

CHOLERA RESEARCH LABORATORY

Director's Report of Laboratory Operations

At the time of the last Technical Committee Meeting it was reported that the Cholera Research Laboratory's Dacca hospital had experienced the largest epidemic in its history in the fall of 1974 and that on October 18 admissions reached 186 with five hospital tents in operation. Although the 1974 epidemic declined from a maximum of 2,682 cases in October to a minimum of 14 cases in January, the numbers immediately began to climb again to produce a continuing situation that culminated once more in an epidemic peak of 1,307 proven cholera cases in the month of October 1975 after which it fell to a current low of 13 cases in January 1976. Table I provides a comparison of the first six months of Fiscal '76 with the corresponding period of Fiscal '75. The peak of the epidemic once more came in October, whereas in all years previous to 1974 the epidemic was four to six weeks later. The Matlab hospital showed the same trend. We do not know the reason for this, but it is interesting that many of the common hypotheses explaining the 1974 epidemic (flooding, very poor nutrition, the occurrence of bustees, etc.) were not nearly as notable in the period of the 1975 epidemic. Apparently the factors involved in the magnitude and seasonality of cholera epidemics are still undetermined. The 1975 epidemic was the second largest in the history of the Dacca hospital.

As will be noted in the attached table, the number of outpatients continues to be very high even during periods when cholera is not a major problem. Handling this number of patients required larger amounts of space than were available in the OPD area of the hospital, and as a result OPD activities have been moved to tents erected over cement flooring slabs. This is working well, but a more permanent type of structure is required.

On the basis of two years' experience with major cholera epidemics, increased OPD attendance, and increased numbers of inpatients, it was obvious that hospital service activities were obstructing opportunities for clinical research. Therefore, a ward area designated exclusively for clinical research patients has been established, and although research patients may occupy areas in other wards, general service patients will not be permitted in the 12-bed research ward. If plans for increasing the number of clinical research physicians can be accomplished, the clinical research ward will be moved to the old OPD location which will permit the use of approximately 18 beds. The research ward in its present location is working out very well with only Dr. Koster and Dr. Rahaman carrying on clinical protocols. One Bengali physician and one senior staff nurse have been assigned to this area as their major responsibility. Dr. Robert Gilman has just arrived with the Hopkins-CMR group and will be involved in clinical research in this area. Additional supporting personnel will be provided.

During this past year the Ministry of Health of the Government of Bangladesh requested the Cholera Research Laboratory to prepare a manual on the treatment of diarrheal disease including cholera that would be suitable for use by physicians and paramedical personnel in field-type treatment center activities. It was prepared through the cooperation of Drs. Mujibur Rahaman, Alam and Miznur Rahman. This manual was based on the assumptions that laboratory facilities would not be available and that maximum use should be made of the oral hydration method. Both the English and Bengali versions of the manual have now been turned over to the government, and it is stated that they plan to distribute it extensively.

The Project Agreement under which the Cholera Research Laboratory is authorized specifies that the Laboratory shall have a Clinical Experimentation Committee consisting of outside physicians and laymen to review all protocols involving use of human subjects for safety and ethical propriety. Efforts to establish such a committee became complicated by the fact that the Government of Bangladesh had assigned these responsibilities to a Review Committee of the Bangladesh Medical Research Council (BMRC) composed entirely of physicians. After lengthy negotiations the BMRC has agreed that their Review Committee will include certain additional people in their deliberations on any protocols from the Cholera Research Laboratory. Below are listed, first, the members of the BMRC Review Committee and, secondly, the additional people that will be included in CRL protocol review.

BMRC Review Committee

1. Dr. Nurul Islam (Chairman) - Director, Institute of Post Graduate Medicine & Research, Dacca
2. Dr. K. Ahmed - Professor of Pharmacology, Institute of Post Graduate Medicine & Research, Dacca
3. Dr. M. Mujibur Rahaman - Head, Clinical Division, CRL, Dacca
4. Dr. Atiqur Rahman Khan - Project Director, National Post Partum & Family Planning Programme, Dacca
5. Dr. Nurul Hoque - Professor of Pathology, Sylhet Medical College, Sylhet
6. Dr. A. Q. Khan - Secretary, Bangladesh Medical Research Council, Dacca

Others

7. Dr. Kamaluddin Ahmed - Head, Nutrition Department, Dacca University, Dacca
8. Dr. A. Samad - Director, Institute of Statistical Research & Training, Dacca University, Dacca
9. Rev. Fr. Richard W. Timm - Director, Christian Organization for Relief and Rehabilitation, Dacca
10. Dr. Ronald J. Garst - Project Director, Suhrawardy Hospital Complex, Dacca

This group now seems to meet the intent of the Clinical Experimentation Committee established in the Project Agreement and has been recommended

by the Director of CRL to the Director of the National Institute of Allergy and Infectious Diseases for his approval. If this is obtained, the final steps towards establishing this committee as the Clinical Investigation Committee for CRL will be completed.

Although the individual research projects are summarized in another portion of the material that is being supplied, the 1975 Report of the Technical Committee asks for a review of research policy and accomplishment. I think that it is appropriate at this point to discuss the Director's concept of research accomplishment, problems and policy as he conceives it for CRL.

In the period before independence CRL was faced with a whole area of problems where the answers were largely unknown. These included cholera and all of the other diarrheal diseases. The initial emphasis was properly placed upon cholera, and with a liberal supply of American-trained scientific personnel, who ranged between bright and brilliant, basic problems were attacked in the pathophysiology of cholera and other diarrheal diseases in the epidemiology of cholera as it was conceived to be at that time and in the basic evaluation of cholera vaccine. This era provided outstanding basic advances in cholera and other diarrheal diseases and laid the foundations for the .4% hospital-treated mortality that has now been repeatedly demonstrated. In the Director's opinion between the basic research of CRL and that carried on in the United States most of the unknowns concerning cholera in regard to hospital and treatment center therapy have been solved. Two areas of basic knowledge concerning cholera yet remain unsettled. One relates to immunity that would be amplified over plain vaccine immunization and the immunity produced by the disease itself. This is probably a subject that is better studied in the developed countries, and CRL should provide the ultimate testing of whatever immunizing agents may be developed. The other is in the area of cholera epidemiology. Evidence is now suggesting that we may have been too anxious to generalize from Snow's experience with the London pump to a conclusion that cholera organisms in water are the direct means whereby infection is produced. More recent information concerning the requirements for infection of human volunteers and the experience amassed over more than 10 years with patient attendants at the Cholera Research Laboratory raise serious questions concerning the source of the dose of cholera organisms entering the mouth of a person who becomes infected. It should be pointed out that in 1963, 1964 and 1965 similar questions were raised, but the investigations of cholera epidemiology were submerged and eventually discontinued both because of preoccupation with epidemiology essential to vaccine trials and the lack of technical methods for the quantitation of small numbers of cholera organisms. During the past year, between other problems, Dr. McLaughlin and the Microbiology Branch have made good progress in the development of the technical methods that are required for quantitation of small numbers of cholera organisms. As a result, true epidemiological studies are now in their early stages. This will include not only the study of water but also food and fomites in both rural and urban areas.

A third problem relating not only to cholera but to other diarrheal diseases is a critical requirement, that if the excellent basic research on cholera therapy is to have much significance in Bangladesh and other less developed countries, there must be ways of bringing therapy to the people who need it. The philosophy of the use of treatment centers has dominated the previous thinking of CRL and still dominates the thinking of the World Health Organization. It may be valid for certain less developed countries. It is not valid for Bangladesh where it is abundantly clear from two successive cholera epidemics that government treatment centers are inadequate in number and staffing to meet the demand. Though not the perfect answer, unsupervised oral hydration therapy appears to offer the possibilities of some therapy in locations where there would otherwise be no therapy available. Programs are in progress to develop a salts-glucose mixture with a flavor, color and preservative, to select a suitably rugged container and to develop simplified instructions for use.

Though cholera is the glamorized killer disease, it is not responsible for the majority of debility or mortality produced by diarrheal diseases in less developed countries. Although precise figures are not known on the basis of laboratory cultures, there is excellent reason for believing that in recent years shigellosis (both Shigella dysenteriae Type 1 and Shigella flexneri) has become the major single diarrheal disease responsible for the largest amount of morbidity and mortality. In Dacca, Matlab and Teknaf, which sample three very diverse populations in Bangladesh, cholera plus shigellosis account for no more than 50% of the diarrheal morbidity that comes to medical attention. At present, although the mortality of treated cholera is less than .4%, that of hospitalized shigellosis exceeds 8%, and the mortality of other hospitalized diarrheal disease exceeds 3%. There is clearly the need for improved treatment of shigellosis and a need to develop means for controlling these lesser-known diarrheal diseases. At the present time the Cholera Research Laboratory, though much hampered by the lack of clinical research physicians, is attempting to develop means for lessening shigellosis mortality and improving shigellosis therapy. Although the research on leukemoid reactions is scientifically interesting and may result in lessened mortality where sophisticated hospital therapy can be used, CRL has not yet faced the more basic question of how to improve the morbidity and mortality situation by therapy that may be used in the field. Research by Drs. Koster, Rahaman and McLaughlin have recently revealed specific shortcomings in shigellosis chemotherapy that may be correctible if advantage is taken of our present knowledge of chemotherapy mechanisms.

Not only is the treatment of shigellosis unsatisfactory, but little is known of its epidemiology in areas like rural Bangladesh. Studies made in other areas have suggested food and personal contact as the main transmission routes, and, unlike cholera, relatively few organisms will initiate infection. The rather sketchy epidemiology which was done at the time of the St. Martin's epidemic suggested a major role

for water in the transmission of this disease. More systematic epidemiological data from the Teknaf project also appears to be implicating tanks as involved in shigella transmission. Just as it may be that water has been overrated in cholera transmission, it may be underrated in the transmission of shigellosis. While a fresh hard look at the epidemiology of cholera is still the highest epidemiological priority in the diarrheal disease field, CRL is beginning to extend its epidemiological investigation to shigellosis.

The role of water, particularly drinking water, is a recurrent theme in the epidemiology of fecal-oral diseases. This is undoubtedly justified. However, the situations differ in different settings, and the possible fallacy of assuming a pre-empting importance for drinking water may be becoming apparent in the studies being carried on in Matlab concerning tubewells. It has been thought that the provision of pure drinking water through the construction of tubewells could not help but have a favorable influence on health and diarrheal disease. Large sums of money have been spent on this assumption. In Matlab at least, this favorable effect cannot be demonstrated under circumstances where other water sources are available and used for other household purposes. It would appear that other routes of transmission of diarrheal disease are of so much greater importance that the role of drinking water becomes insignificant.

In regard to diarrheas caused by agents other than cholera, shigella and salmonella, those caused by toxigenic E. coli are now well recognized. Rather intensive work on toxigenic E. coli infection has been going on at CRL for at least the last two years. This represents a major attempt of this Laboratory to make inroads into the area of so-called diarrheas of unknown etiology. The nature of the coli enterotoxins is being investigated in numerous laboratories, and therefore it has been considered that such work is not a proper subject for CRL research. However, since this Laboratory has large numbers of diarrheal cases, means of diagnosis and epidemiology have been explored in some detail. It is now clear that this type of infection accounts for a significant proportion of diarrheal disease, mostly in adults, but it will not be known for some time whether these infections are epidemic in nature or constitute a continuing baseline of diarrhea throughout the year. In these studies it is of significance that diarrheas were detected which on the basis of both electron microscopy and acute and convalescent serological studies appear to be caused by a reo-virus like agent. Thus, another etiology operative in Bangladesh has been uncovered. Further work along these lines is planned by Dr. Gilman, a guest investigator from the Hopkins-CMR.

Following the basic philosophy of attempting to bring the fruits of scientific research within the reach of persons of lesser financial and social advantages, CRL has encouraged re-investigation of the question of whether sucrose could replace glucose in anti-diarrheal oral therapy solutions and cooperated with the World Health Organization on a trial of a low-sodium, glucose-containing intravenous rehydration solution,

which it was hoped might become a "universal solution" for rehydration of both children and adults. While there may still be extensive discussion of the point, the studies done by Dr. Palmer and his associates demonstrated that with severely purging patients the failure rates of oral solutions containing glucose or sucrose were insignificantly different and related more to the degree of purging than to any other factor that was analyzed. Since in many parts of the world sucrose is inexpensive and available, whereas glucose is not, these studies may extend the use of oral rehydration into areas where it heretofore has not been practical. The studies of the low-sodium glucose-containing I.V. solution in comparison to the CRL formula revealed deficiencies in both solutions if they are to be considered as "universal solutions". These studies suggest the desirability of the higher sodium content of the CRL solution and the desirability of glucose at even a higher concentration than in the W.H.O. experimental formula.

It has been recognized for a long time that the Cholera Research Laboratory had potential for scientific research well beyond the area of diarrheal disease. The two areas of greatest significance, both in Bangladesh and in other developing countries, are nutrition and population control. In the opinion of the Director, although a few forays have been made into the area of nutrition, CRL has not yet developed much in the way of a unique and constructive approach to malnutrition. The Meharan growth studies are potentially valuable in describing the growth and development pattern of rural Bangladesh children and thus providing a baseline for future studies of a more interventional character. They also relate the occurrence of febrile and diarrheal diseases to development. In addition, a happenstance occurrence in the Teknaf area involving a Burmese refugee camp demonstrated that nutrition can be improved in pockets of starvation by local purchase rather than the slow and expensive importation of food which appears to be the common relief practice under such conditions. In addition to these, some systematic work has gone on attempting to relate the occurrence of anergy to nutritional status as measured primarily by anthropometric methods. While there are undeniable opportunities for a variety of descriptive programs and programs that will test the relationship between various aspects of malnutrition to diarrheal disease, it is felt that considerably more thinking and planning are necessary in this area than has been accomplished so far.

The situation is quite different, however, in regard to work in demographic and population control studies. Here the Laboratory has two very well defined programs that have been selected because of the unique properties of the Matlab F.S.A. One is the testing of the theory that area saturation with contraceptives (primarily pills) would be adequate to exploit the natural demand for contraception to an extent that this procedure would have a significant favorable affect upon birthrate. This program is being supported by a research contract with AID and required a considerable amount of field staff effort from July to December to obtain the initial information and to carry on the initial instruction and distribution. This was well accomplished under the direction of Dr. Huber, and from January on the program will become

rather routine with the exception of periodic surveys to monitor changes in usage. This study demonstrated for the first time that the pyramidal supervision system beginning with the dais could not only transmit information from a family up to the computerized data bank, but could also transmit education and materials downward to the family.

The other population study is a clearly defined effort to quantitate the effect of breastfeeding on the period of puerperal infertility and the nutritional state of the babies. This is a baseline study in preparation for an interventional program to be carried out in association with Drs. Mosley and Tyson of Johns Hopkins wherein lactational hormone pills will be tested for their ability to enhance and prolong lactation, thus increasing the period of puerperal infertility and simultaneously improving infant nutrition.

It should be noted that the major organizational effort for both of these population programs is being accomplished during a period of time when cholera immunization field trials are not underway. Therefore, the initiation of these programs has not interfered with the capability of CRL to carry on immunization field trials and has permitted the introduction of a new and useful type of research during a period when the field staff would have otherwise been under-occupied. Now that the basic organization for these studies has been completed it is not expected that they will interfere with immunization field trial capability in the future. It is a source of some concern that cholera immunization field trials were not carried on last year and will not be performed this year. The availability of material for field trial use is not within the control of CRL, but it is hoped that the U.S. Cholera Panel will be able to provide materials for CRL study so that this program will not be interrupted for very long. It is important to keep a certain momentum going in a program of this sort.

The comments above provide a brief resume of the research situation at CRL at present. The situation in regard to the recruitment of scientific investigators is of major importance to the ability of CRL to conduct research. This past year has been fraught with frustrations in this area. Both the Technical Committee and the Director have agreed that the recruitment of additional clinically-oriented research physicians is essential for the revitalization of the clinical research program. In spite of intensive efforts at recruitment carried on by the Director and others it has not been possible to interest any suitable clinicians. Also, efforts are being made to recruit a microbiologist to replace Dr. McLaughlin at the end of his tenure this coming August.

Recruitment difficulties seem to be based upon three things: first, the lack of machinery for recruitment in the United States and other developed countries; secondly, the "poor press" that Bangladesh has received concerning its poverty and its political instability; and third, by the difficulty envisioned by candidates in obtaining a suitable position at the conclusion of their stay in Bangladesh. This latter

factor has turned out to be the critical one in causing two research clinicians to opt for appointment by way of the Hopkins-CMR rather than CRL since the CMR guarantees a person one year of employment at Hopkins at the conclusion of his stay in Bangladesh. Approaches have been made to the National Institutes of Health concerning the possibility of a guarantee of one year's employment at NIH at the conclusion of duty in CRL. With the turnover that an organization like NIH has this would cost them nothing either in money or "job slots" and would assist CRL tremendously.

Although difficulties with recruiting in the United States are very serious, it is a pleasure to report that the Overseas Development Ministry of the United Kingdom has agreed to attempt to recruit (and is willing to support) a research-oriented British physician and a bio-chemist for deputation to CRL, if so requested by the Government of Bangladesh. This request is now in the hands of U.K. representatives. Here again, however, recruiting is expected to be difficult.

While little is yet known of the details, Dr. Rowley has indicated that the University of Adelaide may have support adequate to permit him to have a member of his staff at CRL at least part of the time. Several other approaches to recruitment are also being made.

During this past year consideration was begun concerning the long-range future of the Cholera Research Laboratory. The present Project Agreement terminates 30 June 1977 and calls for the initiation of negotiations concerning extension to begin 1 July 1976. USAID is concerned over its large share in supporting a costly enterprise such as CRL, and in cooperation with the National Institute for Allergy and Infectious Diseases, conducted a meeting on 31 October 1975 to acquaint other potential donors with the research possibilities of CRL. At that time they requested the Director to formulate a five-year research program in considerable detail. This program is still under formulation, and it is hoped that the Technical Committee and its consultants will be willing to provide constructive assistance in reviewing and improving this plan.

Date

3/2/76

M. H. Newbury

Director

TABLE 1

Month	Outpatient Visits			Cholera			Deaths					
							Shigella			Other		
	Dacca	Matlab	Total	Dacca	Matlab		Dacca	Matlab	Total	Dacca	Matlab	Total
July '74	3580	846	4426	36	145		-	3		14	2	16
Aug. '74	4403	1234	5637	186	117		-	3		14	3	17
Sept. '74	4599	914	5513	986	432		2	6		12	2	14
Oct. '74	4990	600	5590	2682	727		-	4		20	1	21
Nov. '74	4649	378	5027	945	205		-	13		28	4	32
Dec. '74	4812	478	5290	251	92		-	8		22	-	22
Jan. '75	4204	621	4825	14	43		-	9		17	3	20
Totals	31237	5071	36308	5100	1761		2	46		127	15	142
July '75	5490	531	6021	150	32		1	6		15	-	15
Aug. '75	4680	515	5195	223	32		-	7		18	-	18
Sept. '75	4479	504	4983	732	194		1	8		19	-	19
Oct. '75	5004	635	5639	1307	404		1	6		8	3	11
Nov. '75	3515	435	3950	472	129		1	7		14	2	16
Dec. '75	4174	488	4662	99	24		-	8		11	1	12
Jan. '76	3708	454	4162	13	-		-	3		7	2	9
Totals	31050	3562	34611	2996	815		4	45		92	8	100