CHOLERA RESEARCH LABORATORY
DACCA, BANGLADESH

ANNUAL REPORT
FOR
FISCAL YEAR 1976

(This report covers the period from
1 July 1975 - 30 September 1976)

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CHOLERA RESEARCH LABORATORY
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I INTRODUCTION

From the time of nationally disturbed conditions associated with Bangladesh independence in 1971 to a period shortly before the re-establishment of the Cholera Research Laboratory (CRL) as a research organization (15 May 1974) through the bilateral project agreement between the Governments of Bangladesh and the United States of America, little research activity occurred at CRL. The staff and facilities remained intact and the Laboratory operated primarily as a service center in Bangladesh treating diarrheal diseases patients in its hospitals at Dacca and Matlab. From the beginning of FY75 to the present, continuing efforts have been directed towards re-instituting research, developing an appropriate institutional program and, in general, through improvement of its physical facilities and administrative operations, placing CRL once more in a posture for further scientific progress.

With the re-institution of a research program after a hiatus of approximately three years, certain re-orientations of research activity have occurred. These have been in response to developments in diarrheal disease research progress in other laboratories and in recognition of the needs of Bangladesh and other developing countries as they have become better perceived. This does not imply a drastic change in research emphasis since the recognition of the desirability of many "new" programs is documented in the pre-independence activities of CRL. Rather, it is considered to be the logical progressive development of scientific activities in the light of a more current appraisal of the Laboratory's potential and mission. The trends that appear to be most important are:

1. In assigning research priorities, a greater weight applied to research offering possibilities of interventive action.

2. Greater emphasis on work with the non-cholera diarrheal diseases.

3. A corresponding reduction in the preoccupation with cholera per se.

4. An increase of interest in the inter-relationships between diarrheal disease, nutrition, and fertility.

II SCIENTIFIC PROGRAM

A detailed report of research is presented annually to the Technical Advisory Committee, and a volume entitled "Proceedings of the Scientific Review and Technical Advisory Committee" is compiled each year as a thorough scientific report. The following information is a Director's overview of the CRL research programs with comments on specific findings and trends which are considered to be important.

A. Diarrheal Disease Research

Although the initial mission of the CRL was to conduct research on cholera, it has become increasingly clear that this disease is but one of the many facets of the total diarrheal disease problem in Bangladesh and other developing countries. Through the 1960s, cholera research, particularly that dealing with hospital based therapy and immunization, was the primary effort of the Laboratory. The development of both intravenous and oral rehydration has been a recognized achievement; and field trials of vaccines were outstanding in defining the effectiveness and limitations of both the existing and prototype immunogens. The work on improved methods of therapy led to research on the mechanism of action of cholera enterotoxin, and in subsequent studies the Laboratory did much to define the pathophysiology of this disease. Considerable advances were also made in epidemiology and immunology of cholera. It can fairly be stated that the research of the Cholera Research Laboratory, together with the occurrence of the seventh cholera pandemic beginning in 1968, did much to spark the revival of interest in cholera and diarrheal disease research and action intervention throughout the world.

Significant changes have occurred in recent years in the overall pattern of diarrheal disease seen at the CRL. The most notable of these changes were the emergence of El Tor biotype V.cholerae, which completely replaced its classical predecessor, and the dramatic increase in the admission rate of patients suffering from dysentery which, unlike cholera and other acute watery diarrheas, is severe and associated with relatively high hospitalized mortality rates. Both of these phenomena have influenced the course of diarrheal disease research at the CRL. A shift to the El Tor biotype of cholera, which produces a milder form of diarrhea and persists in the environment longer than the classical

biotype, has necessitated renewed definition of the epidemiology of the disease. With the advent of increased rates of dysentery, primarily due to Shigella sp., the CRL has embarked on a vigorous program to describe fully the morbidity and mortality associated with this disease and to define optimal modes of therapy for the Bangladesh situation.

1. Clinical Research Program

The correction of dehydration and the proper maintenance of water and electrolyte balance continue to be the mainstays of therapy for most diarrheas seen at the CRL. Several studies to refine this mode of therapy were conducted recently at the CRL.

a. WHO Collaborative Trials of I.V. Therapy: Investigators at the Dacca Cholera Hospital compared the CRL intravenous solution (Dacca solution) to one which is widely recommended by the World Health Organization (WHO). The WHO solution contains less sodium and potassium than Dacca solution and, unlike Dacca solution, contains 5% dextrose. Clinical trials showed the two solutions to be equally effective in correcting initial dehydration, maintaining hydration and in correcting electrolyte imbalance. This study demonstrated that the WHO solution which may be applied in a wider range of clinical situations than cholera or other acute, severe, dehydrating diarrheas alone, appears to be as effective as Dacca solution in cholera therapy. Therefore, health authorities faced with cholera, in addition to other diseases, may choose to stock the WHO fluid which may be used in a wider spectrum of conditions requiring administration of intravenous fluids.

b. Advances in Oral Therapy: In recent years the most significant advances in rehydration therapy have been in the development and popularization of oral glucose-electrolyte solution. In the last decade the CRL was a pioneer in this important field of research, and in the recent past investigators at the Laboratory have continued to contribute significantly to the refinement of this mode of therapy.

In many countries of the developing world bulk glucose is expensive and is not readily available. In many of these countries sucrose (table sugar) is a logical substitute. A comparison of glucose and sucrose solutions conducted in the

Dacca and Matlab Hospitals demonstrated glucose to be slightly better than sucrose, but the differences, while statistically significant, were small and unimpressive when one considers the real world situation where sucrose-electrolyte solution may be a more practical alternative to uncorrected dehydration. Based on these results it seems reasonable to use glucose-electrolyte solution if it is available at a reasonable cost, but sucrose-electrolyte solution should be considered an acceptable, efficacious second choice.

Although the efficacy of oral therapy has been demonstrated in supervised settings, questions remain as to the minimal level of supervision needed for its administration. These oral hydration studies have been important in establishing confidence in oral therapy in moderately to severely dehydrated patients. They have also suggested the potential usefulness and margins of safety of unsupervised use of oral therapy in the field.

c. Shigella Dysentery: Since the advent of the marked increase in the number of patients presenting with dysentery, several studies have been undertaken describing the hospital course of patients with shigellosis and amebiasis. Last year CRL researchers described three serious complications seen in patients severely ill with shigellosis, especially those with dysentery due to Sh. dysenteriae, type 1. Subsequent studies have attempted to understand more fully these observations in order to treat them rationally and effectively.

The leukemoid reaction was noted in 30% of shigellosis patients, and preliminary data suggests this finding accompanies endotoxemia. Although the leukemoid reaction was present more frequently in severely ill patients, its occurrence did not predict either hemolysis or renal failure. Recent studies indicate the hemolysis which was described earlier in shigellosis patients is probably micro-angiopathic in nature. This complication is seen frequently enough in the recent experience at the CRL to document the need to have blood transfusions available to significantly reduce the hospitalized mortality of shigellosis. Kidney biopsies taken within four hours post-mortem from children dying with hemolysis and renal failure were studied with immunofluorescence. No immunoglobulin deposit was found although fibrin deposits were noted. This and other evidence supports the hypothesis

that this lethal complication is produced by activation of clotting and is not secondary to immune-complex disease.

d. Antibiotic Trials: Efforts to document and improve modes of therapy were particularly vigorous, and several studies of the role of specific antibiotics in treating cholera and shigellosis were undertaken. V.cholerae is universally sensitive to the tetracycline group of antibiotics which are administered four times daily in treatment regimen. Tetracycline was also demonstrated to be effective against sensitive strains of Shigella sp. In attempting to define an effective but inexpensive treatment program, any change in treatment which reduces the degree of nursing supervision or lessens the amount of expensive medicine taken without supervision is an important contribution. Doxycycline, a long-acting tetracycline-like drug, is administered only once a day instead of four times daily and acts directly on cell mucosa of the small intestine. Demonstrated by studies to be effective as tetracycline in treatment of these diseases, Doxycycline in single daily doses can reduce personnel costs and ensure that the antibiotics are taken by the patient. Further doxycycline studies are to be initiated at CRL.

The antibiotic sensitivity patterns of Shigella sp. and other pathogens were monitored routinely. Almost all of the recent isolates of Shigella dysenteriae, type 1 (Shiga bacillus) strains were resistant to tetracycline and 50% of all other serotypes of Shigella were resistant to the drug. Virtually all isolates of Shigella were sensitive to ampicillin. Because the Shiga bacillus cases were more seriously ill, ampicillin was used as the drug of first choice in suspected cases. A trial of tetracycline was used first in milder cases thought to be due to other serotypes. The antibiotic therapy was changed if indicated by the sensitivity results which were known 72 hours after admission.

In attempting to reduce the significant amount of mortality and serious morbidity seen in shigellosis patients, a controlled trial of routine doses of ampicillin (50 mg/kg/day) and a high dose (150 mg/kg/day) was conducted. This trial failed to detect any difference between the two doses with respect to number of days of diarrhea, disappearance of blood from the stool, number of days a patient was bacteriologically positive or the persistence of fecal leucocytes. None of the patients in the study developed a serious complication but the

evidence suggests high doses of antibiotic would not reduce the significant morbidity and mortality observed in the hospital. The severity of disease at the time of admission seemed to influence the rate at which complications developed during hospitalization more than blood levels of antibiotics.

We are fortunate that to date virtually all Shigella sp. isolates in Bangladesh are sensitive to ampicillin. However, elsewhere in the world many strains are resistant to this antibiotic and some patients are allergic to the penicillin group of antibiotics. A controlled clinical trial of timethoprem-sulfasoxizole (Bactrim TM) was initiated recently in the Matlab hospital to evaluate this drug as an alternative choice to ampicillin.

e. Amebiasis: Amebiasis was found to be more prevalent among patients presenting to the CRL hospital than previously suspected. Young children and men over forty were particularly prone to necrotic ulcerative disease, but older children experienced no complications. Investigators correlated the extent of involvement of the rectal mucosa at the time of admission with the subsequent clinical course. Skin test reactivity was noted to be depressed in both children and adults compared to patients of similar age with milder disease. It is anticipated that future studies will focus on describing in greater detail the overall morbidity and mortality associated with amebic infection and developing effective means to avert the serious complications of this disease.

2. Laboratory Research

To support the extensive plans to study toxigenic E.coli diarrheas, the CRL has put into operation two diagnostic techniques. The Chinse hamster ovary (CHO) tissue culture assay for heat labile (LT) E.coli enterotoxin is now available to investigators as a routine laboratory test. Investigators have provided a sound rationale for examining pools of E.coli isolates rather than assaying each colony individually, and the resulting increased efficiency has allowed the microbiology laboratory to process many more specimens without loss in accuracy in making the correct diagnosis. More recently, the infant mouse assay for heat stable (ST) E.coli enterotoxin was put into operation successfully. This replaces the cumbersome, expensive canine ileal loop assay.

These two techniques allow investigators to detect both ST and LT positive strains and provide the scope to expand investigations of E.coli diarrhea which accounts for a substantial proportion of diarrheal cases in Bangladesh.

As studies of shigellosis progressed to the stage of making field observations among a large population to define the epidemiology of this disease, it became apparent that a serological tool would facilitate the work. CRL investigators have developed a sensitive hemagglutination assay which is specific for infections with Shiga's bacillus. Seroepidemiology studies are currently underway to define the role of this host parameter in the epidemiological pattern of shigellosis using group A. type 1 infections as a model.

3. Field Trials

a. Oral Rehydration Therapy: In preparation for a large field study of unsupervised use of oral therapy, the CRL developed a product which would be acceptable to the average Bangladeshi and would be easy to use properly. After a series of preference studies and refinement of a series of pictorial instructions to supplement the verbal instruction of field workers, pilot lots of the powdered mixture of CRL formula glucose and electrolytes was packaged in bottles with moisture proof seals under contract by a local pharmaceutical firm.

A study was conducted to document the effectiveness of oral therapy administered without supervision in correcting initial dehydration among the outpatients in Dacca. Patients who were rehydrated during a five-hour stay in the OPD were followed up in their homes for five days during which time they continued to take oral therapy as required. All but a small percentage of patients were successfully treated with this regimen. Because the product made, according to the CRL formula, was not fully developed at the time, this study used packages of Oralyte which were made available by the Bangladesh Government.

Following the favourable response of the outpatient study, the CRL studied the effect of a household based scheme to treat diarrhea in a population of approximately 5,000 in Matlab. This controlled study compared the effectiveness of CRL oral

therapy and kaolin-tincture of cardamon mixture which has been distributed by CRL field workers for many years. The preliminary results of this study indicate both oral therapy and the placebo were equally effective in correcting mild and moderate dehydration when ad lib free water or breast milk were available. A considerable proportion of families mixed the solution improperly and one infant among approximately 225 patients who were treated with oral therapy had an elevated serum sodium after starting treatment. Although the study will be continued in the next cholera season to observe the impact of oral therapy during a cholera epidemic, we plan to use the WHO formula for sodium concentration in subsequent lots of the CRL product unless we find evidence that a higher concentration of sodium is needed in cholera cases.

The field studies have been very useful in defining the optimal place for oral therapy in the scheme of diarrheal disease treatment. The tentative conclusion must be the great majority of diarrheal disease episodes require no special treatment to prevent dehydration. In balancing the potential risk of offering oral therapy to all cases of diarrhea against the small proportion of cases who would benefit from its use, it appears as though the proper place for this form of treatment may be in the black bag of a resident part-time health worker in the village who has been trained to detect moderate to severe dehydration when he is summoned to the patient's home. Based on available evidence, it may not belong in the medicine cabinet in every home for use in every case of diarrhea.

b. Dysentery Therapy, Impact of Simplified Management: Working out of the simple treatment facility at Teknaf, investigators were able to document a reduction in case/fatality rates of approximately 90% when compared to those observed in a similar area twelve miles away which did not have access to the treatment center. In Teknaf, a simple regimen or oral rehydration and the judicious use of tetracycline and ampicillin lowered considerably the mortality associated with dysentery for a cost of less than $ 0.12 per patient contact for medicine and supplies. Attempts are underway to extend the treatment into neighbourhoods using field staff to treat dysentery in the homes in the same manner used in the clinic.

c. Cholera Toxoid Vaccine Trial: The CRL planned and conducted a field trial to evaluate a highly purified, prototype cholera toxoid as an immunizing agent as the first of a series of projects in FY75. The lack of favourable results with this toxoid caused the cancellation of plans for re-immunization in FY76 and indicated the need for much further basic research on cholera toxoid. This is presently underway in Laboratories in the United States, England and several other countries, but this research did not produce an agent which was deemed worthy of a field trial in FY76. During the past year, however, two different field trial designs were planned at the request of the U.S.-Cholera Panel before it was finally ascertained that an adequate supply of a suitable material would not be available for a field trial in FY77. We expect to conduct a field trial of a combined cholera vaccine-cholera toxoid in Matlab in FY78.

4. Epidemiological Research

a. Cholera in Dacca: The cholera epidemics of FY75 and FY76 in Dacca city were the two largest in the history of the Laboratory. The CRL provided not only services to meet the outbreaks but at the same time initiated the research activities afforded by these two outbreaks. Previously the CRL had difficulty in locating the residences of patients based on addresses taken at the time of admission to the hospital. The Community Studies Branch instituted a simple, inexpensive technique to register descriptive addresses of patients and was successful in locating approximately 85 percent of dwellings. This breakthrough provided the opportunity for investigators to adequately describe the epidemics and to document an increased risk of acquiring cholera among people who eat meals outside of their homes. It also provided a mechanism for effective hospital-based surveillance which could be used by local health authorities to facilitate epidemic control measures.

The findings of the urban cholera epidemiology studies prompted the municipal government to request our assistance in implementing control measures during the latest large epidemic. Much of the concern expressed by government officials throughout the world during the current cholera pandemic stems from the appearance of cholera in crowded urban settings. While detailed studies of the epidemiology

of endemic cholera in rural Bangladesh have done much to identify host and environmental factors important in the transmission of the disease, there remains a great deal to be done to define the epidemiology in an urban environment. The methodology developed at the CRL appears to have general applicability as a means of locating the homes of any hospitalized patients and may be a useful epidemiological tool in similar cities having random street plans and non-descriptive home address designation.

b. Diarrhea in the Rural Areas: The CRL has begun to generate data of the incidence of episodes of diarrhea and dysentery based on field surveillance rather than hospital admissions or outpatient visits. The data, which were generated from 12 villages in Matlab with a population of 20,000 and four areas of Teknaf Thana with a population of approximately 40,000, suggest an annual incidence of between 100 to 200 episodes of diarrhea per 1,000 persons per year. Thus diarrheal disease continues to be a major health problem in Bangladesh by almost any standard.

The data relating overall incidence of all types of diarrhea suggested a strong seasonal trend. Twice as many episodes of diarrhea occurred during the dry, low-water months as during the monsoon. As expected, diarrhea was largely a pediatric problem. It was not expected, however, that rates generated from active household surveillance are ten times as high as rates calculated from hospital or outpatient visits. It is sobering to note only ten percent of diarrheal cases seek hospital-based medical attention in an area in which transportation and effective treatment is free. These data emphasize the need to decentralize the delivery of treatment to make a maximal impact on morbidity and mortality of diarrheal disease. We intend to place the CRL approach to the treatment of diarrhea in proper perspective by relating morbidity rates generated from field, hospital and OPD cases to the proportion of episodes of diarrhea for which specific therapy is recommended.

The Matlab investigators, in collaboration with other laboratories, documented the existence of diarrhea caused by reovirus-like agents. Similar to the experience in developed countries, infants were noted to be particularly susceptible to this infection. A panel of infants and young children is being followed quarterly with serological and stool specimens

to note the season and age at which individuals acquire the infection with theseviruses. The early evidence indicates viral diarrheas may account for a considerable amount of the total diarrheal morbidity.

5. Environmental Studies

a. Cholera: The association between the occurrence of cholera and cholera contaminated water appears to be incontrovertible. However, there is accumulating evidence that cholera may not be caused or prevented by merely drinking or not drinking contaminated water, particularly since various bacteriological studies have tended to indicate the number of organisms in water in infected areas sometimes may be quite small. The CRL has begun an extensive study of the environmental epidemiology of this disease using relatively newer techniques of quantitative microbiology focusing not only upon water but the whole environment, including food, that surrounds people at risk.

This project has two main thrusts. First is systematic studies at water sampling stations located in a limited number of traditionally high risk areas using techniques of modern ecological study, including multi-level and sediment sampling. These studies are associated with chemical, physical and meterological measurements as well as studies of zoo- and phytoplankton. Although much of FY76 was devoted to technique development, the systematic sampling began before cholera was reported in these areas and will continue throughout the year. It is hoped these studies will contribute information concerning the yet unexplained seasonality of cholera epidemics and the time relationships between the occurrence of cholera cases and the detection of Vibrio cholerae in water.

The second type of environmental study involves the baris (Bengali: dwelling house) of selected persons admitted to the Matlab hospital. Previous work indicated a high probability of secondary cases in these areas. For several days following the admission of a cholera case, selected baris were subject to intensive epidemiological, environmental, and microbiological studies which paid particular attention to food, household water, local water sources, waste disposal and fomites, as well as the occurrence of symptomatic and

asymptomatic cholera infections. Such studies examine the local environment before and during the occurrence of secondary cases rather than retrospectively. Although only a few baris have been studied to date, isolations of V.cholerae have been obtained almost exclusively from domestic water supplies and their natural sources. The environmental transmission of V.cholerae appears to be much more directly related to water than is probably the case with other diarrheal diseases. It is notable that the organisms involved are of the El Tor biotype rather than of the classical strains that prevailed when previous studies were attempted at the CRL and other laboratories.

b. Shigella dysentery: During the course of the field work in Teknaf, the two tanks (ponds) near the clinic were found to be associated with an increased incidence of shigellosis. Those using either of the two tanks experienced a rate of confirmed Shigella sp. infection of 72/1000/year while those using other sources of water experienced a rate of 32/1000/year. Detailed data of the amounts of water taken into the home for drinking, cooking and washing indicated an inverse relationship between rates of shigellosis and the volume of water consumed in the home. This is the first objective evidence in Bangladesh relating the volume of water available for domestic uses and shigellosis rates, and it confirms similar observations labelling the disease as "water washed" which were made elsewhere in the developing countries.

c. UNICEF Collaborative drilled well study: In twenty villages of the Matlab field surveillance area, the CRL evaluated the effectiveness of the Bangladesh Government effort to improve rural water supplies by increasing the availability of hand-pump drilled wells. This study indicated that drinking well water was not associated with any reduction in the incidence of diarrheal episodes. The data are not completely analyzed, but the tentative conclusion is that virtually all rural Bangladeshis are exposed to contaminated surface water through bathing, cooking, washing and other domestic and personal uses and any marginal benefit which might be associated with drinking bacteriologically safe water is too small to detect. The findings of this and other CRL studies should be considered in future attempts to intervene in the transmission of cholera and other infectious enteric diseases in Bangladesh.

B. Population and Nutrition Research

1. Demographic Studies

The CRL has maintained registration of births, deaths and migration in the rural field study area in Matlab Thana, Comilla District, continuously since 1966. The vital events registration covers a population of over 250,000 in 233 villages. For the first five years the birth rate was relatively stable at about 45/1000 and the death rate averaged about 15/1000, giving an average rate of natural increase of 3%. Beginning in 1971 there have been marked fluctuations in both rates. The crude death rate rose 40% during the war of 1971 and there was again a similar sharp rise with the food shortages in 1974/75. Recently the death rate has declined toward earlier levels. Most striking has been a dramatic decline in fertility during and following the period of food shortage. In 1975/76 the birth rate fell to a low of 27/1000 but recently has shown signs of recovery with improved availability of food. The Matlab population data base has become an increasingly valuable resource each year. Because of the birth registration, the exact ages are now known for approximately 30% of the population which resides in the surveillance area and detailed studies of population, nutrition and infectious diseases interrelationship are underway.

2. Biological determinants of Fertility

The average live birth interval is approximately three years in rural Bangladesh. This is surprisingly long in a non-contracepting society. A prospective follow-up of 2,000 women in the Matlab area has revealed that the major factor associated with long birth spacing is prolonged breastfeeding with lactational amenorrhea averaging 18-20 months. Additional factors are seasonal absences of the husband for work and a seasonal variation in conceptions which is not fully explained. Special longitudinal investigations have been undertaken to determine if the nutritional status of the women relates to their fertility performance. Poor nutrition has been shown to be related to delayed onset of menarche. Among poorly nourished women as compared to better nourished women, the data available so far however, suggest that there is no difference in the two major components of the birth interval - the duration of lactational amenorrhea and in the waiting time

to conception once menstruation resumes. These studies underline the importance of breastfeeding for both infant nutrition and birth spacing in this population and indicate that this factor must be taken into consideration when any contraceptive programs are proposed.

3. Government of Bangladesh Collaborative Contraceptive Study

The Cholera Research Laboratory is conducting a research project in collaboration with the Government of Bangladesh to determine the level of acceptance and the demographic impact of a program of distributing oral contraceptives on a house to house basis. Beginning in October 1975, oral contraceptives were distributed by the Matlab field staff to every family in over 100 villages. Fully 65% of married fecund women agreed to keep a supply of oral contraceptives in their home although there was no commitment to use them. Subsequent surveys have revealed the prevalence of contraceptive use among those women rose from 1% to 15% following the introduction of universally available oral contraceptives. Not enough time has elapsed to assess any change in birth rates from this program. The Matlab field study area was chosen for this research because the registration of births will allow the documentation of the demographic impact of such a scheme. More importantly, indepth surveys will permit an assessment of the acceptability or non-acceptability of such a program and can be used to guide additional approaches towards assisting families in exercising their free choice in reproductive performance. The results of this study are already beginning to be useful in the field of family planning.

4. Child Growth and Development

One of the many complex inter-relationships among health parameters which is thought to be important in Bangladesh is the interplay between nutritional status and infectious disease. Longitudinal studies of infants and children in village Meheran in Matlab have continued to explore the mutual influence of nutritional status and diarrheal morbidity on growth and development of Bangladeshi children. To date only preliminary findings are available. These include the documentation of a distinct plateau in growth rates which starts at about six months of age and is not correlated with visits to the small clinic in the village

and probably relate to inadequate infant nutrition. We anticipate the household based diarrhea morbidity surveillance coupled with nutritional studies will reveal a consistent pattern and allow the investigators to fully identify the etiologies of this slowing in the rate of growth.

III TRAINING

A. WHO Inter-Regional Course

In September 1976, CRL in association with WHO presented an eleven day Inter-Regional Course on the Epidemiology of Diarrheal Diseases. It was attended by 17 Public Health physicians and scientists from 15 countries in Asia, Africa and South America. With the additional participation of Dr. Y. Watanabe of WHO Geneva, the faculty and assisting staff were entirely CRL personnel. The course covered a wide area of the diarrheal disease problem and was presented at a relatively advanced level. This was the first course on this subject sponsored by WHO. The evaluation by participants and WHO observers was very favourable and repetition at regular intervals has been discussed.

B. Bangladesh Trainees

In local level, CRL provided two weeks of laboratory instruction for 19 students of the Paramedical Institute of the Bangladesh Ministry of Health and two weeks of training to the Bangladesh Rural Advancement Committee trainees. In addition, ward training of 1-3 days was provided to classes of several schools of nursing in Bangladesh. CRL has provided individual instruction to at least 13 scientists and graduate students of various universities, mostly within Bangladesh. The periods of training have ranged from a few days to three months.

C. International Trainees

CRL has continued to be attractive to students interested in field experience in developing countries. During this year Ms. Sandra Huffman, graduate student from Johns Hopkins University, has continued her activities with CRL as a demographer trainee and Mr. David Everett and Ms. Margaret Phillips, medical students from the University of Adelaide, spent four months at the Laboratory. In addition, Mr. Richard Daniel, a microbiology student from Surrey University in England, has begun a six month period of training. Inquiries

concerning training opportunities are frequent and plans for two additional trainees in FY77 are in progress. It is a pleasure to report that the activities of these trainees have contributed very considerably to the research of the Laboratory.

D. Training Manual

Another activity of FY76 was the writing of a manual for the diagnosis and management of diarrheal diseases that represented a simplified version of the practices in the hospitals of CRL. It was prepared by CRL physicians and was designed for the use of Bangladeshi physicians and trained health workers. It assumed that no Laboratory facilities would be available and placed major emphasis on powers of clinical observation. This manual has been translated into Bengali and the Ministry of Health of Bangladesh has had 40,000 printed for distribution.

IV PATIENT CARE

In FY75, the Cholera Research Laboratory Hospital in Dacca handled the largest cholera epidemic in its history. The epidemic of FY76, while not as large as the previous year, was still the second largest in CRL history. Like the FY75 epidemic, it reached its peak in October and was predictable in August. Fortunately, admissions covered a broader time period than in 1975 and it was necessary to use only one hospital tent to accommodate the overflow from the wards. Hospital activities in Matlab were considerable, but not record-breaking. The experience of the FY75 epidemic was of great value in handling this situation. Adequate supplies and facilities were available and no acute emergencies developed.

The FY76 hospital and outpatient department activities are tabulated in Table 1. It will be noted that outpatient attendance continued high and that non-cholera disease including shigellosis is a continuing major feature of diarrheal disease, both in Dacca and Matlab. Since non-cholera diarrhea has become an almost continuous source of hospital admissions throughout the year, the general level of hospital and OPD activity remains high even in the absence of cholera epidemics.

TABLE 1

CHOLERA RESEARCH LABORATORY
DACCA & MATLAB PATIENT ACTIVITY

FISCAL YEAR, 1976
(July 1, 1975 to September 30, 1976)

	Inpatients				Out-patients	Total
	Total	Cholera	Shigella	Others		
Dacca	11,047	3,079	1,246	6,722	69,730	80,777
Matlab	3,888	966	214	2,708	8,666	12,554
Total	14,935	4,045	1,460	9,430	78,396	93,331
*Deaths	357	16	92	249	-	-

* Death rate per CRL Inpatient 2.39%.

V ORGANIZATION

A. SCIENTISTS

The Scientific investigators responsible for the scientific program are listed below:

Willard F. Verwey, Sc.D.	Director, CRL
Clinical Division	
M. Mujibur Rahaman, M.B.B.S., Ph.D.	Head, Clinical Div.
A.K.M. Jamiul Alam, M.B.B.S.	Chief Physician (Dacca)
Md. Rafiqul Islam, M.B.B.S.	Deputy Chief Physician (Dacca)
Serajul Islam, M.B.B.S.	Clinical Research Assistant
Epidemiology Division	
George Curlin, M.D., M.P.H.	Head, Epidemiology Div.
K.M.A. Aziz, M.A.	Head, Matlab Field Surveillance Branch
Moslemuddin Khan, M.B.B.S.	Head, Community Studies Branch
A.K.M.A. Alauddin Chowdhury, M.Sc.	Head, Statistics Branch
Douglas Huber, M.D., M.P.H.	Epidemiologist
A.S.M. Mizanur Rahman, M.B.B.S.	Chief Physician (Matlab)
Md. Yunus, M.B.B.S.	Deputy Chief Physician (Matlab)
Laboratory Division	
K.M.S. Aziz, Ph.D.	Head, Laboratory Div.
Imdadul Huq, M.Sc.	Head, Bacteriology Branch
Ansaruddin Ahmed, M.B.B.S.	Head, Immunology Branch
Abdullah Al-Mahmud, M.Sc. (Vet. Sc.)	Head, Animal Resources Branch
James C. McLaughlin, Ph.D.	Microbiologist
William Spira, Ph.D.	Microbiologist

The CRL research effort involves substantial collaboration with Scientists in Bangladesh and worldwide.

The following is a list of scientists who contributed to the research program as guest investigators or collaborating scientists, or whose own research was facilitated by the CRL.

Ahmed, Fariduddin, Ph.D., Professor, Dept. of Physiology, Institute of Post Graduate Medicine & Research, Dacca.

Ahmed, Kamaluddin, Ph.D., Professor, Director, Institute of Nutrition & Food Sciences, Dacca University, Dacca.

Ali, Shahadat, M.Sc., Dept. of Zoology, Dacca University, Dacca.

Ahmed, Jasimuddin, M.Sc., Institute of Statistical Research & Training, Dacca University, Dacca.

Chakma, Subrata, Dr., Divisional Officer, Malaria Eradication Programme, Dacca.

Cain, Mead, Ph.D., visiting Scholar, Bangladesh Institute of Development Studies, Dacca.

Chen, Lincoln, M.D., M.P.H., Population Program Officer, Ford Foundation, Dacca.

Choudhury, Rafiqul H., Ph.D., Bangladesh Institute of Development Studies, Dacca.

Colwell, Rita, Professor, Dept. of Microbiology, University of Maryland, U.S.A.

Gilman, Robert, M.D., Johns Hopkins University, Baltimore, U.S.A.

Kapikian, A.G., M.D., National Institute of Health, Bethesda, Maryland, U.S.A.

Khan, Atiqur Rahman, Dr. P.H., Division of Population Control & Family Planning, Bangladesh Government.

Koster, Frederick, M.D., Johns Hopkins University, Baltimore, U.S.A.

Lee, John, V., Ph.D., Public Health Laboratory Kent, U.K.

Miwatani, Professor, Osaka University, M.B.D. School, Japan.

Morris, George, Dr., Epidemiology Bureau, Center for Disease Control, Atlanta, U.S.A.

Oppenheimer, J., Ph.D., Associate Professor, Johns Hopkins University, Baltimore, U.S.A.

Palmer, Darwin, M.D., Johns Hopkins University, Baltimore, U.S.A.

Tawil, G.S., Dr., Regional Adviser in Health Laboratory Services, World Health Organization, New Delhi, India.

B. Personnel

On January 31, 1977, CRL had 540 fulltime employees and 290 contractual Female Field Workers. Of the total CRL staff, 248 are working in research areas. They may be classified as follows:

1.	Scientists (Investigators)	18
2.	Physicians	12
3.	Technicians	96
4.	Scientific support	122
		248

The rest of the staff are Administrative and Maintenance personnel for the support of the research work. They are classified as follows:

1.	Officers	15
2.	Mid-level	63
3.	Lower level	214
		292

C. Staff Development

Opportunities for staff development, while limited, have been available to local CRL staff. In former years, several scientists received advanced training abroad. In FY76 staff

training was primarily available in the technical and administrative areas. In FY76 CRL has enrolled its personnel in the courses indicated in Table II.

TABLE II

CRL Staff Course or Training Taken

Name	Name of the Course	
Mr. Rabindra Nath Majumder Head, Supply Management Branch	Inventory & Store Management	2 Weeks part time
Mr. Aurangzeb Md. Alamgir Special Assistant Supply Management Branch	Inventory & Store Management	2 Weeks part time
Mr. Abul Hashem Special Assistant Finance Management Branch	Accounting	4 Weeks part time
Mr. Md. Abdul Jabbar Special Assistant Personnel Management Branch	Personnel Management & Industrial Relations	2 Weeks part time
Mr. Abul Kalam Azad Head, Personnel Management Branch	Diploma in Personnel Management	9 Months (Partly completed)
Mr. Abul Kalam Azad Head, Personnel Management Branch	Financial Management	2 Weeks part time
Mr. A. Rashid Khan Head, Finance Management Branch	Financial Management	2 Weeks part time
Mrs. Obaida Kabir Private Secretary to Head, Clinical Division	Office Management & Communications	2 Weeks part time
Dr. K.M.S. Aziz Head, Laboratory Div.	Introduction to Data Processing	2 Weeks part time

TABLE II Contd.

Name	Name of the Course	
Mr. Mizanur Rahman Statistical Assistant Statistical Branch	Population Research & Evaluation	6 Weeks full time

D. Directing Council

The Outline of Operations under the Bilateral Project Agreement activating the Cholera Research Laboratory provides that it shall be governed by a Directing Council appointed by participating Governments. Almost from its beginning, the Directing Council has consisted of representatives of the Government of Bangladesh, the United States of America and the United Kingdom. The Government of Australia has been invited to name a member but, up to this time, has not elected to do so.

The persons and their tenures, who have served on the Directing Council in the 27 months of its existence, are shown below:

Name & Country Associated	Tenure From	To
Dr. K.A. Monsur Director of Health Services (Preventive) Government of Bangladesh	June 1974	April 1975
Dr. Mostaqul Huq Director of Health Services (Preventive) Government of Bangladesh	June 1974	-
Dr. Ataur Rahman Chief of Health Planning Commission Government of Bangladesh	June 1974	September 1975

Name & Country Associated	Tenure From	To
Mr. Michael R. Jordan Chief of Health & Population USAID, Dacca	June 26, 1974	-
Mr. Hilary J. Cunningham Budget & Fiscal Officer American Embassy, Dacca	June 26, 1974	June 1975
Mr. H.A. Moisley First Secretary (Aid) British High Commission Dacca	Aug. 8, 1974	February 1976
Dr. M. Golam Muazzam Secretary Bangladesh Medical Research Council Government of Bangladesh	Jan. 7, 1975	June 1975
Mr. Joe O. Hill Budget & Accounts Officer USAID, Dacca	July 30, 1975	September 1976
Dr. Abdul Quader Khan Secretary, Bangladesh Medical Research Council & Director, Institute of Epidemiology, Disease Control & Research Government of Bangladesh	Aug. 22, 1975	-
Dr. Zakir Hossain Chief of Health Planning Commission Government of Bangladesh	March 8, 1976	
Mr. Michael C. McCulloch First Secretary (Aid) British High Commission Dacca	March 15, 1976	

E. The Scientific Review & Technical Advisory Committee

The Scientific Review & Technical Advisory Committee for the CRL is stated by the Project Agreement to be appointed by the Director of the NIH from Nominations received from each participating government and organization. The appointment of this Committee has been delegated to the Director of the National Institute for Allergy & Infectious Diseases (NIAID). In FY76 the Committee consisted of:

1. Dr. John P. Craig, (Chairman), Department of Microbiology & Immunology, Downstate Medical Center, State University of New York.

2. Professor Derrick Rowley, Department of Microbiology, University of Adelaide, Australia.

3. Professor Sir R.E.O. Williams, Director, Public Health Laboratory Services, Colindale, United Kingdom.

4. Dr. M.A. Latif, Director, Institute of Public Health, Government of the People's Republic of Bangladesh.

5. Dr. Carl E. Miller (ex-officio) Cholera Program Officer, Geographic Medicine Branch, NIAID, Bethesda, Maryland, U.S.A.

The Committee held its meeting at the Cholera Research Laboratory from 25 February to 3 March, 1976 and the following consultants were present:

Dr. Philip S. Brachman, Director, Bureau of Epidemiology, Center for Disease Control, U.S.A.

Dr. Nevin S. Scrimshaw, Chairman, Department of Nutrition & Food Sciences, Massachusetts Institute of Technology U.S.A.

Dr. Edward W. Hook, Chairman, Department of Internal Medicine, University of Virginia, U.S.A.

Dr. John C. Snyder, Harvard University School of Public Health, U.S.A.

F. Clinical Investigation Committee

The Project Agreement states that the Director of CRL is to appoint a Clinical Investigation Committee after consultation with participating nations and the Director of NIH and that this Committee should have an adequate representation from Bangladesh to ensure that the ethics of the country are observed and the rights of citizens protected. At the present time, all CRL Research Protocols involving human subjects are reviewed by an internal Protocol Committee consisting of both expatriates and Bangladeshis and including physicians and non-physicians. After approval by this Committee and the Director, the protocols are submitted to the Review Committee of the Bangladesh Medical Research Council (BMRC) which is responsible for review and approval of all experimentation involving human subjects in Bangladesh. In the case of Protocols submitted by CRL, review is carried on by the BMRC plus three additional persons.

The Members of the Scientific Review Committee of Bangladesh Medical Research Council are as follows:

Prof. Nurul Islam, Director of the Institute of Post-Graduate Medicine and Research, Dacca.

Prof. Shamsuzzoha, Director of BMRC and Secretary of the Scientific Review Committee.

Prof. Nurul Haque, Professor of Pathology, Sylhet Medical College.

Prof. Kamaluddin Ahmed, Professor of Pharmacology, Institute of Post-Graduate Medicine and Research, Dacca.

Dr. M.M. Rahaman, Head, Clinical Division, Cholera Research Laboratory, Dacca.

Additional members for reviewing of the protocols submitted by CRL are as follows:

Dr. A. Samad, Director, Institute of Statistical Research & Training, Science Annex Building, Dacca University, Dacca, Bangladesh.

Reverend Richard W. Timm, Roving Consultant, CORR-CARITAS, Dacca, Bangladesh.

Dr. Kamaluddin Ahmed, Director, Institute of Nutrition & Food Science, University of Dacca, Bangladesh.

G. Financial Support

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MANUSCRIPTS PUBLISHED
FY76

Aziz KMS: Assay of enterotoxin in animal models. Bangladesh Pharm J 5(2): 27-28, April 1976

Aziz KMA: Deaths from drowning in rural Bangladesh. Bangladesh Observer, 28 Dec 1975

Aziz KMS and Rahaman MM: Ensuring better health for all. The Bangladesh Times, 19 August 1975

Chowdhury AKMA, Khan AR and Chen LC: Effect of child mortality experience on subsequent fertility. Pop Studies 30(2): 249-261, June 1976

Curlin GT, Chen LC and Hussain SB: Demographic crisis: the impact of the Bangladesh Civil War (1971) on birth and deaths in a rural area of Bangladesh. Pop Studies 30(1): 87-105, 1976

Fariduddin KM, Rahaman MM and Ahsanullah ABM: Study of energy expenditure and food intake of some working class people of Bangladesh. Bangladesh Med Res Council Bull (1): 24-31, April 1976

Greenough WB, Hirschhorn N, Gordon RS, Lindenbaum J and Ally KM: Pulmonary oedema associated with acidosis in patients with cholera. Trop Geog Med 28(2): 86-90, June 1976

Khan MM, Rahaman MM, Aziz KMS and Islam S: Epidemiologic investigation of an outbreak of Shiga bacillus dysentery in an island population. The Southeast Asian J Trop Med & Pub Health 6(2): 251-256, June 1975

Levine RJ, Khan MR, D'Souza S and Nalin DR: Cholera transmission near a cholera hospital. The Lancet 2(7976): 84-86, 10 July 1976

Levine RJ, Khan MR, D'Souza S and Nalin DR: Failure of sanitary wells to protect against cholera and other diarrheas in Bangladesh. The Lancet 2 (7976): 86-89, 10 Jul 1976

Nalin DR, McLaughlin JC, Rahaman M, Yunus M and Curlin G: Enterotoxigenic Escherichia coli and idiopathic diarrhoea in Bangladesh. The Lancet 2(7945): 1116-1119, 6 Dec 1975

Palmer DL, Koster FT, Alam AKMJ and Islam MR: Nutritional Status: a determinant of severity of diarrhea in patients with cholera. J Infect Dis 134(1): 8-14, Jul 1976

Rahaman MM and Chakma S: Food intake of the Chittagong Hill tribes of Bangladesh. Bangladesh Med Res Council Bull 2(1): 35-41, June 1976

Rahaman MM, Khan MM, Aziz KMS, Islam MS and Kibriya AKM: An outbreak of dysentery caused by Shigella dysenteriae type 1 on a coral island in the Bay of Bengal. J Inf Dis 132(1): 65-70, Feb 1975

Ryder RW, Sack DA, Kapikian AZ, McLaughlin JC, Chakraborty J, Rahman ASMM, Merson M and Wells JG: Enterotoxigenic Escherichia coli and reovirus-like agent in rural Bangladesh. The Lancet 1(7961): 659-662, 27 March 1976

PAPERS PRESENTED IN SCIENTIFIC CONFERENCES
FY76

Aziz KMS: "Toxins in blue-green algae." Seminar on Food and Energy from Unconventional Sources with Application of Nuclear Techniques. Bangladesh Atomic Energy Commission. Dacca. July, 1976

Aziz KMS: "Preliminary observation on the heterotrophic existence of Microcystis aeruginosa Kutzing." First Bangladesh Science Conference of the Bangladesh Association for Advancement of Science. Dacca. March 28-31, 1976

Aziz KMS: "Vibrio population and toxicity of cholera stool." Annual Meeting of the Bangladesh Medical Association. Dacca. December, 1975

Aziz KMS and Huq I: "Microbiology of diarrhea and dysentery in Bangladesh." Symposium on the Impact of Microbiology in the Development of Bangladesh. Dacca. March 29, 1976

Aziz KMS and Rahaman MM: "Evaluation of a health project in Teknaf." Seminar on Methodology of Evaluation, Institute of Statistical Research and Training. Dacca University, Dacca. August 4, 1976

Chowdhury AKMA: "Effect of child mortality experience on subsequent fertility: an emperical analysis of Pakistan and Bangladesh data." Seminar on Infant Mortality in Relation to the Level of Fertility. Bangkok, Thailand. May 6-12, 1976

Curlin GT, Levine R, Aziz KMA, Rahman ASMM and Verwey WF: "Field Trial of Cholera Toxoid." U.S.-Japan Cooperative Medical Science Program. New Orleans, Louisiana. November 4-6, 1975

Huq MI: "Culture collection in a medical microbiology laboratory." 3rd International Conference on Culture Collection. Bombay, India. March 14-18, 1976

Khan AR and Huber DH: "Household contraceptive distribution in rural Bangladesh, six months experience." Battellee Workshop, Household Availability of Contraceptives. Manila, June 7-10, 1976

Khan MU and Curlin GT: "Urban cholera epidemic, Dacca, 1974." U.S.-Japan Cooperative Medical Science Program. New Orleans, Louisiana, November 4-6, 1975

Khan MU: "Urban cholera epidemic, Dacca, 1974." Annual Meeting of Bangladesh Medical Association, Dacca. December, 1975

Palmer DL, Koster FT, Islam AFMR, Rahman ASMM and Sack RB: "Comparison of sucrose and glucose in the oral electrolyte therapy of cholera and other severe diarrhea." U.S.-Japan Cooperative Medical Science Program. New Orleans, Louisiana, November 4-6, 1975

Rahaman MM and Aziz KMS: "Ecology of famine." American Association for the Advancement of Science. Boston, February 18-24, 1976

Rahaman MM, McLaughlin JC and Aziz KMS: "Antibiotic susceptibility of Shigella isolated in Dacca and the recommended treatment of dysentery." Annual Meeting of the Pediatric Society of Bangladesh. Dacca. February, 1976

Ryder RW, Sack DA, McLaughlin JC, Chakraborty J, Kapikian AZ, Wells J, Rahman ASMM and Merson MH: "Enterotoxigenic Escherichia coli and reovirus-like agent in rural Bangladesh." U.S.-Japan Cooperative Medical Science Program. New Orleans, Louisiana, November 4-6, 1975

Sack DA, McLaughlin JC and Sack RB: "Enterotoxigenic E.coli at a Cholera hospital." 15th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C., October, 1975