cotton sheet to maintain modesty. A vomit basin should also be available.

SOME FACTS ABOUT BELIZE

GEOGRAPHICAL

Location:	15° 52′ 9″ and 18° 29′ 55″ North Latitude 87° 28″ and 89° 13′ 67″ West Longitude
Area:	8,866 square miles (including 266 square miles of islands).
Length:	174 miles at longest point.
Width:	68 miles at widest point.
Physical features:	Coral reefs (largest unbroken Barrier Reef in the Western Hemisphere) and atolls; belt of low coastal areas; flat, dry coastal plains; elevated mountainous mass (highest point: Victoria Peak 3,680 feet); ravines, river gorges, waterfalls.
Climate:	Sub-tropical with temperatures ranging from 50°F (10°C) to 75°F (24°C). Located in "Hurricane Belt".
Rainfall:	Annual rainfall ranges from 60″ (North) to 160″ (South).

ECONOMIC

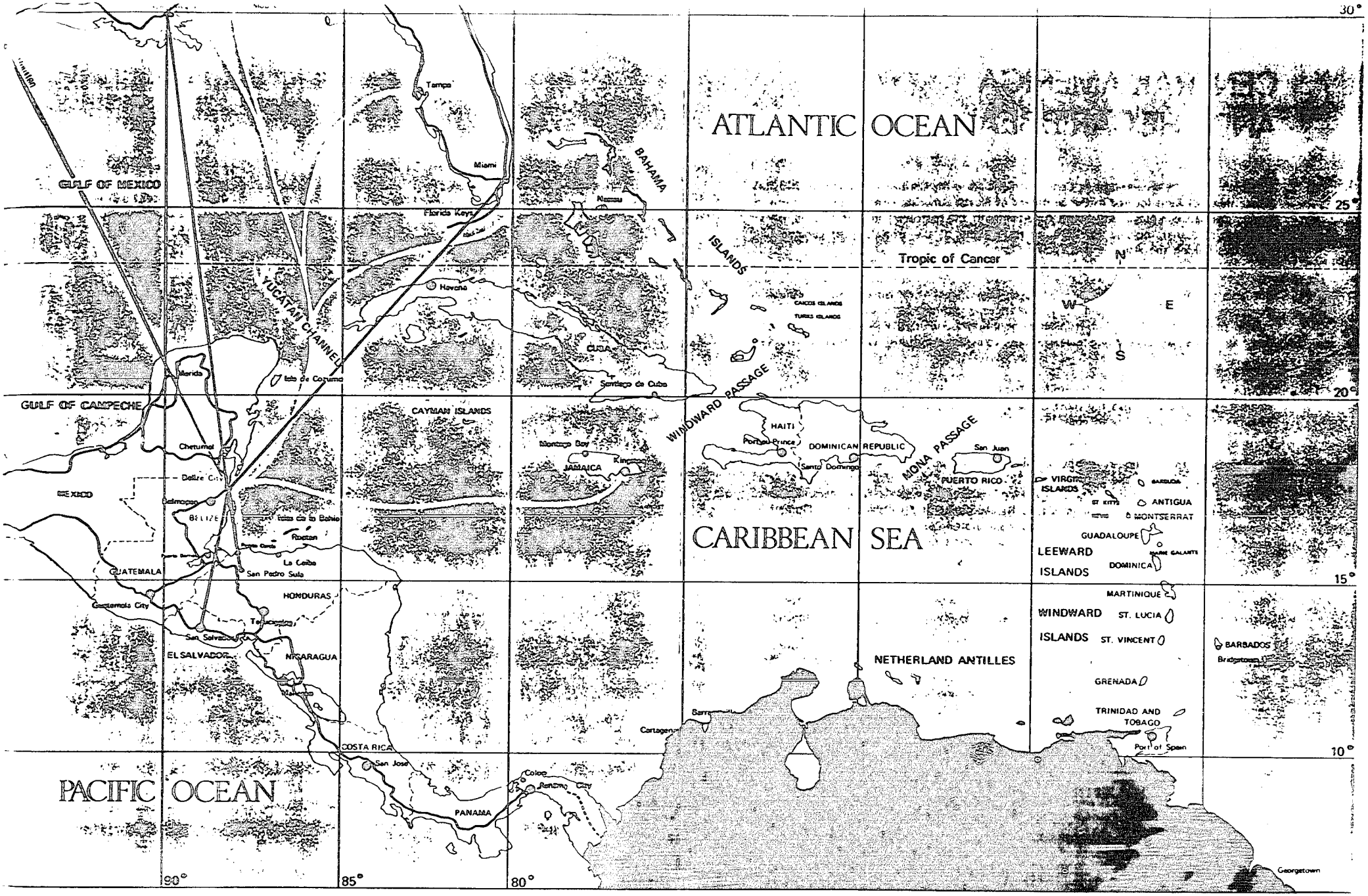
Main products:	Sugar, fishery, citrus, bananas, rice, light industry.
Natural resources:	Forestry, fishery, land.
Currency:	Belize dollar; 1 BZE$ = US$ 0.50

SOCIAL

Population:	145,353 (National Census 1980).
Population density:	16 per square mile
People:	Afro-Belizeans (Creoles), Mestizos, Maya, Garinagu, Asian, Europeans and others.
Capital:	Belmopan (population 3,000) established 1970 as administrative centre.
Largest city:	Belize City (population 40,000) — former capital and main commercial centre.
Literacy:	90 % English (official), Spanish, Creole, Maya and Garifuna

POLITICAL

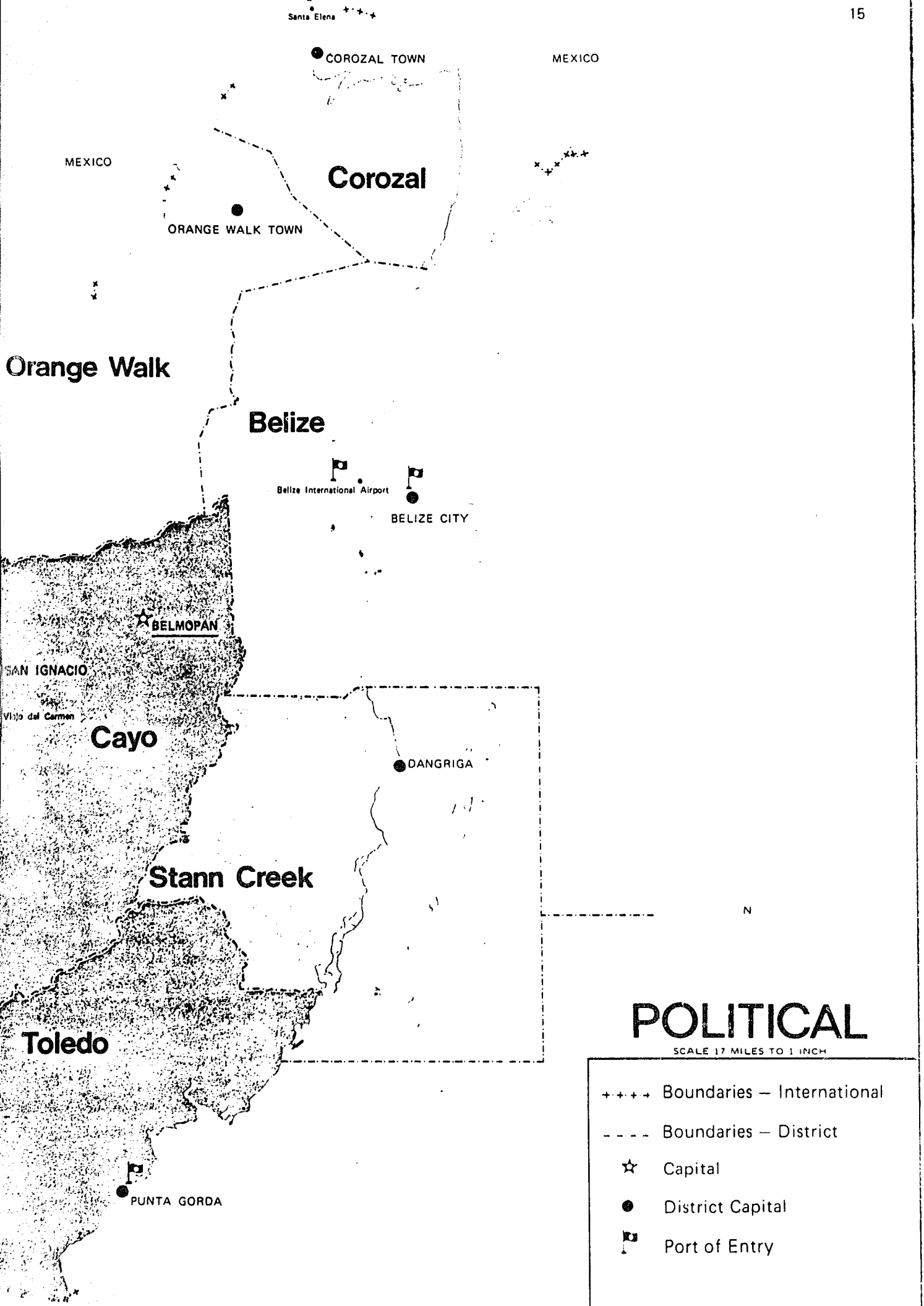
Borders:	Mexico at North and Northwest Guatemala at South and West Caribbean Sea at East
Government:	Parliamentary Democracy with Cabinet headed by Prime Minister; bi-cameral National Assembly: Senate (nominated) and House of Representatives (elected). Date of Independence: September 21, 1981.
Elections:	National elections held within every five years; municipal elections for City Council, Town Boards and Village Councils periodically.

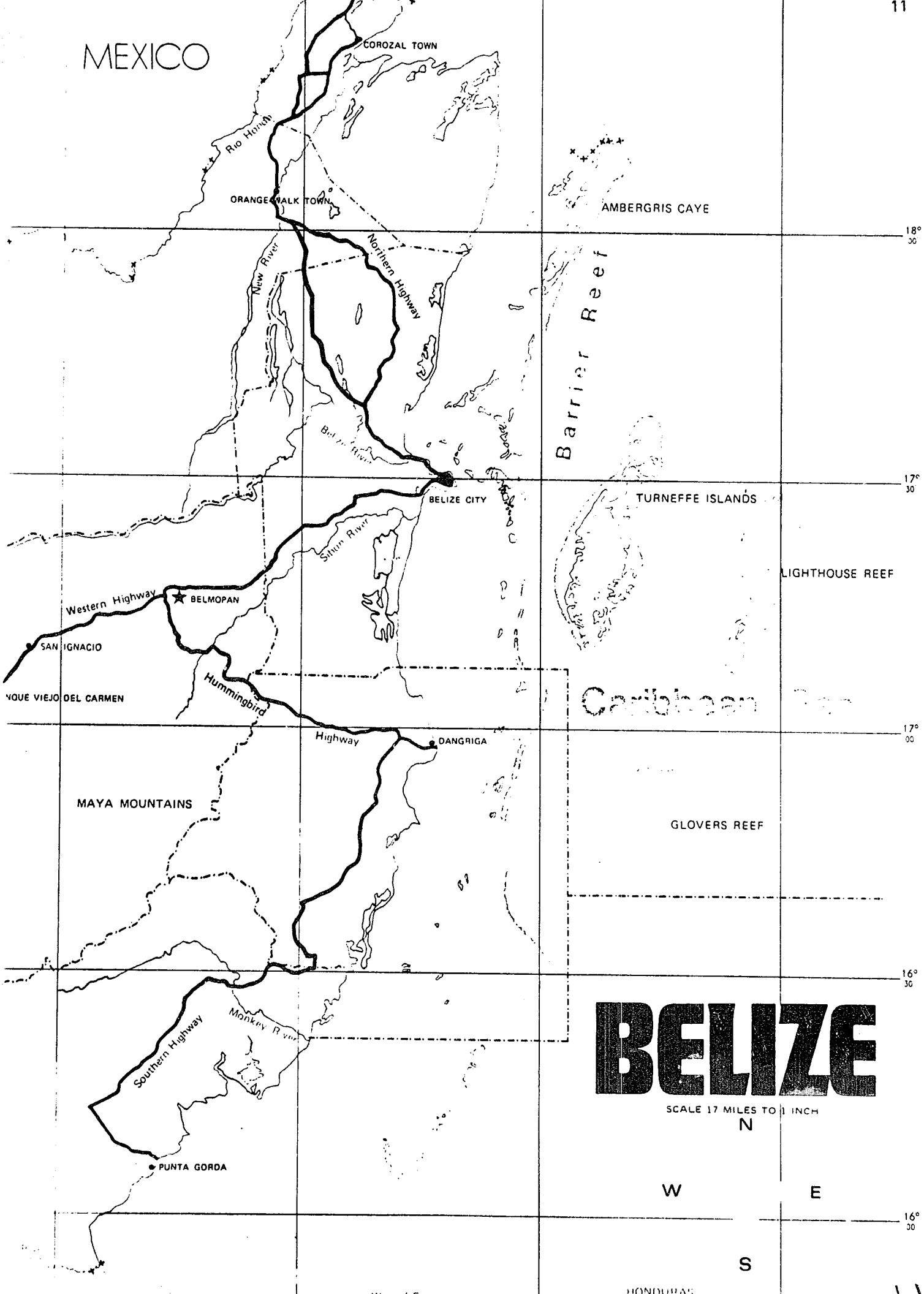


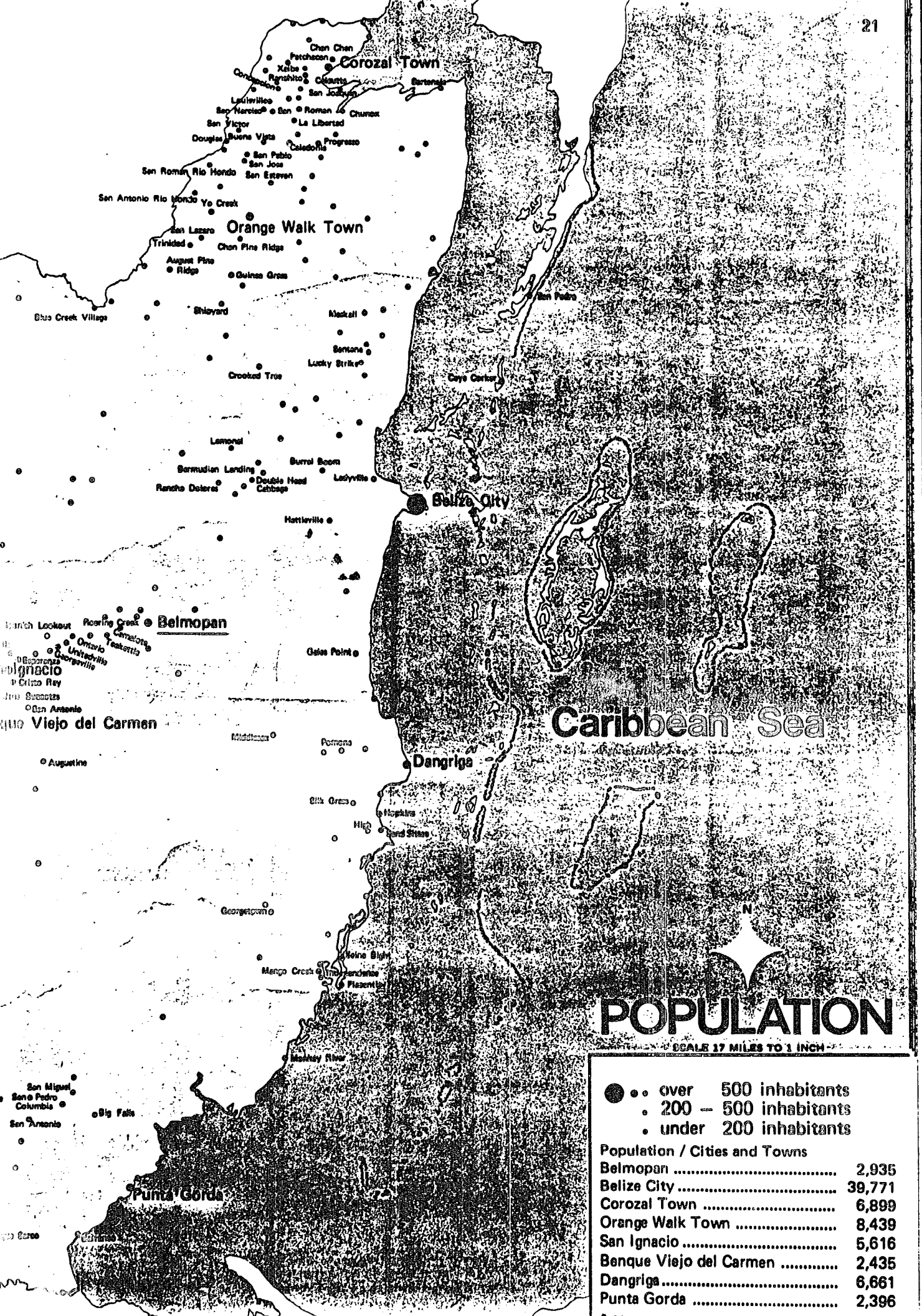
CENTRAL AMERICA AND THE CARIBBEAN

Capital — Main Roads — Direct Air Service from Belize City

Main City — Main Sea Lanes from Belize City — Main [illegible] by Airlines Serving Belize


Santa Elena
COROZAL TOWN
MEXICO
MEXICO
Corozal
ORANGE WALK TOWN
Orange Walk
Belize
Belize International Airport
BELIZE CITY
BELMOPAN
SAN IGNACIO
Cayo
DANGRIGA
Stann Creek
N
POLITICAL
SCALE 17 MILES TO 1 INCH
Toledo
Boundaries — International
Boundaries — District
Capital
District Capital
Port of Entry
PUNTA GORDA


MEXICO
COROZAL TOWN
Rio Hondo
ORANGE WALK TOWN
AMBERGRIS CAYE
18° 30'
New River
Northern Highway
Barrier Reef
Belize River
17° 30'
BELIZE CITY
TURNEFFE ISLANDS
Sibun River
LIGHTHOUSE REEF
Western Highway
BELMOPAN
SAN IGNACIO
NOQUE VIEJO DEL CARMEN
Hummingbird
Highway
DANGRIGA
17° 00'
MAYA MOUNTAINS
GLOVERS REEF
16° 30'
Southern Highway
Monkey River
BELIZE
SCALE 17 MILES TO 1 INCH
N
W
E
S
PUNTA GORDA
16° 30'
HONDURAS


Corozal Town
Orange Walk Town
Belmopan
Belize City
Caribbean Sea
Dangriga
Punta Gorda
San Pedro
Caye Caulker
Ladyville
Burrel Boom
Double Head Cabbage
Hattieville
Lucky Strike
Crooked Tree
Lemonal
Bermudian Landing
Rancho Dolores
Blue Creek Village
Shipyard
Maskall
Sartaneja
Guinea Grass
August Pine Ridge
Chan Pine Ridge
Trinidad
San Lazaro
Yo Creek
San Antonio Rio Hondo
San Roman Rio Hondo
San Estevan
San Pablo
San Jose
Progreso
Caledonia
Douglas
Buena Vista
San Victor
La Libertad
Chunox
San Roman
San Narciso
Louisville
Chan Chen
Petchacan
Xaiba
Ranchito
Calcutta
Bartolome
Gales Point
Ontario
Teakettle
Unitedville
Georgeville
Esperanza
Cristo Rey
San Antonio
Viejo del Carmen
Middlesex
Pomona
Augustine
Silk Grass
Hopkins
Sand Stone
Georgetown
Mango Creek
Independence
Placentia
Mahlsey River
San Miguel
San Pedro Columbia
San Antonio
Big Falls
Bahamas
Ranger Creek
Lookout
N
POPULATION
SCALE 17 MILES TO 1 INCH
over 500 inhabitants
200 – 500 inhabitants
under 200 inhabitants
Population / Cities and Towns
Belmopan 2,935
Belize City 39,771
Corozal Town 6,899
Orange Walk Town 8,439
San Ignacio 5,616
Benque Viejo del Carmen 2,435
Dangriga 6,661
Punta Gorda 2,396

SUPPLEMENT TO THE BELIZE REPORT July 17, 1991

Enclosed are reproductions of photos which I took during my trip to Belize showing some important attributes which will affect the occurrence and incidence of cholera in this country.

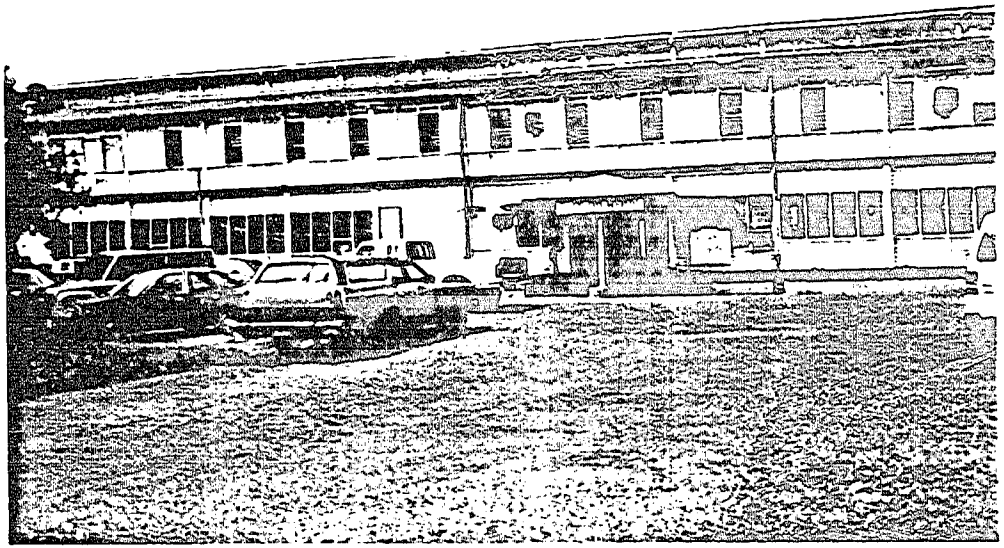
Page 1 shows some of the medical facilities in Belize. Belize City Hospital (upper left) is the major hospital in Belize. A rural health center (upper right) serves rural residents. The Bureau of Public Health (lower left) is the center for public health programs in the country, and central laboratory (lower right) is the location for carrying out cholera isolations.

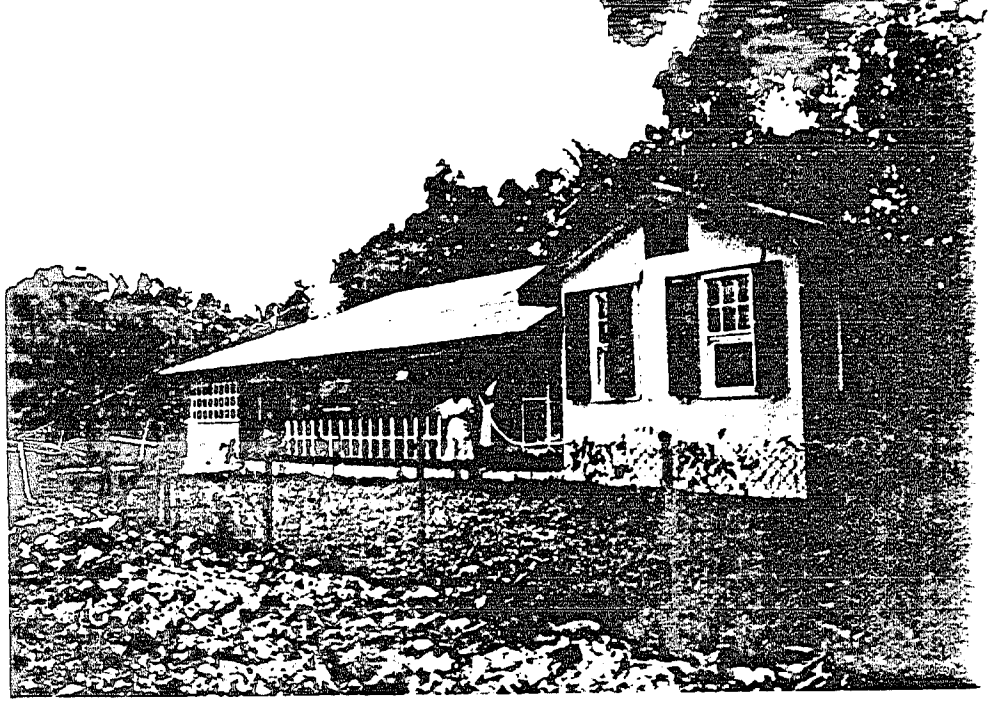
Page 2 shows some of the water supplies most commonly found in rural areas. Two styles of hand pumps are shown along with the rain water collection devises used to collect and store rain water. A water cooler, consisting of a hollowed gourd, (lower right) has a narrow opening, and thus, prevents hands from contaminating the water after it is collected. Of course the narrow neck does not protect the water if it is already contaminated at the source.

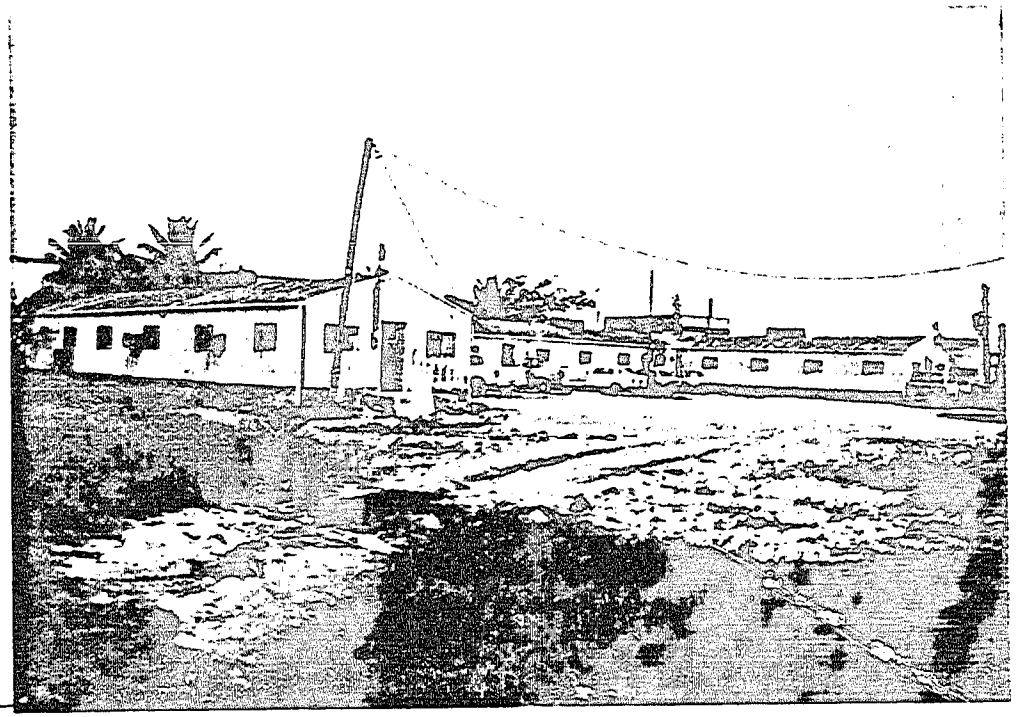
Page 3 shows some of the more modern water systems in Belize. The water treatment plant (lower left) provides treated and chlorinated water to Belize City using water obtained from the Belize River (upper right). The rudimentary water system with its pump and water storage unit (upper right) distributes water to

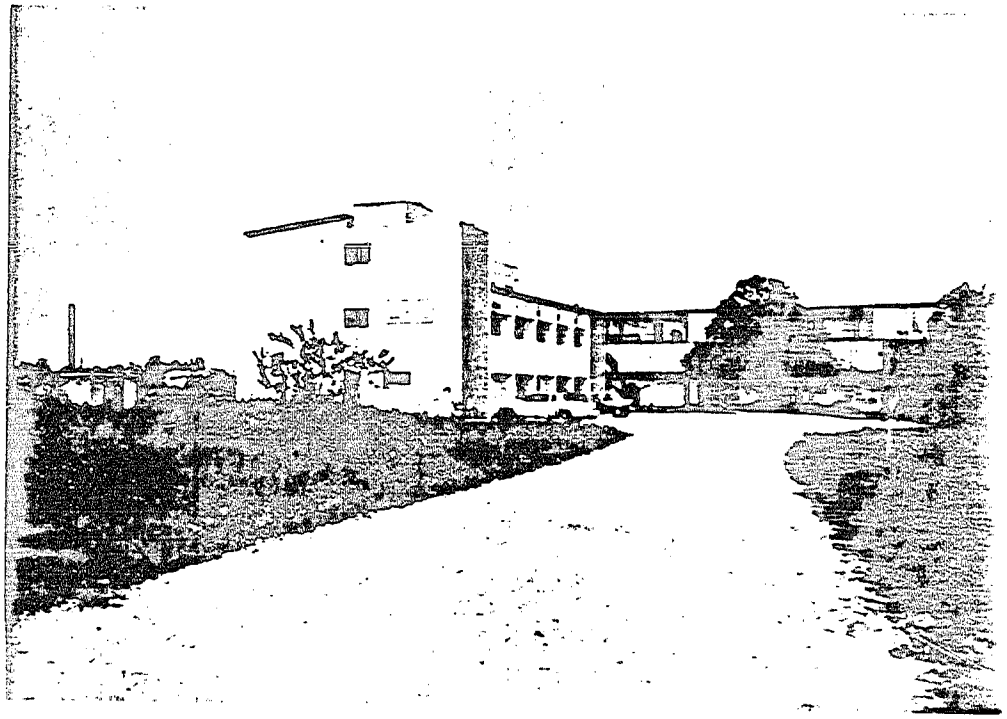
faucets along the road (lower right) to each house hold unit, but not into the house unless the customer provides additional plumbing. These rudimentary water systems do not chlorinate routinely.

Less safe water such as open wells (upper right) and surface rivers and ponds (upper left) are also used, but I do not know the proportion of the population using these less safe sources. A municipal sewage system does serve Belize City; however, the open sewers still are used by many persons and drain directly into the sea (lower right). Posters warning about the dangers of cholera are common in Belize City (lower left).

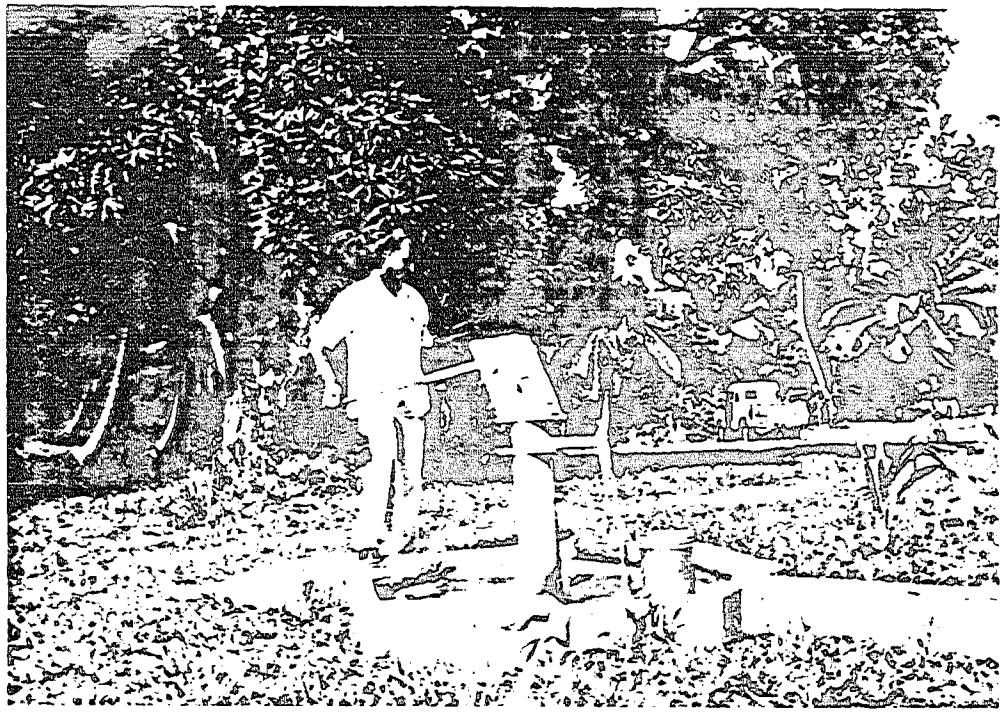


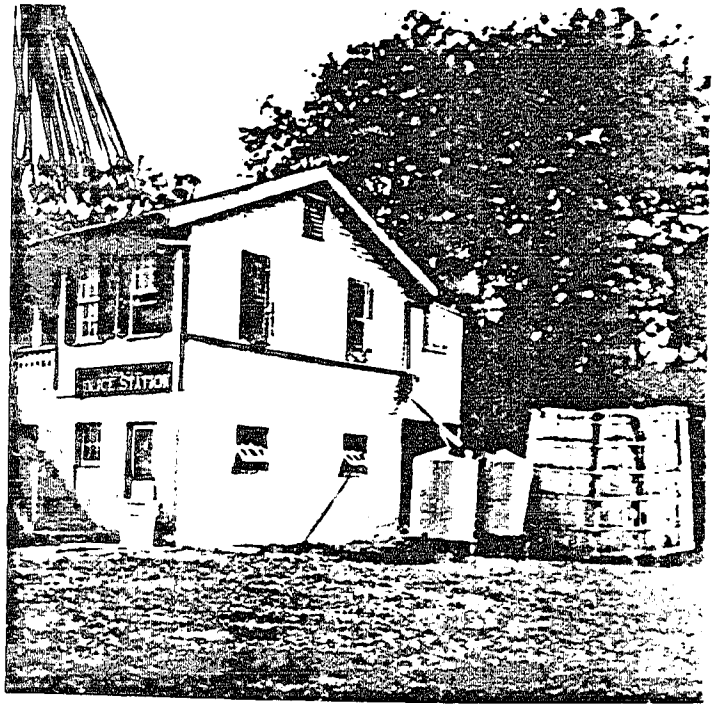


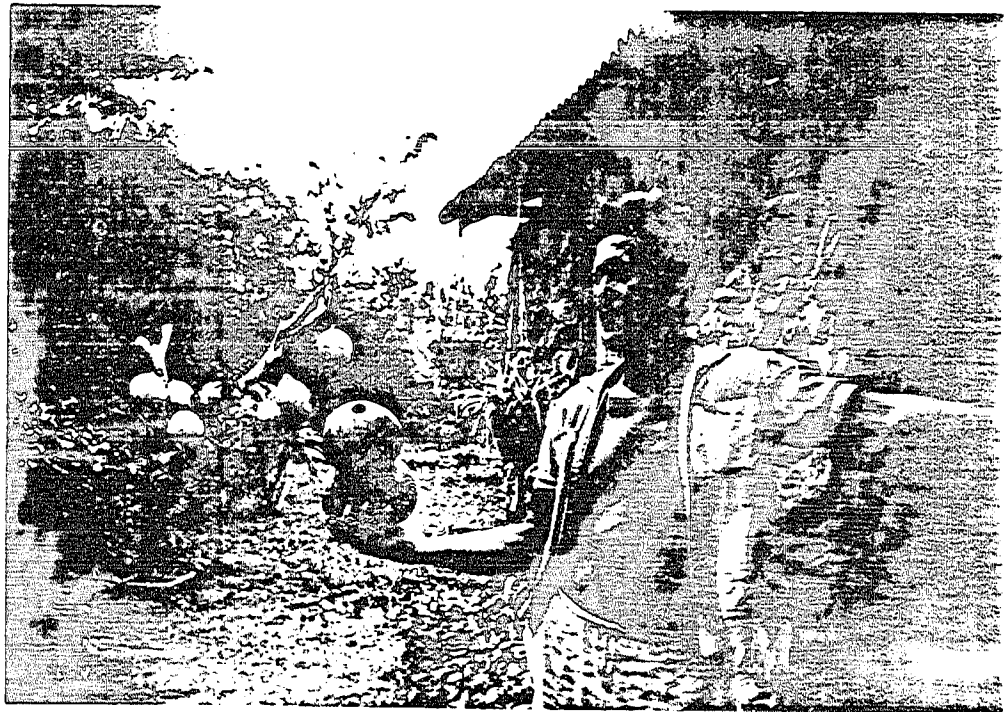


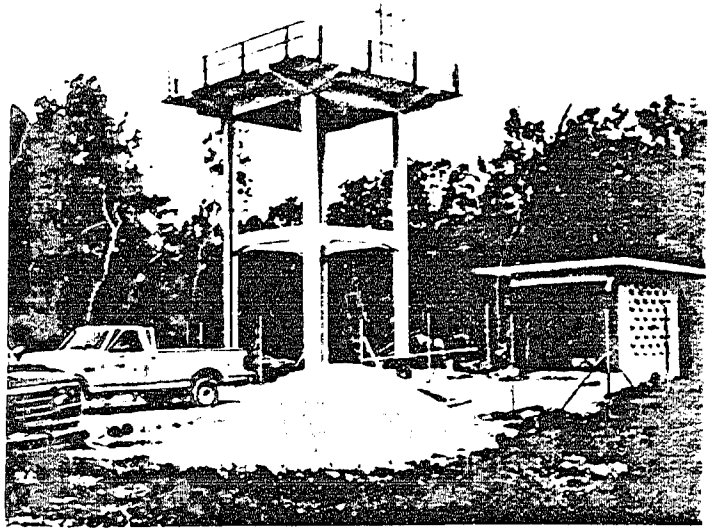


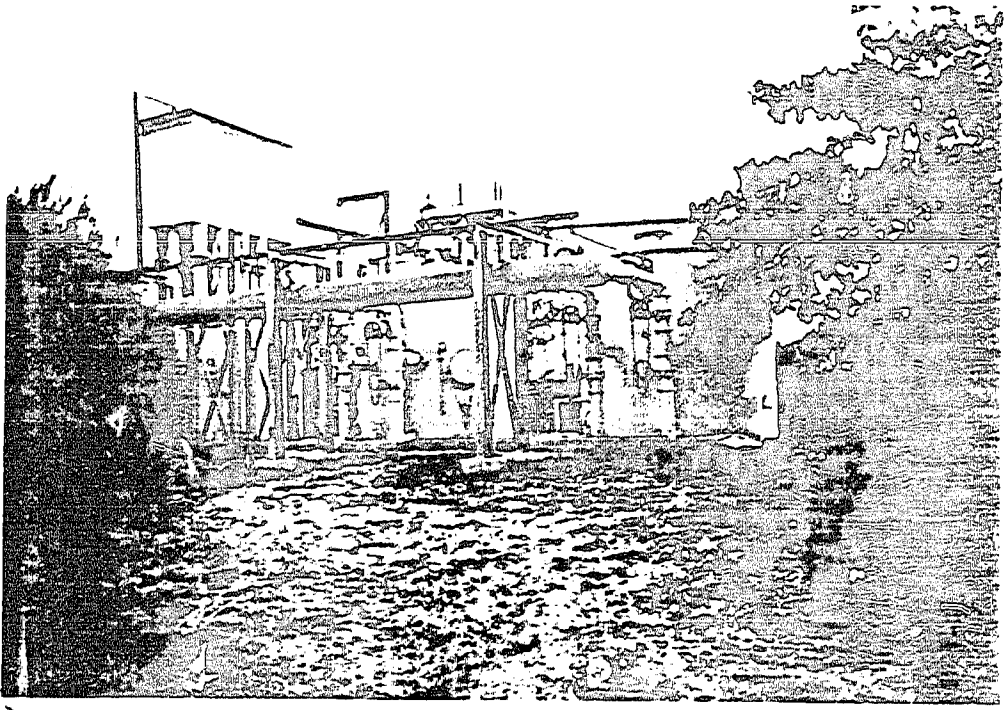
page 2

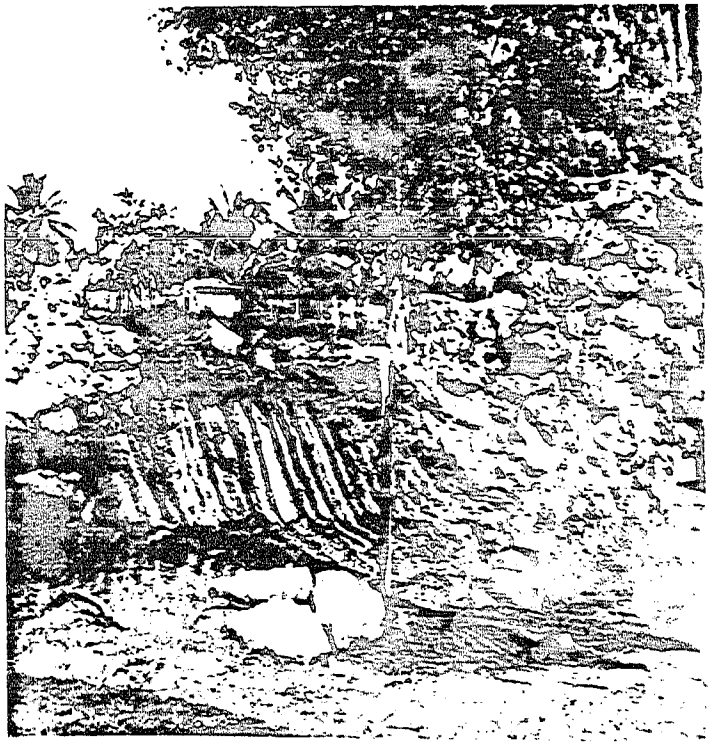












CHOLERA
LOCKLEAZLE HISTORY