

REPORT OF THE  
INTERNATIONAL SCIENTIFIC REVIEW MEETING  
CHOLERA RESEARCH LABORATORY  
DACCA, BANGLADESH  
FEBRUARY 6-14, 1978

Cholera Research Laboratory  
GPO Box 128  
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## SUMMARY OF MAJOR RECOMMENDATIONS

An International Scientific Review Meeting was held in Dacca, Bangladesh, from February 6 through 14 to review the scientific activities and competence of the Cholera Research Laboratory and make recommendations for the future. Twenty-six scientists participated in this meeting (Appendix 1). Some of the major recommendations are abstracted below:-

1. The meeting recommends the internationalization of the CRL and the new institution be called the International Center for Diarrheal Disease Research (ICDDR). This recommendation is made in recognition of the fact that diarrheal diseases constitute a major world health problem and there is a need for an international institution which addresses this problem (V.1).
2. The principal objective of the International Center would be governed by a concern for improving health of the community. The preoccupation with diarrheal disease prevention and control implies the necessity to identify determinants of diarrheal disease distribution in the community, besides undertaking clinical and laboratory research, and should also include the development of appropriate technologies of intervention for prevention and control and <sup>their</sup> testing in community situations (V.4).
3. Another important objective of the Center would be to provide training to Bangladeshi and other nationals in the areas of its activities and competence in collaboration with national, regional and international organizations (V.5).
4. It is important that the Center's research agenda be problem-orientated and address problems of priority and does so in a manner that is most likely to develop applicable interventions with reasonable prospect of success. This could be achieved by designing studies with the involvement of health service implementors. Furthermore, to ensure this orientation on a continuing basis, the meeting advises that individuals known for their social responsibilities and concerns be included on the scientific review committees and co-ordinating committees (V.6).
5. The meeting agreed that research in diarrheal diseases, in the broadest sense, should be of paramount importance in the proposed International Center. Past and current work in this area has been outstanding in regard to scientific quality and applicability to health problems in Bangladesh and other developing countries. Current and proposed research programs in this area offer the prospect of defining the etiology, pathophysiology and treatment of virtually all acute diarrheal illnesses. The results of such research will be directly applicable to a major health problem in Bangladesh and in other developing countries (IV.1.2).

6. The meeting favours biological and demographic population studies at the Center provided they are relevant to diarrheal diseases and related health problems. The meeting recognizes the demographic data now available and yet to be collected are unique. A great deal of information of both practical and theoretical importance is available from this source and the meeting endorses continuation of this activity. It recommends that more social data be gathered and that the data be made available to other institutions in Bangladesh and in other countries, to permit full utilization of this unique resource (IV.2.7 and IV.2.2).

7. The meeting recommends that the International Center address itself to the study of diarrheal diseases as they relate to food and nutrition. Relevant factors include food availability and food consumption at the household level, food utilization and the nutritional status. Studies should also examine the reduction of nutrient energy intake associated with diarrhea and, for instance, the economic and/or productivity effects of temporary disability due to diarrheal disease. Also, the effect of diarrhea on food utilization, nutrient loss, nutrient diversion, or nutrient wastage deserves investigation (IV.3.4 and IV.3.5).

8. The meeting generally agreed that the results of scientific research should be developed to the point that they could be used by health professionals and by the public. At the point where interventions become practical and applicable, a strong effort should be made to help local agencies to use such information effectively. The Center should aim to produce effective interventions together with a methodology for their introduction, evaluation, and incorporation into the local health care service (IV.4.2 and IV.4.4).

9. In establishing the Center there are several special considerations such as the possibility of the Center drawing away local talent from national centers. This may be guarded against by the development of positive and mutually collaborative partnerships between the Center and local institutions so that a spirit of complementarity prevails and local initiatives and capabilities are facilitated by the Center's presence. There are several ways by which these complementary relationships may be established, some of these are: full exchange of information, secondment of research and teaching staff, joint research undertakings, contractual research by national institutions, sharing of equipment, facilities and personnel. In addition, a joint committee representing the Center and local institutions for program co-ordination in Bangladesh could continuously monitor the program and projects and recommend necessary adjustments and suggest specific collaborative arrangements (V.8 and V.9).

## I BACKGROUND: THE CHOLERA RESEARCH LABORATORY

- I.1 The Cholera Research Laboratory (CRL) was established in Dacca in 1960 by joint agreement between the Governments of Pakistan and the United States Agency for International Development (USAID), and was the executing agency of a cholera research program sponsored by SEATO. Following the war of Bangladesh Independence in 1971, a new agreement was negotiated between the Government of Bangladesh and USAID and signed in 1974. This agreement will expire in September, 1978, and USAID funds under the present agreement will run out in December, 1978.
- I.2 The CRL facility in Dacca is located within the Institute of Public Health complex. It comprises laboratories, a small hospital and out-patient treatment center, a library, a data processing center, animal house, administrative offices and a workshop. In addition, the CRL has operated the Matlab Field Research Station and field hospital since 1963, and the Teknaf Field Research Station and field laboratory since 1974. The population in both field research areas has been maintained under demographic surveillance, and under disease surveillance for a number of field research programs.
- I.3 Initially orientated to cholera research in all its aspects, the CRL has more recently turned its research focus and expertise towards other diarrheal diseases, and through its population data base towards population dynamics, fertility and nutrition.
- I.4 The CRL has a number of research programs which are health services research projects (in the sense of the experimental provision of health services) or have a significant component of the activities in this field, e.g.
- Cholera and diarrheal disease treatment at CRL.
  - Matlab family planning program.
  - Teknaf water supply and sanitation program.
  - Teknaf shigella surveillance project.
  - Development and testing of simple oral electrolytes for home use.
- I.5 There is no doubt as to CRL's high international reputation in the field of cholera research, or that the

CRL is now establishing a similarly high reputation with respect to research into other important diarrheal diseases, and its more recent research interests including population and family planning, and environmental sanitation projects.

I.6 With the expiry of the existing agreement, the United States and Bangladesh Governments have proposed the reorganization of the CRL as an international center. A Subcommittee on Internationalization, jointly sponsored by the Government of Bangladesh and the CRL, has taken the opportunity to invite representatives of international agencies to consider its reorganization, and now seeks scientific opinion on its research objectives, emphasis, and relationships with other institutions in Bangladesh and elsewhere. At the same time, the CRL has experienced conflicts of direction and emphasis among its staff and potential conflicts with the development of other institutes in Bangladesh. There has been some public criticism of the CRL's role in health research and training, with accusations that the CRL by its very presence is retarding health research and development in Bangladesh. Although matters of opinion, the CRL has taken these criticisms seriously enough to invite views on their validity.

I.7 A preliminary informal meeting with representatives of potential donor agencies, and others, was held in December, 1977, to review a draft charter and a draft prospectus for the proposed Center.

I.8 The meeting which is the subject of the present report was convened by the CRL to review the scientific activities and competence of the CRL and make recommendations for the future.

## II BACKGROUND: HEALTH IN BANGLADESH

II.1 The health situation in which CRL now operates, and proposes to continue to operate as an international center, requires a brief outline to provide a perspective for the body of this report.

II.2 The population of Bangladesh is approximately 80 million, with a density around 1400 per square mile, the highest figure for a predominantly rural country. Only 8% live in urban centers of 5000 people or more. Annual per capita income is under US \$ 100, and per-capita expenditure on health (from revenue) is around 50%.

II.3 Availability of trained medical manpower such as doctors and auxiliaries (nurses) is not satisfactory to

meet the requirements of the country, especially in the rural areas. Other facilities such as hospital beds are not enough to meet the need. Organized health care services are being developed with the target to eventually provide a health center and attached auxiliary staff for each 20,000 population.

II.4 The ten leading causes of death (from a localized survey in 1976), and their rates per 100,000 population, as per Companiganj project in Noakhali district, have been estimated as:-

|                                 |     |
|---------------------------------|-----|
| Diarrheal disease               | 412 |
| Pneumonia                       | 282 |
| Measles (epidemic year)         | 131 |
| Birth injury, prematurity, etc. | 113 |
| Malnutrition                    | 84  |
| Tetanus                         | 84  |
| Stroke                          | 75  |
| Fever                           | 66  |
| Senility                        | 56  |

II.5

|                       |                          |
|-----------------------|--------------------------|
| Crude birth rate      | 46 per 1000              |
| Crude death rate      | 18 per 1000              |
| Natural increase rate | 2.8%                     |
| Infant mortality      | 140 per 1000 live births |
| Maternal mortality    | 6 per 1000 live births   |

II.6 To further complicate this picture, the country is generally deficient in communications and rapid transport links, and suffers from recurrent natural catastrophes such as famine, flood, and cyclone.

### III REVIEW METHODS

III.1 The objectives of the Review Meeting were:-

- a) To critically review the current scientific program of the CRL.
- b) To examine the rationale for the transformation of the CRL into an International Center for Health Research (ICHR).
- c) To review the proposed objectives for the ICHR.
- d) To provide guidelines for the balanced development of a scientific program of the ICHR to meet these objectives.
- e) To recommend requirements for scientific staff and institutional resources to fulfill the proposed objectives of the ICHR.

III.2 The Review Meeting was held at Dacca, Bangladesh, 6-14 February, 1978.

III.3 The Review Meeting had as participants 26 scientists from fifteen countries and was also attended by all available senior staff of CPL. Participants are listed in Appendix I.

III.4 Background material provided to participants before and during the Review Meeting is listed in Appendix II.

III.5 On the first two days of the meeting, February 6 and 7, summaries of general reports and research programs were presented by CPL staff, and clarified or amplified as necessary. This period included short visits to a recurring cholera focus across the Buri Ganga river at Keraniganj served by a Terres Des Hommes Health Center and to Dacca Medical College and Shishu hospitals.

III.6 On February 8 and 9, participants divided into three groups:-

Group 1 - Discussion of Diarrheal Disease Program and visit to Matlab Field Research Station, Matlab Thana, Comilla District.

Group 2 - Discussion of Population Studies Program, discussion of organizational aspects and visit to Matlab as above.

Group 3 - Visit to Teknaf Field Research Station, Teknaf Thana, Chittagong District.

III.7 On February 10, Groups 1 to 3 reported and discussed their observations and conclusions at a plenary meeting. Participants then reconvened as five small groups to consider and make recommendations on:-

- a) Training and Outreach Activities.--
- b) Administration.
- c) Demographic Data Processing.
- d) Nutrition Studies.
- e) Organization and Structure.

III.8 These and earlier reports were discussed and drafted as the final report on February 11, 12 and 13.

#### IV RECOMMENDATIONS

##### IV.1 DIARRHEAL DISEASE RESEARCH

IV.1.1 In reviewing the current and proposed scientific programs, the following considerations were used as guidelines in determining recommendations:-

- a) Applicability to health problems in Bangladesh and other developing countries.
- b) Scientific quality.
- c) Involvement with local institutions in project planning, execution and evaluation.

IV.1.2 The meeting agreed that research in diarrheal diseases, in the broadest sense, should be of paramount importance in the proposed International Center. Past and current work in this area has been outstanding in regard to scientific quality and applicability to health problems in Bangladesh and other developing countries. Current and proposed research programs in this area offer the prospect of defining the etiology, pathophysiology and treatment of virtually all acute diarrheal illnesses. The results of such research will be directly applicable to a major health problem in Bangladesh and in other developing countries. Critical reviews of proposed scientific objectives in five major areas are as follows:-

##### IV.1.3 Clinical Studies

IV.1.3.1 The proposed International Center (IC) has a unique opportunity to define the clinical aspects, pathophysiology mechanisms and therapeutic requirements in acute non-cholera diarrheas including those caused by rotavirus, NAG vibrios, NAG parahemolyticus vibrios, ST producing E. coli, and shigella. These agents together with V. cholerae are responsible for the vast majority of acute watery diarrheal illness both in Bangladesh and in other developing countries. The meeting emphasizes that such studies provide the background for more precise etiologic diagnosis, effective field treatment, and appropriate environmental control measures for these diseases, without demanding sophisticated and expensive laboratory techniques.

IV.1.3.2 In the area of oral therapy there has been extensive progress made in recent years and there is a clear necessity for a field trial in Bangladesh of oral fluids in diarrheal disease. The particular advantage of CRL for further studies of this type is its centralized

treatment facilities with large numbers of seriously dehydrated children with diarrhea and the strong clinical tradition which will enable the numerous problems which are likely to arise in the widespread use of oral therapy to be decisively investigated. Furthermore, such studies can be related to etiological agents. The defined communities provide an excellent basis for assessing oral therapy in the community and there are several health care delivery systems within which the operational research problems of oral therapy can be fully determined.

IV.1.3.3 The meeting agrees with the current plans to study an even simpler oral rehydration regimen, employing a mixture of water, table salt and brown sugar, under carefully observed conditions, in patients with mild to moderately severe dehydrating diarrhea. Although the usefulness of this solution in the management of diarrhea has not been documented, its potential practical value should receive consideration. The meeting also feels that the effectiveness of the Standard Oral Rehydration Solution (ORS) in children with rotavirus diarrhea should be carefully documented; the results of this evaluation will be of great practical value throughout the world.

IV.1.3.4. The laboratory along with government hospitals and dispensaries is now rendering treatment to acute diarrheal diseases in Dacca and Matlab with a total population of approximately 3.5 million.

#### IV.1.4. Epidemiology

IV.1.4.1 The epidemiologic program has been, and continues to be, outstanding in scientific quality and unique in the observations which it provides. The meeting recommends continuation of the current long-term epidemiologic field studies on rotavirus and enterotoxigenic E. coli infections. The studies offer the unique prospect of defining both the epidemiology and the protective immune mechanisms in these two diarrheal illnesses which, collectively, appear to account for most episodes of childhood diarrhea in many parts of the world.

IV.1.4.2 More generally, work concentrating on the epidemiology and transmission of the enterotoxigenic E. coli and the rotaviruses should comprise studies of people, their behaviour, and the environment. The observations made should also be applicable to behavioural aspects of cholera transmission. These studies are not only valuable in themselves, but should act as a baseline for environmental interventions and their assessment and also for programs to change behaviour. Team work

by an epidemiologist, social anthropologist, environmental engineer, and microbiologist is needed in a limited number of villages so that their studies are closely integrated and compatible for analysis.

IV.1.4.3 The presently proposed epidemiological studies of the toxigenic E. coli and rotaviruses fit well into this program and are endorsed. Complementary behavioural observations and environmental microbiology should be run concurrently with the village studies if at all possible.

IV.1.4.4 Where opportunities present, epidemiological studies carried out in two (or more) locations should be methodologically comparable and, thus, complementary to each other. Environmental alterations to reduce infection transmission should be undertaken as soon as adequate (>1 year) baselines are available. The interventions should usually be low cost changes capable of widespread replication, though occasionally more expensive changes may be needed to test hypotheses efficiently.

IV.1.4.5 Evaluation of interventions should be made in sufficient detail to understand processes involved in success or failure and give a clear guide to improved interventions.

IV.1.4.6 In the past, field work at Matlab has been predominantly descriptive except for the vaccine trials. In the future there should be strong emphasis on a range of interventions studied on a small scale in epidemiological detail. This will require very close co-operation between those with different disciplinary backgrounds and orientations. While the initial aim must be to find effective interventions, they must be developed with due regard for replicability on a large-scale and costed and evaluated with care. This will make heavy demands on the research workers in terms of attitude as well as range of disciplines. They will need to be sensitive to several ways of thinking about disease problems and none is likely to have a complete background in this on arrival at the institute. Consequently, an interdisciplinary working group is central to effective work on the epidemiology of interventions.

IV.1.4.7 The Teknaf area seems suitable for epidemiological studies of diarrheal diseases and related health problems, with an emphasis in surveillance and interventions. A rural field research station has been functioning since 1974. The material and human resources of the station are adequate for epidemiological research and offer great potentialities for expansion of activity

into the area of appropriate rural technology like health interventions. The infrastructure for collection, storage and retrieval of scientific data is excellent. The treatment facilities provide community services which are indispensable to maintain field operations; this activity is supported by a field laboratory. At present, the effort results in the collection of demographic, anthropometric, morbidity, and socio-anthropologic data. These data, particularly those relating to cultural factors, are of potential value for understanding of transmission, control, and prevention of diarrheal disease. More research along this line is justified.

IV.1.4.8 Available information, however, permits the design of intervention strategies that could result in a significant reduction in diarrheal disease transmission. These interventions should meet the following:-

(a) they should be simple; (b) of low cost; (c) taking into consideration beliefs and traditions of the population; (d) they should yield preliminary results within a period of not more than three years; and (e) the rural technology introduced should be self-sustaining. The present experimental design should thus be modified to conform with some of the above specifications. The emphasis of the intervention should be an improvement of sanitary conditions surrounding the child, which calls for an improved maternal knowledge of child-rearing and care. The instruments of the intervention (for instance, latrines, tube-wells) should be carefully installed to ensure their optimal use, thus avoiding pitfalls in the interpretation of the outcome.

#### IV.1.5 Immunology

The meeting strongly endorses the current immunologic studies, and recommends that future immunologic research be guided by the following broad principles:-

- a) The major objectives should more clearly define the local intestinal immune mechanisms and to determine their role, if any, in protection against the acute diarrheal illnesses which are commonly observed in Bangladesh and other developing nations. It is only on the basis of such studies that the development of more effective anti-diarrheal vaccines can be anticipated.

- b) In such studies of local intestinal immune mechanisms, effective collaborative arrangements with scientists in other parts of the world should be established. A great deal of current research in this area requires highly trained research technicians, as well as expensive and highly sophisticated equipment, the duplication of which is neither necessary nor desirable.
- c) It was brought to the notice of the meeting that the CRL is implementing a cholera vaccine field trial under the guidance of the Bangladesh Medical Research Council, the National Institutes of Health (USA) and the Wellcome Laboratories (UK). This meeting recommends that no subsequent major vaccine field trials should be planned until a more thorough understanding of the intestinal immune response to V. cholerae and/or its enterotoxin has been reached. It is felt by the meeting that, on the basis of current information, the best candidate vaccine for future trials may be a combination of subunit toxoid and killed bacteria.

#### IV.1.6

##### Bacteriology

The meeting feels that current and proposed bacteriologic studies are all of sufficient scientific and practical merit that they should be continued. It made the following specific comments:

- a) The current work of polyphasic characterization of V. cholerae, NAG vibrios and related organisms is of great potential practical value, is not apt to be carried out equally well elsewhere, and, therefore, deserves a very high priority. For essentially the same reasons, the proposed work on environmental microbiology deserves major emphasis.
- b) The meeting endorses the concept of developing a facility to study microbial genetics, especially in regard to studies of plasmid transfer among enterobacteriaceae, in Bangladesh. It was felt that the unique opportunities for carrying out such studies in this environment would justify their expense. The meeting recommends, however, that the development of a framework of collaborative arrangements, both with local institutions and with scientists in other countries should precede a major investment in such a facility.

#### IV.1.7

#### Physiological Studies

The meeting recognizes that a particular strength of the CRL has been the ability of its scientists to pursue a problem from the clinical, through the cellular, to the molecular biological level. It is strongly felt that this strength should be preserved in the proposed International Center. Pursuant to this objective, the capacity for carrying out relevant physiological studies must be maintained. The meeting feels that two such studies deserve considerable emphasis at the present time.

- a) The pathogenesis of diarrhea caused by rotavirus is fundamentally different from that due to Vibrio cholerae and enterotoxigenic E. coli. The scientists at CRL are in a unique position to define the pathophysiology of diarrhea caused by rotavirus, and studies should be directed to this goal. The results of such studies could lead to a more effective means of treating this illness which appears, both in Bangladesh and in other developing countries to be the major cause of diarrheal illness in children under two years of age.
- b) The failure of oral rehydration alone in a significant proportion of patients with severe diarrheal disease has pointed to the potential practical value of an antisecretory agent which could be used as an adjunct to oral glucose-electrolyte therapy. The meeting endorses the study of potential adjuvant antisecretory agents in the proposed International Center.

#### IV.1.8

#### Conclusion

The proposed Center has a unique opportunity to provide the background knowledge for vaccination, control and treatment of diarrheal diseases in the world. With the development of effective collaborative arrangements, locally, nationally and internationally, this goal should be achieved.

#### IV.2

#### POPULATION STUDIES

##### IV.2.1

In reviewing the various protocols, the following conditions were used in deriving recommendations:-

- a) relevance to diarrheal diseases and related topics;
- b) applicability to health problems in Bangladesh and other developing countries.

c) early and thorough involvement with local institutions in project planning and execution; and

d) scientific quality.

#### IV.2.2 Demographic Surveillance

The meeting recognizes the demographic data now available and yet to be collected, are unique. A great deal of information of both practical and theoretical importance is available from this source and the meeting endorses continuation of this activity. It recommends that more social data be gathered and that the data be made available to other institutions in Bangladesh and in other countries, to permit full utilization of this unique resource.

#### IV.2.3 Determinants of Natural Fertility

The meeting notes that this study has so far produced useful information with regard to biological factors associated with natural fertility. It considers that a household survey of the study area (fourteen villages) would be desirable in order to establish the level of natural fertility to provide a bench mark for the national family planning program. The meeting recommends close co-operation between the Center and the Bangladesh Institute of Development Studies, the National Institute of Population Research and Training, the Ministry of Health and Family Planning etc. in the analysis of these and other demographic data.

#### IV.2.4 The Contraceptive Distribution Project

Full consensus was not obtained on this work in that some members generally endorsed it as written whereas the majority recommended that the project design be altered to concentrate on monitoring the effect of improved maternal and child mortality. The majority also felt that this study should be co-ordinated with the national family planning program now underway through co-operation with the National Institute of Population Research and Training, and the Ministry of Health and Family Planning, and be concordant with the government policy of integrating family planning with other health services.

#### IV.2.5 Reproductive Endocrinology

IV.2.5.1 The meeting believed that the proposed work, although not strictly within the mandate of the Center as defined,

is of great importance and would throw light on several aspects of reproductive biology largely unattended to so far, particularly as applied to developing countries.

IV.2.5.2 The project involves, however, the establishment of an entirely new and complex laboratory capability in reproductive endocrinology with staff and equipment, and would by its very nature be of long-term duration. It is, therefore, strongly recommended that the protocol and project requirements be planned and developed jointly with the endocrinologists at the National Institute of Diabetic, Metabolic and Endocrinological Diseases with a view to basing this project in the latter Institute, and thereby augmenting the Institute's staff and equipment. Such an arrangement would ensure pooling of resources and ensure long-term continuity of reproductive endocrinology in the country.

#### IV.2.6 Sex Socialization and Fertility Behaviour

The meeting endorses the interesting anthropological study on this topic, and suggests the inclusion of attitudes on population problems in the survey. The meeting recommends expansion of the Center's behavioural sciences program through increased staff and collaboration with other institutions.

#### IV.2.7 Conclusions

The meeting favours biological and demographic population studies at the Center provided that they are relevant to diarrheal diseases and related health problems.

#### IV.3 NUTRITION

IV.3.1 Many intestinal infectious agents induce acute diarrhea and dysentery which may lead to malabsorption. Such events are responsible for the following abnormalities: vomiting, anorexia, fluid and tissue loss, nutrient depletion, food wastage and nutrient diversion.

IV.3.2 It is apparent that some of these physiological alterations can also occur with certain asymptomatic or sub-clinical infections. In any event, the abnormalities are important contributors to the causation of malnutrition.

IV.3.3 Epidemiological observations in several countries suggest that a reduction in incidence of intestinal infection and diarrheal disease may lead to better nutrition and growth and to lower childhood mortality.

IV.3.4 The meeting recommends that the International Center address itself to the study of diarrheal diseases as they relate to food and nutrition. Relevant factors include food availability and food consumption at the household level, food utilization, and the nutritional status.

IV.3.5 Studies should also examine the reduction of nutrient energy intake associated with diarrhea and, for instance, the economic and/or productivity effects of temporary disability due to diarrheal disease. Also, the effect of diarrhea on food utilization, nutrient loss, nutrient diversion, or nutrient wastage deserves investigation.

IV.3.6 Research should also be carried out on the relationship of host factors, primarily nutrition and immunity, to the outcome of intestinal infection. Furthermore, investigations must be conducted on the effect that various agents of diarrhea might have on particular deficiencies or on the overall nutrition and growth of children.

IV.3.7 A primary goal of studies on etiology and pathogenesis of malnutrition is to know better the contribution of intestinal infection in order to give the appropriate priority for problem solving. In this regard, operational and evaluation research focusing on control and prevention should include monitoring the nutritional state. Intervention studies aiming at a reducing of diarrheal disease in the community should attempt to measure overall improvement in:-

- a) maternal and fetal malnutrition;
- b) childhood mortality;
- c) nutritional status (food intake, hematologic parameters, clinical signs);
- d) growth and development; and
- e) immunologic competence.

IV.3.8 The role of nutrition in host resistance to enteric infection is often emphasized. An improvement of the nutritional status could lead to an increased capacity to cope with diarrheal disease and could lower duration of disease and mortality due to diarrhea. Intervention studies in the field of nutrition, if made, must contemplate monitoring of incidence, natural history and outcome of diarrheal disease.

IV.3.9 The meeting recommends that nutritional studies focus in particular upon maternal and fetal malnutrition, and breast-feeding<sup>and weaning</sup> practices. In this regard, health services research should be carried out to develop the appropriate technologies required to improve child feeding practices, child care, early home rehydration, personal and environmental sanitation, and other relevant factors that will lead to an improved nutrition and host resistance.

IV.4 HEALTH SERVICES RESEARCH IN DIARRHEAL DISEASES

IV.4.1 The meeting viewed this activity as the experimental provision of health care to relatively small population units, and included applicability testing, clinical trials to determine efficacy, efficiency, and cost effectiveness, and also demonstration or pilot projects.

IV.4.2 The meeting generally agreed that the results of scientific research should be developed to the point that they could be used by health professionals and by the public. At the point where interventions become practical and applicable, a strong effort should be made to help local agencies to use such information effectively. Examples here are the oral and intravenous fluid therapies and, possibly, rural environmental sanitation programs investigated at Teknaf.

IV.4.3 Functional or collaborative links between the Center and demonstration or pilot projects in or outside Bangladesh, are of great potential value to both parties in generating a two-way flow of ideas and scientific information, and the meeting recommends the establishment of such links.

IV.4.4 The outcome of intervention studies is not just demonstration that they work in a particular site, because many low-cost prevention and control measures are likely to be site-specific. Rather, the Center should aim to produce effective interventions together with a methodology for their introduction, evaluation, and incorporation into the local health care service. For example, if protected tanks with restricted beds of water hyacinth are found to reduce cholera incidence, the Center's research should not only demonstrate this conclusively, but work out the methods needed to assess the applicability of this finding at other places relatively rapidly, the steps required for successful implementation through existing services, and their maintenance over time.

IV.4.5 Where applicable, the development of well-defined operational research programs will have an obvious practical value and also provide an interface for stronger collaboration between the proposed Center, local health professionals, and governmental health care programs. The meeting encourages the further development of operational research programs in the following areas:-

- a) The meeting supports the proposed water and sanitation intervention study in the Teknaf area. This study, if properly carried out, could serve as a model for further studies in other areas, of the value, or lack thereof, of various sanitary interventions in the control of diarrheal disease (see paragraphs IV.1.4.7 and IV.1.4.8).
- b) The meeting feels that an evaluation of the effectiveness of oral fluid therapy, as provided by government health workers in a rural area other than Matlab, should be carried out soon as a collaborative effort between scientists of the proposed Center (who would provide the training and evaluation) and health workers of the Government Health Service. The meeting emphasizes that, for several reasons, an evaluation of oral fluid therapy should be carried out as soon as appropriate collaborative arrangements can be developed. When appropriate, the provision of routine therapy of diarrheal diseases should be turned over to the Government of Bangladesh.

IV.4.6 Problems associated with experimental intervention programs may be:-

- a) Inability to sustain, terminate or hand over programs requiring continuous support
- b) Cross-reactions between two or more programs ongoing in the same study area.
- c) Overloading of populations such as Matlab or Teknaf with intervention programs because of the attraction of their demographic data bases.

These problems indicate the need for collaborative planning of intervention programs.

IV.4.7 There is no suggestion that the Center should become responsible for large-scale health service delivery. The Center should be aiming to provide guidance rather than services themselves.

IV.5 DEMOGRAPHIC SURVEILLANCE AND DATA PROCESSING

- IV.5.1 The meeting has reviewed the Demographic Surveillance System in Matlab (DSS) and many of the data processed up-to-date from the DSS. It was favourably impressed by both the care and thoroughness of the data collection and by the high quality of the returns. The DSS that started in 1966 now includes a population of about 270,000 persons in about 50,000 households in 233 villages, and records annually about 38,000 events (birth, death, marriage, migration).
- IV.5.2 It is currently envisaged that the population under the DSS be reduced by about 40% to effect a saving in operational cost. The meeting feels strongly that the DSS be continued and regrets the possibility of the reduction.
- IV.5.3 Processing of the data collected by the DSS as well as demographic, hospital and administrative records, uses partly computer facilities outside the CRL and partly CRL's own data processing equipment (sorting machines). This has been found unsatisfactory and limits the scope to which the data may be effectively utilized.
- IV.5.4 For these reasons, the meeting believes that it is highly desirable for the International Center to obtain adequate computer facilities, either of its own or in participation with one or more other organizations such as the Bangladesh Institute of Development Studies (BIDS).
- IV.5.5 The type of computer, its operational and maintenance costs and the possible co-operative managements should be explored by a task force appointed jointly by the International Center and BIDS.
- IV.5.6 The socio-economic information collected by the DSS should be further expanded, up-dated at the regular censuses and fully utilized. An improved coding system should be developed to describe socio-economic status (e.g. occupational classification) in collaboration with other Bangladeshi institutions working in this field (BIDS, Bureau of Statistics, etc.).
- IV.5.7 Cause of death is now inadequately indicated. It is highly desirable to know the most probable causes of death for young children and also for deaths associated with pregnancy or child birth. For this

purpose, it would help to have lay personnel reporting the death and indicating which set of major symptoms were present (e.g. fever, vomiting, diarrhea) so that better trained coders can code the most probable causes from these symptoms.

IV.5.8 Some additional personnel are recommended such as one senior demographer-statistician and, when the computer is obtained, at least one fulltime programmer.

IV.5.9 In its demographic research and, in particular, in connection with collation and use of social and economic data, the Center should maintain close co-operation with the Bangladesh Institute of Development Studies, the Bangladesh Fertility Research Program, and the Institute of Statistical Research and Training.

#### IV.6 TRAINING AND COMMUNICATION

IV.6.1 The Center has a clear obligation to share its specific technical activities in relation to diarrheal disease and related health fields with the host country and the rest of the world. A key component of these outreach activities will be training, by which the meeting means the implantation of knowledge and skills in the minds of receptive individuals so that they may effectively carry out skilled tasks.

IV.6.2 The training program involves two main components: training in relation to research and service-orientated training.

##### IV.6.3 Training in Research

IV.6.3.1 It is clear that one of the important ways in which the Center can contribute to research in diarrheal diseases is by training those who will subsequently be involved in diarrheal disease research and related fields. This will include specific commitment to the training of Bangladeshi research workers. The meeting distinguishes between relatively long-term education of those taking up the Center's specific research fields, short-term specific training in techniques, and training of research support staff.

IV.6.3.2 In education of research workers, the Center should accept potential research workers from Bangladesh, from other developing countries, and from developed countries. The Center should aim to have roughly equal numbers of research trainees from each of these three sources. Entry should be limited to research workers of potential

excellence and originality and final selection should be made by the Center. The meeting envisages that many more candidates than places will be available and selection on research potential will be necessary.

IV.6.3.3 Among the areas of research training, special attention should be directed to population-based research areas such as epidemiology where there is a disproportionate scarcity of workers.

IV.6.3.4 It is strongly recommended that negotiations be initiated as soon as possible with the Bangladesh authorities to recruit Bangladesh physicians to work in epidemiology in the Center for a minimum of two years. This could be followed by a period of special training (i.e. one year) at an appropriate university at no expense to the trainee, who would then have an additional period of pay back time to the Center. A career ladder will have to be developed for these physicians.

IV.6.3.5 Provision of research education underlies the need for long-term staff. A three-year research training period cannot be satisfactorily supervised by a senior worker on a two-year appointment. Many sources of funding for these research trainees are likely to be available; nevertheless, the Center should also have its own training funds to avoid competition with funds for research workers. The total training budget of the Center should amount to a substantial proportion of its total funds.

IV.6.3.6 Fellowships should be available for medical and non-medical graduates from the Center and from other agencies and governments. They should be either post-doctoral or they should be worked out in association with suitable institutions. The Center should not contemplate granting its own academic qualifications.

IV.6.3.7 Due account must be taken of the career opportunities of trainees and usually they will have an appropriate post allocated in their own country prior to acceptance.

#### IV.6.4 Short-term Training

The facilities and expertise of the Center make it very suitable for short-term courses, seminars, and workshops on particular techniques, both for research and for implementation. Such short courses may be either national or international in nature, and utilize the Center's expertise in epidemiology, field work, clinical diagnosis and management of diarrheal diseases,

enteric bacteriology and the like, in collaboration with national institutions where appropriate.

#### IV.6.5      Training of Research Support Staff

The shortage of skilled technical help is likely to impede research in diarrheal disease and allied fields and the Center will need to continue to develop an appropriate role in the specific training of technicians.

#### IV.6.6      Service-orientated Training

IV.6.6.1      Because of the present local situation, with the concentration of diarrheal disease in the cholera hospital, the Center has obligations in service-orientated training in Bangladesh. These need to be adequately met in such a way as to increase the capacity of the country to meet its own needs.

IV.6.6.2      In Bangladesh, lectures, long and short courses, seminars, and demonstrations should be offered to medical, nursing and other health institutions or other allied institutions. The work of the Center will involve not only training physicians and other appropriate health personnel, but also the development of training and education for families of hospital patients to give suitable fluid therapy for diarrheal diseases. At present, most patients in Dacca with diarrheal diseases come to the CRL. It is highly desirable that such treatment should be made available on a larger scale in the other Dacca hospitals and health care facilities by the appropriate authorities, and the Center will need to respond to requests for advice and assistance in this respect.

IV.6.7.      The staff of the projected Center should devote an appropriate proportion of their working time to training and teaching activities. However, their primary function should be research, both in the acquisition and the application of new knowledge and skills.

#### IV.6.8      Communications

IV.6.8.1      Clearly, communication should be improved between the International Center and relevant institutions, particularly in Bangladesh and the rest of the world.

IV.6.8.2      The meeting feels that the International Center should support Bangladeshi scientific journals by the submission of papers and probably some subsidization.

#### IV.6.9      General

IV.6.9.1      A list should be made and kept of all persons who have been trained by the CRL so that they can be used in times of need.

IV.6.9.2      The Center should establish policy as to when and to what extent the data it generates should be made available to outside organizations.

#### V      ORGANIZATIONAL ISSUES

V.1            The meeting recommends internationalization of the CRL and the new institution be called the International Center for Diarrheal Disease Research (ICDDR). This recommendation is made in recognition of the fact that diarrheal diseases constitute a major world health problem and there is a need for an international institution which addresses this problem. In view of the fact that the WHO has initiated a diarrheal disease control program, including research, the ICDDR would make a significant contribution nationally as well as internationally.

V.2            The more specific title is preferred because it indicates the focal concern of the institution. It should be noted, however, that some members of the meeting prefer retention of the more general title already proposed.

V.3            Diarrheal diseases constitute one of the major causes of death, particularly in infants and young children, and are also closely linked with malnutrition and high fertility. In almost two decades, the CRL has developed a strong research base in cholera and certain diarrheal diseases in the laboratory and in field situations. This work would be extended into investigation of the full array of diarrheal diseases and related problems.

V.4            Thus, the principal objective of the ICDDR would be governed by a concern for improving the health of the community. The preoccupation with diarrheal disease prevention and control implies the necessity to identify determinants of diarrheal disease distribution in the community besides undertaking clinical and laboratory research, and should also include the development of appropriate technologies of intervention for prevention and control and their testing in community situations.

- V.5 Another important objective of the ICDDR would be to provide training to Bangladeshi and other nationals in areas of its activities and competence in collaboration with national, regional and international organizations.
- V.6 Experience confirms that institutional insularity reflected in unresponsiveness to human welfare, whatever the reason, can render the aims and objects of centers for health research largely redundant and futile. It is therefore important that the ICDDR research agenda be problem-orientated, and address problems of priority and does so in a manner that is most likely to develop applicable interventions with reasonable prospects of success. This could be achieved by designing studies with the involvement of health service implementors. Furthermore, to ensure this orientation on a continuing basis, the meeting advises that individuals known for their social responsibilities and concerns be included on the scientific review committees and co-ordinating committees.
- V.7 The CRL has, in the course of its past work, also developed considerable expertise in collecting demographic information, particularly at Matlab and Teknaf, which has produced important information in nutrition and population studies. In expanding this work, the Center should establish appropriate collaborative relationships with national institutions active in nutrition research and in demographic and biologic studies in population research.
- V.8 In establishing the ICDDR, there are several special considerations such as the possibility of the Center drawing away local talent from national centers. This may be guarded against by the development of positive and mutually collaborative partnerships between the Center and local institutions so that a spirit of complementarity prevails and local initiatives and capabilities are facilitated by the Center's presence.
- V.9 There are several ways by which these complementary relationships may be established. Some of these are: full exchange of information, secondment of research and teaching staff, joint research undertakings, contractual research by national institutions and sharing of equipment, facilities and personnel. In addition, a joint committee (representing the Center and local institutions) for program co-ordination in Bangladesh could continuously monitor the program and projects, and recommend necessary adjustments and suggest specific collaborative arrangements.

- V.10        The training program of the ICDDR should first and mainly be centered around providing opportunities to a variety of health professionals to acquire skills in clinical, laboratory, epidemiological, and field research. A close consultative relationship should be developed with the national health service administration to further the field activities, and to promote short-term exchange of scientists, teachers and other professionals.
- V.11        Regional and international collaboration will take the form of dissemination of relevant information and knowledge, by meetings, visits, seminars, and workshops. Working through the host government, the WHO could assist through appropriate channels. By these various orientations and concerns, the ICDDR will relate itself to real human problems and address to their solutions without losing scientific quality and concentration of effort.
- V.12        The long term future of the Center was not considered by the meeting. As for the actual size of the scientific and support staff of the Center, and the scope of its facilities, these will be dependent on the scientific program which will be developed and the financial support the Center is able to attract.

Appendix I

PARTICIPANTS IN THE  
INTERNATIONAL SCIENTIFIC REVIEW MEETING  
FEBRUARY 6-14, 1978

Barua, Dr. D., Medical Officer, Bacterial & Venereal  
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Microbiology, University of Goeteborg, Gulhedsgaten, Sweden

Hossain, Dr. Monowar, Chairman, Bangladesh Institute of  
Development Studies, Dacca, Bangladesh

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Islam, Professor Nurul, Director, Institute of Post-Graduate  
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Khan, Dr. Atiqur Rahman, Director, Bangladesh Fertility Research Program, Dacca, Bangladesh

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Mata, Dr. L.J., Director, Instituto de Investigaciones en Salud (INISA), University of Costa Rica, San Jose, Costa Rica

Moodie, Dr. Peter M., Deputy Director, Department of Tropical Medicine, School of Public Health and Tropical Medicine, University of Sydney, Sydney, Australia (Reporter)

Myat, Dr. Aung, Epidemiologist, World Health Organization, Dacca, Bangladesh

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Ruzicka, Dr. L.T., Senior Fellow, Department of Demography, Research School of Social Sciences, Australian National University, Canberra, ACT, Australia

Saroso, Dr. Julie Sulianti, Head, National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia (Chairman)

Zahra, Dr. A., Director, Division of Communicable Diseases, World Health Organization, Geneva, Switzerland

Appendix II

DOCUMENTS STUDIED FOR THE  
INTERNATIONAL SCIENTIFIC REVIEW MEETING  
FEBRUARY 6-14, 1978

1. Cholera Research Laboratory Annual Report 1977.\*
2. Informal Report - Summary of Discussion of the Informal Meeting relating to the development of an International Center for Health Research from the Cholera Research Laboratory, December 6-8, 1977.\*
3. Draft Prospectus - An International Center for Health Research.\*
4. Director's Introductory Statement.
5. Guidelines for the International Scientific Review.
6. Reports of Diarrheal Disease Program.
7. Abstracts and Progress Reports of Protocols on Diarrheal Diseases:
  - a) Diarrheal Disease Transmission
  - b) Host Susceptibility
  - c) Diarrhea Therapy
8. Diarrhea Program Presentation.
9. Report on Outreach and Training Program.
10. Report on Nutrition Program.
11. Abstracts and Progress Reports of Protocols on Nutrition.
12. Report on Population Program.
13. Abstracts and Progress Reports of Protocols on Population.
14. Report on Matlab Activities.
15. Report on Teknaf Activities.

16. Report on Dacca CRL Facilities.
17. Background Report on Health and Health Services Delivery in Bangladesh.
18. Curriculum vitae of Director, Deputy Director, Scientific Directors, Investigators ~~and Branch~~ Heads.
19. CRL Organizational Chart.
20. Various Research Protocols.

\* Circulated to participants before the meeting.

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INTERNATIONAL SCIENTIFIC REVIEW MEETING  
Cholera Research Laboratory  
Dacca, Bangladesh

February 6-14, 1978

DIRECTOR'S INTRODUCTORY STATEMENT

Introduction

The documentation provided to the International Scientific Review Meeting, particularly the Prospectus, provides considerable detail regarding the history and development of the Cholera Research Laboratory so I will not review it here. In essence, the CRL is now in its eighteenth year having been established in 1960. Throughout this time period it has basically operated under bilateral Project Agreements, initially between the Governments of the United States and Pakistan, and subsequently between the United States and Bangladesh. These Project Agreements had a life of three or four years.

In the first decade of its existence, the CRL was operating under the auspices of the South-East Asia Treaty Organization (SEATO) and was governed by an International Governing Council made-up of representatives of the SEATO nations and chaired by the Director-General of SEATO. Following the Independence of Bangladesh, the new Project Agreement in 1974 established a Directing Council consisting of representatives of the United States, Bangladesh, and the United Kingdom who are resident in Bangladesh.

Throughout the entire life of the CRL, the technical and scientific control has been under the National Institutes of Health in Bethesda, Maryland, USA. The NIH appointed the Director and, in the first decade of the CRL's existence, seconded four to six scientists to carry out the scientific program. Beginning in 1965, the Center for Disease Control, Atlanta, Georgia, joined the scientific program seconding two to three scientists to guide the epidemiological program.

Oversight of the scientific program throughout this entire period has been provided by a Technical Review Committee consisting of scientists from the United States, the United Kingdom, Australia and Bangladesh which is appointed by the National Institutes of Health.

During the first ten years of the CRL's existence, there was a strong and close link with the NIH, not only through the secondment of scientists from the NIH staff, but also through

a close working relationship with the Cholera Advisory Committee of the NIH which was an active group meeting three to five times a year to discuss and monitor every aspect of the CRL research program.

With the Independence of Bangladesh, the formal relationships were temporarily broken. Simultaneously, the NIH underwent considerable reorganization and the Cholera Advisory Committee was dissolved and all scientific positions at the CRL were withdrawn. Two CDC scientific positions have been maintained, however up until the present time. The outcome of these changes resulted in the CRL having to independently recruit its scientific staff and develop its scientific program. When the current Project Agreement was established in 1974, the NIH maintained nominal scientific control through appointing the Director and the Technical Advisory Committee, but did not provide the strong sustained support that previously existed with the assignment of scientists and the operation of the Cholera Advisory Committee. As a result, it can be reasonably said that the CRL to a considerable degree lost its focus and suffered a considerable drop in scientific productivity in recent years.

#### Advantages and Disadvantages of the Operating Arrangements of the CRL

In considering what should be the future structure of the proposed International Center for Health Research, it is useful to review the advantages and disadvantages of the previous operating arrangements for the CRL. There obviously were a number of distinct advantages. The CRL operating under a temporary Project Agreement had full autonomy for all of its operations, quite free from the constraints of governmental bureaucracy. This permitted the CRL to recruit its own staff, under its own pay scales, establish its own personnel regulations without considering labour laws or labour union activities, obtain supplies and equipment, duty-free without restriction, and generally have full freedom to carry out whatever operations were necessary for a productive research program. The strong links with NIH and CDC ensured the immediate availability of carefully screened and highly qualified scientists for carrying out the research program. Further, the institutional ties with the enormous research capacity at the NIH provided strong scientific back-up and the intellectual stimulation required to generate new ideas and initiatives. Within this framework, the research agenda generally tackled "universal" problems related to cholera, looking at various aspects of pathogenesis therapy, epidemiology and immunology.

Looking at the performance, the CRL obviously had a highly productive research program. It made fundamental advances in cholera pathogenesis, leading to major developments in both intravenous and oral therapy. Further, the CRL contributed to fundamental knowledge in cholera epidemiology and immunology. This scientific knowledge has had a global impact on the management of cholera epidemics. Basically, it has rationalized the

control of epidemics and has removed the panic related to the disease with all of the political and economic implications.

There were, however, major disadvantages of this operation. Since the CRL operated under three years agreements, there was always a short-term perspective both in the minds of the scientists as well as the CRL staff who have always found their future insecure. No attention was given to "institutionalization" of the CRL. For example, there was no goal to create long-term research capacity either in CRL or in Bangladesh.

Since most of the scientists were short-term expatriates there was a failure to see the full dimensions of the cholera and diarrheal disease problems, particularly in their social and cultural context; rather, the dominate initiative for the research agenda came from ideas generated outside of Bangladesh. Within this context, it is not surprising that there was little concerted effort to actually seek to solve the problems of cholera and diarrheal disease as they existed in Bangladesh. Finally, given the autonomy of the CRL, it is not surprising that there were very weak links with research or health related institutions in Bangladesh.

#### The Current Situation

In looking at the CRL today it is clear that we are both the beneficiaries as well as the victims of our history. The CRL is now entering its eighteenth year. It has a large institutional infrastructure with clinical facilities, laboratories, field operations, administrative maintenance and logistic support. There are over 500 fulltime staff. These facilities represent a major potential resource for productive research. It should be noted, however, that while the institutional structure is large, it cannot be called well-developed; rather it has simply grown in various directions and accumulated activities and operations on the basis of short-term projects, but no overall rationale currently exists. These points notwithstanding, the potential capacity for highly productive research is enormous.

With reference to scientific leadership, the CRL has about two dozen scientists; half of these, however, are expatriates under contracts of two years or less. With reference to the future, there has been no organized staff development program and only one scientist is in a training development activity which he took on his own initiative.

#### The Proposal for the Future

The current Project Agreement for the CRL terminates in 1978. USAID, the major donor to the CRL, has recognized for a number of years that their support for this institution has been a major exception to their usual policy for support of

project activities. Specifically, projects are designed to have a limited lifetime, generally only a few years. The CRL has now gone for eighteen years. Recognizing the substantial institutional capacity that has evolved, the United States Government and the Government of Bangladesh have agreed that steps should be taken to see if a more permanent institutional base could be established for the CRL. The general terms of their discussion were that there should be a consideration of the history of the CRL as an international autonomous institution. On this basis, the Government of Bangladesh has developed a proposal that the CRL be restructured as an International Research Center, chartered in Bangladesh, but governed by a fifteen member International Board of Governors, the majority from developing countries, with three designated by Bangladesh. Within this framework, the Center would solicit international support from multiple donors.

Concurrent with the restructuring of the governing framework must be a restructuring of the program and operations of the institution. The points to consider are: First, the development of scientific leadership and research capacity within CRL; secondly, the development of a problem-centred and problem-solving orientation to the research program; third, the development of strong institutional ties with research and health related institutions, both in Bangladesh and the developing world, with a particular goal to strengthening scientific manpower and research in these institutions.

#### The Objectives of the International Scientific Review

Over the past year a number of structural and organizational changes have been made in the CRL to begin moving toward the development of a more permanent International Research Center meeting the objectives outlined above. There has been the establishment of a standardized procedure for development and critical review of scientific protocols as well as strengthening of the guidelines and procedures for ethical review of all research involving human subjects. The scientific staff of the laboratory have been reorganized into research working groups with a problem-centred orientation. This latter reorganization, however, was only initiated in October, 1977, so that the current activities do not begin to fully reflect this reorientation of priorities. Overall, the CRL still maintains the same fundamental structure and method of operation that it has over the years.

It is in this context that the International Scientific Review Meeting is asked to examine the CRL as a research resource and provide guidance for the future International Centre for Health Research, Center, chartered in Bangladesh, but governed by a fifteen member International Board of Governors. The specific guidelines for this Scientific Review and the questions which the meeting is asked to address in this Review are provided on the appended sheet.

Concurrent with the restructuring of the governing framework must be a restructuring of the program and operations of the institution. The points to consider are: First, the development of scientific leadership and research capacity within CRL; secondly, the development of a problem-centred and problem-solving orientation to the research program; third, the development of strong institutional ties with research and health related institutions, both in Bangladesh and the developing world, with a particular goal to strengthening scientific manpower and research in these institutions.

COMMENTS BY DIRECTOR, CRL, ON DRAFT DOCUMENTS  
AND DISCUSSION TO DATE  
FEBRUARY 12, 1978

The general document on "Organizational Issues" expresses legitimate concern about "institutional insularity". To avoid this, there is the recommendation that "It is therefore important that the ICDDR research agenda be problem-orientated and address problems of priority and does it in a manner that is most likely to develop applicable interventions with reasonable prospects of success".

In order to maintain a problem-solving orientation, there must be built in to the institution structures to ensure that the scientists are involved with the problems in the first place. As noted in my Introductory Statement, one of the major weaknesses of CRL in the past has been that most of the scientists were expatriates and knew about the problems in the literature and in the laboratory, or in the patient, but not about the problems in the field. Thus, not surprisingly, the research agenda tackled these "universal" problems but missed almost totally the problems "in the field". Therefore, we have the current situation where the CRL hospital in Dacca is seeing ten times more cases than we were a decade ago and the hospital in Matlab three times more cases and we do not know why, nor do we have any solutions.

While the recommendations of the Scientific Review Meeting do, indeed, seem to capitalize on the strengths of the CRL, my concern is are they not also perpetuating its weaknesses?

It is clear that the group examining the problems of diarrhea therapy recognized the importance of the CRL having an institutional structure that was involved constantly in providing comprehensive services for diarrheal disease care. This is actually quite an expensive proposition. To maintain the general ward (intensive care) at the CRL it will cost approximately \$100,000 a year and will provide comprehensive sickness care for only 0.25% of the diarrhea cases seen annually.

What is the justification? It was simply and directly stated: "It was felt that the relatively high cost of the general ward could be justified by the potential improvements in therapy which might be derived from careful observations of the more critically ill patients." Stated another way: The CRL required this institutional structure being constantly and comprehensively involved with services to a problem in order to create the research agendas that would lead to the solution to the problem.

Recognizing the importance of problem-related institutional structures, should not the same rationale apply to health care as well as disease care? More specifically, should not the CRL invest at least an equal amount to provide comprehensive health care to a community (say 100,000) under the rationale "that the relatively high cost of community health services could be justified by the potential improvements in prevention which might be derived from careful observations of the community at large".

In the establishment and maintenance of either of these institutional structures, it would have to be recognized that some or many of the services provided in both cases might be useless. Further, of course, such an approach initially involves a multiplicity of interventions applied simultaneously which makes the research more complex. These realities, however, should not detract the Center from setting-up such institutional structures built on the knowledge that we have (or think we have) and then carrying out analytical studies and manipulating variables in order to detect and answer the unanswered questions.

The above proposition is, in essence, addressing the question: "To what degree does the new International Center approach the problem of diarrheal diseases and related problems from a disease orientation versus a health orientation?" If it is to primarily have a sickness orientation, then a major component of its resources should obviously go towards hospital-based activities including the provision of comprehensive hospital-based services for sick people. If on the other hand there is to be a balanced effort directed towards disease prevention and maintaining health, then at least an equal fraction of its comprehensive service delivery resources should be directed towards establishing a similar institutional structure in the community from which research questions related to prevention may be derived.

It is my view that the major misunderstanding about the entire nutrition research agenda involves exactly this lack of clarity about the balance of a hospital-based therapy orientated research agenda versus a community-based prevention orientated research agenda. If prevention was foremost in the minds of the Scientific Review Group, I feel there would have been absolutely no misunderstanding about the high relevance of the recommendations of the Nutrition Group. They were simply proposing a research program in the context of field orientated health service delivery to improve nutrition, particularly in the vulnerable groups, as a means of preventing diarrhea morbidity and mortality. To say that this approach is not a relevant agenda for the International Center which is concerned with the prevention of diarrheal diseases, is the same thing as saying that any nutrition related research designed to improve survival of the critically ill patients on the general ward is also irrelevant to the diarrhea therapy program.

In summary, I am asking the Scientific Review Group to give further consideration to the relative balance of disease versus health orientation. I recognize that it is easier for most of us as individual scientists to visualize a sharp focus when thinking about a disease while the concept of health is so global that it is baffling, yet the diarrheal diseases are fundamentally an in-product of a complex combination of biological, ecological, social, economic and cultural factors that can only be approached by a comprehensive involvement in the setting in which it occurs; that is, in the community itself.

We all agree that an International Center devoted to this problem in the developing world should, as a first step, be located in a country where the problem exists. Are we, however, only proposing a half-way step if the International Center does not have institutional structures for research generating the ideas and solving the problems in all of their complexity right out in the community with the problem.

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## GUIDELINES FOR THE INTERNATIONAL SCIENTIFIC REVIEW

### Objectives:

1. To critically review the current scientific program of the CRL.
2. To examine the rationale for the transformation of the CRL into an ICHR.
3. To review proposed objectives for the ICHR.
4. To provide guidelines for the balanced development of a scientific program of the ICHR to meet this objective.
5. To recommend requirements for scientific staff and institutional resources to fulfill the proposed objective of the ICHR.

### PROPOSED DRAFT OUTLINE OF THE INTERNATIONAL SCIENTIFIC REVIEW REPORT, WITH SOME ISSUES TO BE CONSIDERED

#### I. Critique of the recent and currently active CRL research and outreach activities.

This may be done in the framework of the current Active Working Groups:

1. Diarrheal Diseases
  - a. Disease Transmission
  - b. Host Defense
  - c. Therapy
2. Population
3. Nutrition
4. Outreach
  - a. Training
  - b. Communication/Information
  - c. Extension of Services

#### Questions and Issues:

1. Are these areas of high priority?
2. Are the protocols well designed?
3. Is the research being carried out under sufficiently high scientific standards?

4. Are the results of work being adequately disseminated to scientists, institutions or agencies that need it?
5. Where are strengths and weaknesses in:
  - a. Establishment of priorities and balance of effort.
  - b. Multidisciplinary approaches.
  - c. Scientific staff and institutional resources
  - d. Linkages with national and international institutions.

## II. Rationale for an ICHR

### Questions and Issues:

1. Why create an ICHR?
2. Is there relevant international experience to provide a precedent or justification for an ICHR?
3. Is it possible for the ICHR to strengthen independent research capacity in Bangladesh and in the region? If it is possible how can that best be done? If it is not possible can the existence of the ICHR be justified?
4. What are the alternatives to the ICHR to carry out the proposed research and outreach activity in LDC? How might the institutional capacity of the CRL fit with these alternatives?

## III. Objectives of the ICHR

### Questions and Issues:

#### A. Research

1. Are the specific research areas (diarrheal diseases, nutrition, and population) appropriate problem areas for the focus of the ICHR? Do these research areas
2. form a rational and logical combination? Should other infectious diseases, or non-infectious disease be included?
3. What should be the basis for determining which research program and projects should be carried out by the ICHR in these areas?
4. How does the ICHR establish its research priorities within these problem areas to avoid diffusion of effort and resources?

### Questions and Issues:

1. Why create an ICHR?
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4. What are the priority research questions in these areas that can best be addressed by the ICHR?
5. What programmatic efforts or projects will be required to answer these?

#### B. Outreach

1. What are the training capacities that are urgently needed in the LDC? Which of these could be most effectively met by the ICHR?
2. How should the ICHR set priorities for training efforts?
3. What should be the scope and content of outreach activities such as information dissemination through newsletters, publications, national and international seminars, etc.?
4. What should be the role of the ICHR in extension activities such as extension of rehydration centers, etc.?

#### General:

1. What should be the balance of ICHR's effort in research vs. outreach activities?

#### IV. Structure of the Research/Outreach efforts

1. To what degree should the ICHR be goal oriented with highly structured research programs versus providing maximum latitude for creative scientists to develop individual (and perhaps unrelated) research projects?
2. Is the Working Group structure conducive to focused research yet facilitating a plurality of approaches and ideas?
3. Should clinical and/or field research activities be linked to service delivery programs? How may such links best be achieved to most effectively use the limited resources of the ICHR for research and training?
4. What should be the relative balance of laboratory and clinical research (with a biological based disease orientation) versus field research (with a social and ecological based health orientation)?

5. To what degree should the research encompass broader areas such as personal health education, community motivation, or health systems research?
6. Should ICHR decentralize, and set up more field research areas? How is a balanced effort defined and established?
7. How should the ICHR relate to other research institutions in the host country and other LDC's, particularly with reference to setting research priorities? Should the ICHR be secondary and complementary to these efforts, or should it move ahead independently in special problem areas?
8. How should, the ICHR relate and respond to health program priorities in the host country, and in other L.D.C.? How should it relate to WHO and other international agencies in this regard?
9. Should the ICHR consider satellite institutions in other L.D.C.'s?

V. Staff and Institutional requirement

1. Given the proposed objective of the ICHR, what are the institutional requirements with regard to:
  - A. Personnel:
    - areas of scientific interest
    - professional experience and ability
    - balance of national origin
  - B. Physical resources:
    - space
    - equipment
    - logistics
  - C. Administrative support for local operations and international linkages.

## DIARRHEAL DISEASE PROGRAM

### INTRODUCTION

In a recent publication it has been estimated that 18 million people die of diarrhea each year in the non-industrialized countries. Bangladesh contributes significantly to this toll. In rural Bangladesh each person will have diarrhea once a year. This is deceptive since diarrhea afflicts children more often than adults. Thus a child may have more than 2 attacks per year while an adult has less than one. Assuming a duration of 8 days per episode the prevalence of diarrhea in Matlab thana, a rural area of Bangladesh, was 2 percent for adults and 4 percent for preschool children (Table 1). Hospitals see only a small fraction of these illnesses. Where rates can be accurately calculated only 0.8 percent of all episodes of diarrhea come to a treatment center.

In the 1960's the contribution of diarrhea to overall mortality in Bangladesh was quite constant ranging from 20 to 26 percent. During the crises of the early 70's this rose from 35 to 45 percent, the increase being due almost entirely to Shigella dysentery. Now the situation seems more comparable to that prevailing in the 1960's. Viewed from those hospitals which are run by the CRL, however, the situation has a different face. Beginning with the crises of the 1970's there has been an extraordinary growth of hospital visits (Figure 1). Assuming that metropolitan Dacca has a total population of about two million and that potentially 1 percent of the diarrhea is severe enough to cause a person to seek treatment it is apparent that 20,000 visits per year could be expected. Thus since 1972 the catchment area of the Dacca hospital has enlarged, a higher rate of diarrhea exists or there is a greater tendency for patients to use the hospital. In Matlab the same increase in hospital usage has occurred. Since the composition of the population is known there the cause of this increase can be ascertained. In any case viewed from the side of a large treatment unit the rapid growth of visits has already assumed alarming proportions and shows no signs of levelling off.

Let us now look at the causes of this problem. Diarrhea is primarily due to infection and would not exist if the agents of disease were kept from the host. In Bangladesh there is a widespread mingling of faecal wastes with the water used for drinking, bathing, washing of clothes and dishes, or any other purposes. Food is easily contaminated by water or by hands that have been in contaminated water. If any diarrheal diseases, such as may be true of the rotavirus, are

spread by air or contact then conditions are optimal here due to crowding. Thus the fundamental cause of spread of disease is due to the lack of control of waste disposal and separation of human wastes from food and water. In addition there may be enhancement of the problem because of lowered host resistance. This is thought to be primarily a function of undernutrition. It should be pointed out however, that there is also an increased resistance to many pathogens because of frequent exposure and acquired immunity. In fact in well nourished travellers from countries such as Bangladesh it has been shown that the occurrence of travellers diarrhea is much less frequent. Finally there is the presence of highly virulent pathogens here that are not so common in countries with effective sanitation.

In the early 1960's when the Cholera Research Laboratory was established we were ignorant of the causes of almost 80 percent of the diarrhea seen. This has changed. Now a pathogen can be found in 80 to 90 percent of the diarrheas presenting to our treatment centers. In considering which organism causes diarrhea, in what proportion of the population, one must bear in mind variations in the distribution and relative proportions of different agents, from month to month as well as over longer periods. Thus after the independence of Bangladesh diarrhea due to shigella increased dramatically. Cholera waxes and wanes in a 3 to 5 year cycle. Such trends must be recognized and be defined with respect to the newly recognized agents such as the rotavirus or enterotoxigenic E.coli. This is of obvious importance when trying to interpret the effect of interventions whether in a community or a National basis.

This is not sufficient because the reason for changes in disease patterns rests not only on the agent but on human behaviour which in the past two decades has been periodically affected by war, cyclones, and famine. Social and religious customs form a continuous context which may be the most important determinant of disease. It is a special reason for focus since man has adapted behaviour to improve his lot and will continue to do so. Knowledge of how behaviour may encourage or discourage diarrheal illness may speed this process.

The Cholera Research Laboratory has contributions to an understanding of and impact on diarrhea disease includes:

1. Demonstrating that antibiotics shorten the duration of purging in cholera. This finding has been put to use within and outside of Bangladesh.

2. Demonstrating that in large populations under adverse conditions, the mortality due to cholera can be reduced to less than 1% by health workers with brief training in intravenous fluid therapy. Appropriate intravenous fluids have been devised, tested and introduced into standard use.
3. Basic knowledge about electrolyte transport during diarrhea has led to the simple inexpensive replacement of salt and water losses in diarrhea by mouth. The treatment has spread rapidly across the world.
4. Defining the limited protective capacity of current commercial and experimental vaccines against cholera.
5. Demonstrating the association of *V.cholerae* with water usage and the relative case to carrier ratios of Classical and El Tor cholera in rural Bangladesh.
6. Showing that introduction of a single safe water source has little if any impact on diarrhea in the context of rural Bangladesh.
7. Putting cholera/diarrhea into the general context of overall mortality and fertility.
8. Confirming in humans the now generally accepted mechanism for diarrhea in cholera.
9. Demonstrating that enterotoxin-producing *E.coli* and rotavirus are major causes of diarrhea here, and describing the spectrum and distribution of disease due to these agents.
10. Discovering a new syndrome with a high mortality in children that is commonly associated with shigellosis here.
11. Identification of hypoglycemia as an important risk factor in diarrhea.
12. Demonstration that antibiotic reduces deaths in shiga dysentery.

In the context of these past accomplishments now let us look at present goals and challenges. These include:

1. We must see that the simplest effective treatment measures are placed in the hands of those at risk.

2. We must continue to define the causes of illness with particular emphasis on defining the way in which different agents spread seeking opportunities for effective preventive interventions.
3. A vigorous effort to understand better how an individual protects himself against disease by both natural defenses such as gastric acid and acquired defenses such as the local and systemic immune systems must be made. We remain woefully ignorant of one of the most important defense systems of the body, the local immunity of the gut.
4. The influence of nutrition on resistance to diarrhea and the influence of diarrhea on nutrition must be better defined.
5. Before the millenia of total sanitation arrives specific and focal interventions in the environment that can reduce the spread of disease must be identified.
6. Diarrhea must be viewed as one part of a complex of infections that cause death in Bangladesh.
7. The effect of caring for diarrhea effectively on acceptance of other health and family planning measures should be studied.

Work on diarrhea must not proceed with blinders on since the overall goal in any research on health is not cure or prevention of the disease in which there is a particular interest but in the overall improvement of health. Some simple solutions to the diarrhea problem could have adverse consequences in other spheres. All efforts must be looked at from the point of view of what leads to better health over the long run for the people involved. In this context let us now look at some of the specific questions about diarrheal diseases that we are currently focusing upon and where this may tend to lead us over the next two to five years.

Three general areas of work have been defined and groups of scientists formed to approach these.

1. The ways in which diseases are transmitted.
2. The ways in which diseases exert their effects on people and how they can be effectively treated, and
3. How do individuals and populations resist diarrheal diseases.

## DISEASE TRANSMISSION

First let us look at the thinking of the working group that has been focusing on the ways diseases are transmitted. The long range goals of this group are:

1. To define the agents responsible for the various kinds of diarrhea seen in Bangladesh; and define their natural cycles.
2. To delineate the ways in which they are spread in the different communities of Bangladesh.
3. To seek effective and applicable interventions by which the cycles of disease can be interrupted.

It is apparent from Table 2 which lists currently active work that a main focus is on the spectrum of diseases and manner of spread of agents that have only recently been shown to cause diarrhea here. These are the rotavirus and enterotoxigenic E.coli. They are being studied within the matrix of the more classical and defined causes of diarrhea, and taken together with these explain 80-90% of all watery diarrhea seen. Surveillance data now being gathered will define shorter term seasonal cycles. Longer cyclical changes will require surveillance on these and other agents continuing for many years. We hope to initiate in collaboration with the Government surveillance units coupled to model treatment centers in different areas to accomplish this objective and to define geographic distribution. Such units will be necessary to assess long term natural trends or any effects of particular interventions that might be implemented locally or on a national scale.

With respect to the specific pathogens involved, each presents some aspects that remain unique. Each agent needs to be studied both as a separate entity and as a part of a matrix diarrheal disease. For example, when we say that under-nutrition is associated with an increase in diarrhea we find that in Matlab the increase in diarrhea during famine conditions in 1974 was primarily due to one agent, shigella. Large cholera outbreaks did not characterize that period. In a time of relatively good nutrition in the population this year we have seen the largest outbreaks of cholera in Matlab in our twelve years of experience in this area. At present we have no idea of what relationship the new agents (rotavirus and E.coli) may have to under-nutrition or other social and environmental variables. It is very important to tease out any correlations between particular agents and specific social and economic conditions.

## Cholera

The CRL has accumulated an enormous amount of longitudinal data on cholera in both Dacca and Matlab over a 12 to 15 year period. This data needs to be critically analyzed. Cyclical shifts between Inaba and Ogawa serotypes have occurred and marked variations in the frequency and location of cases have been seen. A major shift in biotype from classical strains to El Tor has occurred. The existing data from Matlab needs to be examined with an eye toward making relationships between characteristics of communities which have been affected heavily as compared to those which have not been. Such comparisons will focus on water usage and waste disposal. We have seen that rates of cholera are lower when tank water is used for bathing, washing and cooking. Thus villages with access to tanks may exhibit lower cholera rates.

From a more basic science point of view there is need to determine the susceptibility of patients to cholera infection following a previous infection. The re-infection studies to date have been inadequate since they have been primarily hospital based and have not properly taken into account the question of serotype specific immunity. Data from prison studies is conflicting as to the importance of serotype specific immunity. What we need to do is to follow intensively a cohort of patients who have been recently infected with cholera with periodic diarrheal surveillance, culturing and serology to see what the true re-infection rate is. It would be ideal if we had both Inaba and Ogawa organisms occurring at the same time in doing this study. There is also a need to design studies which might shed some light on why cholera does not commonly infect children in the first two years of life like E.coli and rotavirus (Table 3). One approach might be to define potential risk factors (e.g. bathing) and comparing them in young (less than 2 years) and older children. In other words what we would like to know is what factors allow older children to get cholera, but protect younger children. These studies of course have to be combined with immunologic studies of breast milk and local immunity.

Based on the information obtained we then must come up with good feasible ideas for intervention measures to prevent cholera transmission. It really is not sufficient to say that since studies have shown that tubewells do not work that we must give up the idea of other intervention measures. For one we might consider intensive educational programs in select areas to increase motivation for proper water usage and sewage disposal along the lines that is being done for the CDP Project. Providing access to tanks and improving the separation of bathing, washing, cooking and drinking water from feces in such villages may achieve a great deal and be

possible while advance sanitation is not. Such measures require expertise in the social and behavioural sciences. This must be developed in order to effectively approach such studies.

### Rotavirus and Enterotoxigenic E.coli

The studies currently underway will provide the basic descriptive epidemiologic information on the new pathogens (rotavirus and enterotoxigenic E.coli). The most critical questions to be answered are concerning what effects these agents may have on nutrition, morbidity, and mortality in the first two years of life. Conversely over a longer range it will be important to know what variations in the nutritional status of the population may have on the incidence and severity of these newly identified causes of diarrhea. A study in which 200 children will be followed in each of 2 villages for a period of a minimum of 1 year is contemplated. We will attempt to determine the cause of all their episodes of diarrhea by looking for known bacteriologic and virologic agents, follow their growth and development, measure their small intestine absorption following diarrhea, and look at their food intake patterns. In addition we will divide the two villages into an oral fluid and non-oral fluid villages; the oral fluid village children will receive oral fluid for every episode of diarrhea and the control village residents will receive a placebo. The study will hopefully define the relationship between diarrheal disease etiology, nutrition, feeding patterns, malabsorption, and diarrhea treatment.

One other study being considered in Dacca is to compare rates of rotavirus and E.coli diarrhea in higher and lower socio-economic groups. This would be particularly interesting for rotavirus which is known to be a common cause of diarrhea in developed countries. One could examine the relationship between breast feeding patterns, socio-economic status, and rotavirus rates.

### Other Vibrios

Because of the close relationships between V. cholerae and other vibrios that are present in patients with cholera-like diarrhea these have a special interest although they are responsible for a smaller proportion of the watery diarrhea than V.cholerae, rotavirus and E.coli. We see that watery diarrheas of equal severity to classical cholera are caused by V.cholerae NAG, and E.coli and that this is mediated by a toxin that is remarkably similar in antigenicity, mode of action and chemistry. One of the basic questions, then, is whether the genetic code for this toxin is the same and if it

may be transmitted in nature between vibrios and E.coli and perhaps other enteric bacteria. Such genetic exchanges between bacteria whether by means of bacteriophages or plasmids compound epidemiologic analysis, since it is conceivable that a pathogenic trait can itself have a reservoir in nature outside of the organism that is normally associated with a disease.

A second question which arises is whether we can expect further shifts in the biotype of the predominant cholera vibrio in the future. Taxonomically, the species V.cholerae contains organisms distributed on a spectrum from the highly host-adapted V.cholerae biotype cholerae (classical cholera) to apparently non-pathogenic free-living aquatic vibrios. In the past, the emergence of the hardier, less virulent El Tor biotype as the dominant agent of cholera caused dramatic changes in the epidemiology of this disease. Other pathogenic biotypes may rise to importance in the future as new permutations of environmental resistance and virulence factors develop. On the other hand, it may be possible to engineer a relatively innocuous strain which will compete successfully for the same ecological niche as the pathogenic biotypes and eventually supplant them. Exploring these questions will require first and extensive analysis of the molecular basis for these organisms' pathogenicity and environmental robustness, as well as the potential for genetic exchange between them.

#### Parasites and Protozoa

Parasitic diseases which are the classical focus of tropical medicine may seem to have been slighted. In fact the sort of studies that are most urgently needed are not those that will look again at the distribution of various parasites in a population but ones that will define what is the relation of any given parasite to actual morbidity. Since we plan to focus attention on protein loss and since there have been recently studies on E.histolytica which is a known cause of dysentery it is likely that this protozoa will receive a priority in future studies.

#### Chronic Diarrheas

There are still a group of patients that seek treatment with the complaints of more chronic diarrhea associated with much mucus but no blood. Often from such cases no pathogens are found. This is at present a problem that needs to have a good description and a cause or causes assigned.

#### Traveller's Diarrhea

As an interesting sideline our attention may be given

to traveller's diarrhea. It is of interest that one of the most important causes of watery diarrhea in Bangladesh, enterotoxigenic *E.coli*, is also the most common cause of traveller's diarrhea of "turista". A further observation is that the severity of *E.coli* diarrhea in Bangladeshi's is much greater than that ordinarily seen in travellers from richer countries. It would be of interest to find out whether travellers coming into Bangladesh from such countries acquire a disease of milder severity with the same organism that is producing cholera-like illness in the local population. If this is true then there may be important host factors characterizing the individuals coming from industrialized countries that can be related to the severity of illness.

### Environmental Studies

In addition to concentrating on individual causes of diarrhea attention will be given to important environmental correlates of different kinds of diarrheal illness. The most obvious of these are of course, the management of human wastes and the quality of water. In Teknaf studies are already planned which will relate diarrhea rates to the provision of tubewells and sealed sanitary latrines. Teknaf is quite different from Matlab in that water is less available in this area and there is no major flooding during the monsoon season. For this reason the use of surface water for washing, bathing and cooking may be easier to control. If this is the case then the introduction of tubewells may have a much more important impact on rates of diarrhea there than has been the case in water-drenched areas such as Matlab. There is a need for more knowledge about the pattern of fecal contamination of various water sources. Conditions which affect the survival of different pathogens need to be defined and may provide effective intervention measures to control the spread of disease.

### Other Diseases

Finally over a longer range there is an interest in the overall causes of death and disability due to infections in the Matlab area as well as other areas in Bangladesh. Next to diarrhea the most important causes of death are related to respiratory infections and fevers. At the present time a little is known about the causes of either of these clinical states. Some components of these such as whooping cough which are expected to be highly prevalent are clearly subject to a cheap and simple intervention. Diphtheria is also prevalent in Bangladesh and as one considers the priorities for immunization of a population the question of interaction of different vaccines becomes very important. Beyond this

there is an important question with some vaccines such as measles or pertussis that an undernourished population may either be more subject to a serious side-effects or not respond within appropriate immune defence. Extensions into these areas will very much depend on linkages to the causes of diarrheal disease and opportunities that present themselves due to epidemics as they are observed in the areas of study.

### Social and Behavioural Aspects

It is realized that at present our ability to study or mount interventions that rest on a social and behavioural sciences base is very limited. We require scientists with such expertise to join us here to begin formulation of studies in these areas. In the past significant basic descriptive anthropology has been done here but to date little of this knowledge has been applied to the interruption of disease.

### HOST DEFENSE

The Working Group on Host Defense currently has the protocols underway that are listed in Table 3.

Man has evolved genetically to defend himself against many potential agents of disease in his environment. In the case of diarrheal disease the two most salient primary defenses of the intestinal tract against infection are the very low pH or high acidity in the stomach which is capable of killing most of the enteric pathogens which commonly cause disease. Secondly a microflora characterizes his intestinal tract that competes effectively for ecological space against the majority of potential pathogens. In addition to this there is a defense which responds to acquired infections this is made up of a local and systemic immune system that operates both in the body fluids as antibodies and complement and through various defensive cellular systems.

### Gastric Acid

At the present time several protocols are in progress looking at the relationship between diarrheal disease and the capacity of individuals who have these diseases to secrete free acid in the stomach. In the past it has been observed that patients who have cholera have a definite reduction in gastric acidity. This observation has been confirmed again in the current protocols. It is known that gastric acidity can be affected by various medications and nutrients. It is also probable that malnutrition decreases gastric acidity. Thus defects in ability to produce acid due to undernutrition may well be an important predisposing factor to diarrheal illness.

The longer-term goal of these studies will be to develop methodologies which can be taken into the field such that high risk populations to the various kinds of diarrheal illness can be categorized in terms of their gastric acid secretion so that this can be related to incidence of attacks of diarrhea. Specific nutrients which improve gastric acid secretion in malnourished individuals need to be sought and the causes of hypoacidity ascertained in different kinds of malnutrition. Drugs such as xanthines which stimulate gastric acid might be considered in place of antibiotics as preventive measures in populations of high risk environments. Since diarrhea is a major cause of death before the reproductive age the population here should be heavily selected for high acid secretory ability. This may correlate with the high prevalence of ulcer disease here.

### Microflora

At the present time no studies relating to normal microbial flora of the gut are underway nor are any in the planning process. This is a very difficult and complex area. Many of the most important organisms indigenous to man are not yet grown even in the most sophisticated laboratories. It has also been extremely difficult to introduce predictable alterations of indigenous gut flora. However, since studies of diarrhea in nurseries have been carried out in which normal human lactobacillus has been introduced and shown to decrease attack rates, attention to this is mandatory. Manuevers involving normal human micro flora are of particular interest since in the environment here fecal-oral transmission is favoured it is very likely that introduction of a healthy micro flora in one individual in the family might well propagate to many individuals in a village. If such a micro flora has an important role in defense against disease the implications are obvious. It might also be noted that thinking of this sort might be extended to the environment and as expertise in bacterial genetics improves the possibility of utilizing microbes which are harmless to man but which occupy the current ecological niches of human pathogens might be introduced into the environment and be every effective in interrupting the spread of illness. To convert thoughts like this into practical scientific investigations will require a great deal of thought and consultation at a basic microbiologic level and a further evolution of technology in bacterial genetics before such approaches can be realized.

### Immunity

With respect to the immune systems we currently have a major field intervention in the form of a vaccine trial which is testing what appears to be an optimal, parenteral vaccine

directed against cholera. This is really in a sense the ultimate trial growing out of previous trials which began here and in other places in the early 1960's. Already there are several concerns about the ultimate usefulness of parenteral vaccines. One of these concerns at a basic level is the possibility that parenteral vaccines may impede the development of local intestinal immunity. In the Matlab vaccine field trial area this hypothesis can be tested and plans are underway for the test of such questions.

From the present vaccine trial several important observations are to be made that were not possible in previous trials. The first of these will be on the development of local intestinal immunity to cholera toxin and LPS. The second will be on immunity in breast milk of immunized lactating mothers. These studies have grown out of recent developments in the field of gut immunology. Methods of investigating local immunity of the intestinal tract have been established here during the past year. It is anticipated that this embryonic start will grow into one of the major research thrusts of the laboratory over the next five years.

Data from humans who have been subjected to cholera in the United States has indicated that the local immune response is probably most important in protection against cholera. By extension it is likely that the same may be true in other enterotoxigenic diarrheas. In several countries a significant effort is in progress to develop stable vaccine strains of vibrio cholerae and E.coli. Thus coupled with an improved basic understanding of how the gut responds to antigens carried by pathogens is the prospect of potentially powerful oral vaccine against diarrheal disease. Another aspect of this is the possibility that there may be cross-protection at least to the toxins produced by several of the important pathogens. This seems a real possibility since the toxic noieties of E.coli, vibrio cholerae and vibrio cholera NAG are closely related antigenically.

Other determinants of whether or not disease follows colonization by a toxigenic bacteria relate to factors which allow bacteria to adhere closely to the intestinal mucosa. These factors are called adhesins or colonization factors. Little is known as yet about common antigenicity between the colonization factors of the different toxigenic bacteria. As basic information has been obtained however on cholera and the related toxigenic bacteria it seems more rather than less likely that approaches can be devised that may give some kind of broad protection against the watery diarrheas.

Initial work in this area will depend heavily on very well equipped and sophisticated laboratories backing up, intensive clinical studies carried out in the research units of the Cholera Research Laboratory. When possible concurrently field studies will also be done. It is likely, however, that several years may be needed before the appropriate tests for carrying studies of gut immunity into the field can be devised. However the close association of basic research on local immunity in the intestinal tract through collaboration between workers here and in the United States, Sweden, United Kingdom and Australia should bring rapid application to the field of developments as they occur.

#### DIARRHEA PATHOGENESIS AND THERAPY

The current concerns of this working group can be seen from the list of protocols that are currently either actually underway or ready to be implemented (Table 2).

##### Extension of Therapy

The highest priority of this working group at the present time is to see that the cheap, simple and effective means of treating watery diarrhea are made available to all individuals at risk within Bangladesh. A special sub-group has been formed which is exploring the different available strategies by which diarrhea treatment can be provided to all those at risk. Clearly this is a job that cannot be done simply by having CRL deliver treatment to an increasing number of individuals with diarrhea. The key to this will be finding a way in which the current knowledge of effective treatment of diarrhea can be propagated throughout all communities in this country.

At the present time we are exploring ways to further simplify the treatment of diarrhea patients by the establishment of Treatment Centers. We believe that such centers can be staffed primarily by individuals without formal training in medicine or nursing under the supervision of one or two trained nurses. Under epidemic conditions simple treatment centers were established in the Matlab-Chandpur area and were found to be highly effective. However, this was at a time when the government mounted a massive mobilizing medical students and many paramedical personnel. The present challenge will be to define community resources which would allow the establishment of simple centers as a backup to what can be done at home and as sites for education in the community.

As another approach at the CRL Treatment Center a program has been initiated which will require the attendants of patients to both mix and administer the oral rehydration necessary for the care of the sick individual. Since we are currently seeing close to 150,000 patients per year, including Dacca and Matlab, it is apparent that even if a few individuals learn how to do this and communicate this to their neighbours propagation may occur at a "grass roots" level. Many questions which must be resolved, some of these are as follows:

1. Should the main effort be toward establishing the local packaging of the more complex salt and glucose mixtures that have been advocated by the World Health Organization and by ourselves?
2. Should the treatment be simplified such that a family member might mix salt and locally available sugar with water in the appropriate combination to be given to a diarrhea patient?
3. Should treatment be visualized as always having to be provided through an outside party i.e. should the treatment be medicalized or should it be considered a home remedy that every family is able to administer at the first sign of diarrhea?
4. What sort of backup should be available for those cases in which oral rehydration fails? At present this will occur in about 25% of the most severe cholera cases but in only 1 or 2% of the most severe diarrhea due to other organisms.
5. What part of the overall care of individuals in Bangladesh should be related to the treatment of diarrhea?
6. What are other components in treatment such as diet, local medicines, etc. How do beliefs affect acceptance?

#### Clinical Studies

Underpinning these efforts have been a series of studies in the clinical research unit here. Carefully controlled double-blind comparisons between the efficacy of sucrose and glucose based electrolytes solutions have been carried out in children and adults with many different kinds of diarrheal illness. At the present time it can be said that although on the average there seems to be a slight advantage to glucose based solutions, a significant difference cannot be demonstrated between these two modalities in a large series of patients (Table 5). On the basis of these studies the treatment units

of the Cholera Research Laboratory have switched over entirely to sucrose based electrolyte replacement solutions. We are at the present time gaining experience in vast numbers of patients with these new solutions. As can be seen from Figure 2 there is an upper limit in rate of fluid loss above which both sucrose and glucose based oral solutions fail. This has to be borne in mind when approaching the treatment of cholera and provision made for intravenous hydration.

The next step in the sequence is to observe the effectiveness of simple salt-sucrose solutions without potassium or bicarbonate added. Locally available inexpensive products will be used in the form of lobon and gur. It is anticipated that since in most patients with acute watery diarrhea neither acidosis nor important potassium depletion is present initially, with adequate hydration return of electrolyte balance to normal will be achieved by normal homeostatic mechanisms and diet without the need of the added special salts. Should this prove to be the case then we can confidently go forward with an exceedingly simple and inexpensive program based on locally available materials.

At the present time we favour this strategy over the more complex one which involves establishing factories for the production of packets of the more complex more ideal mixture as the first step and then establishing an effective distribution system to all parts of the country that would reach down to the household level. Such an approach is also being pursued but we have doubts that it can be realized in the immediate future.

#### Diarrhea Therapy and Nutrition

A crucial part of the evaluation of oral rehydration will be to determine the effect of consistent application of this modality on the nutritional status of a cohort of young children. In Matlab, a longitudinal study is being devised which will compare several well-matched villages with respect to different interventions in the treatment of diarrhea in the early years of life. Data from the Philippines has suggested that the regular use of oral rehydration in the diarrheas of infancy and childhood will result in improved nutritional status. This hypothesis will be subject to critical scrutiny in these longitudinal studies. These studies will also indicate whether diarrhea treatment may be more effective in one or another kind of diarrheal illness. Larger scale field trials of oral rehydration in diarrhea are conceived of as growing out of the work in communities where treatment centers may be established and different strategies employed to establish optimum oral rehydration.

## Antisecretory Agents

One of the clear limitations of oral rehydration is the fact that particularly in cholera patients having a very high rate of fluid loss it may be impossible to keep up with these losses simply due to the limitations of the absorptive capacity of the intestinal tract. Thus, if agents could be devised which would diminish even by a factor of 30 or 40% the very high secretion rate seen in cholera a great deal of intravenous therapy would be obviated. Hence a priority for research in the Clinical Research Unit will be the exploration of various potential anti-secretory drugs. Candidates for such trials at the present time would seem to be nicotinic acid, some of the prostoglandin inhibitors, and local anesthetic remedies which seem to have some documentation that they may indeed reduce the rate of fluid loss. Studies of such interventions can be carried out in a very few patients that have a very high rate of purging in careful balance studies.

At the present time no one has established a clinically useful anti-secretory drug for use in cholera and related diarrheas. This is despite a very detailed knowledge of the mechanisms by which the cholera toxin produced fluid loss from the gut. In developing such agents it is important to remember that diarrhea itself may be a protective mechanism when not so extreme as to kill the patient. Thus caution will have to be exercised in exploring any really potent anti-secretory drugs. We already know that anti-motility drugs tend to enhance the severity of shigellosis.

In seeking ways to interfere with the secretory processes of the gut it will be necessary to further define certain basic mechanisms for regulating gut secretion and absorption. Such studies are very much dependent on new assay techniques for hormones which are responsible for these functions. It is anticipated that as methodology becomes available for looking at newly discovered regulating substances for the intestinal tract studies will be carried out to define the patho-physiology related to such regulators in the various kinds of diarrhea which are observed in Bangladesh. Although in initial stages such studies are likely to seem quite academic, it will be through a better understanding of the alterations of gut physiology in diarrhea that we may appropriately intervene to reduce the fluid losses which are incurred by the enterotoxigenic pathogens.

## Shigella Dysentery

If one looks at the patients who have come to the attention of the Cholera Research Laboratory over the past 5 years it is apparent that a very large, important proportion suffer from non-watery diarrhea or dysenteries. When individuals have fever, abdominal pain, blood and mucous in the stool the

shigellae are usually found. During the major outbreak of shiga dysentery in 1974 and 1975 this Laboratory showed that devastating effects of the disease in the Teknaf area and defined an approach that reduced mortality. A new severe complication syndrome characterized by leukemoid reaction of the granulocyte series and a very rapid hemolysis of red cells with fragmentation was described. Death in such circumstances was associated with renal decompensation, uremia and very severe anemia. It was found that the hemolytic-uremic syndrome correlated quite well with the early appearance of endotoxin in the blood stream during the acute dysenteric phase of disease. It was also shown that circulating immune complexes probably played no particular role in the disorder. A relatively effective treatment was devised which since it involved transfusion and antibiotics was very costly.

Blood cultures in shigellosis have indicated that bacteremia may not be as infrequent as previously thought. However, there are many patients who appear to have gram negative shock but are not bacteremic. A great deal more work is necessary to clarify the clinical syndromes of shigellosis. It is also necessary to further define the pathogenesis of this disease particularly from the point of view of the earlier stages of invasion and proliferation of the bacteria in the intestinal tract. Intervention strategies are a big problem although recently studies here have shown that one dose of ampicillin seems to be effective clinically as a five day course. It is equally apparent that the shigello bacilli very rapidly acquire resistance to all known antibiotics.

Thus any overall strategy of prevention or cure by antibiotic therapy seems doomed to failure over the long run. For this reason there must be new approaches. Possibilities would lie in recognizing those particular factors possessed by the shigellae which attach to receptors in the intestinal epithelium and produce invasion. By defining these then antibodies or other receptor blocking maneuvers can be devised which might prevent attachment and invasion. Since basically shigellosis is a self-contained disease and the main problem is the severity of the reaction to the invasion phase a better understanding of the cascade of events which follow invasion and produce shock and subsequent hemolytic-uremia syndrome may also provide ways for intervening even after invasion has occurred in an effective and less expensive way than are available at the present time.

### Enteric Fever

Diarrhea due to salmonella seems rare in Bangladesh and we have not as yet done any studies to define the incidence of

enteric fevers or what proportion might be due to invasive salmonellae. We do see typhoid fever with some frequency. Remaining as an area which requires further definition is the large number of patients which come with the complaints of soft stool, a great deal of mucous, abdominal pain and sometimes low-grade fever. To date this syndrome has not correlated well with any of the commonly recognized pathogens either parasitic or bacterial. We know nothing about the clinical course or consequences of this illness. Nor are we aware of its age incidence or distribution in the community. This is perhaps the largest undefined area of diarrheal illness remaining.

### Complications of Diarrhea

A comment is warranted with regard to the complications associated with diarrheal illness. Since we are seeing between 8 and 10,000 patients per month in Dacca alone we also see a great many complications. At the present time these cases are admitted to a general ward and we see approximately 200 of them each month. These are primarily small children with dysentery or chronic diarrheas often without a pathogen who are severely under-nourished. They frequently have septicaemia or respiratory infections and over the past years have been cared for in the classical approach of the highest technology possible. Of course, in Bangladesh this amounts to considerably less in technology than intensive care with cost purchases in the \$ 500 - 600 patient day in the West. However, in proportion to the effort and expense devoted to taking care of the majority of uncomplicated cases, immense resources are involved in this effort.

It is quite clear that none of the District Hospitals are equipped to mount such an effort. We also do not know what is important in what we do and what may not be important. A current priority has been set to try and dissect which maneuvers truly contribute to the survival over the longer term of the patients that we care for. I personally have an overriding suspicion that some of the simple and less expensive things are more important than the more complex ones. Our plans in the future in this area will be to make simplifications in the care process carefully watching for any increased morbidity or mortality.

In most instances, however, the patients that arrive in the severely malnourished state with chronic diarrhea are situations which if recognized in their local communities several months earlier could have been prevented with cheap and simple interventions. Our long term effort must be to establish such interventions in the communities from which such patients come.

## SUMMARY

The diarrheal diseases program is presently focusing upon defining the role of several new pathogens which contribute to the matrix of diarrheal illness in rural Bangladesh. We are seeking to understand the ways in which each responsible agent is spread in the community with the goal of defining simple and effective interventions that will interrupt the cycle of disease. The relationships of the various causes of diarrhea to states of malnutrition, poor growth and mortality particularly in the younger age groups are a high priority. Strategies to provide the known simple and effective modalities for the care of watery diarrhea in every household in Bangladesh are being developed. Since such a task is enormous this implies a close co-operation with not only the institutions and government of this country but directly with individual and communities as well. Simplifications of this already simple treatment are being explored with the ultimate goal of making each family self-sufficient in the treatment of simple diarrhea in this and other countries.

Studies directed at understanding the role of local intestinal immunity in diarrheal illness are a major effort and will increase over the next five years. It is expected that this effort will lead to the testing of both killed and live, oral vaccines against various diarrheal diseases within this time frame.

Basic studies in the pathogenesis of diarrheal disease will continue in an effort to define points in the cycle of disease which can be effectively altered to prevent illness or reduce morbidity and mortality. Over the longer term it is anticipated that studies will extend into the invasive bacteria that enter the body through the gut and cause fever such as typhoid and other enteric fevers. It is also anticipated that as increased understanding of local immune processes occurs that some of the techniques applied to the gut may be applicable to the respiratory tract and that the studies of selected, important respiratory diseases may be undertaken at a later time.

Table 1

Annual Diarrhea Incidence (episode per person) by age  
in Urban and Rural Bangladesh

| Incidence          |                 | Rural (1975)                   |                 |                     |                 |                               |
|--------------------|-----------------|--------------------------------|-----------------|---------------------|-----------------|-------------------------------|
| Urban<br>(1964-66) | Rural<br>(1975) | Prevalence <sup>a</sup><br>(%) | Popn<br>(000's) | Episodes<br>(000's) | Episodes<br>(%) | Morbidity<br>(000s<br>person) |
| 1.62 )             | 1.86            | 4.1                            | 11.4            | 86.7                | 39              | 344                           |
| 0.90 /             |                 |                                | 35.2            |                     |                 |                               |
| 0.38               | 1.07            | 2.4                            | 36.0            | 38.5                | 17              | 302                           |
| 0.10 <sup>b</sup>  | 0.52            | 1.1                            | 41.3            | 21.5                | 10              | 177                           |
| 0.09               | 0.56            | 1.2                            | 139.5           | 78.2                | 35              | 370                           |
| 0.31               | 0.90            | 2.0                            | 263.4           | 224.9               | 101             | 1000                          |

Source: Urban data from: W.H. Mosley and M.U. Khan, "Diarrheal Studies in Rayer Bazaar," Cholera Research Laboratory, Dacca, 1977.

Rural data from: G.T. Curlin, K.M.A. Aziz, and M.R. Khan, "The Influence of Drinking Tubewell Water," paper presented at the Twelfth Joint Conference on Cholera: U.S.-Japan Cooperative Medical Science Program, Sapporo, Japan, October 1976.

- a. Assumes diarrhea duration of 8 days per episode  
b. For 10-19 year age group.

TABLE 2

DIARRHEA THERAPY

| <u>Protocol Number</u> | <u>Title</u>                                                                                   | <u>Principal Investigator</u> | <u>Period of Study</u> |
|------------------------|------------------------------------------------------------------------------------------------|-------------------------------|------------------------|
| 77-003                 | Single Dose Doxycycline for Cholera                                                            | D. Sack                       | Mar 77 - Oct 77        |
| 77-004                 | A Clinical Trial of Trimethoprim & Sulphamethoxazole (Bactrim) in the Treatment of Shigellosis | Md. Yunus                     | Oct 76 - July 78       |
| 77-017                 | Sucrose vs Glucose Electrolyte Oral Solution - in the diarrhea of infants                      | D. Sack                       | July 77 - Dec 78       |
| Planned                | Lobon-Gur (Common salt + Brown Sugar) Oral rehydration solution in the diarrhea of adults.     | R. Islam                      | Feb 78 - Mar 78        |
| Planned                | Studies on Hypoglycemia in Diarrhea                                                            | A.K.M.J. Alam<br>R. Islam     |                        |
| Complete               | Single Dose Ampicillin in Shigellosis                                                          | R. Gilman                     |                        |
| 77-018                 | Sucrose vs Glucose Electrolyte Oral Solution - in the diarrhea of adults                       | S. Islam                      | Sep 77 - July 78       |

TABLE 3

Etiology of Diarrhea  
Matlab Hospital  
All VTS Patients  
November 17 - December 27, 1977

| <u>AGE</u> | <u>Rota</u>  | <u>Cholera</u> | <u>Others*</u> | <u>Unknown</u> | <u>Total</u> |
|------------|--------------|----------------|----------------|----------------|--------------|
| 0-3m       | 2** (7.4)*** | 0 (0)          | 2              | 4              | 8            |
| 4-6m       | 20 (102.3)   | 1 (5.1)        | 6              | 33 17          | 44           |
| 7-9m       | 50 (249.9)   | 3 (15.0)       | 5              | 17 41          | 99           |
| 10-12m     | 40 (312.0)   | 2 (16.0)       | 2              | 63 19          | 63           |
| 1-2y       | 123 (155.7)  | 9 (11.4)       | 11             | 72             | 215          |
| 2-3y       | 3 (2.7)      | 8 (7.2)        | 3              | 14             | 28           |
| 3-6y       | 2 (2.1)      | 13 (13.4)      | 1              | 11             | 27           |
| 4-5y       | 1 (1.1)      | 23 (25.0)      | 1              | 8              | 33           |
| > 5y       | 0 (0)        | 55 (2.2)       | 32             | 68             | 155          |
| Total      | 241          | 114            | 63             | 254            | 672          |

\* Includes shigellae, salmonellae, NAG, LT/ST enterotoxigenic E. coli by slide agglutination.

\*\* No. of cases

\*\*\*Number in parenthesis represents projected annual incidence per 1000 population.

TABLE 4

DIARRHEAL DISEASE TRANSMISSION

| <u>Protocol Number</u> | <u>Title</u>                                                                                                        | <u>Principal Investigator</u> | <u>Period of Study</u> |
|------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------|------------------------|
| 77-012                 | Epidemiology of Enterotoxigenic <u>Escherichia coli</u> Diarrhea                                                    | R. Black                      | Aug 77 - July 79       |
| 77-013                 | Polyphasic Characterization of <u>Vibrio Cholerae</u> , NAG, & Related Organisms.                                   | W. Spira                      | Sept 77 - Oct 78       |
| 77-022                 | Life Cycle of F. Buski                                                                                              | R. Gilman                     | Sept 77 - Oct 78       |
| 77-023                 | Comparison of Selective Plating Media for Isolating <u>Vibrio Cholerae</u> and Characterization of Isolated Strains | M. Merson<br>G. Morris        | Dec 77 - Jan 78        |
| 77-024                 | Epidemiology - F. Buski                                                                                             | R. Gilman                     | Sept 77 - Sept 78      |
| 77-025                 | Epidemiology & Family Studies of Enterotoxigenic <u>Escherichia coli</u>                                            | R. Black                      | Oct 77 - Dec 77        |
| 77-031                 | Enterotoxigenic & Enteropathogenic <u>Escherichia coli</u> , Serotypes, Antibiotic Sensitivity & Disease            | M. Merson                     | Oct 77 - Mar 78        |
| 78-003                 | Epidemiology of Rotavirus Diarrhea                                                                                  | M. Merson                     | Dec 77 - Mar 78        |
| Planned                | Water and Sanitation Intervention (Bangladesh)                                                                      | M.M. Rahaman                  | Mar 78 - Feb 80        |

TABLE 5

HOST SUSCEPTIBILITY

| <u>Protocol Number</u> | <u>Title</u>                                                                                                | <u>Principal Investigator</u> | <u>Period of Study</u> |
|------------------------|-------------------------------------------------------------------------------------------------------------|-------------------------------|------------------------|
| 77-006                 | The Sereny Test: A Model for Determining Virulence & Immunologic Protection from Invasive Enteric Organisms | D. Sack                       | July 77 - May 78       |
| 77-011                 | Local Immune Response in Cholera                                                                            | D. Sack                       | May 77 - May 79        |
| 77-029                 | Gastric Acid in Enteric Disease                                                                             | R. Gilman                     | Sept 77 - May 78       |
| 78-004                 | Pre-test of Cholera Vaccines for the 1978 Cholera Vaccine Field Trial                                       | M. Merson                     | Jan 78 - Apr 78        |
| 78-005                 | Local Immune Response to the Field Trial Cholera Vaccines                                                   | D. Sack                       | Jan 78 - Jan 79        |
| 1974 Vaccine Trial     | Mass Vaccination with Tetanus Toxoid Effect of one or two Injections on Neonatal Mortality                  | R. Black                      |                        |
| Planned                | Cholera Vaccine Field Trial                                                                                 | M. Merson                     | May 78 - Jun 80        |

Fig. 1

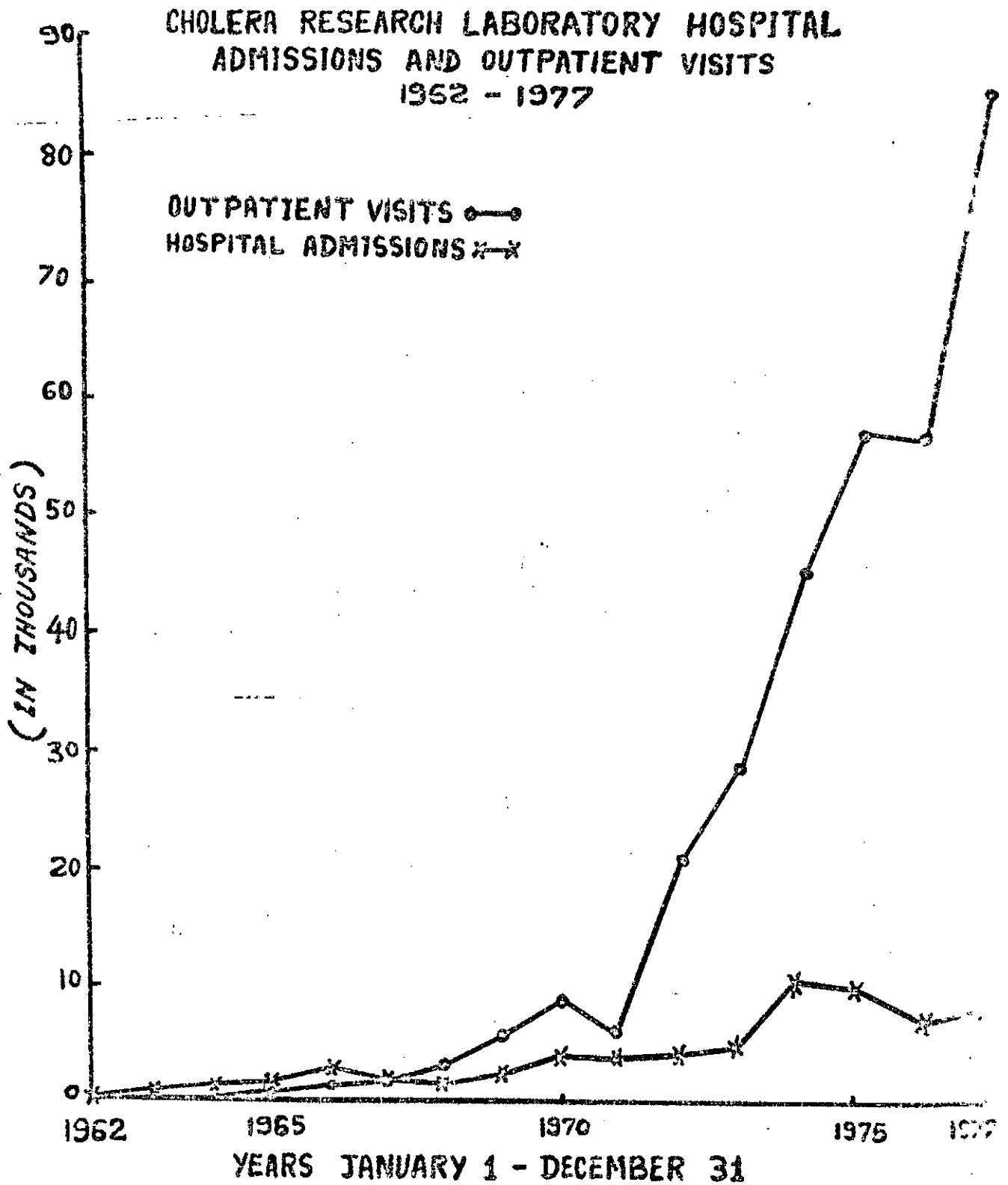
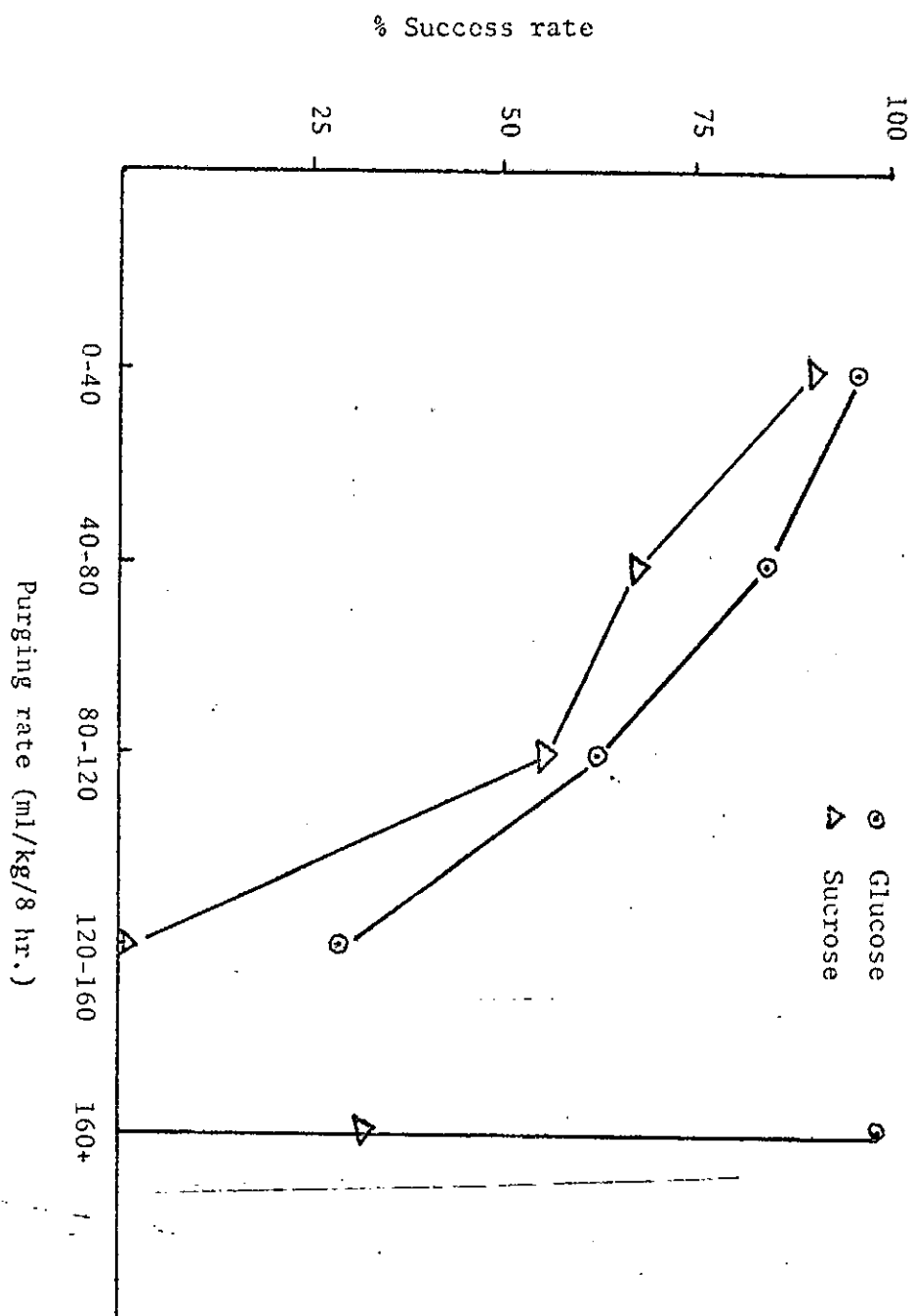


FIGURE 2

ASSOCIATION BETWEEN SUCCESS AND PURGING  
IN ADULTS WITH SEVERE WATERY DIARRHOEA



# DIARRHEAL DISEASE TRANSMISSION

| <u>Protocol Number</u> | <u>Title</u>                                                                                                        | <u>Principal Investigator</u> | <u>Period of Study</u> |
|------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------|------------------------|
| 77-012                 | Epidemiology of Enterotoxigenic <u>Escherichia coli</u> Diarrhea                                                    | R. Black                      | Aug 77 - July 79       |
| 77-013                 | Polyphasic Characterization of <u>Vibrio Cholerae</u> , NAG, & Related Organisms.                                   | W. Spira                      | Sept 77 - Oct 78       |
| 77-022                 | Life Cycle of F. Buski                                                                                              | R. Gilman                     | Sept 77 - Oct 78       |
| 77-023                 | Comparison of Selective Plating Media for Isolating <u>Vibrio Cholerae</u> and Characterization of Isolated Strains | M. Merson<br>G. Morris        | Dec 77 - Jan 78        |
| 77-024                 | Epidemiology - F. Buski                                                                                             | R. Gilman                     | Sept 77 - Sept 78      |
| 77-025                 | Epidemiology & Family Studies of Enterotoxigenic <u>Escherichia coli</u>                                            | R. Black                      | Oct 77 - Dec 77        |
| 77-031                 | Enterotoxigenic & Enteropathogenic <u>Escherichia coli</u> , Serotypes, Antibiotic Sensitivity & Disease            | M. Merson                     | Oct 77 - Mar 78        |
| 78-003                 | Epidemiology of Rotavirus Diarrhea                                                                                  | M. Merson                     | Dec 77 - Mar 78        |
| Planned                | Water and Sanitation Intervention (Bangladesh)                                                                      | M.M. Rahaman                  | Mar 78 - Feb 79        |

# EPIDEMIOLOGY OF ENTEROTOXIGENIC ESCHERCHIA COLI DIARRHEA

Robert E. Black, M.D.

## ABSTRACT

Diarrhea caused by enterotoxigenic Escherchia coli (ETEC) is probably an important cause of morbidity and mortality in developing countries. In previous studies in Bangladesh ETEC were isolated from 20 to 70% of patients with acute watery diarrhea without other known pathogen isolated.

Application of laboratory techniques for identification of ETEC currently available at the Cholera Research Laboratory to a sample of patients in Matlab, along with the demographic data currently available, will permit a study of the epidemiology of ETEC diarrhea in an endemic area. To obtain reliable information about age, sex seasonal and geographical incidence of ETEC diarrhea, the study will be conducted over a two year period (February 1977 to January 1979). Data tabulations, analysis and publication is expected to take an additional six months (until July 1979).

## PROGRESS REPORT

Residents of the Matlab Field Surveillance Area who are treated for diarrhea or dysentery at Matlab hospital are routinely cultured for Vibrios, Salmonella, and Shigella. Since February, 1977, a systematic sample of these rectal cultures have also been tested for enterotoxigenic Escherchia coli (ETEC) by the Chinese Hamster Ovary Assay and the Infant Mouse Assay.

During the first five months of surveillance, 39% of inpatients and 32% of outpatients were infected with ETEC. The proportion of inpatients positive for ETEC was 54% for adults (age 10 and over) and 27% for children. The results from these five months have been used to estimate the annual incidence by age of Matlab visits (inpatient and outpatient) for illness associated with ETEC (Table 1). For all these toxin types, (ST only, ST/LT, LT only) the annual incidence is highest for children less than two years of age and drops markedly by age 5-9 years. However, ETEC of all three toxin types continue to affect adults and, with ST/LT and ST only ETEC the incidence appears to be higher in adults than in 5-9 year old children.

After one year is completed, the results will be analyzed to determine the incidence by age, sex, and religion of diarrheal disease associated with ST only, ST/LT and LT only ETEC. We will also attempt to determine if the severity of diarrhea is influenced by age, sex, enterotoxin type, season, presence of intestinal parasites or nutritional status and to define the seasonal and geographical pattern of ETEC in Matlab.

ESTIMATED ANNUAL INCIDENCE BY AGE OF MATLAB HOSPITAL VISITS  
FOR ILLNESS ASSOCIATED WITH ENTEROTOXIGENIC E. COLI, 1977

E. COLI TOXIN TYPE

| <u>AGE</u><br><u>(YRS)</u> | <u>Pop</u><br><u>(1976 est)</u> | <u>ST</u><br><u>(per 1000)</u> | <u>LT</u><br><u>(per 1000)</u> | <u>ST/LT</u><br><u>(per 1000)</u> | <u>TOTAL</u><br><u>(per 1000)</u> |
|----------------------------|---------------------------------|--------------------------------|--------------------------------|-----------------------------------|-----------------------------------|
| < 2                        | 13,687                          | 33.7                           | 18.2                           | 15.2                              | 16.2                              |
| 2-4                        | 26,007                          | 2.3                            | 1.3                            | 2.9                               | 6.6                               |
| 5-9                        | 36,388                          | 1.4                            | 0.3                            | 0.7                               | 2.4                               |
| 10-19                      | 72,489                          | 1.2                            | 0.4                            | 1.4                               | 3.0                               |
| 20-29                      | 32,468                          | 2.1                            | 0.7                            | 1.5                               | 4.4                               |
| 30+                        | 79,342                          | 1.8                            | 0.4                            | 2.1                               | 4.4                               |
| <hr/>                      |                                 |                                |                                |                                   |                                   |
| Total:                     | 260,387                         | 3.3                            | 1.5                            | 2.4                               | 7.2                               |

POLYPHASIC CHARACTERIZATION OF VIBRIO CHOLERAE  
NAG AND RELATED ORGANISMS

W.M. Spira, Ph.D

ABSTRACT

The purpose of this collaborative study with the University of Surrey, England, is to establish a rational taxonomically-oriented classification for the so-called "non-agglutinating" varieties of Vibrio cholerae which adequately characterizes their potential as human pathogens. An immediate practical benefit of this classification will be the subsequent development of diagnostic schemes for the determination of the pathogenic members of the group.

Isolates of V. cholerae NAG and related organisms will be obtained from patients at the CRL, from aquatic sources, and from established culture collections elsewhere in the world to provide a wide spectrum of isolates representing different environmental backgrounds. In addition, the patients at CRL from whom NAG vibrios are isolated will be placed under careful observation during the course of their illness to develop a thorough clinical picture of documented NAG diarrhea.

The pool of isolates will be subjected to a battery of standard confirmatory tests based on traditional laboratory methods in vibrio classification. They will then be tested for biological activity in animal models (infant rabbit, rabbit ileal loop, mouse lethal test), for the production of toxic substances (CHO and adrenal cell assays, ELISA assay for cholera-like substances, suckling mouse assay, and rabbit vascular permeability assay), and for adherence factors (adhesion of intact mucosal tissue or brush border cells, and direct hemagglutination). After this, isolates will be taken to the University of Surrey where they will undergo battery of additional tests designed to characterize biochemical adaptability, resistance to environmental stress and phenotypic properties considered to be variable in this group of organisms.

The data base generated will be coded for computer and subjected to cluster analysis to establish groupings within the V. cholerae NAG which will further characterize those members which are likely to be human-associated or pathogenic. Representatives from each cluster will be used for further genetic analysis. Identification schemes for diagnostic use will be developed from differential characters identified in the taxonomic analysis.

## PROGRESS REPORT

The basic purpose of this study is to define the potential of V. cholerae, NAG as a human pathogen, to identify which members of the group are likely to be pathogenic, and to develop diagnostic schemes for their detection. This study, which was begun ten weeks ago, has so far concentrated on isolating and classifying NAG vibrios from patients admitted to the CRL Treatment Center, and on characterizing the illness with which they are associated. One problem we faced during this period was screening for the relatively infrequent NAG vibrio patient. We had to use darkfield microscopy, which is difficult to apply to these organisms primarily because of low motility in the population. In order not to miss cases, we have had to resort to extremely intensive and lengthy observations coupled with enrichment cultures. Our sensitivity is enough, however, that we have missed only 5% of the NAG vibrios which have later been demonstrated by culture.

Thus far, 40 patients have been admitted to the study. The distribution of isolates is: NAG Neiberg Group (HG) II - 15; HG V - 5; HG VII - 2; V. parahacmolyticus - 13; Aeromonas sp. - 2; unidentified Vibrio-like organisms - 1. Two of the HG II isolations were from mixed infections with Shigella boydii. No other pathogens have been found in the other patients so far, though the tests for rotavirus and enterotoxigenic E. coli are still pending. The stools from which these isolates were obtained were also screened for sub-populations of antibiotic resistant members of the same group. All populations tested harboured sulfoxazole and tetracycline resistant organisms, about half of which were also streptomycin resistant. These are being maintained in order to compare their biological activity with their non-resistant co-isolates, as well as for further characterization of their resistance factors.

# LIFE-CYCLE OF F. BUSKI

R. Gilman, M.D.

## ABSTRACT

F. buski is endemic in Bangladesh. Life cycles' studies are necessary to delineate the intermediate snail host vector. Susceptibility of snail hosts to infection with F. buski miracidium from both endemic and non-endemic regions will establish area susceptibility.

Seasonal snail dynamics and natural infection with cercariae of F. buski will be determined. Plants given by weight will be fed to rabbits to survey a given area for metacysts.

EPIDEMIOLOGY - F. BUSKI

Robert R. Gilman, M.D.

ABSTRACT

A Fasciolopsis buski endemic village will have a census performed. Stool samples from children (0-12) and all women in the village will be examined by formal ether and Methiolate-Iodine-Formalin technique. Ova counts will be determined. Nutritional Anthropometrics will be measured and the hematocrit and total plasma protein determined. Antibody titers to endamebae histolytica and Fasciolopsis buski will be determined. Villagers will be followed quarterly to establish seasonality of acquisition and to follow growth rates.

## PROGRESS REPORT

During the last year a study of Fasciolopsis buski infection was initiated. A review of the literature here and in Calcutta revealed the first reported case in 1958 from the Demra region east of Dacca city. A second report in 1960 also reported a case from Demra High School. Similar reports from the eastern and south-eastern area of Dacca have been reported by others. We have mapped the area from which patients coming to the Cholera Hospital with buski infection are located. We used shigella patients as a control of the hospital catchment area and found most of the patients were in the east and south-east area of Dacca.

Two villages have been studied for F. buski prevalence in this endemic zone. Over 60% of children over three years of age were infected.

The life cycle here is similar to other areas. Planorbidae snails are present in endemic and non-endemic areas. Gymnocephalus cercariae (associated with F. buski) were found in snails segmentina and hippeutis species taken from the endemic area. Segmentina and hippeutis snails from a known non-endemic area (Meheran) did not have gymnocephalus cercariae. However, rates of infection in snails have never been higher than 4% in the endemic area. Miracidium have been hatched from F. buski eggs derived from both flukes and eggs found in stools and have infected snails of hippeutis and segmentina species. In hippeutis, all snails died within two weeks but infective forms were found in eight or eleven crushed snails. In segmentina, infection went to cercarial stage. Metacysts, however, have still not been produced. The hippeutis infected were from the non-endemic area.

Although water chestnut (Trapa natans) grow wild, it is located far from the two study villages and eaten sporadically. The major water plant consumed is water lily or lotus, the national flower. It is often eaten raw like celery. Metacysts have not yet been isolated from it however.

An indirect fluorescent antibody test was developed. It is specific but too insensitive to be used as an epidemiological tool.

Patients with F. buski infection have had flukes expelled after tetrachlorethylene treatment. The mean number of flukes present has been about 100.

Village studies are now being collated to see if nutritional parameters are affected when heavy buski infection is present.

COMPARISON OF SELECTIVE PLATING MEDIA FOR ISOLATING  
VIBRIO CHOLERAЕ AND CHARACTERIZATION OF ISOLATED STRAINS

Michael H. Merson, M.D.

ABSTRACT

Five selective agar plating media will be evaluated for isolating V. cholerae from clinical specimens from patients with cholera-like illness. The plating media to be compared are two commercial brands of thiosulfate-citrate-bile salts-sucrose (TCBS) agar, alkaline-bile salts-tellurite-gelatin agar (Monsur's), Vibrio Parahemolyticus (VP) agar, and the newly developed sucrose-teepoltellurite (STT) agar. The V. cholerae isolates will be examined for rate of sucrose fermentation and toxigenicity. Toxin determinations will be done in the CHO, rabbit skin and ELISA assays. Additional V. cholerae organisms isolated from the environment in 1976 and 1977 will also be tested for toxigenicity. If any non- or slow-sucrose fermenting strains or non-toxigenic strains are isolated, their epidemiology will be investigated.

There is not much point in treating individual cases. The

## PROGRESS REPORT

Data in Table 1 shows the comparative efficacy of the five plating media in isolating V. cholerae. Eiken TCBS, Monsur's and BBL TCBS agars were found to be of almost equal efficacy. There were three stool specimens from which V. cholerae was isolated on Eiken TCBS agar and not on BBL TCBS agar. The VP and STT agars were significantly inferior ( $p < .001$ ) to any of these three agars. There were fifteen specimens from which V. cholerae was isolated on Eiken TCBS or Monsur's agars and not on STT agar. Results of slide agglutination reactions with V. cholerae O1 antisera of colonies taken directly from the primary plating media are shown in Table 2. STT and Monsur's agar were found superior to TCBS and VP agars for direct agglutination.

No slow sucrose-fermentation colonies were isolated. Toxin testing of about 1000 patient isolates revealed one organism that was non-toxigenic in the rabbit skin, CHO and ELISA assays. Toxin testing of approximately 200 water isolates revealed two additional non-toxigenic isolates. Rabbit ileal loop studies are planned for these three isolates.

is not much point in treating individual cases. The

Table 1

Evaluation of 5 Plating Media for Isolation of V. cholerae from 157 specimens

| No.<br>Specimens        | <u>Media</u>               |                          |                       |                      |                          |
|-------------------------|----------------------------|--------------------------|-----------------------|----------------------|--------------------------|
|                         | <u>EIKEN<br/>TCBS agar</u> | <u>BBL TCBS<br/>agar</u> | <u>STT**<br/>agar</u> | <u>VP**<br/>agar</u> | <u>Monsur's<br/>agar</u> |
| 68                      | + *                        | +                        | +                     | +                    | +                        |
| 3                       | +                          | +                        | +                     | -                    | +                        |
| 8                       | +                          | +                        | -                     | +                    | +                        |
| 5                       | +                          | +                        | -                     | -                    | +                        |
| 2                       | +                          | -                        | -                     | +                    | +                        |
| 1                       | +                          | -                        | +                     | -                    | -                        |
| 1                       | -                          | -                        | -                     | -                    | +                        |
| 69                      | -                          | -                        | -                     | -                    | -                        |
| Total Pos.<br>specimens | 87                         | 84                       | 72                    | 78                   | 87                       |

\* indicate V. cholerae isolated on media.

\*\* sucrose teepol tellurite (STT) agar and Vibrio parahemolyticus (VP) agar are both significantly inferior to the TCBS agars and Monsur's agar (P < 0.05).

Table 2

Slide agglutination reaction on individual colonies directly from primary plating media with Vibrio cholerae O1 antiserum

Agglutination Reactions

| <u>Media</u>  | <u>Negative</u> | <u>1+</u> | <u>2+</u> | <u>3+</u> | <u>4+</u> |
|---------------|-----------------|-----------|-----------|-----------|-----------|
| Eiken TCBS    | 20              | 31        | 36        | 8         | 1         |
| BBL TCBS      | 15              | 24        | 41        | 13        | 2         |
| STT agar      | 2               | 1         | 2         | 30        | 54        |
| VP agar       | 12              | 15        | 43        | 15        | 1         |
| Monsur's agar | 1               | 5         | 7         | 28        | 55        |

# COMMUNITY & FAMILY STUDIES OF ENTEROTOXIGENIC ESCHERCHIA COLI

R.E. Black, M.D.

## ABSTRACT

A study to define the rates of clinically apparent and inapparent infection with E. coli producing heat-stable toxin (ST), heat-labile toxin (LT), or both will be conducted in a Bangladesh village (population 1100). Two field workers will live in the village for two months during October-December, 1977 and visit each family daily. At these visits he will culture all cases of diarrhea and previously selected control individuals who have not been ill for the previous week. These rectal cultures will be tested for enterotoxigenic E. coli using the Chinese hamster ovary tissue culture assay for LT and the infant mouse assay for ST at the Cholera Research Laboratory. One isolate per person with enterotoxigenic E. coli will be serotyped by Dr. Bernard Rowe, Colindale Laboratories.

A study of the epidemiology of enterotoxigenic E. coli (predominant strains producing ST and LT) will be done by investigating household contacts and the home environment of patients who are felt to have illness caused by enterotoxigenic E. coli. These index cases will be identified by screening E. coli picked from their stool cultures for one of the four most common serogroups associated with enterotoxigenic E. coli in Bangladesh. The E. coli will be tested by slide agglutination with a pool of antisera against O.6, O.8, O.73 and O.115 E. coli. Once the index case is identified, family members will be cultured for ten days and environmental specimens obtained for the first three days. The isolates of E. coli per specimen will be tested for the same O group as found in the index cases using individual antisera. The pool and single antisera will be supplied by Dr. Rowe who will also confirm one isolate per patient as E. coli and do complete serotyping.

PROCESS . . . CRT

In October, 1977, we began two studies of the epidemiology of diarrhea associated with enterotoxigenic E. coli (ETEC) in the Matlab Field Surveillance Area. A family study was designed 1) to determine the proportion of family members of ETEC positive patients who become ill or infected with ETEC in the ten days following the index case and the relation of these infections to age and initial antitoxin titers, and 2) to determine if ETEC in the environment (animals, food, water) is related to these infections. Index cases are selected by screening E. coli from V. cholerae negative Matlab patients for 4 O groups (6, 8, 78, 115) by slide agglutination and confirming the O group by tube agglutination. Index cases selected by this method have been enterotoxigenic in 90% of cases. To date, 33 index cases have been selected (Table 1) and family contact and environmental isolates have been screened for the same serogroup as the index case. Endotoxin testing of these isolates with the Chinese hamster ovary and the infant mouse assay is in progress.

Also, in October, community surveillance for diarrhea was started in one village. All cases of diarrhea and randomly selected controls have a rectal swab obtained and tested for Salmonella, Shigella, Vibrios, enterotoxigenic E. coli and rotavirus. Specimens are being processed.

Table 1

Enterotoxigenic Escherichia coli Isolates from the Family Study  
by Serogroup and Toxin Type

|         | 6 | 8 | <u>O Group</u> |            | Total |
|---------|---|---|----------------|------------|-------|
|         |   |   | <u>78</u>      | <u>115</u> |       |
| ST/LT   | 4 | 3 | 9              | 1          | 17    |
| ST only | 1 | 2 | 9              | 3          | 15    |
| LT only | 0 | 0 | 1              | 0          | 1     |
| Total   | 5 | 5 | 19             | 4          | 33    |

ENTEROTOXIGENIC AND ENTEROPATHOGENIC ESCHERICHIA COLI  
SEROTYPING, ANTIBIOTIC SENSITIVITY AND  
COMPARATIVE CLINICAL EVALUATION

Michael H. Mellon, M.D.

ABSTRACT

Stools from 1248 persons admitted in a one year period to the CRL Hospital with acute watery diarrhea will be examined for recognized enteric pathogens, including enterotoxigenic E. coli (ETEC), the classical enteropathogenic E. coli (EPEC), rotavirus and parvovirus (Norwalk Agent). Clinical features of illness associated with these organisms will be described. To better determine the importance of ETEC and EPEC as etiologic agents of diarrheal disease, the incidence of these organisms in this population will be compared to the incidence in persons of the same age admitted to another Dacca hospital with non-gastrointestinal illnesses.

The serotypes of ETEC isolated from approximately 350 patients in the study will be compared with serotypes of non-enterotoxigenic E. coli (non-ETEC) isolated from 862 patients with diarrhea of another etiology and 386 persons admitted to another Dacca hospital with non-gastrointestinal illnesses. The efficacy of newly prepared pools of antisera against specific O groups believed to be most commonly associated with ETEC strains will be determined. Antibiotic sensitivity of ETEC and non-ETEC isolates will be compared.

## PROGRESS REPORT

In November and December 304 watery diarrhea cases that were darkfield negative for Vibrio cholerae were admitted to the study. Etiology of these cases is shown in Table 1. Diagnosis has been made in 40% of cases to date. Slide agglutination tests to identify enterotoxigenic and enteropathogenic E. coli isolates from all cases have been initiated. Sera used to identify enterotoxigenic E. coli cases has been newly prepared from enterotoxigenic strains isolated from diarrhea cases in Bangladesh. Toxin-testing of a sample of slide positive and slide negative isolates will begin shortly.

Data has been accumulated for the rotavirus cases. Seven infections were in persons aged five and over. Admission stool electrolyte values (Table 2) indicate less electrolyte loss in these cases than is usually observed in diarrhea cases caused by toxin-producing organisms. We have examined stools from 125 persons with non-diarrheal illnesses, including 37 children aged 0-2, and none have been positive for rotavirus.

Table 1

Etiology of Diarrhea in Moderate to Severely Dehydrated Patients  
seen at Dacca Hospital, November - December, 1977

|              | <u>Chol</u> | <u>Shig</u> | <u>NAG</u> | <u>Rota</u> | <u>Sal</u> | <u>Mixed</u> | <u>Unknown</u> | <u>Total</u> |
|--------------|-------------|-------------|------------|-------------|------------|--------------|----------------|--------------|
| 0-2          | 2*          | 4           | 0          | 30          | 0          | 3            | 52             | 101          |
| 3-4          | 2           | 3           | 1          | 0           | 1          | 1            | 12             | 20           |
| 5-9          | 4           | 5           | 1          | 3           | 0          | 2            | 17             | 32           |
| 10-19        | 5           | 2           | 4          | 1           | 0          | 0            | 18             | 30           |
| 20-29        | 6           | 6           | 2          | 1           | 0          | 0            | 33             | 48           |
| 30-39        | 1           | 2           | 0          | 1           | 1          | 1            | 22             | 28           |
| 40-49        | 0           | 3           | 2          | 0           | 0          | 1            | 17             | 23           |
| ≥ 50         | 2           | 3           | 5          | 1           | 0          | 0            | 11             | 22           |
| <b>Total</b> | <b>22</b>   | <b>28</b>   | <b>15</b>  | <b>37</b>   | <b>2</b>   | <b>8</b>     | <b>182</b>     | <b>304</b>   |

\* Number of cases

Etiology of Diarrhea in Moderate to Severely Dehydrated Patients  
seen at Dacca Hospital, November - December, 1977

|     | <u>Chol</u> | <u>Shig</u> | <u>NAG</u> | <u>Rota</u> | <u>Sal</u> | <u>Mixed</u> | <u>Unknown</u> | <u>Total</u> |
|-----|-------------|-------------|------------|-------------|------------|--------------|----------------|--------------|
| 0   | 4           | 0           | 0          | 0           | 0          | 0            | 4              | 4            |
| 1   | 3           | 1           | 1          | 1           | 1          | 1            | 12             | 20           |
| 2   | 5           | 1           | 1          | 3           | 0          | 2            | 17             | 32           |
| 3   | 2           | 4           | 1          | 1           | 0          | 0            | 13             | 30           |
| 4   | 6           | 2           | 1          | 0           | 0          | 0            | 11             | 22           |
| 5   | 2           | 0           | 1          | 1           | 0          | 1            | 7              | 17           |
| 6   | 5           | 2           | 5          | 1           | 0          | 0            | 13             | 25           |
| 7   | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 8   | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 9   | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 10  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 11  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 12  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 13  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 14  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 15  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 16  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 17  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 18  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 19  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 20  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 21  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 22  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 23  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 24  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 25  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 26  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 27  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 28  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 29  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 30  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 31  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 32  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 33  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 34  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 35  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 36  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 37  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 38  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 39  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 40  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 41  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 42  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 43  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 44  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 45  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 46  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 47  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 48  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 49  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 50  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 51  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 52  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 53  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 54  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 55  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 56  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 57  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 58  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 59  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 60  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 61  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 62  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 63  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 64  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 65  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 66  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 67  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 68  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 69  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 70  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 71  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 72  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 73  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 74  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 75  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 76  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 77  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 78  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 79  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 80  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 81  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 82  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 83  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 84  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 85  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 86  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 87  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 88  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 89  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 90  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 91  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 92  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 93  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 94  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 95  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 96  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 97  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 98  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 99  | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |
| 100 | 1           | 2           | 2          | 1           | 0          | 0            | 6              | 12           |

Table 2

Admission Stool Electrolytes of 21 Rotavirus Cases\*

|             | <u>Meq/Liter <math>\pm</math> 1 S.E.</u> |       |     |
|-------------|------------------------------------------|-------|-----|
| Sodium      | 35.0                                     | $\pm$ | 5.7 |
| Potassium   | 34.7                                     | $\pm$ | 5.3 |
| Bicarbonate | 10.3                                     | $\pm$ | 2.9 |
| Chloride    | 30.8                                     | $\pm$ | 6.6 |

\* Mean plasma specific gravity patients of these cases was 1.028

# EPIDEMIOLOGY OF ROTAVIRUS DIARRHEA

Michael H. Merson, M.D.

## ABSTRACT

This study will define the epidemiology of rotavirus diarrhea in rural Bangladesh. Fifty cases of rotavirus diarrhea presenting at the Matlab Hospital will be identified by the ELISA assay during the winter season. The clinical course of hospitalized cases will be documented. Breast milk from lactating mothers of rotavirus cases and nasal secretions from cases will be screened for rotavirus and rotavirus antibodies by the ELISA assay. Dietary histories will be obtained from all rotavirus cases. All household contacts and bari contacts age five or less of all index cases will be examined for rotavirus infection by stool examination and serology. Stools from animals belonging to families of rotavirus cases will be examined for rotavirus and any rotavirus detected will be compared by RNA genotype analysis to rotavirus from cases. This study will provide information on the ratio of symptomatic/asymptomatic cases in rotavirus diarrhea, the transmission of the organism in the family and bari in man and animals, and the role of serum antibody in protection from disease. Cases of rotavirus diarrhea will also be identified by stool examination and serology in a village that has ongoing surveillance for E. coli diarrhea and other pathogens. Weights will be taken in young children using a standard schedule during and after diarrhea to examine the effect of rotavirus and other diarrheas on weight gain.

## PROGRESS REPORT

Since November 17, 1977 we have examined stools obtained from all VTS diarrhoea cases visiting the Matlab Hospital for rotavirus antigen by the ELISA assay. Results of this work for patients seen from November 17 - December 28 are shown in Table 1. Fifty-three per cent of children 0-2 years were infected with rotavirus and ninety-eight per cent of the rotavirus cases occurred before age 2. The projected annual incidence (perhaps inaccurate if this is an epidemic period) was highest in the last six months of the first year of life. Almost all children below age 2 were breast feeding and those below age 6 months were usually exclusively breast feeding. If the present rate exists throughout the year and no reinfection occurs, approximately 2/3 of children are seen at the hospital with rotavirus infection sometime in the first 2 years of life.

Two hundred and twelve of the cases (88%) had no clear evidence of dehydration or were mildly dehydrated when seen. All of these received glucose containing oral fluid for about 4 to 8 hours and despite the presence of vomiting in about 30% of cases, only 5% required subsequent hospitalization for intravenous fluid. The remaining 29 patients initially received intravenous fluid and then were maintained on oral fluid. We are presently evaluating a sucrose containing oral fluid for treatment of rotavirus patients.

Studies of transmission of rotavirus in the families and basis of hospital cases are presently in progress. The contrast in the age distribution of rotavirus and cholera is evident (see table) and suggests that different factors may be involved in transmission of these two diseases.

Etiology of Diarrhea  
Matlab Hospital  
All VTS Patients  
November 17 - December 27, 1977

| <u>AGE</u> | <u>Rota</u> | <u>Cholera</u> | <u>Others*</u> | <u>Unknown</u> | <u>Total</u> |
|------------|-------------|----------------|----------------|----------------|--------------|
| 0-3m       | 2**(7.4)*** | 0 (0)          | 2              | 4              | 8            |
| 4-6m       | 20(102.3)   | 1 (5.1)        | 6              | 17             | 44           |
| 7-9m       | 50(249.9)   | 3 (15.0)       | 5              | 41             | 99           |
| 10-12m     | 40(312.0)   | 2 (16.0)       | 2              | 19             | 63           |
| 1-2y       | 123(155.7)  | 9 (11.4)       | 11             | 72             | 215          |
| 2-3y       | 3(2.7)      | 8 (7.2)        | 3              | 14             | 28           |
| 3-4y       | 2(2.1)      | 13 (13.4)      | 1              | 11             | 27           |
| 4-5y       | 1(1.1)      | 23 (25.0)      | 1              | 8              | 33           |
| > 5y       | 0(0)        | 55 (2.2)       | 32             | 68             | 155          |
| Total      | 241         | 114            | 63             | 254            | 672          |

\* Includes shigellae, salmonellae, NAG, LT/ST enterotoxigenic E. coli by slide agglutination.

\*\* No. of cases

\*\*\*Number in parenthesis represents projected annual incidence per 1000 population.

# WATER AND SANITATION INTERVENTION (BANGLADESH)

M. Mujibur Rahaman, M.B.B.S. M.Sc. Ph.D

## ABSTRACT

Four communities in Teknaf and Shahpuridwip have been selected as experimental sites to be provided with a) water derived from handpumps, b) water from handpumps with water-sealed latrines and sanitary education, c) latrines only, and d) sanitary education only. Incidences of diarrhea and dysentery will be used to evaluate the impact of these intervention measures. Nutritional status will be measured periodically along with rate of skin infection and severity of worm load. Control areas will be the nearly comparable villages without the above intervention measure.

Diagnosis of the causes of diarrhea and dysentery will be carried out by bacteriological and virological techniques. Impact of these intervention measures alone or in combination should be reflected in the attack rates of diarrhea and dysentery as well as other parameters when compared to those of the control villages.

HOST SUSCEPTIBILITY

| <u>Protocol<br/>Number</u> | <u>Title</u>                                                                                                         | <u>Principal<br/>Investigator</u> | <u>Period of Study</u> |
|----------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------|------------------------|
| 77-006                     | The Sereny Test: A Model for<br>Determining Virulence & Immunologic<br>Protection from Invasive Enteric<br>Organisms | D. Sack                           | July 77 - May 78       |
| 77-011                     | Local Immune Response in Cholera                                                                                     | D. Sack                           | May 77 - May 79        |
| 77-029                     | Gastric Acid in Enteric Disease                                                                                      | R. Gilman                         | Sept 77 - May 78       |
| 78-004                     | Pre-test of Cholera Vaccines for the<br>1978 Cholera Vaccine Field Trial                                             | M. Merson                         | Jan 78 - Apr 78        |
| 78-005                     | Local Immune Response to the Field<br>Trial Cholera Vaccines                                                         | D. Sack                           | Jan 78 - Jan 79        |
| 1974<br>Vaccine<br>Trial   | Mass Vaccination with Tetanus Toxoid<br>Effect of one or two Injections on<br>Neonatal Mortality                     | R. Black                          |                        |
| Planned                    | Cholera Vaccine Field Trial                                                                                          | M. Merson                         | May 78 - Jun 81        |

THE SERENY TEST: A MODEL FOR DETERMINING VIRULENCE AND  
IMMUNOLOGIC PROTECTION FROM INVASIVE ENTERIC ORGANISMS

David A. Sack, M.D.

ABSTRACT

In this study we intend to compare the virulence as measured by the ED 50 in a sereny test of fifteen selected isolates of shigella and three isolates of invasive E. coli. In addition, we plan to determine the protection induced by one infection against a subsequent challenge with either a hemologous strain or heterologous invasive strain in bacteria. This study will help to elucidate one factor in the virulence of invasive enteric infections and further would explore the possibility of cross protection between shigella infections and E. coli infections.

## PROGRESS REPORT

The dose response curve has been determined for four invasive strains of bacteria (S. dys I 57053, S. flex 58127, S. sonnei 19882 and invasive E. coli O25:H-). Using five fold dilutions and inoculating one eye of five guinea pigs per group, the ED<sub>50</sub> results were remarkably similar among the strains tested (being approximately 10<sup>6</sup>/eye). The duration until conjunctivitis varied with the inoculum; however, no guinea pig became positive later than four days post inoculation. Of interest, however, was a marked difference in the duration of clinical conjunctivitis being  $\geq 14$  in S. flex and seven to ten days in the other three strains.

In limited reinoculation experiments using S. dys I, homologous protection is not complete since many eyes previously infected, again developed conjunctivitis with reinoculation.

Some serendipitous observations made during this study are that stools from patients with dysentery may give a positive sereny test; however, the reaction is delayed from ten to thirty days. This delayed positive reaction may occur with a stool which contains either Shigellae or even ameba and the pathogens can then be recovered from the positive eye of the guinea pig. This has only been seen to occur with guinea pigs deprived of Vitamin A and Vitamin C, but not in healthy guinea pigs. These serendipitous observations represent very few animals in an uncontrolled dietary regimen, however, so follow-up studies are needed.

## LOCAL IMMUNE RESPONSE IN CHOLERA

David A. Sack, M.D.

### ABSTRACT

Using several assays of immunologic function, recently adapted for use with cholera, we plan to quantitate the local intestinal as well as systemic immune response to cholera in humans. Acquired immunity to cholera is one of the defense mechanisms against reinfection with V. cholerae, and both local intestinal immunity (IgA) and systemic immunity are likely stimulated by the disease. While rises in serum anti-bacterial and antitoxic are well documented following the disease, the local immune response, which may be more important in protection, is less well understood. Various cholera vaccines have been developed for human use; however, the best and longest lasting protection is afforded by a previous episode of the disease, which gives excellent protection for at least one year. Documentation and quantitation of the local immune response to cholera would seem crucial to the evaluation of new cholera vaccines, especially if they are to be administered locally. Since antitoxic and antibacterial immunity may act synergistically, both types of antibodies would need to be measured. Assays which will be used include the following: Antitoxin - neutralization, hemagglutination, enzyme-linked immunosorbent (or radio immune assay) hemolytic plaque assay, and fluorescent antibody; Antibacterial-vibriocidal, enzyme-linked immunosorbent and vibriolytic plaque assay. The assays will be done using the following clinical specimens: serum, peripheral lymphocytes, duodenal secretion, and breast milk. These studies should form the basis for quantitating the local antitoxic and antibacterial immune response in human cholera and provide a basis for comparing the response in different population and nutritional groups, as well as providing a basis for the evaluation of potential new cholera vaccines designed to stimulate local immunity.

## PROGRESS REPORT

Ground work has been laid, specimens are being collected, but no significant data are available for analysis.

... 8 Septo-

... is not much point in treating individual cases. The

## GASTRIC ACID IN ENTERIC DISEASE

R. Gilman, M.D.

### ABSTRACT

A case control method will be used to evaluate gastric acid in patients with enteric disease. Adult patients with cholera, amebic dysentery, enterotoxigenic E. coli and shigellosis (30 in each group) will be compared in their ability to produce gastric acid after a 50mg betazole stimulus. They will be studied the morning after admission, seven days, one month and in a few cases three months after hospital admission. Gastric levels will also be determined.

## PROGRESS REPORT

Patients with cholera, amebiasis, toxigenic E.coli and acute shigellosis had gastric acid studies performed.

The major deficiency in acid production has been found in patients with acute cholera. Nine of 32 of these patients were hypochloric (less than 5 mEq/hour). Patients with cholera tended to increase their mEq/hour one month after disease. Hypochloric cholera patients appear to have a variable response one month after recovery. Two patients stayed hypochloric while three others were able to increase their acid output to over five mEq/hour. These patients tended to be older and often less well-nourished than the cholera patients. One of six patients with E.coli toxigenic diarrhea failed to produce over 5 mEq/hour after either histalog or pentagastrin stimulation.

Sequential studies of gastric acid production in malnourished children have also been performed. Nearly half the children studied did not decrease their pH below 2.5. In addition, lack of gastric stimulation was also supported by their inability to clear bacteria from the stomach after 1.0mg/kg of histalog.

Hypochlorhydria persists in most children well after recovery in weight has occurred.

Interpto-

There is not much point in treating individual cases. The

PRE-TEST OF CHOLERA VACCINES FOR THE  
1978 CHOLERA VACCINE FIELD TRIAL

Michael H. Merson, M.D.

ABSTRACT

Three new cholera vaccine products manufactured by Wellcome Foundation, London, will be field tested to confirm their safety and determine their immunogenicity in approximately 1,030 Bangladeshis living in the CRL Vaccine Trial Surveillance (VTS) area. These vaccines are: (1) an aluminum hydroxide adjuvanted, formalin-treated cholera toxoid; (2) an aluminum hydroxide adjuvanted cholera whole cell vaccine, and (3) a vaccine containing both the toxoid and whole cell vaccine. Tetanus toxoid will be administered as a placebo vaccine. All vaccinees will receive two 0.5 ml injections of one of the cholera vaccines or of tetanus toxoid at six week intervals. Physicians will examine each vaccinee on the day of inoculation, for four days following, and fourteen days after each injection. Fingertip blood specimens will be obtained on the day of each inoculation and two weeks after for determination of vibriocidal and antitoxin responses to the vaccines. If the cholera vaccines are found to be safe, a large scale field trial will be conducted with the vaccines prior to the fall 1978 cholera season.

PROGRESS REPORT

Pre-test of cholera vaccines for the 1978 Cholera Vaccine Field Trial started on January 23, 1978.

# LOCAL IMMUNE RESPONSE TO THE FIELD TRIAL CHOLERA VACCINE

David A. Sack, M.D.

## ABSTRACT

This study is planned to determine the effect of the field trial cholera vaccines on the local antitoxic immune system. The study will be divided into two sections. Part "A" will be an assessment of antitoxin titers in breast milk samples of lactating women receiving the vaccines. Part "B" will be an assessment of antitoxic immunity in blood, saliva and intestinal washings from a group of healthy volunteers in Dacca who receive the vaccine in an identical manner. It is hoped that these studies will help explain the results observed in the vaccine field trial and will help in understanding the basic mechanism of the local immune system in relation to cholera.

PROGRESS REPORT

New protocol. Work will start in the immediate future.

w pro-

MASS VACCINATION WITH TETANUS TOXOID -  
EFFECT OF ONE OR TWO INJECTIONS ON NEONATAL MORTALITY

R.E. Black, M.D.

Preliminary data for protocol preparation

During the 1974 cholera toxoid field trial, children age 1-14 years and adult women were randomly assigned to receive cholera toxoid or 0.5 ml tetanus and diphtheria toxoids (aluminum phosphate absorbed, for adult use) by jet injection. Subsequent birth cohorts from women vaccinated with one or two injections of either preparations are being analyzed to determine the effect of tetanus toxoid on neonatal mortality. In all groups (cholera toxoid 1 or 2 injections, tetanus toxoid 2 injections, and tetanus toxoid 1 injection) the neonatal mortality has decreased since 1974-75. However, this decrease has been most marked in the groups given tetanus toxoid (Table 1).

Since deaths from neonatal predominantly occur from the fourth to the fourteenth day of life, mortality from this time period is being analyzed separately (Table 2). It appears that 2 injections of tetanus toxoid given to non-pregnant women are highly protective against neonatal tetanus for at least 18-24 months after vaccination. One injection of tetanus toxoid appears to have been as protective as 2 injections for 6-18 months after vaccination; however, this effect is not apparent 18-24 months after vaccination.

Table 1

Neonatal Mortality by Mother's Vaccine Status in Four Birth Cohorts  
from the Matlab Field Surveillance Area, October 1974 - September 1976.

| <u>Birth Cohort</u>     | <u>Vaccine* Status of Mother</u>                    |                                                |                                               |
|-------------------------|-----------------------------------------------------|------------------------------------------------|-----------------------------------------------|
|                         | <u>Cholera toxoid</u><br><u>(1 or 2 injections)</u> | <u>Tetanus toxoid</u><br><u>(2 injections)</u> | <u>Tetanus toxoid</u><br><u>(1 injection)</u> |
| October 74 - March 75   | 79.4** (22/277)                                     | 125 (11/88)                                    | 71.9 (12/167)                                 |
| April 75 - September 75 | 86.5 (64/740)                                       | 39.9 (18/451)                                  | 40.0 (11/275)                                 |
| October 75 - March 76   | 53.7 (49/912)                                       | 47.2 (28/593)                                  | 30.9 (8/259)                                  |
| April 76 - September 76 | 55.6 (70/1260)                                      | 27.2 (24/882)                                  | 66.5 (22/331)                                 |

\* Given August - September 1974.

\*\* Per 1000 Live Births.

Table 2

Mortality at 4-14 days of age by Mother's Vaccination Status in Four  
Birth Cohorts from the Matlab Field Surveillance Area.  
October 1974 - September 1976.

| <u>Birth Cohort</u>                             | <u>Vaccine* Status of Mother</u>             |                                         |                                        |
|-------------------------------------------------|----------------------------------------------|-----------------------------------------|----------------------------------------|
|                                                 | <u>Cholera toxoid</u><br>(1 or 2 injections) | <u>Tetanus toxoid</u><br>(2 injections) | <u>Tetanus toxoid</u><br>(1 injection) |
| October 74 - March 75*<br>(pregnant women)      | 26.1** (7/268)                               | 0 (0/82)                                | 37.0 (6/162)                           |
| April 75 - September 75<br>(non-pregnant women) | 46.2 (35/758)                                | 9.1 (4/440)                             | 7.5 (2/267)                            |
| October 75 - March 76<br>non-pregnant women)    | 19.1 (17/889)                                | 7.0 (4/573)                             | 7.9 (2/254)                            |
| April 76 - September 76<br>(non-pregnant women) | 28.4 (35/1231)                               | 3.5 (3.866)                             | 24.9 (8/321)                           |

\* Given August - September 1974

\*\* per 1000 children surviving to age 4 days.

## CHOLERA VACCINE FIELD TRIAL

Michael H. Merson, M.D.

### ABSTRACT

Prior to the 1978 fall cholera season, all adult, non-pregnant women and children aged 1-14 living in the Matlab VTS area will be given in a double blind manner two intramuscular 0.5 ml injections six weeks apart of one of four vaccine preparations: a formalin treated cholera toxoid (TOX), a cholera whole cell vaccine made with inactivated Inaba and Ogawa organisms (WCV), a mixture containing the toxoid and whole cell vaccine (TOX-WCV), or tetanus toxoid (placebo). All four preparations will be adjuvanted with aluminum hydroxide. All products will be safely tested in a small population (ca. 1000) prior to the major field trial. The efficacy of the three cholera vaccines in preventing cholera and/or decreasing the severity of illness will be compared by counting cholera cases who are treated at the Matlab Hospital or are identified during intensive stool culture and serology studies in cholera infected bars. The protective effect of the toxoid against disease caused by heat-labile (LT) enterotoxin-producing Escherchia coli will be determined by stool culture of diarrhea cases visiting the Matlab hospital. Serosurveys will be done over a one-year period to determine the duration of serum vibriocidal and antitoxin responses to the three cholera vaccines tested.

Recepto-

There is not much point in treating individual cases. The

DIARRHEA THERAPY

| <u>Protocol<br/>Number</u> | <u>Title</u>                                                                                   | <u>Principal<br/>Investigator</u> | <u>Period of Study</u> |
|----------------------------|------------------------------------------------------------------------------------------------|-----------------------------------|------------------------|
| 77-003                     | Single Dose Doxycycline for Cholera                                                            | D. Sack                           | Mar 77 - Oct 77        |
| 77-004                     | A Clinical Trial of Trimethoprim & Sulphamethoxazole (Bactrim) in the Treatment of Shigellosis | Md. Yunus                         | Oct 76 - July 76       |
| 77-017                     | Sucrose vs Glucose Electrolyte Oral Solution - in the diarrhea of infants                      | D. Sack                           | July 77 - Dec 77       |
| Planned                    | Lobon-Gur (Common salt + Brown Sugar) Oral rehydration solution in the diarrhea of adults.     | R. Islam                          | Feb 78 - Mar 78        |
| Planned                    | Studies on Hypoglycemia in Diarrhea                                                            | A.K.M.J. Alam<br>R. Islam         |                        |
| Complete                   | Single Dose Ampicillin in Shigellosis                                                          | R. Gilman                         |                        |

## SINGLE DOSE DOXYCYCLINE FOR CHOLERA

David A. Sack, M.D.  
Sirajul Islam, M.B.B.S.  
Hassan Rabbani, M.B.B.S.  
Asma Islam, M.B.B.S.

### ABSTRACT

Sixty patients will be studied in a randomized, unblinded, antibiotic trial for the treatment of cholera comparing single dose doxycycline (4 mg/kg) with multiple dose doxycycline (2 mg/kg/dose, daily for 4 days). Multiple dose doxycycline has previously been found equal in effectiveness with tetracycline. Patients will be compared with respect to duration of diarrhea, duration of positive stool culture for vibrio, volume of I.V. fluid used and volume of diarrheal stool. If effective, single dose doxycycline would further simplify and lower the cost of the treatment of cholera.

by Strepto-

## PROGRESS REPORT

Sixty-five patients with cholera were treated with either single dose 200 mg doxycycline (or 4 mg/kg is less than fifteen years) or multiple dose doxycycline 500 mg over four days (or 10 mg/kg if less than fifteen years) in a randomized prospective trial to determine the efficacy of single dose treatment. Patients receiving single dose therapy required similar volumes of intravenous fluid, purged similar volumes of diarrheal stool and had similar durations of diarrhea. Although the mean duration of stool culture positive for Vibrio was similar for the two groups; in both groups several patients continued to excrete V.cholerae in the stool for more than three days. Blood levels of antibiotic demonstrate that the doxycycline is absorbed in spite of the rapid transmit time associated with severe diarrhea. These results suggest that although tetracycline remains the drug of choice for cholera, since it both shortens the disease and eradicates the organism, doxycycline is a reasonable alternative in certain circumstances, and that a single dose of 200 mg (4 mg/kg in children) is effective clinically.

A CLINICAL TRIAL OF TRIMETHOPRIM + SULPHAMETHOXAZOLE  
(BACTRIM) IN THE TREATMENT OF SHIGELLOSIS

Dr. Md. Yunus

ABSTRACT

Various strains of shigella SP. are developing resistant to all useful antibiotics including Ampicillin. So, proven alternative antibiotic should be defined and available when ampicillin resistance is being noted. The purpose of this study is to determine the clinical and bacteriological effectiveness of Bactrim against shigellosis in comparison to ampicillin. The drugs will be compared both clinically and bacteriologically in 200 confirmed shigella bases. Case selection will be done by a preset random selection. 111 subjects clinically suggestive of shigella dysentery of all age and sex except children below 3 months of age and pregnant women, will be required for the trial. There is possibilities of some potential risks mainly of physical nature due to adverse reaction of the drug and therapeutic failure. But the likelihood of such risk is very minimum and is not severe. If any signs of adverse reaction develop or therapeutic failure is suspected, the drug will be stopped at once and an alternative drug will be prescribed. A signed informed consent statement from the subject or from the parents or the authorised legal guardian, if the subject is minor, will be obtained. If the drug is found effective, the individual subject will be benefited by being cured from the disease in particular and the society in general having a proven alternative effective drug for the disease. The study requires the use of blood, urine, stool etc.

## PROGRESS REPORT

From the data so far available it can be said that the combination of Trimethoprim and Sulphamethoxazole (Bactrim) is effective in shigellosis because all the patients under trial in both the groups were cured without any clinical or bacteriological failure. But it is not the time to comment anything where Bactrim is equally effective or superior or less effective than ampicillin since the number of cases so far completed is few. All the strains of shigella isolated are sensitive to Bactrim though one shigella flex is resistant to ampicillin. Ampicillin resistant flex strain is probably new in Bangladesh.

SUCROSE ELECTROLYTE SOLUTION IN CHILDREN WITH  
SEVERE WATERY DIARRHEA. RESULTS OF A DOUBLE BLIND  
COMPARISON WITH GLUCOSE ELECTROLYTE SOLUTION

David A. Sack, M.D.

ABSTRACT

We plan a double blind trial to compare the effectiveness of an oral glucose electrolyte solution (WHO formula) with sucrose electrolyte solution in the hydration of infants with cholera, rotavirus, E. coli and other severe watery diarrheal diseases in Bangladesh. Approximately 100 patients with cholera, 100 patients with rotavirus and 100-200 patients with other watery diarrheal diseases, with ages between three months and four years will be admitted into the study. Because of the seasonal nature of many of the diarrheal diseases, most of the cholera cases will be selected during the cholera season (October, November) and most of the other cases will be selected during January, February and March. The primary determinant of failure of a treatment will be the need to begin (or resume) I.V. hydration; however, other factors such as absorption of sugars and patient's acceptance of therapy will also be examined.

## PROGRESS REPORT

111 children aged three months to four years with acute dehydrating watery diarrhea were included in a study to determine the efficacy of sucrose electrolyte solution in rehydration and maintenance hydration. Patients with  $>10\%$  dehydration were initially given 70% of their requirements by the intravenous and were scheduled to receive the balance of rehydration and all maintenance fluids by the oral route. Patients with 7.5% dehydration were scheduled to receive only oral therapy. Failure was defined as the need for unscheduled intravenous fluids. 102 children had cholera. The groups were well matched according to diagnosis, degree of dehydration, duration of illness prior to hospitalization, admission Sp.gr. and  $CO_2$  levels.

The clinical success rates are shown in Table 1. None of the differences are statistically significant.

Table 1  
Clinical Success Rates

|                                              | Sucrose     | Glucose     |
|----------------------------------------------|-------------|-------------|
| Overall success rate                         | 40/55 (73%) | 43/56 (77%) |
| Success in patients with<br>>10% dehydration | 28/41 (68%) | 35/48 (73%) |
| Success in patients with<br>7.5% dehydration | 12/14 (86%) | 8/8 (100%)  |
| Success in patients with<br>cholera          | 39/53 (74%) | 36/49 (73%) |

The purging rates did not vary with the two treatment groups; however, patients who failed had a purging rate approximately twice that of the patients who succeeded as shown in Table 2.

Table 2  
Mean Intake and Output Measurements  
in Patients who Succeeded or Failed

|                                                     | Sucrose   |          | Glucose   |           |
|-----------------------------------------------------|-----------|----------|-----------|-----------|
|                                                     | Succeeded | Failed   | Succeeded | Failed    |
| Total diarrheal<br>purging                          | 190(+25)* | 320(+41) | 182(+23)  | 379(+41)  |
| Purging during worst<br>eight hours                 | 65(+6)    | 120(+18) | 64(+6)    | 120(+12)  |
| Vomiting during worst<br>eight hours                | 7.3(+3)   | 21(+8)   | 3.9(+1.5) | 8.0(+4.5) |
| Total Intake of Oral<br>Fluid                       | 337(+32)  | 245(+32) | 343(+31)  | 305(+37)  |
| Intake of Oral Fluid<br>during first eight<br>hours | 90(+6)    | 85(+12)  | 89(+6)    | 76(+9)    |

\*ml/kg (+SE)

During the study, one patient admitted with severe dehydration from cholera died. The child who was taking sucrose solution died of hypoglycemia, with convulsions and aspiration, but did not die from dehydration. No patients failed on either oral fluid from malabsorption of carbohydrate.

The study has shown that sucrose solution can be used effectively in hydration of children in conjunction with intravenous fluids. The death which occurred re-emphasizes the need to guard against hypoglycemia in children with cholera.

SUCROSE ELECTROLYTE SOLUTION IN ADULTS WITH  
SEVERE WATERY DIARRHEA. RESULTS OF A DOUBLE BLIND  
COMPARISON WITH GLUCOSE ELECTROLYTE SOLUTION

Sirajul Islam, M.B.B.S.

ABSTRACT

We plan a double blind trial to compare the effectiveness of an oral glucose electrolyte solution (WHO formula) with sucrose electrolyte solution in the hydration of adults with cholera, E. coli and other severe watery diarrheal diseases in Bangladesh. Approximately 150 patients with watery diarrheal diseases, with ages between sixteen years and fifty years will be admitted into the study. The primary determinant of failure of a treatment will be the need to begin (or resume) I.V. hydration; however, other factors such as absorption of sugars and patient's acceptance of therapy will also be examined.

## PROGRESS REPORT

148 adult male patients with acute watery diarrhea including cholera, with  $>7.5\%$  dehydration, were included in a study to determine the efficacy of sucrose electrolyte oral solution in rehydration and maintenance hydration. Patients with severe ( $>10\%$ ) dehydration were initially given 70% of their requirements by intravenous route to reverse shock. Persons with moderate ( $\geq 7.5\%$ ) dehydration were scheduled to receive only oral therapy. Failure was defined as the need to give unscheduled intravenous therapy. 75 patients received sucrose solution, 73 received glucose solution in a randomized double blind manner. Bacterial etiologies are listed in Table 1. The groups were well matched for age, weight admission dehydration, specific gravity and  $CO_2$ .

Table 1

Sucrose solution n=75      Glucose solution n=73

|             |                 |                 |
|-------------|-----------------|-----------------|
| V. cholerae | 36              | 43              |
| ETEC        | 20              | 14              |
| Shigellae   | 2 (1 with ETEC) | 2 (2 with ETEC) |
| NCV         | 3 (1 with ETEC) | 0               |
| Salmonellae | 1               | 0               |
| Unknown     | 15              | 16              |

by Siropro-

The clinical success rates showed no significant difference between the two groups as shown on Table 2.

Table 2  
Success of oral therapy in adults  
receiving either sucrose or glucose electrolyte  
solution

|                                                    | Sucrose solution | Glucose solution |
|----------------------------------------------------|------------------|------------------|
| Overall success rate                               | 56/75 (75%)      | 61/73 (84%)      |
| Success rate for severely<br>dehydrated patients   | 38/51 (75%)      | 36/45 (80%)      |
| Success rate for moderately<br>dehydrated patients | 18/24 (75%)      | 25/28 (89%)      |
| Success rate for patients<br>with cholera          | 22/36 (61%)      | 30/43 (70%)      |

Failure of oral therapy occurred in two ways; either the patients failed to become rehydrated (this was usually due to excessive vomiting) or the patients failed to maintain hydration (this was usually due to excessive purging, >100ml/kg/8hr period). Failures were usually in patients with cholera (26/31 failures had cholera).

There was no evidence that sucrose increased the purging rate when compared to glucose. The solutions were equally well tolerated. Neither electrolyte imbalance, nor abnormalities of serum glucose were seen in either group. One patient was documented to malabsorb sucrose, but did not become dehydrated with the excess purging.

This study has shown that sucrose electrolyte oral solution can be used effectively in most cases of severe diarrhea in adults, but that both must be used in conjunction with I.V. therapy when appropriate to treat patients with severe dehydrating diarrhea.

LOBON-GUR (COMMON SALT + BROWN SUGAR)  
ORAL REHYDRATION SOLUTION IN THE DIARRHEA OF ADULTS

Dr. R. Islam

ABSTRACT

A clinical trial to observe the effectiveness of an oral solution containing only common salt and Brown sugar without added bicarbonate/citrate or potassium chloride, is planned on adult diarrhea patients with mild to moderate dehydration of any etiology. Approximately 50 patients with mild to moderate dehydration (Plasma sp. gravity less than 1032) will be taken for the study. Failure will be considered when the solution will fail to correct initial dehydration or maintain hydration or electrolyte imbalance at any time of the study and these patients will be treated with the indicated standard intravenous and/or oral replacement solutions.

## PROGRESS REPORT

This protocol is in the review process at present and will start as soon as it is approved.

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by Streptoc-

There is not much point in treating individual cases. The

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## STUDIES ON HYPOGLYCEMIA IN DIARRHEA

A.K.M.J. Alam, M.B.B.S.  
R. Islam, M.B.B.S.

### ABSTRACT

Patients with clinically symptomatic hypoglycemia have been identified. Descriptive information has been gathered. It is a common complication of diarrhea in children and requires treatment. One group of patients has been found to be distinct. These have eaten a local plant (Ghagra). This plant produces a malignant form of hypoglycemia with a high mortality. It is seasonal occurring in the fall as the water recedes.

No protocol has been prepared as yet for further studies on specific hypotheses.

## SINGLE DOSE AMPICILLIN IN SHIGELLOSIS

Robert H. Gilman, M.D.  
Hassan Rabbani, MBBS

### ABSTRACT

At present there is evidence that prolonged therapy with high doses does not appear to change the course of shigellosis. A single case of ampicillin may well be sufficient to produce clinical cure in most cases of shiga and flexneri dysentery. This protocol examines this possibility.

In this study a single dose regimen will be compared with the standard 100 mg/kg ampicillin dose given four times daily for five days. Safety guards provided are treatment with a standard regime if cultures are positive for more than three days or intravenous therapy if abdominal distension occurs. Relapses will also be treated using the standard regime. Benefits are mainly to society but for the individual include the possibility of a lower rate of side effects than with the standard regimen. Forty patients in each age group with positive isolates for shiga bacillus will be studied.

Children will be used in this study since this is the primary group towards which such therapy should be directed.

## PROGRESS REPORT

A randomized, non-blind comparative study comparing a large single dose of ampicillin with a 5 day divided dose schedule for the treatment of shigella dysentery has been performed. Of 129 patients, 91 patients were considered eligible for study.

There were 50 adults, 26 received a single dose and 24 the multiple dose schedule. There were 41 children, 23 received the single dose therapy and 18 who received the multiple dose therapy. Single dose therapy was 100ug/kg per day divided into four equal doses given for five days. The groups were homogeneous except that more children in the multiple dose group had fever on admission.

Both children and adults had a satisfactory response to a single large dose of ampicillin compared to patients treated routinely. There was, however, a larger number of shigella isolations after treatment in patients who had received a single dose of ampicillin.

Studies of ampicillin-resistance in fecal coliforms in single and multiple dose groups showed less resistance in the single dose group on day four and seven after admission to hospital. Within one week of stopping antibiotic, both groups had predominantly ampicillin sensitive fecal coliforms.

SHIGELLA ISOLATED FROM PATIENTS WITH ACUTE COLITIS

PATIENTS WITH CULTURE FOR SHIGELLA

|          |               | <u>Number of Days After Therapy</u> |            |          |          |                     |
|----------|---------------|-------------------------------------|------------|----------|----------|---------------------|
|          |               | <u>Number of Patients</u>           | <u>1-2</u> | <u>3</u> | <u>7</u> | <u>14</u> <u>21</u> |
| CHILDREN | Single Dose   | 23                                  |            |          |          | (15) (11)           |
|          |               |                                     | 4          | 1        | 2        | 1 1                 |
|          | Multiple Dose | 18                                  |            |          |          | (13) (11)           |
|          |               |                                     | 2          | 0        | 1        | 0 0                 |
| ADULTS   | Single Dose   | 26                                  |            |          |          | (19) (18)           |
|          |               |                                     | 5          | 2        | 3        | 1 0                 |
|          | Multiple Dose | 24                                  |            |          |          | (18) (18)           |
|          |               |                                     | 5          | 0        | 0        | 0 1                 |

( ) = Number of patients examined as outpatients

CHARACTERISTICS OF  
AMPICILLIN SINGLE DOSE AND MULTIPLE DOSE GROUPS

|                                                                                                                   | No. of Patients | Mean Age in Years | Duration of Disease (Days) | Frequency of Stool/day | Mean Pus Cells per HPF | Mean Fecal Leucocytes per HPF | Mean White Cell Count | No. of Patients with Fever on Admission Day |
|-------------------------------------------------------------------------------------------------------------------|-----------------|-------------------|----------------------------|------------------------|------------------------|-------------------------------|-----------------------|---------------------------------------------|
| The following data are based on 100 cases. The standard deviation is not much point in treating individual cases. |                 |                   |                            |                        |                        |                               |                       |                                             |
| S.D.                                                                                                              | 23              | 5                 | 6                          | 22                     | 49                     | 6                             | 19.1                  | 9                                           |
|                                                                                                                   |                 | $\pm 3$           | $\pm 4.5$                  | $\pm 13$               | $\pm 35$               | $\pm 4$                       | $\pm 6.2$             |                                             |
| Multiple Dose                                                                                                     | 18              | 5                 | 4                          | 18                     | 40                     | 5 <sup>+</sup>                | 15.5                  | 11                                          |
|                                                                                                                   |                 | $\pm 2$           | $\pm 2$                    | $\pm 14$               | $\pm 20$               | $\pm 3$                       | $\pm 7.5$             |                                             |
| S.D.                                                                                                              | 26              | 33                | 4                          | 25                     | 62                     | 7                             | 12.8                  | 15                                          |
|                                                                                                                   |                 | $\pm 16$          | $\pm 2$                    | $\pm 21$               | $\pm 38$               | $\pm 7$                       | $\pm 4.2$             |                                             |
| Multiple Dose                                                                                                     | 24              | 37                | 4                          | 20                     | 59                     | 5                             | 11.9                  | 9                                           |
|                                                                                                                   |                 | $\pm 16$          | $\pm 2$                    | $\pm 15$               | $\pm 35$               | $\pm 4$                       | $\pm 4.0$             |                                             |

Standard Deviation

TABLE II

DISTRIBUTION OF SHIGELLA ISOLATED IN SINGLE DOSE STUDY

| <u>THERAPY GROUP</u>    | <u>CHILDREN</u>      |                  | <u>ADULT</u>         |                  |
|-------------------------|----------------------|------------------|----------------------|------------------|
|                         | SINGLE DOSE<br>GROUP | MULTIPLE<br>DOSE | SINGLE DOSE<br>GROUP | MULTIPLE<br>DOSE |
| Total Shigella Isolated | 23                   | 18               | 26                   | 24               |
| Shigella Shiga          | 13                   | 8                | 8                    | 13               |
| Shigella Flex.          | 10                   | 9                | 12                   | 10               |
| Shigella Dys.           | 0                    | 0                | 0                    | 0                |
| Shigella Boydi          | 0                    | 1                | 4                    | 1                |
| Shigella Sonnei         | 0                    | 0                | 2                    | 0                |
| Others                  | 0                    | 0                | 0                    | 0                |

TABLE III

|          |               | <u>No. of<br/>Patients</u> | <u>FOURTH DAY</u> |            |             | <u>SEVENTH DAY</u> |            |             |
|----------|---------------|----------------------------|-------------------|------------|-------------|--------------------|------------|-------------|
|          |               |                            | <u>WBC</u>        | <u>PUS</u> | <u>F.L.</u> | <u>WBC</u>         | <u>PUS</u> | <u>F.L.</u> |
| Children | Single Dose   | 23                         | 17.1<br>+6.0      | 11<br>+9   | 1<br>+4     | 16.9<br>+4.7       | 4<br>+7    | 1<br>+.3    |
|          | Multiple Dose | 18                         | 19.5<br>+8.7      | 14<br>+26  | 1<br>+4     | 19.06<br>+4.25     | 7<br>+21   | 1<br>+4     |
| Adults   | Single Dose   | 26                         | 11<br>+4.0        | 11<br>+4   | 1<br>+2     | 10.6<br>+4.7       | 20<br>+4   | .3          |
|          | Multiple Dose | 24                         | 10.6<br>+4.7      | 13<br>+12  | 1<br>+1     | 10.5<br>+2.7       | 2<br>+4    | .4          |

## OUTREACH PROGRAM

The outreach program will be ICHR's effort to share research products or recommendations with the world in general and the developing world in particular, specially in the Bangladesh context. The Laboratory has committed \$60,000 for this year for outreach activities. The outreach will consist of (1) Training, (2) Extension and (3) Communications.

### INTRODUCTION

The existing International Agricultural Research Centers have been proposed as a model for the ICHR. A quote from a report by Bo Bengtsson for the Swedish Agency for Research Cooperation with developing countries (1977 - page 57) is directly relevant to outreach programs:

"... If the national research basis is weak, further investments to and expansion of international agricultural research - at the expense of national systems - may not serve to develop research capacity in third world countries. Rather, support to international research systems may delay the build up of national capacity, contributing to the emigration of researchers and distorting national investment ...".

The most important reason for an outreach program is the attempt to deal with this problem. No one would question that research capacity in Bangladesh, South Asia and in the South East Asia region needs to be strengthened. It is quite likely that unless active efforts are made by the ICHR to strengthen this capacity, the net effect of the new center will be detrimental to Bangladesh and to the region.

There are other considerations, however, which are almost as important:

1. Relevance of research: Research conducted in isolation from actual problems is rarely of much use. The most important contributions of the Cholera Laboratory up to now have come directly out of a program dealing with a specific problem - the intravenous and oral fluid treatment of cholera.
2. Human subjects: Most of the research conducted by the Laboratory will involve human subjects. It is not possible

to conduct this kind of research in a foreign country without clear evidence that the subjects of the research benefit from it.

3. Delivery of technology: The Laboratory must accept some responsibility for the way in which technological advances produced are utilized and for the consequences of this utilization.

## TRAINING

Training will include courses, lectures, demonstrations, practical experience, research work leading to Master's and Ph.D. degrees and post doctoral research.

The Cholera Research Laboratory has certain unique advantages to offer for training in certain areas both in a Bangladesh context and in the context of developing countries in general and South and South East Asia in particular. Maximum benefit for the cost would be for Bangladeshis with the amount of benefit decreasing with increasing distances because of travel costs. It is proposed that training efforts will be equally divided with one third for Bangladesh, one third for other developing countries and the last third to the developed countries. CRL funds will only be used for developing countries, with fifty percent for Bangladesh and fifty percent for developing countries. Trainees from developed countries will be expected to independently raise all the costs of training at CRL, including overhead. However, some trainees will be accommodated on an exchange basis.

Training efforts, wherever appropriate, will be in collaboration with an institution in Bangladesh or an institution in the developing countries. Augmentation of local training programs in Bangladesh will be given a high priority.

The Laboratory in the past has conducted training of various kinds on an ad-hoc basis, which has included training of medical students, interns, doctors, and on an occasional basis fellows sent by WHO or other institutions. It has also trained, for various technical abilities, technicians from other institutions in the fields of pathology, clinical biochemistry and microbiology. There have been students from abroad who had done their thesis work for their Ph.D. degree. The Laboratory has also accepted National Science and Technology fellows from Bangladesh for training in appropriate fields for their career development. In addition there has been some degree of training for nurses and field workers and in-service training in the field of biochemistry and laboratory technology.

Training will be imparted in the following areas where the Laboratory has unique facilities and personnel:-

A. Clinical Work

CRL has been the pioneer in formulation of the Intravenous fluid and oral therapy. One hundred and ten thousand patients were treated for diarrheal disease at the Matlab and Dacca hospitals in 1977. All developing countries are encouraged to use this resource for the improvement of diarrheal disease therapy in local institutions.

Training should not be restricted to physicians, and could include:

1. Training of nurses and paramedical personnel (health auxiliaries) in the management of diarrheal diseases;
2. Training of indigenous practitioners, from Dacca and Matlab, particularly.
3. Training of families of hospital patients to give oral therapy for diarrheal diseases.

B. Field Work

CRL has two field areas where demographic surveillance work is ongoing. Quite a number of epidemiological studies have been carried out. There is a data bank where the data from the field is stored and handled by the Statistical Branch at CRL. These are unique facilities for training in the following areas.

1. The epidemiology of diarrheal diseases;
2. Field Surveillance;
3. Statistical methods and data handling.

C. Laboratory Work

There are several training institutions in Bangladesh where various aspects of Laboratory work is taught. In collaboration with these institutions, CRL can train in particular areas where practical training has not been particularly strong or is absent. In the past the Laboratory has provided training to students from the Paramedical Institute, the Armed Forces Institute of Pathology, Dacca University, Dacca Medical College, the Atomic Energy Center, and to individuals assigned by WHO.

Courses in the following areas can now be offered:

1. Enteric Bacteriology and Immunology;
2. Clinical Biochemistry;
3. Clinical Pathology;
4. Breeding and Care of Animals for medical research;
5. Elementary Laboratory Technology and Laboratory Safety;

6. Many institutions in the developing countries suffer from lack of preventive maintenance services for medical or other scientific equipment. CRL has unique facilities for training in repair and maintenance of particular equipments.

It is expected that most of the training programs will be in collaboration with other institutions at home and abroad.

#### D. Research Fellowships

Fellowships will be offered by the Cholera Research Laboratory and the British Council. It is hoped that WHO and other interested organisations from the developing countries or the developed countries will also provide fellowships. Training on an exchange basis between CRL and any other institution that falls within the framework of the objectives of the Laboratory will be possible. The CRL fellowships could be divided into several grades:

1. Pre doctoral fellowships for medical graduates and for non-medical graduates. Since MBBS courses take one year longer in comparison to the M.Sc. degree, MBBS fellows should be rated a little higher than the M.Sc. fellowship. These fellows could work for career development in various research areas in CRL or they could utilize their research work to produce a thesis for the next higher degree in the Institute of Post-Graduate Medicine or in any University in Bangladesh or elsewhere. Arrangements for accreditation with affiliated universities will have to be made. Coordination committees between institutions will be needed and it may be desirable to set up a multilateral coordinating committee in which one member from each of the collaborating institutions will be represented. \*
2. CRL will also offer fellowships for post doctoral candidates. We already have one post doctoral fellow from a developed country. We plan to have post doctoral fellowships for persons from within Bangladesh and from the developing countries.

#### EXTENSION

Another major category of outreach for the ICHR will be health service delivery (preventive and curative) in areas which are a particular interest of the ICHR. The Laboratory has an obligation to try to develop practical recommendations for the prevention and treatment of the diseases under study. This can't be done in isolation from active efforts to carry out these recommendations. It will not be possible for us to provide

\* Membership to this committee could also be based on disciplines instead of institutions. .../5.

support for service programs in all the areas in which we have an interest, but it is essential that we develop active association with service programs and in some instances it will be desirable for the Laboratory to organize programs in collaboration with Government and private organisations. Two activities have been proposed for immediate action:

1. At Dhaka, it is likely that the research program will be able to make recommendations for a practical rural sanitation program to control shigellosis dysentery. A proposal for a shigellosis control program to cover the entire population of 80,000 is being developed.
2. In the Dacca metropolitan area, almost all patients with cholera who go to any hospital come to the Cholera Laboratory. Many patients with dysentery and less serious diarrheas are also treated there. Eighty-six thousand patients were treated in the hospital last year, and the same number are expected to be treated this year.

It is essential to have to decentralize diarrhoea treatment, to make oral fluid treatment available at home and to develop a sanitation program which will bring cholera under control.

In addition to these programs for which IEHR will have a direct responsibility, there are several independent health service delivery programs in Bangladesh, which are conducting research and which could benefit from an association with us. The collaboration between the evaluation unit of the Compagnon Project and CRL is an example of this.

#### Communication

Communication is now achieved by publication, in scientific journals, the CRL report series and annual reports. There has not been much publication in the popular press in local language. A lot of the information about diarrhoea treatment available from the radio, television and other mass media can be utilized to get the message across to the people. Liaison with professional and non-professional societies, holding of lectures, seminars, symposia etc. will be other means of communication.

Large-scale inter-ethnic interaction in the health sciences will be essential. Organization of joint conferences, participation in regional conferences and publications of the Laboratory's findings with the region will be necessary. The present series of Cholera Laboratory reports is useful, but it

might be desirable to publish a quarterly journal of the International Health Research Center which will present the results of new research and also present certain information available to the Laboratory that is useful to other scientists - such as the sensitivity of bacteria encountered in the various regions in which the Laboratory is working and the demographic data generated from Matlab and other areas.

Follow-up of individuals and evaluation of all training and extension work must be an integral part of the program. A directory of trained people will be kept and the translation of their newly learned skills from CRL to the community and country concerned will be evaluated.

# NUTRITION

| <u>Protocol Number</u> | <u>Title</u>                                                                                                                            | <u>Principal Investigator</u>   | <u>Period of Study</u> |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|------------------------|
| 77-010                 | Lactose Malabsorption in Bangladeshi Villagers as Determined by Breath Hydrogen Testing                                                 | K. Brown                        | July 77 - Jan 78       |
| 77-030                 | Gastric Acid in Protein Calorie Malnutrition                                                                                            | R. Gilman                       | Oct 77 - Mar 78        |
| 77-026                 | Nutritional Consequences of Low Dose Whole Milk Dietary Supplements given to Lactose-Malabsorbing Children.                             | K. Brown                        | Sept 77 - Mar 78       |
| Planned                | Studies in Nutrition & Lactation                                                                                                        | K. Brown                        |                        |
| Planned                | Classification of Energy-Protein Malnutrition by Anthropometry and its Usefulness in Prognosticating Subsequent Morbidity and Mortality | A.K.M.A. Chowdhury<br>L.C. Chen | Jan 78 - Apr 78        |
| Planned                | Quantitation of $\alpha_1$ -Antitrypsin to detect the gastrointestinal protein loss in diarrhoea and dysentery                          | M.A. Wahed                      | Feb 78 - Aug 78        |

LACTOSE MALABSORPTION IN BANGLADESHI VILLAGERS  
AS DETERMINED BY HYDROGEN BREATH TESTING

Kenneth H. Brown, M.D.

ABSTRACT

The recently developed technique of hydrogen breath testing will be used to determine the prevalence of lactose malabsorption among Bangladeshi villagers. The results will be related to the subjects' age, nutritional status, and history of recent diarrhea.

## PROGRESS REPORT

1. A validation study in which results of breath hydrogen testing for lactose malabsorption and glucose-galactose malabsorption were compared to standard tolerance tests of absorption (i.e. blood glucose rise following oral ingestion) has been carried out in sixty Bangladeshi and expatriate children and adults. The tests show agreement in approximately eighty percent of the subjects. In most instances of non-agreement, the BHT indicated malabsorption, but the LTT showed normal glucose rise. In half of these cases the subjects experienced symptoms of lactose intolerance. Thus, the BHT is probably more sensitive and more specific than the LTT.

2. The village study was initiated in September, 1977. Anthropometric measurements and diarrhea histories were obtained from approximately 2,000 Matlab villagers who were then stratified by age, nutritional status, and history of recent diarrhea.

3. Breath hydrogen tests have been successfully completed in over 200 villagers. The tests were easy to administer and proved to be an acceptable field technique.

4. Results of the studies are currently being coded prior to tabulation. Preliminary analysis indicates that most of the adult population malabsorbs lactose regardless of nutritional status or diarrhea history. Children generally absorb lactose normally until about three years of age, when they acquire malabsorption. Results of children's absorption studies related to nutritional status and diarrhea history are not yet available.

NUTRITIONAL CONSEQUENCES OF LOW DOSE,  
WHOLE MILK DIETARY SUPPLEMENTS  
GIVEN TO LACTOSE-MALABSORBING CHILDREN

Kenneth H. Brown, M.D.

ABSTRACT

A study is planned to determine whether dietary supplements of whole milk given to lactose malabsorbers will be nutritionally advantageous. Lactose malabsorbing and normal, control children will receive a vegetable and rice diet either alone or with supplements of lactose-free or lactose-containing milk during these sequential balance periods. Calorie, fat and nitrogen balances will be determined; and breath hydrogen tests will be performed to evaluate dietary carbohydrate absorption.

## PROGRESS REPORT

1. Six children - four malabsorbers and two controls - have completed the study, and an additional six subjects are currently staying in the metabolic ward at C.N.U.
2. Clinical parameters from the first group of subjects indicate that lactose malabsorbers successfully tolerate the diet including lactose-containing simulated milk, but they do have mildly increased stool weights, decreased intestinal transit times, and increased breath hydrogen concentrations. Nevertheless, growth rate (i.e. weight gain) is equally enhanced by the lactose-containing and lactose-free simulated milk supplement.
3. Analysis of laboratory specimens for nitrogen, fat, and calorie balances are in progress.

# STUDIES IN NUTRITION AND LACTATION

K. Brown, M.D.

## ABSTRACT

A study is proposed whereby the relationships between maternal diet, maternal nutritional status, breast milk volume and composition, and infant growth rates will be examined in a series of poor Bangladeshi women. The mother-infant pairs will be examined semi-monthly for a period of three to four months post-partum. Maternal dietary intakes will be recorded and anthropometric examinations of mothers and infants will be performed. Babies will be weighed before and after every feed for a twenty-four hour period in order to determine breast milk consumption. Then milk will be extracted by mechanical pump for an additional twenty-four hour period, and an aliquot of the pooled sample will be saved for nutrient analysis. After the infant is approximately four months of age, the effect of maternal diet supplementation on milk volume and composition will be determined in a controlled in-patient study.

## PROGRESS REPORT

1. Studies have been in progress for approximately nine months and eleven women have completed their in-patient stay. An additional six women will complete their in-patient period in one week.

2. Although the study mothers are small by Western standards (weighing approximately 40 kg), their percentage expected weights-for-heights are only slightly below Western standards. Nevertheless, milk consumptions by infant age are less than reported in Western countries. Most infants maintain growth curves parallel to Western norms for only the first three months of life.

3. Milk analyses demonstrate markedly reduced fat concentrations, slightly reduced nitrogen concentrations, and slightly increased lactose concentrations as compared to previously published studies of Western mothers.

4. Seven of eleven mothers demonstrate significant increases in milk production (and generally stable concentrations of proximate principles) following maternal dietary supplementation with increased calories and protein.

5. Dietary recall data of study mothers have not been completely tabulated. Because of marked variability in the early data, weighed intake studies have also been initiated in the subjects' homes.

6. Future studies will attempt to determine whether independent supplementation of either protein or calories alone will also enhance the volume of milk secretion.

QUANTITATION OF  $\alpha_1$  ANTITRYPSIN TO DETECT  
THE GASTROINTESTINAL PROTEIN LOSS IN  
DIARRHOEA AND DYSENTERY

M.A. Wahed

ABSTRACT

Loss of plasma protein into the G.I. tract occurs in several disorders. The extent or magnitude of loss in shigellosis and amebiasis have never been measured. Moreover currently available methods to detect the protein loss into the gut are cumbersome, expensive, imprecise, technically hazardous due to use of radioactive materials and long steady state. Keeping in view of the above facts, a new method which uses the presence of antitrypsin which resists enzymatic proteolysis has been developed. Loss of vascular protein can be measured by comparing the ratio of antitrypsin in stool and serum. The antitrypsin can be measured using a radial immuno-diffusion (RID) technique.

### PROGRESS REPORT

This study is in the review process preliminary observations have shown a significant protein loss during acute shigellosis but not during cholera by the  $\alpha$  antitrypsin assay.

# GASTRIC ACID IN PROTEIN CALORIE MALNUTRITION

R. Gilman

## ABSTRACT

Gastric secretion of 25-30 children with severe Protein-Calorie-Malnutrition (PCM) will be determined at the Nutrition Research Unit. A mercury tipped tube will be passed and basal gastric acid output determined. An injection of 1.5mg/kg of betazole (histalogue) will be given and stimulated gastric acid output collected. Patients will also have basal gastrin levels determined. Gastric contents will be quantitatively cultured for gram-negative organisms before and after histalogue injection. Children, 80% height for weight or over, will have gastric juice tube placed and both basal and stimulated gastric secretion determined. These children will be matched either for weight or age and are the controls for the malnourished child.

CLASSIFICATION OF PROTEIN-CALORIE MALNUTRITION BY  
ANTHROPOMETRY AND ITS USEFULNESS IN PROGNOSTICATING  
SUBSEQUENT RISK OF MORBIDITY AND MORTALITY

A.K.M. Alauddin Chowdhury &  
Lincoln C. Chen

ABSTRACT

Utilizing already collected cross-sectional anthropometric field data and longitudinal vital registration and diarrheal disease hospitalization information on a cohort of 2,000 children ages 13-22 months in the Matlab field surveillance area, this study examines the relative usefulness of various classification systems for protein-calorie malnutrition. The cross-sectional information includes child anthropometry (weight, height, arm circumference) and selected socio-economic and maternal data collected during November 1975 - January 1976 and the longitudinal data include death and hospital reports maintained by CRL from November 1975 through November 1977. Comparisons are made between children classified similarly and differently by varying systems to determine factors associated with classification discrepancies. The validity of various systems is assessed by comparing their capacity to discriminate and prognosticate future morbidity (hospitalization for diarrheal disease) and mortality (child death). The analysis, moreover, attempts to identify additional, readily and reliably obtained survey information related to family or maternal characteristics which would strengthen the discriminatory power of child anthropometric measurements alone. Unlike many other studies, this investigation has the advantages of exact age information, longitudinal morbidity and mortality data, a cohort of children during a nutritionally vulnerable period, and supplementary socioeconomic and maternal information.

PROGRESS REPORT

2. New Protocol. Work just started.

## NUTRITION WORKING GROUP

Bangladesh, like many other countries in South and Southeast Asia, has a serious nutrition problem. In Table 1 is shown the prevalence of energy-protein malnutrition among preschool children reported by a recent Bangladesh national nutrition survey. If classified according to the system devised by Waterlow, 57.9% of children were moderately or severely stunted; 5.8% wasted, and 15.8% both wasted and stunted. Only 20.5% of children could be classified as normally nourished or mildly malnourished.

Although the nature, magnitude, and cause of malnutrition varies across geocultural boundaries, the fundamental causes of malnutrition in Bangladesh are similar to many other countries, where predominantly agrarian densely-settled populations struggle with social inequality, low agricultural productivity, unsanitary environments, heavy disease burdens, monotonous cereal-based diets, and sub-optimal utilization and distribution of existing resources. As such, the long-term solution to the nutrition problems will be dependent upon political and socioeconomic development. Research and experience however, have repeatedly shown that improved standards of living alone may not necessarily lead to nutrition wellbeing; this is well substantiated by the alarming nutrition problems among populations consuming (over consuming) affluent diets. The goal of nutrition activities therefore, requires direct and indirect policies, programs, and other inventions while at the same time ensuring that such activities are consistent with, indeed part of, the long-term solution.

What is an appropriate role for the ICHR in contributing to an improvement of the nutrition problem in Bangladesh and other countries facing similar problems? To begin with, it should be made clear that the ICHR does not intend to develop a comprehensive nutrition program. Bangladesh already has two nutrition institutes and Asia has several of the world's leading scientific centers for nutrition research. Rather, the role of ICHR should be to meet program gaps and to be used as an instrument in strengthening national bodies. The scientific work to be conducted at ICHR moreover, should be closely linked with the diarrheal diseases and the institutional infrastructure thus far developed. These linkages have a strong scientific and institutional rationale.

(1) Because of its frequency, age-specificity, and pathophysiology, diarrheal disease is undoubtedly the most important infectious cause of malnutrition globally. Diarrheal diseases compromise nutritional status by reducing food intake, malabsorption, and metabolic wastage of nutrients.

(2) Nutritional status, conversely, is an important determinant of host defense against diarrheal and other infectious diseases.

(3) Breastfeeding and weaning practices protect against infection and is also a crucial determinant of child and maternal nutritional wellbeing.

(4) The field, clinical, and laboratory infrastructure of CRL may provide unique opportunities for certain types of nutrition research. One such example is the Matlab demographic Surveillance System where cross-sectional censuses and longitudinal vital registration of vital events has been maintained among a rural population of 280,000 for a decade.

#### Framework

Three critical strands in the complex web of malnutrition are: (1) the availability of food resources to a family; (2) the effective utilization of such resources within a family; and (3) the efficiency of nutrient utilization by the human body.

The level of resources available to a family obviously depends upon socio-political issues, such employment, land tenure, income distribution, production and technology. While critically important, it is difficult to see a clear role for the ICHR in this process, except that insofar as research highlights the consequences and causes of the problem, so that it may generate greater political and social commitment to its solution. Until such changes are generated, it is likely that the malnutrition problem will continue to be with us.

Irrespective of the socio-political system, the effectiveness and efficiency of nutrient utilization by a family and an individual are critically important. It has been repeatedly demonstrated that diarrheal disease compromise nutritional status by reducing food intake, the absorption of nutrients in the gastro-intestinal tract, and the efficient metabolic utilization processes are also linked with food behaviour and distribution within families. More efficient

utilization of food available to a family may be determined by beliefs and practices related to dietary behaviour during such processes as illness, pregnancy and lactation.

### Program

The role of the ICHR would be primarily directed at studying the development and application of technologies related to improving the efficiency and effectiveness of food utilization by families and individuals, playing particular attention to diarrheal disease intervention technologies and their optimalization within a specific geocultural environment.

### Impact of Infection Control on Nutrition

Several technologies against diarrheal disease are being developed and planned for field testing by the CRL. These include oral rehydration, water and sanitation, and immunoprophylaxis against cholera. A nutritional component to these interventive studies would seem to offer a high yield of useful information. For example, it is postulated that oral therapy may reduce diarrheal morbidity and mortality as well as improve nutrition because it would reduce loss of appetite and it offers a vehicle for education about feeding practices during diarrhea. Because diarrheal disease is like an iceberg where morbidity greatly exceeds mortality, it is not clear whether the technology would in the end really exert much of an impact on mortality, since the fluid and electrolyte loss associated with severe dehydrating diarrheas may be refractory to oral therapy alone. Improvement of morbidity and nutrition therefore, may be the most important benefits to be obtained with the application of such a technology and nutrition research therefore, assumes a critical role in any assessment of oral therapy. Similarly water and sanitation interventions will need to incorporate a strong nutritional component, including such outcome variables as nutritional status, malabsorption, as well as diarrheal disease attack rates. These studies of intervention will include the development of practical approaches to promote continued breastfeeding and sound dietary practices during and following the course of illness, in order to compensate for the nutrient demands of such episodes. Such investigations will require indepth nutritional, social, and anthropological skills to adequately define the technical, institutional and cultural constraints.

## Dysentery and Nutrition

The mechanism responsible for malnutrition among children with watery diarrheal illness is better understood than that associated with dysentery. Dysentery, in contrast to diarrhea, is not only associated with loss of fluids and electrolytes but also with the loss of large amounts of protein. An attack of dysentery, which may occur several times during the preschool period is associated with not only loss of protein through the gut but also increased catabolism due to systemic involvement as well as low intake of diet during the illness. caused by poor appetite and/or actual withholding of food. Studies may be undertaken to determine the magnitude and mechanisms of loss of plasma protein, body nitrogen and other ingested foods during an attack of dysentery. Also the effect of inexpensive, rapid treatment on these losses should be studied. Parts of these studies may have to be carried out in a metabolic ward of a hospital with consenting parents. In the field, the study should focus on the cultural practices associated with the episodes of dysentery with collection of qualitative and quantitative data on the intake of foods. Another area of study is the "chronic" low-grade but exhausting diarrhea associated with moderate or severe malnutrition. This syndrome has been repeatedly observed during the vicious spiral of diarrhea-malnutrition but the etiologic agents or pathophysiology have not been adequately delineated.

## Food Practices

The distribution of nutrients is primarily a household decision. Its importance is underscored by the fact that even families with sufficient total food availability may have malnourished children. Intra-family food practices, therefore, relates to the effective utilization of food resources available to a family. Three aspects of intra-family distribution appears to be particularly crucial for virtually all nutrition-related programs. First is an understanding of the beliefs and decisions that determine "normal" distribution across seasons in rural areas where crop production and food availability may fluctuate markedly. Second, are food distribution practices during various states such as lactation, pregnancy and illnesses. Third, the impact of various health, education and food intervention programs on intra-family food practices and on the net increases of food consumption and nutritional wellbeing of the most vulnerable nutritional sub-groups, mothers and children.

A series of prospective indepth village-based studies are planned to develop a sound methodology for measuring intra-family food practices in subsistence rural households and to identify patterns and determinants of the process. From such studies, approaches toward improving nutrition may be developed, such as improving the diet of mothers during lactation and pregnancy, presenting the withdrawal of breastfeeding and food during illness. An additional aspect of these studies are a need to integrate technology with other program activities for the appropriateness, effectiveness, and safety of technology depends upon such an understanding.

### Diarrheal Disease and Malabsorption

It is well established that malabsorption of nutrients in the gastrointestinal tract is highly prevalent in poor countries. The causes of this defect and its significance in terms of nutrient wastage are still not fully delineated. When afflicted by acute diarrheal illnesses, individuals already suffering from malabsorption may experience a further deterioration of gastrointestinal absorptive capacity, thereby further compounding the problem. A line of investigation will be undertaken to delineate the epidemiology and pathophysiology of this problem and, as importantly, to measure its significance in terms of nutrient wastage and compromised nutrition status. These studies will involve test diet measurements in a metabolic ward setting, nutrient absorption tests, such as the "hydrogen breath test" recently established at the CRL, and field studies. These studies are essential not only to potentially reduce the level of nutrient loss but also to better assess the nutrient requirements arising from differing health, malabsorption, and other environmental conditions. These baseline studies would also lead to the development of field studies of possible types of intervention, such an antibiotic prophylaxis for children who experience repeated bouts of diarrhea or more effective feeding practices and programs during acute illness.

### Breastfeeding and Nutrition

No other socio-biological practice is as important as breastfeeding in determining the nutritional wellbeing of mothers and children. Breast milk is acceptable, inexpensive, readily available, and possesses unparalleled nutritive and anti-infectious properties. Furthermore, breastfeeding has contraceptive effects, protecting the health of mothers and children against the deleterious consequences of short birth-

spacing. Because of its crucial role in the control of infection, malnutrition, and high fertility, breastfeeding deserves high research priority.

A series of field based studies linked with laboratory supported facilitative will be undertaken to identify the levels, patterns and determinants of breastfeeding in rural and urban populations. Of particular concern is the identification of optimal patterns and lengths of breastfeeding, focusing on such issues as the timing, type and nature of dietary supplementation of mothers and/or children. There is limited data to suggest that the volume of breast milk may be related to maternal dietary intake of protein while, perhaps, the fat content (and, therefore, calories) in milk may be influenced by maternal caloric intake. Almost nothing is known about what determines the duration of lactation, although indirect evidence suggests that it is primarily related to the frequency, duration and intensity of nipple stimulation by the nursing child.

A systematic investigation of maternal dietary variations and breast milk production will be undertaken in both clinical and field settings. In the clinical setting this will involve controlled variations in the diet and observation on variability in milk production. In the field setting this will involve correlations between maternal dietary practices and breast milk production.

The implications of these investigations can be substantial if infant nutrition can be effectively improved simply by providing additional quantities of ordinary food to the mother, as opposed to having to provide powdered milk or other specially prepared diets for young infants. Further, this approach is particularly relevant in rural settings where breastfeeding typically extends well through the second year of an infant's life. A parallel line of investigation will be social and programmatic research on means to provide breastfeeding, particularly among urban families undergoing rapid socio-economic change.

### Conclusion

The broad thrusts outlined earlier circumscribes, in our opinion, an appropriate arena for ICHR's work in nutrition. Several aspects of the current activities (see Appendix 1) deserve comment. First, although CRL has been involved in direct nutrition research since the early 1960's (sub-clinical malabsorption, national nutrition survey 1962-64, field anthropometry, nutrition and host resistance), the

CRL has not as yet evolved a coherent nutrition program. The current working group contains some nutritionist members, but only one member devotes all of his time to nutrition work. Secondly, it is clear that the current and proposed future program is linked closely to other CRL activities. Nutrition is a massive field requiring the skills and efforts of many. As such the ICHR can only be one participant, contributing its share to problem solution.

Finally, we are seeking the advice of this International Review Committee in refining the future orientation of this program. Some crucial questions are:

(1) What should be the program-scope of ICHR's work? Which nutrient deficiency: energy-protein, vitamin-A, iron deficiency anemia?

(2) What types of disciplinary and scientific skills should be brought to bear on the problem? Which orientation: field, clinical, biomedical?

(3) How much of the effort should be directed to interventions, technology development, and evaluation and assessment?

(4) What are some productive relationships between the ICHR and the Bangladeshi nutrition institute and other national and regional nutritional bodies?

# APPENDIX 1

## NUTRITION

| <u>Protocol Number</u> | <u>Title</u>                                                                                                                            | <u>Principal Investigator</u> | <u>Period of Study</u> |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|------------------------|
| 77-010                 | Lactose Malabsorption in Bangladeshi Villagers as Determined by Breath Hydrogen Testing                                                 | K. Brown                      | Jul 77 - Jan 78        |
| 77-026                 | Nutritional Consequences of Low Dose Whole Milk Dietary Supplements Given to Lactose-Malabsorbing Children                              | K. Brown                      | Sep. 77 - Mar 78       |
| 77-030                 | Gastric Acid in Protein Calorie Malnutrition                                                                                            | R. Gilman                     | Oct 77 - Mar 78        |
|                        | Studies in Nutrition & Lactation                                                                                                        | K. Brown                      |                        |
|                        | Classification of Energy-protein Malnutrition by Anthropometry and its Usefulness in Prognosticating Subsequent Morbidity and Mortality | A.K.M.A. Chowdhury            |                        |
|                        | Quantitation of $\alpha$ -antitrypsin to Detect the Gastrointestinal Protein Loss in Diarrhea and Dysentery                             | L.C. Chen.                    | Jan 78 - Apr 78        |
|                        | Meheran Growth Study.                                                                                                                   | M.A. Wahed                    | Feb 78 - Aug 78        |
|                        |                                                                                                                                         | M.U. Khan                     | Oct 73 - Dec 77        |
| *                      |                                                                                                                                         | R. Black                      |                        |
| *77-027                | Determinants of Natural Fertility                                                                                                       | A.K.M.A. Chowdhury            |                        |
| *                      | Water and Sanitation Intervention                                                                                                       | Mujibar Rahaman               |                        |

\* Also listed under other Working Groups

## POPULATION WORKING GROUP

Bangladesh is the eighth most populous nation in the world with 80 million people living on 55,000 square miles of land. Like many other parts of Asia (particularly certain parts of India, Pakistan and Indonesia), the demography of Bangladesh is characterized by high fertility and mortality (Appendix I). Over the past decade, rural Bangladesh has experienced high fertility and mortality and despite aggressive programmatic effort these health indicators have remained unchanged. In meeting the health need of this and similar populations, four issues are of significance:

1. What are the social and biological determinants of human reproduction?
2. What are the causes of high mortality and morbidity?
3. Within the context of available knowledge and technology, how can health and family planning services be delivered efficiently and effectively?
4. How appropriate, acceptable, effective and safe are modern and traditional health and contraceptive technologies, both theoretically and within any given socioeconomic and cultural setting?

These questions constitute the core of the proposed scientific program of ICHR's Population Working Group. This paper speculates on how ICHR may best contribute to these issues. To do so, the paper draws heavily upon the ongoing work of ICHR. A list of ongoing protocols is given in Appendix A along with abstract summaries and progress reports; details of these protocols may be scrutinized in subsequent sessions of this Review. Utilizing the information generated by these and other completed CRL studies, this paper reflects upon how current activities may be fortified and/or modified and thus projected into the future.

### Determinants of Human Reproduction

How interventions may be more effective requires a fundamental understanding of the epidemiology of human reproduction. Just as malaria and smallpox cannot be controlled by random application of insecticides and vaccines, so too the indiscriminate delivery of modern contraceptive technologies cannot be expected to meet the contraceptive needs of a given population. The need for knowledge is underscored by the fact that reproductive patterns in Bangladesh and

many other less developed populations differ markedly from those of affluent populations. For example, despite low contraceptive practice, the total fertility rate in rural Bangladesh averages 6.3 per woman, far below the maximum biological level of about 10.6 as noted among Hutterites, a non-contracepting affluent population reproducing close to the biological maximum.

The factors responsible for these marked differences are depicted in Figure 1. In this figure are diagrammed biological states associated with the components of a birth interval - amenorrhea, menstruating interval, and gestation. These biological components of reproduction are crucial because all factors that ultimately affect fertility, behavioural and biologic, must operate through these components to affect fertility. In the absence of direct fertility control behavior, an average rural Bangladeshi woman takes about 36 months between successive births. This length contrasts with only 21 months for noncontracepting Hutterites. The longer birth intervals, and thus lower fertility, in Bangladesh is due primarily to the lengthy period of postpartum amenorrhea, averaging 17-22 months. CRL research has documented that the lengthy period of temporary sterility is due to intensive and extended breastfeeding. Abbreviation of amenorrhea is noted with brief or non-intensive lactation or involuntary cessation of breastfeeding precipitated by premature infant death. Contrary to an earlier hypothesis, studies in Matlab have shown that maternal malnutrition does not have a direct or major effect on postpartum amenorrhea.

Figure 1

|                      | Birth                 | First menses          | Conception | Birth |
|----------------------|-----------------------|-----------------------|------------|-------|
|                      | ↓                     | ↓                     | ↓          | ↓     |
|                      | Postpartum Amenorrhea | Menstruating Interval | Gestation  |       |
| Bangladesh (36 mths) | 18                    | 9                     | 9          |       |
| Hutterites (21 mths) | 6                     | 6                     | 9          |       |

How would research elucidating these biological components of reproduction contribute to meeting the health needs of a population. First, the information generated is needed to improve program strategies, such as the optimal timing of postpartum contraception. Secondly, a basic

understanding of reproduction would facilitate the development and application of more appropriate contraceptive technologies and would improve the use of existing technologies. Finally, such research is essential for social science studies of reproductive behaviour - why people want children and why they don't. Some examples are in order.

Unlike women in affluent countries, the average rural Bangladeshi woman spends most of her reproductive lifetime amenorrheic, either from breastfeeding or pregnancy. Oral pills, a modern technology, induces monthly menses - a distinctly less common biological state in most less developed countries. It is not surprising therefore that oral pills may be inappropriate (daily administration for people who have no illness!); culturally unacceptable (induction of menses when amenorrhea is a more common physiologic state); less than optimally effective (overlap of protection afforded by the pills and postpartum amenorrhea); and possess different benefit/risk ratios (possible interference with breastfeeding and transfer of steroid hormones and/or metabolites in breast milk).

Another example is shown in Table 1 which presents unpublished CRL data showing a positive association between fertility and landholding. Wealthy rural families apparently have higher fertility than their poor counterparts. Such correlative findings, not uncommonly, have generated spurious conclusions, such as: poor families cannot afford many children; rich families are healthier and are able to reproduce more; improving the economic condition of the poor may actually increase fertility. Based upon an investigation of the biological components of reproduction however CRL research has demonstrated that one explanation for lower fertility among the poor is more intensive and extended breastfeeding. This fertility differential therefore reflects behaviour differences unrelated directly to fertility desires but more to child nutrition. If explicit reproductive behaviour were responsible for this differential, one would observe changes of the length of the menstruating interval, not postpartum sterility.

Table 1

| Fertility            | Landholding (acres) |     |       |       |     |
|----------------------|---------------------|-----|-------|-------|-----|
|                      | None                | <1  | 1-1.9 | 2-2.9 | 3>  |
| Total Fertility Rate | 6.8                 | 7.1 | 7.3   | 7.4   | 7.7 |

The future ICHR agenda in this area will be to elucidate the basic epidemiology of human reproduction. This would involve continuation of the demographic surveillance system registering longitudinally vital events in a rural population. The ongoing longitudinal field studies on lactational amenorrhea, breastfeeding, factors associated with the onset of ovulation following amenorrhea, fecundability, fetal wastage, birth and the factors associated with live births and offspring survival would be continued. The current work would lead to two future lines of investigation. First would be indepth field studies of fertility behaviour, controlling for biological variables. Such studies would involve indepth social research integrating such concerns as economic value of children, the role and status of women, the role of high mortality, and sociocultural factors. Second would be a linkage of field studies with clinical and laboratory reproductive-biology to address questions such as the timing in the return of postpartum ovulation, the biologic regulation of breastfeeding and postpartum amenorrhea, factors responsible for subfecundity, and reproductive function in relation to health and nutrition. How these future thrusts will evolve from the ongoing program is synthesized at the end of this paper.

#### Determinants of Morbidity and Mortality

Like many other less developed countries, the life expectancy in Bangladesh is 53.4 and 49.3 years for males and females, respectively (Appendix II). These abbreviated life expectancies are due nearly entirely to high infant and child mortality for survivors at age 5 expect to survive to an average of 65 years. The age-sex specific death rates for rural Bangladeshi children under 5 years are shown in Table 2. High infant mortality in Bangladesh is particularly concentrated in the neonatal period and 1-4 year mortality is also very high. The presumption is that maternal malnutrition, poor obstetrical care, low birth weight, and neonatal tetanus are important contributors to neonatal mortality and the synergism of infection and malnutrition are the major contributors to childhood mortality.

Like reproduction, socioeconomic and cultural factors affecting mortality may be more important than biologic ones. A closer scrutiny of sex differentials in Table 2 underscores this fact. The very high female death rates in comparison to males presumably reflect inequality of dietary and health care practices which in turn are symptomatic of sexual inequality within the society. Although oversimplified, the remarkable data in Table 2 shows that even within existing resource and knowledge constraints, rural Bangladeshi families

could theoretically reduce female child mortality by half without any program intervention whatsoever. Similar inequalities have been shown between social and economic classes; and these may be more marked than sexual ones. Future research would need to dissect out such differentials and, like reproduction, elucidate how socioeconomic and cultural factors operate (via nutrition, environmental sanitation, crowding, health practices) to affect mortality.

Table 2

|                           | Infant and Child Mortality |       |        |           |
|---------------------------|----------------------------|-------|--------|-----------|
|                           | Total                      | Male  | Female | F/M Ratio |
| Under 1 year <sup>a</sup> | 137.9                      | 142.5 | 132.9  | 93        |
| under 1 mo.               | 78.1                       | 87.9  | 67.8   | 77        |
| 1-11 mo.                  | 59.8                       | 54.6  | 65.1   | 119       |
| 1-4 years <sup>b</sup>    | 25.4                       | 18.3  | 32.9   | 180       |
| 1 year                    | 31.6                       | 22.9  | 40.6   | 177       |
| 2 year                    | 34.8                       | 25.7  | 44.4   | 173       |
| 3 year                    | 22.5                       | 16.0  | 29.2   | 183       |
| 4 year                    | 11.6                       | 7.7   | 15.8   | 205       |

<sup>a</sup> per 1,000 live births

<sup>b</sup> per 1,000 population.

How can research contribute to a reduction of high death rates? First, basic field epidemiological studies are needed to delineate the factors associated with high risk of mortality, such as age, parity, birth spacing, seasonality, social class, access to resources, and nature of and access to health care. Second, a clearer delineation of the causes of death could facilitate the selection of more cost-effective intervention programs. Finally, longitudinal surveillance of mortality is essential to assess the impact of various interventions and health technologies.

One example of the value of CRI surveillance system is a recent study of maternal mortality. Despite its clear importance, field studies of the risk factors, and causes of

maternal mortality in rural areas has been virtually absent for program planning purposes. Maternal mortality is an infrequent event, requiring longitudinal surveillance of a large population and difficult to obtain cause-of-death data. Table 3 shows the results of a study of maternal mortality by cause-of-death and timing in relation to pregnancy. This study not only demonstrated that the Bangladesh maternal death rate was in the order of 5.7 to 7.7 per 1,000 livebirths but also that primigravida and grand multigravida women were at highest risk. The unique data enabled the study to project that a family planning program aimed at mothers with 4 or more children could theoretically reduce maternal mortality by 30% while an antenatal program focused exclusively on eclampsia among primigravida could prevent another 30%. In essence the study showed that two highly specific actions could eliminate two-thirds of maternal mortality.

Table 3

Number of maternal death by cause, and time of death, in relation to pregnancy, Matlab thana, 1967-1968 study

| Cause of death              | Antepartum<br>(months of pregnancy) |   |   |   |   |   |   |   |     | During<br>delivery | Postpartum<br>Days Wks Mths |     |   |    | Total |
|-----------------------------|-------------------------------------|---|---|---|---|---|---|---|-----|--------------------|-----------------------------|-----|---|----|-------|
|                             | 2                                   | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 2-7 |                    | 2-4                         | 2-3 |   |    |       |
| Direct obstetric            |                                     |   |   |   |   |   |   |   |     |                    |                             |     |   |    |       |
| Eclampsia                   |                                     |   |   |   |   |   |   | 1 | 7   |                    | 2                           |     |   | 10 |       |
| Obstructed labor and others |                                     |   |   |   |   |   |   | 1 | 1   | 11                 | 1                           | 1   | 1 | 16 |       |
| Postnatal                   |                                     |   |   |   |   |   |   |   |     |                    |                             | 3   |   | 3  |       |
| Ectopic pregnancy           |                                     |   |   | 1 |   |   |   |   |     |                    |                             |     |   | 1  |       |
| Induced abortion            | 1                                   | 2 |   |   |   |   |   |   |     |                    |                             |     |   | 3  |       |
| Indirect obstetric          |                                     |   |   |   |   |   | 1 | 1 |     |                    |                             |     | 2 | 4  |       |
| Not related                 |                                     |   |   |   | 1 | 1 |   |   |     |                    |                             | 1   | 1 | 2  |       |
| All causes                  | 1                                   | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 18  | 3                  | 5                           | 4   |   | 41 |       |

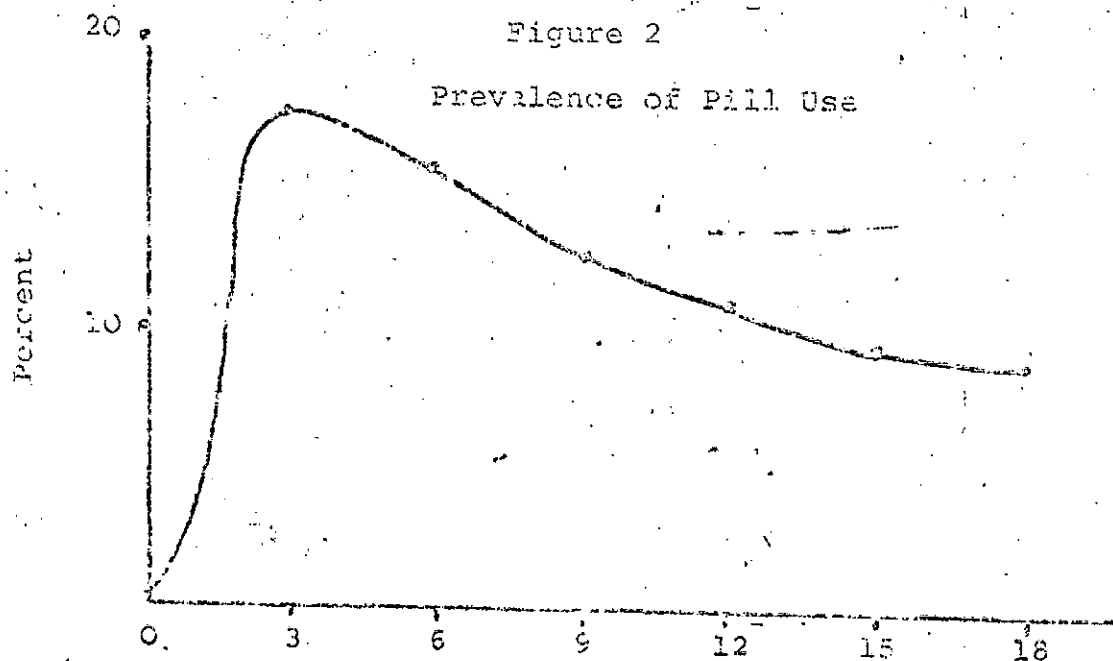
To extend such studies to infant and child mortality would require the development of a classification system for cause-of-death within the context of the CRL demographic surveillance system. Such a system would need to be based on simple information, obtainable by non-professional field workers focusing on highly prevalent illnesses where inexpensive, effective technologies are current available. This broad based system would be complemented by a more intensive

indepth follow-up study of a stratified sample of deaths.

Mortality, of course, only reflects the consequences of severe illnesses. Most health problems, like an iceberg, remain submerged and equal attention should be devoted to the burden of illness imposed upon a society. Increasingly, it is becoming recognized that morbidity may have far more severe consequences in terms of welfare and productivity than mortality alone. The indepth longitudinal demographic surveillance system constitutes an ideal backbone for the testing and development of methodologies for assessing the prevalence, incidence, causes and consequences of disease burden in a society.

### Fertility Regulation Services and Technology

To test the efficiency and effectiveness of a simple fertility control delivery service, the CRI in 1975 initiated a contraceptive distribution project providing through resident female village workers unrestricted household supply of non-clinical contraceptives (oral pills and condom) to all married couples in half of the Matlab surveillance area with the remaining half serving as controls. Two years of program experience showed that: while modest, there exists some demand for contraceptives (24 percent of eligible couples in rural Bangladesh as measured by current use of contraception or an expression of an intent for future use); three months after the household distribution was initiated 17 percent of the eligible women claimed to be using oral pills; after 18 months of program effort the use-prevalence had declined to 8.7 percent (Figure 2). The decline of use-prevalence reflected both a diminishing rate of new acceptors and briefer rates of method continuation over time.



The disappointing performance reflected weaknesses of both the service delivery system and the technologies employed. In-depth surveys indicated that the village workers were too elderly to have ever contracepted themselves; were rarely contacted by women experiencing side-effects preferring instead to rely on the traditional practitioners; were perceived as socially inferior by most potential clients; and may have accorded the extra work, without extra pay, low priority. Acceptors and continuers tended to cluster geographically, reflecting either worker variability or varying community and family attitudes and interactions. Problems were also encountered with the acceptability and use-effectiveness of the oral pill technology. Oral pills were often irregularly or improperly used. Side-effects, such as dizziness, weakness, and irregular menstrual bleeding were troublesome.

One consequence of this research led to a modification of the study design whereby better-trained female workers backed by stronger supervisory and technical support staff are now providing selected health and family planning services in 70 villages (population 80,000). This MCH-FP program includes selected antenatal, maternity, and child health services and also a wider range of family planning services including IUD, sterilization, and menstrual regulation. Improving the scope and quality of services should yield useful information on the efficiency and effectiveness of a village-based MCH-FP program and on the acceptability and appropriateness of a broader array of contraceptive technologies.

The crucial areas of delivery system and technology constitute a future focus of the ICHR. Delivery systems issues to be addressed include: (1) the cost-effectiveness of a simple household distribution program in comparison to a more intensive program offering a fuller range of contraceptive services, selected health services, and more adequate client support and field training and supervision; (2) the feasibility and operational constraints of organizing and implementing such delivery systems; (3) measurement of the demographic impact of these systems; (4) the identification of program variables such as worker qualification, training, supervision that affect program performance; and (5) the importance of community participation and informal networks in performance.

With respect to contraceptive technologies, the aims would be: (1) the determination of the acceptability, use-effectiveness, and side-effects of various modern and traditional contraceptives; (2) the identification of program requirements to optimize the safety and effectiveness of various fertility control technologies; and (3) an assessment of the interaction

between contraception, breastfeeding, and lactational amenorrhea so that optimal strategies to promote both MCH and fertility control may be derived.

Linked with the contraceptive technology program would be a clinical and laboratory program in reproductive biology. Such a program is also considered essential for the determinants of reproduction program. An exploratory phase of the reproductive biology program would involve the development of laboratory capacity for assays of the reproductive hormones. This capacity in turn would be related to clinical and epidemiologic field studies. The reproductive biology program would generate knowledge on the biologic basis of the reproductive patterns of less developed populations and also on how the development and application of modern technologies, often conceived and developed for affluent populations, may be made more appropriate for less developed populations.

### Health Services and Technology

Like experiences elsewhere (Guatemala and India), the CRL experience with mortality reduction programs has not been spectacularly successful. Despite abundant resources and effective technology directed with relative autonomy at a highly prevalent disease in Matlab thana, the impact of CRL curative diarrheal health services probably has reduced crude death rates by less than 20%. The factors responsible are multiple, including insufficient health promotion and prevention, overcentralized services, single-disease orientation (ignoring such important problems like neonatal tetanus), lack of community participation, and unfavorable socioeconomic forces. Based upon this experience future work in this area should be guided by certain general principles. First, since the responsibility of health services rests with the people, community, and national organizations, CRL's activities needs to be oriented toward strengthening these indigenous bodies. Second, because national bodies may have different constraints than an autonomous research organization, the work of CRL needs to be made as relevant as possible. Third, services based in hospital facilities will by their very nature restrict access and utilization. Thus, whatever technology is developed and field tested will be more acceptable and effective if mothers, household members, or non-professionals can understand and apply these technologies directly themselves. Fourth, in developing any system consideration should be given to strengthening, utilizing, and linking the existing (traditional) health service structure. Finally, community participation, and control, should be a critical ingredient to facilitate responsiveness, access and utilization.

The Matlab and Demnuf demographic systems and the village-based MCH-TP program provide preliminary field bases for the conduct of studies on the delivery and impact of health services and technologies. Two lines of investigation seem worthwhile pursuing in the future. First would be an assessment of the delivery system constraints and impact of the village-based MCH services program being implemented in Matlab. The underlying demographic base affords a unique opportunity to measure program impact. While the program contains deficiencies with regard to the guidelines outlined earlier, it has the distinct advantage of collaboration with the Bangladesh Government, ensuring some relevance and ready transfer of findings. Other less structured activities, to be discussed in the "Training and Outreach" session need also to be developed.

The second line of investigation would be undertaken in close cooperation with other ICNR Working Groups. Specific interventions now being implemented or planned including cholera vaccine, water and environmental sanitation, or rehydration need to be field tested under a variety of delivery system modalities - as single interventions or within the context of broader services, based in homes, hospitals, commercial outlets, traditional practitioners or via field workers. The demographic data of the surveillance system would provide one of the foundations for the assessment of these field trials.

#### Summary and Conclusion

Table 4 presents the current scientific program of the CRL as it contributes to the four program thrusts outlined in this paper. An "X" indicates the contribution made by current protocols to these four main goals. Although clearly related, the ongoing program will require substantial development to meet the projected needs, which are summarized in Table 5. Implicit in the development of Table 5 are several considerations deserving articulation: the comparative advantage of the CRL; the ongoing activities of the CRL; optimal utilization of CRL resources, particularly in the field; potential usefulness; and role in developing national capabilities. Regarding the last criterion, it should be noted that some cooperative arrangements have already been formed with Bangladeshi organizations. The contraceptive distribution project is a joint program with the Ministry of Health and Population; data from the demographic surveillance system are being made available to scientists at the Bangladesh Institute of Development Studies; the reproductive biology program is being developed in consultation with an informal consultative group of interested Bangladeshi scientists; the

anthropology study is linked with the University of Rajshahi. It is expected that such arrangements would be further consolidated with future protocols.

The program proposed here is admittedly broad and ambitious. A comprehensive attack in all of the areas would require at least twice the level of resources and staff envisaged for this working group. We hope that the International Scientific Review Group would offer guidance as to the importance, relevance, and appropriateness of these programs so that priorities within and between Working Groups may be established.

Table 4

| <u>Current Protocols</u>    | <u>Determinants of</u> |                                | <u>Service and Technology</u> |               |
|-----------------------------|------------------------|--------------------------------|-------------------------------|---------------|
|                             | <u>Reproduction</u>    | <u>Morbidity<br/>Mortality</u> | <u>Fertility</u>              | <u>Health</u> |
| Demographic Surveillance    | X                      | X                              | X                             | X             |
| Determinants Fertility      | X                      |                                |                               |               |
| Contraceptive Distribution  | X                      | X                              | X                             | X             |
| Survey Pregnancy Prevalence | X                      |                                |                               |               |
| Reproductive Biology        | X                      |                                | X                             | X             |
| Anthropological Study       | X                      |                                |                               |               |
| Response Bias               | X                      |                                |                               |               |
| Marriage                    | X                      |                                |                               |               |
| Life Cycle                  | X                      | X                              |                               |               |
| Family Structure            | X                      |                                |                               |               |
| Joint Activities            |                        | X                              |                               | X             |

Table 4

| <u>Current Protocols</u>    | <u>Determinants of</u> |                                | <u>Service and Technology</u> |               |
|-----------------------------|------------------------|--------------------------------|-------------------------------|---------------|
|                             | <u>Reproduction</u>    | <u>Morbidity<br/>Mortality</u> | <u>Fertility</u>              | <u>Health</u> |
| Demographic Surveillance    | X                      | X                              | X                             | X             |
| Determinants Fertility      | X                      |                                |                               |               |
| Contraceptive Distribution  | X                      | X                              | X                             | X             |
| Survey Pregnancy Prevalence | X                      |                                |                               |               |
| Reproductive Biology        | X                      |                                | X                             | X             |
| Anthropological Study       | X                      |                                |                               |               |
| Response Bias               | X                      |                                |                               |               |
| Marriage                    | X                      |                                |                               |               |
| Life Cycle                  | X                      | X                              |                               |               |
| Family Structure            | X                      |                                |                               |               |
| Joint Activities            |                        | X                              |                               | X             |

Table 5

- I. Determinants of Human Reproduction
  - A. Longitudinal surveillance of fertility.
  - B. Indepth studies of fertility and marriage behaviour.
  - C. Reproductive biology linked with clinical and field studies.
- II. Determinants of Morbidity and Mortality
  - A. Longitudinal surveillance of mortality.
  - B. Cause-of-death investigations.
  - C. Health behaviour and socio-economic, cultural antecedents of death.
  - D. Studies of morbidity methodology and social impact.
- III. Fertility Services and Technology
  - A. Village-based family planning and health services research.
  - B. Contraceptive technology linked with program intervention and reproductive biology.
- IV. Health Services and Technology
  - A. Village-based MCH-FP services.
  - B. Health service access and utilization research
  - C. Impact of specific technologies.

# APPENDIX II

Assumed Life Table based on age-specific death rates for 1974 in SAS (Table)

| Age   | Probability<br>of dying<br>1,000 $nq_x$ | Survivors<br>$l_x$ | Life<br>expectation<br>$e_x$ | Probability<br>of dying<br>1,000 $nq_x$ | Survivors<br>$l_x$ | Life<br>expectation<br>$e_x$ |
|-------|-----------------------------------------|--------------------|------------------------------|-----------------------------------------|--------------------|------------------------------|
| MALES |                                         |                    | FEMALES                      |                                         |                    |                              |
| 0     | 117.28                                  | 100,000            | 53.4                         | 110.44                                  | 100,000            | 49.3                         |
| 1     | 22.64                                   | 88,272             | 59.5                         | 44.87                                   | 88,956             | 54.4                         |
| 2     | 25.38                                   | 86,274             | 59.8                         | 43.43                                   | 84,365             | 55.9                         |
| 3     | 15.89                                   | 84,054             | 60.4                         | 23.80                                   | 81,275             | 57.4                         |
| 4     | 7.89                                    | 82,748             | 60.3                         | 15.63                                   | 78,934             | 58.1                         |
| 5     | 23.47                                   | 82,111             | 59.3                         | 31.54                                   | 77,700             | 58.0                         |
| 10    | 5.24                                    | 80,184             | 56.2                         | 8.86                                    | 75,249             | 54.9                         |
| 15    | 5.63                                    | 79,764             | 51.5                         | 17.35                                   | 74,582             | 50.3                         |
| 20    | 5.93                                    | 79,311             | 46.7                         | 13.13                                   | 73,289             | 46.2                         |
| 25    | 11.48                                   | 78,836             | 42.0                         | 14.05                                   | 72,180             | 41.8                         |
| 30    | 14.99                                   | 77,931             | 37.5                         | 21.52                                   | 71,166             | 37.4                         |
| 35    | 27.66                                   | 76,763             | 33.0                         | 20.93                                   | 69,634             | 33.2                         |
| 40    | 32.08                                   | 74,640             | 28.9                         | 34.06                                   | 68,177             | 28.6                         |
| 45    | 52.11                                   | 72,245             | 24.7                         | 33.63                                   | 65,855             | 24.7                         |
| 50    | 75.67                                   | 63,481             | 21.0                         | 53.58                                   | 63,640             | 20.5                         |
| 55    | 103.55                                  | 63,299             | 17.5                         | 94.33                                   | 60,230             | 16.5                         |
| 60    | 152.47                                  | 56,744             | 14.2                         | 154.04                                  | 54,546             | 13.0                         |
| 65    | 222.22                                  | 43,091             | 11.0                         | 226.05                                  | 46,143             | 9.9                          |
| 70    | 283.42                                  | 37,405             | 8.8                          | 393.93                                  | 35,712             | 7.1                          |
| 75    | 423.32                                  | 28,730             | -                            | 603.71                                  | 21,644             | -                            |

POPULATION

| <u>Protocol<br/>Number</u> | <u>Title</u>                                                                                                         | <u>Principal<br/>Investigator</u>             | <u>Period of Study</u> |
|----------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|------------------------|
| -001                       | Demographic Surveillance System -<br>Teknaf                                                                          | M.M. Rahaman                                  | Oct 77 - Sept 80       |
| -001                       | Demographic Surveillance System -<br>Matlab                                                                          | L.C. Chen                                     | Oct 77 - Sept 78       |
| -027                       | Determinants of Natural Fertility                                                                                    | A.K.M.A.<br>Chowdhury                         | Oct 75 - Oct 78        |
| -028                       | Survey of Fertility by Pregnancy<br>Prevalence                                                                       | A.K.M.A.<br>Chowdhury                         | May 77 - Jan 78        |
| A. No.<br>0410             | Contraceptive Distribution Project<br>Matlab                                                                         | S. Bhatia<br>T. Osteria                       | Oct 77 - Sept 78       |
| -008                       | Endocrinological Factors in Relation<br>to Reproduction in Bangladesh                                                | B. Seaton                                     | Feb 78 - Jan 80        |
| -007                       | Sex Socialization and Philosophies<br>of Life in Relation to Fertility<br>Behaviour - An Anthropological<br>Approach | K.M.A. Aziz                                   | Jun 77 - Jun 79        |
| -015                       | An Estimation of Response Bias of<br>Literacy in a Census of Rural<br>Bangladesh                                     | M. Shafiqul<br>Islam                          | Dec 77 - Dec 77        |
| anned                      | Marriage Formation and Dissolution<br>in Rural Bangladesh: Implications<br>for Fertility                             | L. Ruzicka<br>A.K.M.A.<br>Chowdhury           |                        |
| anned                      | A Life Cycle of a Rural Woman<br>In Bangladesh                                                                       | S. Bhatia<br>A.K.M.A. Chowdhury<br>L. Ruzicka |                        |
| anned                      | Family Structure and Fertility<br>in Rural Bangladesh                                                                | L. Ruzicka<br>A.K.M.A.<br>Chowdhury           |                        |

# DEMOGRAPHIC SURVEILLANCE SYSTEM, TEKNAF AND MATLAB

M. Mujibur Rahaman  
Lincoln C. Chen

## ABSTRACT

This protocol rationalizes the operations of two demographic surveillance systems in Teknaf and Matlab thanas. Unlike other protocols, this proposal does not address or examine a specific research hypothesis. Rather its aim is to articulate the purposes, rationale, and costs of two field surveillance programs - institutional resources of the CRL. The protocol provides summary information on the history of the surveillance systems; ongoing scientific activities; advantages and limitations of the systems for various purposes; and issues that require exploration over the coming year. The protocol proposes that a Demographic Surveillance Committee be constituted to optimize resource utilization and to facilitate coordination within and between CRL programs.

## DETERMINANTS OF NATURAL FERTILITY

A.K.M. Alauddin Chowdhury

### ABSTRACT

This protocol amendment proposes the continuation of an ongoing longitudinal field research program on the epidemiology and demography of the intermediate variables of human reproduction in rural Bangladesh. The study design involves monthly follow-up of 2,500 women of reproductive age in 14 villages of the Matlab surveillance area. Since October 1975, monthly data on reproductive status (amenorrhea, menstruation, or pregnant) breastfeeding, spousal separation, contraception, maternal morbidity and anthropometry, child survivorship and anthropometry have been collected. The goals of the program are: (1) to measure the intermediate variables of reproduction (postpartum amenorrhea, menstruating interval, gestation, fetal wastage); (2) to identify the importance of selected social and biological factors in affecting these variables; and (3) to develop new methodologies for the measurements of reproduction and for research into the determinants of fertility. A smaller component of this study involves the biological and social determinants of menarche.

## PROGRESS REPORT

### A. MENARCHE STUDY

Sample Size - 1200

Date of Start - April 1976

Date of Completion - October 1978

#### variable

#### Data Collection Methods

Nutrition (Anthropometric)

Every month for a cohort of 1200 girls age 10-20 wt, ht, and Ac were taken

Onset of menses

Date of menses

Every month for same cohort were asked about their menses and date

Marital Status

Every month

Birth Order

Mother's Pregnancy  
history

were asked during the 1st interview

Socio-economic variables

To be added from the census data.

A paper is going to be published in social Biology winter 1977. The paper clearly illustrates the relationship between weight for age and the onset of menarche among girls in rural Bangladesh. It is also indicated that the proportion of young women married within any age is strongly related to the attainment of menarche.

Next paper will look into the effect of growth spurt on menarche controlling other variables.

B. POST PARTUM AMENORRHEA

Sample Size - 2500

Date of Study - Oct. 1975

Date of Completion - Nov. 1975

| <u>Variables</u>        | <u>Data collection method</u>                                                            |
|-------------------------|------------------------------------------------------------------------------------------|
| Lactation               | This is a cross sectional survey of women who have a surviving child 11-18 months of age |
| Menstruation            |                                                                                          |
| Post partum Amenorrhea  |                                                                                          |
| Pregnancy               |                                                                                          |
| Anthropometric (Mother) |                                                                                          |
| Anthropometric (Child)  |                                                                                          |
| Supplementation (Child) |                                                                                          |
| Mothers food            |                                                                                          |
| Mothers Activity        |                                                                                          |
| Mothers illness         |                                                                                          |
| Contraception           |                                                                                          |
| Socio-economic status   | Were added from the census data.                                                         |

This study did not directly measure breastfeeding practices, other factors which could be considered indices for breastfeeding patterns were incorporated into the analysis. A multiple linear regression using menstrual status as a binary dependent variable illustrated that when post-partum interval was controlled, maternal age, socioeconomic status (defined as variations in wealth), and infant supplementation were significantly correlated with the probability of being amenorrheic. As shown in other studies, maternal age was related positively with postpartum amenorrhea. With older women more likely to be amenorrheic than younger women. Richer women and those feeding their infants higher quality supplements exhibited an increased tendency to resume menstruation. With all variables present, maternal nutritional status was able to explain less than 1% of the total variance ( $R^2 = .115$ ). Current maternal/infant morbidity and infant anthropometric status were not associated with the probability of being amenorrheic.

Socioeconomic status was found to be unrelated to maternal nutritional status. This surprising finding may be explained by the generally poor sanitary and environmental conditions prevalent throughout villages in Bangladesh.

A paper is accepted for publication in "Population Studies".

C. BREAST FEEDING PRACTICE

Sample Size - 200 women with parity 2-3 and age 20-29  
Date of State - March 1976  
Date of Completion - August 1977

Variables

Data Collection Method

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| Mother's anthropometric           | Once a month for 18 months by       |
| Child's anthropometric            | measurement and interview           |
| Sex of the child                  |                                     |
| Menstruation                      |                                     |
| Days breast feed (last one month) | This data is collected every month  |
| Days supplemented ( " " " )       | to look the interruption of breast  |
| Mother's illness ( " " " )        | feeding and supplementation time    |
| Father's illness ( " " " )        | to time associated with the illness |
| Child's illness ( " " " )         | of child or mother.                 |
| Contraception ( " " " )           |                                     |
|                                   |                                     |
| Mother's diet                     | Collected by observation during     |
| Mother's activity                 | daytime once a month for 18 months  |
| Crop in stock                     |                                     |
| Breastfeeding                     |                                     |
| (a) Suckling time                 |                                     |
| (b) Number of feeds               |                                     |
| (c) Initiation                    |                                     |
| Child's supplementation           |                                     |

Analysis is in progress by Dr. Huffman in Johns Hopkins University  
from a separate funding by NICHD, USA.

D. BIRTH INTERVAL DYNAMICS

Sample Size - 2200 currently married non menopausal women  
Date of Start - October 1975  
Date of Completion - September 1976 -

Variables

Data collection methods

Fecundity  
Conception and Outcome  
Breast feeding  
Supplementation  
Separation life  
Contraception  
Woman's illness  
Husband's illness  
Child survival  
Anthropometric  
Hematocrit

Monthly interview and measurement  
were done routinely for 2200 women

Serum Albumin  
Serum Protein

5 blood samples were collected from  
each woman for every alternate month  
during the first year of the study

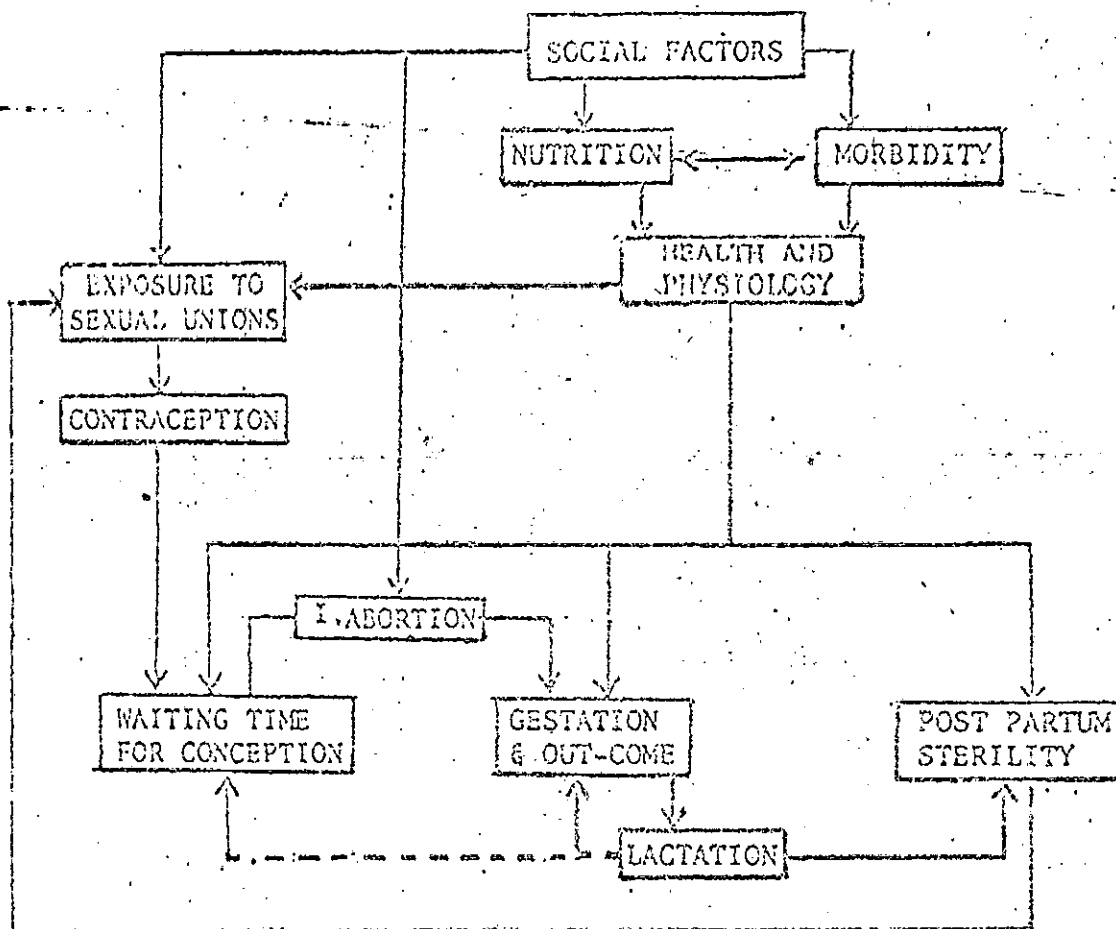
In the preliminary analysis on the 1st year it was found that age  
is negatively related with fecundity and controlling age, parity  
is positively related with fecundity.

Initial Wt

/ as well as Wt. gain seems to have a relation with fecundity.

Elaborate and detailed analysis will be done both by  
multiple classification analysis as well as life table technique  
according to the enclosed model.

A paper is going to be published in the Proceedings of Nutrition  
and Reproduction Conference in NIH USA.



MODEL: Effect of nutrition & morbidity on birth interval by socio-economic status.

## PREGNANCY PREVALENCE SURVEY

A.K.M. Alauddin Chowdhury

### ABSTRACT

The Principal Investigator himself has developed a new method and termed it as Pregnancy Prevalence Survey. Details of the method with its advantages and limitations comparing to other methods is already published (1).

The fertility rates estimated by Pregnancy Prevalence survey were found as good as that of vital registration system in Matlab. This new method should be field tested in an area in which intensive vital events registration like Matlab has not been conducted as such as registration system may introduce bias through frequent questioning about births. Hajigonj thana is adjacent to the Matlab thana and may be expected to share many of the factors regulating fertility with pre-contraceptive distribution Matlab. If it is found to be suitable for field use and if it gives reliable estimates, the method can be expanded to a nationwide basis. It is simple, flexible and relatively low cost.

## PROGRESS REPORT

Sample size - 3200 households

Time:           1st Round Survey May 1977  
              2nd Round Survey Nov. 1977

### V a r i a b l e s

### Method of Data Collection

Household composition

Interviewed twice

Socio economic status

at six months interval

Demographic variables

Pregnancy status.

Last 12 months birth

Pregnancy test

In 2nd round to a sub-sample  
of 500 irrespective of  
reported pregnancy status

Coding of the collected information  
is in progress.

# CONTRACEPTIVE DISTRIBUTION PROJECT, MATLAB

Shushum Bhatia  
Trinidad Osteria

## ABSTRACT

This proposal is a modification and extension of the ongoing protocol Contraceptive Distribution Project (CDP), Matlab (July 1975 - September 1978). The objective of the CDP is "to determine the demographic and health impact of a program that incorporates health services with family planning". The initial study design involved the regular provision through CRL female workers of non-clinical contraceptives (oral pills and condoms) to all married couples on half of the Matlab surveillance area (MSA) with the remaining half servicing as controls.

Two years of experience with this simple but intensive household distribution program suggests that program performance may be improved substantially through several modifications. Accordingly, this protocol proposes that a new cadre of better-trained female village workers, backed by stronger field supervisory and technical staff, be deployed in 70 villages (80,000 population) to provide family planning and selected health services and that a wider array of clinical services, including IUD, sterilization, and menstrual regulation, be provided at the CRL Matlab Treatment Unit. Improving the quality and scope of services would, in essence, establish three study cells: (1) original household distribution (85,000); (2) intensive health and family planning program (80,000); and (3) control (95,000).

It is anticipated that the intensive program in 70 villages would be operational by January, 1978. A baseline survey on family planning practices and reproductive status was carried out on about 20,000 eligible women prior to program implementation. Fortnightly visits to the households will be undertaken to assess contraceptive technology acceptability, use-effectiveness, side effects, pregnancy and lactation status.

# ENDOCRINOLOGICAL FACTORS IN RELATION TO REPRODUCTION IN BANGLADESH

Dr. Brian Seaton

## ABSTRACT

Reproductive biology is a complex, multi-factorial subject. Nowhere is this more true than in Bangladesh where, in addition to the physiological and endocrinological factors which affect reproductive performance in all humans, factors such as malnutrition, disease and behavioural patterns have a marked effect. Whilst much excellent research has already been done in the CRL in the demographic aspects of reproduction in Bangladesh, progress is being hampered by an inability to identify and evaluate the contribution of endocrinological factors to the overall pattern. This protocol seeks to meet this need by (i) establishing a laboratory capability in reproductive endocrinology (ii) establishing baseline data for the endocrinological aspects of the reproductive process in Bangladeshi women (iii) initiating basic and applied research aimed at improving the safety and efficacy of intervention programs in fertility regulation and family planning.

SEX SOCIALIZATION AND PHILOSOPHIES OF LIFE IN RELATION  
TO FERTILITY BEHAVIOUR: AN ANTHROPOLOGICAL APPROACH

K.M.A. Aziz

ABSTRACT

The factors in sex socialization from childhood through the fertile period of life, and philosophical factors about sex and family life, as related to fertility behaviour would be studied. This investigation would be approached through the individual in-depth life history collection from fifty ever-married individuals of both sexes. Further, there would be intensive interviewing of about 200 children between 5 to 13 years of age whose dates of birth are known. Only-volunteers with required criteria would qualify as respondents. The background of respondents would vary in respect of education, income, duration of marriage, number of children born alive, and proportion of living children out of the total born alive. The respondents would be Muslim holding the most common lineage title of Pradhania who mainly depend on small agricultural land holding or agricultural labour. The adult responses would be tape recorded without the identification of respondent and locality. The individuals preferring not to be on tape would be interviewed only by manual recording of responses. Children as well as adult conversation, and behaviour indicative of sex socialization would be observed and recorded. The questions for children would be mostly in structured form, whereas for adults topics of inquiry would be mostly unstructured. The areas of inquiry would include: (1) contribution of exposure to sex in the formation of individual philosophies, (2) sources of sex information and method of its communication, (3) learning of sex roles, and (4) psychological reasons for acceptance or non-acceptance of family planning.

AN ESTIMATION OF RESPONSE BIAS OF LITERACY  
IN A CENSUS OF RURAL BANGLADESH

M. Shafiqul Islam

ABSTRACT

This study was conducted among 11304 persons five years old and over in 1974 on the basis of a five percent systematic sample in 233 villages of Matlab. Census enumerated 3426 literate persons. Subsequent to census, objective tests were offered to 1892 individuals. 30.3 percent literacy rate was found in census through verbal response and 7.5 percent false rate was found in objective tests. A census was carried out by trained experienced male field workers assisted by resident female workers in each village. The work of several census teams were supervised and completed census forms were verified by a senior staff of Cholera Research Laboratory in the field. A pre-tested census proforma was used to collect data in a house to house visit. Every individual and family was identified by a separate number. Census included information on literacy, educational levels, age, sex and religion. Success in objective tests was determined by ability of reading and writing of one or both of the vernacular texts designed for elementary standard on a separate form.

In this investigation effort was made to estimate the level of literacy in the Matlab demographic surveillance area in Comilla district. Through objective tests, the validity of verbal responses on literacy was assessed. The study was undertaken to better understand the precision and accuracy of customarily collected census information.

## PROGRESS REPORT

The aim of this investigation was to determine the level of literacy in a rural area of Bangladesh. Through objective tests, the validity of verbal responses on literacy was assessed and by subsequent analysis, factors associated with response bias were noted. The study was undertaken to facilitate a better understanding of the precision and accuracy of customarily collected census information.

In 1974, the CRL conducted a census among the residents of 233 villages in the Matlab demographic surveillance area. One of the questions posed to all the enumerated was "literacy" and among a sample of 1892 people, a test for literacy was given after the verbal response. Analysis showed 30.3 percent literacy rate according to census enumeration. The objective test result showed 71.5 percent false literacy rate. The highest literacy rate was found among young persons (43.8 percent), the intermediate in adult (30.9 percent) and the lowest rate among the children and elderly persons (about 24.5 percent). Males had much higher literacy rate than females (41.1 percent for 19.3 percent). Male performance was better in literacy test than the females (5.6 percent for 9.9 percent false response rate). Educational level six and over had literacy rate much higher than that of level one to five (96.8 percent to 61.6 percent). In respect of false response, level one to five had a higher rate than that of level six and above (10.7 percent to 1.2 percent). The Muslims showed lower literacy rate than the Hindus (30.3 percent for 32.7 percent) but higher false response rate than the Hindus (7.7 percent for 6.2 percent).

Matlab Field Research Station  
Cholera Research Laboratory

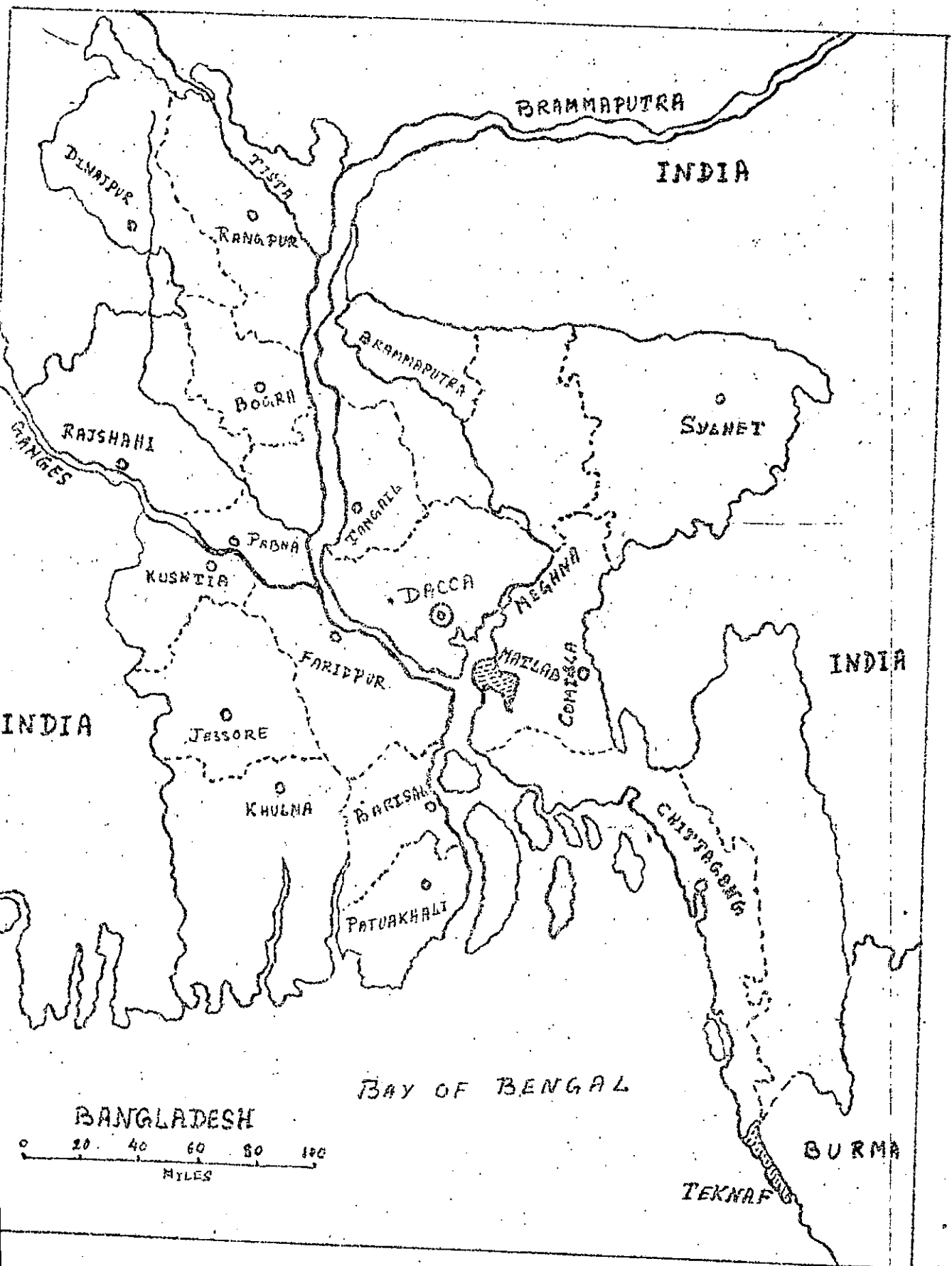
December 1977

## Introduction

Since its establishment in 1960, the Cholera Research Laboratory (CRL) has operated several rural field stations as part of its scientific program. The first and largest rural field research station was established in 1963 in Matlab thana (county), Comilla District. Matlab is situated 45 km southeast of Dacca, the capital of Bangladesh (see Map 1). In 1974 a second research station was established in Teknaf thana, Chittagong District. Teknaf is situated 160 km from Chittagong at the southeastern tip of Bangladesh, bordering Burma to the east and the Bay of Bengal to the west. These two field stations form the basis of most CRL field research in diarrheal disease, nutrition, and population. In addition to these field sites, other rural areas (Rangpur, Sylhet, Chittagong Districts) and urban areas (Dacca and Chittagong Cities) have also served as temporary sites for field research.

The permanent field stations were established to support the research and training functions of the CRL. Field research, linked to basic science and clinical facilities, is crucial to a better understanding to the pattern, causes and consequences of diarrheal disease, malnutrition, and high fertility. Elucidation of effective interventions against these problems also relies heavily on field research. The linkage of field work with health services in a population where specific health problems are highly prevalent also provides a relevant environment for the training of a variety of health professionals and paraprofessionals.

# MAP - I



### MATLAB FIELD STATION

The Matlab field program began in 1963 when 23 villages with a population of about 28,000 were censused as part of a field trial of cholera vaccine. In 1966 a census assigning each individual with a unique identification number was conducted in 132 villages containing 112,000 people. Shortly after this census, the registration of all births, deaths and migrations was instituted. The surveillance population was doubled in 1968 when another 101 villages with a population of 109,000 were censused and included in the registration system. Since 1968 therefore the Matlab surveillance program has consisted of 228 villages\* involving a 1974 population of 264,000. A summary of these censuses is shown in Table 1.

Table 1

Enumerated Census Populations by Sex in the Old (1966),  
New (1968), and Total Areas in Matlab

| <u>Census Year</u> | <u>Area</u> | <u>Total</u> | <u>Males</u> | <u>Females</u> |
|--------------------|-------------|--------------|--------------|----------------|
| 1966               | Old         | 111,722      | 57,122       | 54,600         |
| 1968               | New         | 109,402      | 55,833       | 53,569         |
| 1970               | Old         | 120,694      | 61,036       | 59,658         |
| 1974               | Both        | 263,493      | 134,422      | 129,071        |

\* Although 233 villages were censused in 1968 and 1970, the registration system has been maintained continually in 228 villages.

Concomittant with field surveillance activities has been the provision of diarrheal disease health services. These services, also initiated in 1963, involve a simplified rural treatment unit situated at Matlab Bazaar, staffed by physicians and paraprofessionals. A network of seven substations, dispersed through the surveillance area, provide speedboat and jeep transfer of severely affected cholera and other diarrheal disease patients to the central facility.\* All patients irrespective of their residence within or beyond the CRI Matlab surveillance area receive free treatment at the central facility. It is estimated that the treatment unit, fed by the network of speedboats and jeeps, provides diarrhea treatment services to a population of nearly 1 million people in the region.

Past work in the CRI field programs has made substantial scientific contributions. Cholera research in Matlab has documented that: (1) therapy of severe cholera and other diarrheal diseases can be virtually 100% effective in a rural facility staffed primarily by paraprofessionals; (2) oral rehydration of diarrheal cases with an inexpensive and widely accessible glucose-solution can be effectively utilized in a rural treatment center; (3) the current whole-cell cholera vaccine provides limited protection of brief duration; (4) tubewell installation does not necessarily protect against diarrheal diseases; and (5) quarantine is not an effective control measure against cholera because of asymptomatic carriers. The Matlab field station has also supported important research in population and nutrition, such as:

This costly but effective patient-transfer system was considered essential on ethical grounds for the conduct of selected field investigations (e.g. field trial of cholera vaccine).

(6) identification of the crucial role of breastfeeding in birth spacing; (7) elucidation of the inter-relationship between child mortality, nutrition, and fertility; (8) understanding the level and factors affecting demand for contraception; (9) testing the relative suitability and effectiveness of modern contraceptive technologies; and (10) examination of factors affecting the growth and development of Bangladeshi children.

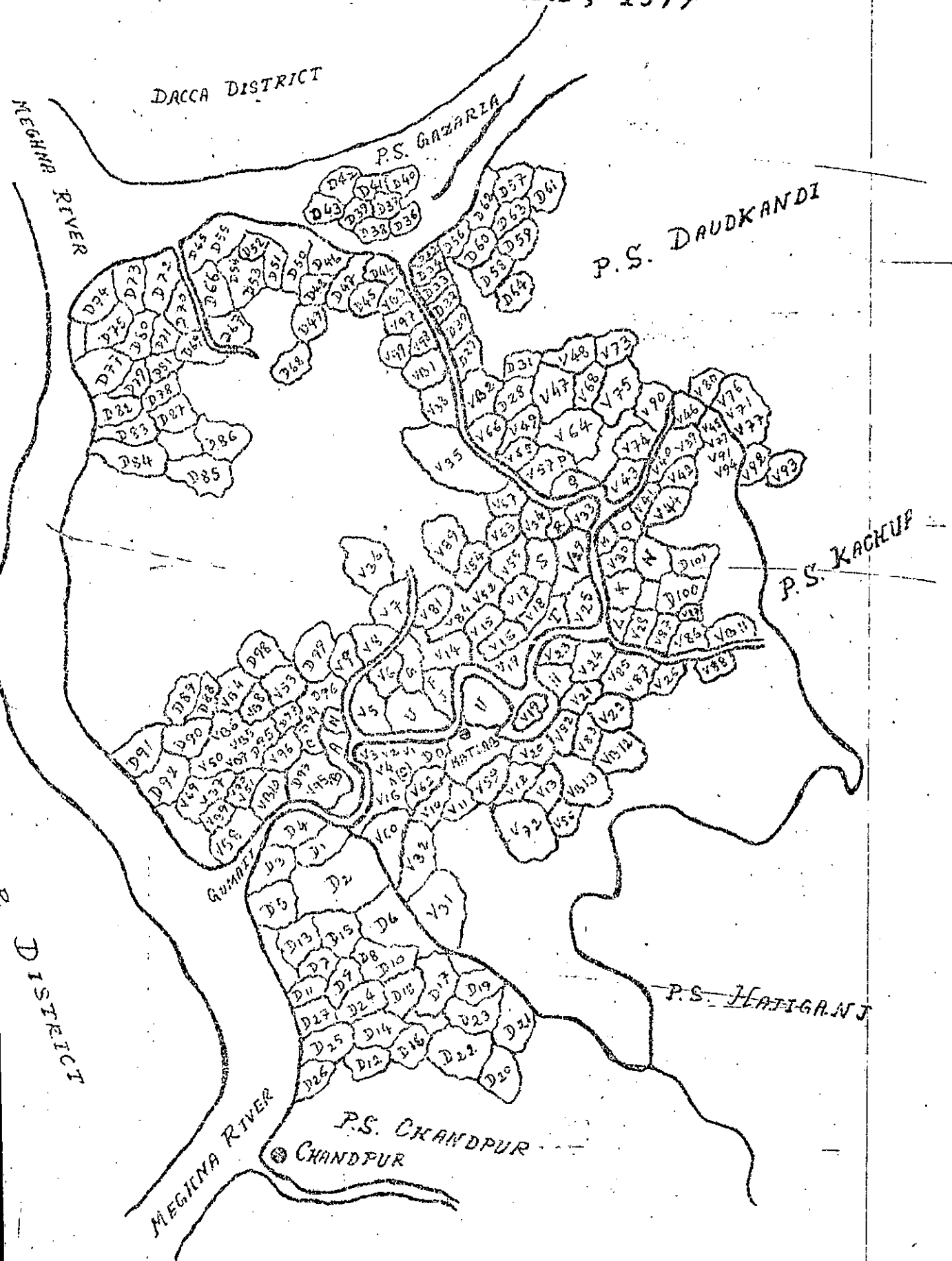
### The Study Area and People

The topography of Matlab thana is low-lying deltaic plain intersected by numerous tidal rivers and canals, fed primarily by the Meghna River, one of the three large rivers draining Bangladesh. A recently constructed motorable road links the thana center with the district headquarter, but communication within the thana is only possible by foot or country boat. The surveillance area consists of 228 villages. Map 2 shows these villages in relation to the major canals and Matlab center, where the CRL research station and treatment facility are situated. Nearly all of these surveillance villages are in Matlab thana but several are in adjacent thanas and not all Matlab thana villages are included in the study area.

The population of the surveillance area is relatively homogenous consisting of indigenous Bangladeshis. More than three-quarters are Muslims and the great majority of the remainder are Hindu. The average population density is 780 per square km. Villages average about 1,200 each. The education level of the study population, while low, is higher than the national average. According to a sample of the 1974

# MAP - II

## MATLAB SURVEILLANCE AREA, 1977



census, 30 percent of the population over age 5 years were literate. Less than half of the population had attended school, however, and the level of literacy was twice as high among males as females. The principal economic activities are agriculture and fishing, the latter being primarily a Hindu occupation. The staple food is rice, grown during the monsoon aman season. A second rice crop or vegetable crop is often possible during the winter boro season. Jute, the cash crop, is usually grown during the spring-summer aus season. An average household owns about 0.7 acres of land. Landholding is however skewed and about 20 percent are absolutely landless. If landlessness is defined as less than 0.5 acres, 42 percent of the households may be classified as landless.

#### Staff and Facilities

CRL shares a thana health center in Matlab Bazaar with the Bangladesh Government. In the CRL half of the Government thana health complex, the ground floor contains patient care facilities, consisting of a simplified treatment and training unit staffed by paraprofessionals, a diarrheal research service unit, and a maternal and child health and family planning (MCH-FP) clinic. On the second floor are situated Clinical pathology and microbiology laboratories, field research offices, a conference/training room, and administrative office. CRL maintains its own generator, maintenance shop, and fuel depot to support field operations. A barge provides accommodations for visiting investigators and across a canal from the health complex are situated additional research offices and storage facilities.

The CRL Matlab field staff are shown in Appendix I. The staff consists of over 100 members organized in three administrative branches: Hospital, Field Surveillance, and Administration. These staff are supported by another 60 support staff. Moreover, in the villages, the CRL maintains nearly 300 fulltime resident female village workers.

#### Scientific Support Program

Two ongoing activities are maintained to support all field research in Matlab. These are the demographic surveillance system and diarrheal treatment services.

Demographic Surveillance: The basic demographic data collection system is a three-tier system. Detection of vital events are the primary responsibility of over 200 female village workers (FW). FW's visit each household in the area daily, except during the monsoon season when visits may be reduced to every two days. These workers, most of whom are illiterate, inquire about births, deaths, migrations, and marriages and record these events in register books (often with the help of literate friends). They also supply kaolin mixture to villagers who complain of diarrhea and refer severe cases to the Matlab treatment unit. The work of FW's is supervised by 16 male field assistants (FA's) who, accompanied by the FW's visit each household monthly to check on the completeness of the registration and to record vital events on standard registration forms. These forms are in Appendix II. The area covered by a FA is called a field unit and contains about 16,000 people (3,000 households). The work of FA's is again checked by senior field assistants (SFA's) who visit each household at least three times annually. All

of these workers in turn are supervised by the Branch Head and the Demographic Surveillance Supervisor, who along with 3 field surveillance assistants (PSA's) randomly check on the quality and completeness of the field work. The crude birth, death, infant mortality, and total fertility rates in Matlab generated by this system since 1966 are shown in Table 2.

Table 2

Trends in Fertility and Mortality in the Matlab Field Study Area, 1966 - 1975<sup>a</sup>

| Year <sup>b</sup> | Crude Birth Rate    | Crude Death Rate    | Infant Mortality Rate | Total Fertility Rate |
|-------------------|---------------------|---------------------|-----------------------|----------------------|
| 1966              | 46.8                | 16.0                | 111                   | 6.7                  |
| 1967              | 45.2                | 17.2                | 125                   | 6.4                  |
| 1968              | 46.4                | 15.7                | 124                   | 6.7                  |
| 1969              | 45.2                | 15.1                | 128                   | 6.6                  |
| 1970              | 43.6                | 14.6                | 131                   | 6.4                  |
| 1971 <sup>c</sup> | 44.5                | 21.3                | 147                   | 6.5                  |
| 1972              | 41.8                | 16.4                | 129                   | 6.1                  |
| 1973              | 47.8                | 14.6                | 129                   | 7.3                  |
| 1974 <sup>d</sup> | 40.1                | 20.0                | 167                   | 6.1                  |
| 1975              | 27.6                | 18.2                | 150                   | 4.2                  |
| 1976              | (43.2) <sup>e</sup> | (14.8) <sup>e</sup> |                       |                      |

- a. These data are for 110 villages (original population 113,000).  
b. Twelve months beginning April of each year.  
c. War  
d. Food Shortages  
e. Provisional data.

Diarrheal Disease Health Services: The Matlab health service program supports and constitutes an integral part of the field research activities. In Matlab center, the bulk of diarrheal disease services are provided by about 15 paraprofessionals supervised by several physicians and supported by about 12 support staff. The number of patients serviced by this program is shown in Table 3.

Table 3

Number of In- and Outpatients Serviced at the  
CRL Matlab Treatment Unit (1966-76)

| <u>Year</u> | <u>Inpatient</u> | <u>Outpatient</u> | <u>Total</u> |
|-------------|------------------|-------------------|--------------|
| 1966        | 961              | 1513              | 2474         |
| 1967        | 950              | 1872              | 2822         |
| 1968        | 1959             | 2745              | 4704         |
| 1969        | 2223             | 3548              | 5771         |
| 1970        | 2893             | 3763              | 6656         |
| 1971        | 2331             | 1836              | 4167         |
| 1972        | 1391             | 2694              | 4085         |
| 1973        | 720              | 2776              | 3496         |
| 1974        | 4763             | 8882              | 13645        |
| 1975        | 4125             | 8872              | 12997        |
| 1976        | 3037             | 7367              | 10404        |

In 1978 a simplified treatment and training unit staffed entirely by paraprofessionals is being developed. Unit staff will assess all incoming patients and, where appropriate, therapeutic decisions will be determined and implemented by paraprofessionals. Basic procedure manuals for this unit are being developed. Paraprofessionals would

also be trained to detect complicated cases too severely ill for simplified treatment. These selected patients would receive care in a study ward which would also service patients who are under research protocols.

Also in 1978 central clinical facilities are being established for selected MCH-FP services. Clinical fertility control services - IUD insertion, ligation, sterilization, and menstrual regulation - along with selected maternity services would be made available at the Matlab central facility. These clinical services will back-up a MCH-FP program being implemented by the CRL in 70 Matlab villages consisting of 80,000 people. This program constitutes the second phase of the Contraceptive Distribution Project where the fertility - mortality impact of an intensified village-based delivery system is being tested. The program involves village-based delivery of selected MCH-FP services by resident female workers backed-up by union-level subcenters.

#### Scientific Projects (1977-78)

A listing of the scientific research and training activities in Matlab is shown in Table 4. Details on these protocols are available in the CRL 1977 CRL Annual Report. In 1977-78, over 20 specific research projects are being undertaken in Matlab. These involve all six scientific working groups of the CRL.

I. Diarrhea Therapy: Plans are currently being formulated to mount field trials of oral therapy as a preventive and therapeutic health technology at the village level. These trials will focus on two aspects of this technology. The first is an assessment of the effectiveness of oral therapy

TABLE 4

Research Projects in Matlab in 1977-78

| <u>Working Group</u>      | <u>Study Title</u>                                                                                        | <u>Protocol No.</u> |
|---------------------------|-----------------------------------------------------------------------------------------------------------|---------------------|
| I. Diarrheal Therapy      | A. Longitudinal Field Trial of Oral Therapy                                                               | Pending             |
|                           | B. A Clinical Trial of Trimethoprim and Sulphamerthoxazole (Bactrim) in the treatment of Shigellosis      | 77-004              |
| II. Host Defense          | C. Cholera Vaccine Field Trial                                                                            | 730503              |
| III. Disease Transmission | D. Epidemiology of Enterotoxigenic Escherichia coli Diarrhea                                              | 77-012              |
|                           | E. Community and Family Studies of Enterotoxigenic <u>Escherichia coli</u> .                              | 77-025              |
|                           | F. Rotavirus Family and Community Study                                                                   | Pending             |
|                           | G. Cohort Infection and Nutrition Study                                                                   | Pending             |
|                           | H. Water Use Behavior Study                                                                               | 77-019              |
|                           | I. Organic Materials and Energy Flow Study                                                                | 77-020              |
|                           | J. Reovirus Serology                                                                                      | Pending             |
|                           | K. Hospital Surveillance of Diarrheal Disease                                                             | Pending             |
| IV. Nutrition             | L. Growth and Development Studies Meheran                                                                 | 77-007              |
|                           | M. Lactose Malabsorption in Bangladeshi Villagers                                                         | 77-010              |
| V. Population             | N. Demographic Surveillance                                                                               | 730502              |
|                           | O. Contraceptive Distribution Project                                                                     | 700505              |
|                           | P. Determinants of Natural Fertility                                                                      | 77-027              |
|                           | Q. Survey of Fertility by Pregnancy Prevalence                                                            | 77-028              |
| VI. Outreach              | R. Short-term diarrheal prevention and treatment training to Bangladeshi physicians and paraprofessionals | Pending             |
|                           | S. Establishment of simplified treatment and training unit                                                | Pending             |
|                           | T. Operations of Baburhat treatment unit for training                                                     | Pending             |

in reducing diarrheal morbidity and mortality, preventing the hospitalization of severe diarrheal cases, and improving the nutritional status of children. The second will test various systems of service delivery and to assess the relative effectiveness and risk of various delivery systems. The aim of the second program will be to optimize safety, acceptance, and use.

II. Host Defense: On three previous occasions the Matlab field station has conducted field trials of cholera vaccines. The efficacy of the whole-cell cholera vaccine currently used throughout the world was established by these trials. In 1978, another cholera vaccine field trial is planned. The trial will involve four population cells: (1) toxoid vaccine; (2) whole-cell vaccine; (3) combined toxoid and whole cell; and (4) tetanus toxoid. The new cholera toxoid vaccine has undergone safety testing in developed countries and appears to hold significant promise in terms of effectiveness. The whole-cell vaccine to be tested is adjuvanted differently from the current vaccine and also holds some promise. The combined vaccine cell will test for synergism between the first two vaccines, and the fourth cell will be the control group. It is anticipated that over 100 field workers will be required over a three month period (May - July 1978) to get the field trial underway.

III. Disease Transmission: In recent years there have been two major scientific break-throughs which have vastly extended the possibilities of detecting a causal agent for diarrheal diseases. The first was the discovery that some strains of the ubiquitous E.coli, which were considered

normal inhabitants of the human intestinal tract, are causal agents of acute diarrheal disease. The second advance was that many acute diarrheas in children are associated with a virus particle called Rotavirus. Preliminary studies indicate that E.coli and Rotavirus diarrheas are highly prevalent, and the latter in particular may play an important causative role in childhood malnutrition. Epidemiologic studies are therefore in progress in Matlab to identify the level, pattern, and modes of transmission of these diarrheal agents. A longitudinal study among a cohort of newborns, moreover, is also being initiated to study immunity and reinfection. Paralleling these epidemiologic studies are behavioral studies on water and sanitation practices. The transmission cycle of cholera in endemic areas for example, is unarguably associated with contaminated water, but the actual path of the organism from one infected host to other susceptibles has not been delineated definitively. Interest in this subject has been sharpened recently by studies at the CRL which show that simply providing safe water for drinking, for example by drilled wells, has not been sufficient to reduce the incidence of cholera when contaminated surface waters in canals and tanks is available for other uses. Water and sanitation behavior are being studied in Matlab through intensive village-level observational research by an in-resident investigator.

IV. Nutrition: In the past, the CRL has conducted several nutrition studies in Matlab involving infection, immunity, and nutritional status. In 1977-78, several studies are either in progress or planned on the potential role of infection, malabsorption, food distribution, and dietary practices on the nutritional status of children. In the study village of Meheran, a three-year longitudinal study on infection, dietary

intake and growth and development among over 400 children under age 10 will be completed in December 1977. The study should yield useful anthropometric information on Bangladeshi children and may provide a basis for analysis of the interaction of infection, particularly diarrheal diseases, and malnutrition. Also to be completed by December is a study of the relationship between nutritional status and lactose malabsorption in several selected Matlab villages. The study will document the level of lactose (a major carbohydrate constituent of milk) malabsorption in rural Bangladesh and may prove useful in determining the utility of milk as a child weanling food. Because new techniques have recently developed in the detection of etiologic agents involved in childhood diarrheas and because such techniques are now available at CRL, another indepth longitudinal cohort study on the effects of infection on dietary practices and growth and development of about 100 newborns is planned in 1978. The study would examine the role of various infectious agents in infant and childhood diarrhea, the development of host immunity, and factors related to reinfection. Parallel investigations would also be undertaken to assess changes of dietary practices and gastrointestinal absorptive functions during diarrhea to estimate the importance of these variables in malnutrition.

V. Population: Population activities in Matlab date back to 1966 when the demographic surveillance system was established. In 1977-78 the surveillance system, while continuing, is being modified to improve its quality and to increase its relevance to CRL's expanding field program. In addition to supporting demographic analyses on fertility, mortality, migration, and marriage by CRL scientists, the system provides essential demographic data for the contraceptive distribution project.

In collaboration with the Ministry of Population, the CRL initiated in October 1975 a house-to-house distribution of oral pills and condoms to half of the study population. Through this program, the level of demand for contraception, optimal delivery systems, and suitability of various modern contraceptive technologies are being assessed. In 1978 the program is undergoing modification involving more extensive contraceptive services, better support for side-effects, and parallel selected MCH services in 70 villages. The last population project in Matlab is in its third year. It is a longitudinal study on the determinants of natural fertility. This study involves monthly visits to 2,500 couples and is examining the role of health, mortality, nutrition, and selected socioeconomic indicators on fertility performance. An extra dividend of this study has been the development of a new fertility survey technique computing fertility from two cross-sectional surveys on pregnancy prevalence. This technique was verified in the surveillance area and is being tested in a non-CRL field site.

VI. Outreach: Although undertaken sporadically in the past, the CRL has been increasingly involved in training of health professionals and paraprofessionals. One impetus to this activity was the large cholera epidemic in Chandpur Subdivision in fall 1977. The outbreak was not only met by intensifying CRL services in Matlab but the CRL treatment center rapidly trained Bangladeshi physicians, medical students, and paraprofessionals who were assigned to Government facilities in the epidemic area. Both for training and service purposes, the CRL also established a temporary simplified rural treatment unit at Baburhat (at the southern tip of the surveillance area). This unit served as a useful field training facility and also helped to meet the large

number of severe cholera cases requiring emergency treatment. As a continuation of this program the CRL Matlab treatment unit is being developed into two components. The first will be a simplified treatment-cum-training unit staffed entirely by paraprofessionals. The second will be a clinical unit for complicated patients requiring physician attention and for patients involved in various scientific protocols. Construction of the treatment-cum-training unit should be completed by the end of December 1977.

Cholera Research Laboratory  
Matlab Field Station  
Staff Roster - December 1977

Field Surveillance Branch

Mohammad Rahman, Head

Supervisors

Carder  
Chakraborty  
Rahman Khan

Field Surveillance Assistants

S. Sattar  
Sarker  
M. Nurul Islam  
ul Hoque  
Rahman I  
ul Hossain

Other Field Assistants

l. Ziaque  
l. Majid  
l. Momen  
l. Ranjan Das  
l. Uddin Akhanda  
l. em Ali  
Matlur Rahman  
uat Ali  
uzul Islam  
Ismail  
Rahman  
Ali  
nder Hayet  
idullah  
iya Begum

Field Assistants

l. Bari  
l. Baten  
l. Halim  
l. i  
l. i  
r. Rezaul Mia  
s. Samad  
s. Shahid  
Taher  
Kashem  
M. Aminul Islam Khan  
Patwary  
Rahman Bakaul  
ullah Sarker  
Rahman  
n Kamrun Nessa (Mrs.)  
Khorsheda (Mrs.)

Field Assistants Contd.

Dilwar Hossain  
Dinesh Ch. Shaha  
Fazlur Rahman  
Firoz Mia  
Golam Hossain  
Hoshmeera Salma (Mrs.)  
Idris Ali I  
Idris Ali Mia II  
Khaleda Khanom (Mrs.)  
Khalidur Rahman II  
Kh. Shahadat Hossain  
K.J.M. Mannan Pathan  
K. Mokbul Hossain  
Kohinoor Begum (Miss)  
Lutfun Nahar Khanom (Mrs.)  
Marisha Chakraborty  
Mazedul Hoque  
Memorajan Das  
Monowara Begum  
Nazqis Akter (Mrs.)  
Nasiruddin  
Nazrul Islam  
Nurul Hoque  
Osman Gani Bhuiyan  
Parash Ch. Chakraborty  
Rashida Akter (Miss)  
Ruhul Amin  
Serajul Hoq  
Serajul Islam  
Shahana Ahmed  
Shenidur Rahman  
Shauzuddin Ahmed  
Siddiqur Rahman  
S.M.A. Aziz  
S.R. Patwary  
S.R. Paul  
Swapna Das (Mrs.)  
Tofazzal Hossain Khan  
Zahirul Hoque  
Zainal Abedin I  
Zainal Abedin II  
Zebun Nessa Zinnat (Mrs.)

Special Staff

Anowara Khanam  
Jahanara Begum  
Kohinoor Rahman (Mrs.)

Special Staff Contd.

Rufia Begum (Mrs.)  
Sati Chakraborty (Mrs.)  
Shahida Begum Shahana (Mrs.)

Clerical Staff

A.K.M. Mozibul Hoque  
Fazlur Rahman  
Md. Shahidullah Khan

Female Village Workers

Anowara Begum  
Arati Rani Mallik  
Ayesha Akter  
Ayesha Begum  
Basona Rani Gope  
Begum Amana Khanoom  
Begum Easmin  
Begum Monowara Akter  
Begum Seraji  
Bina Rani Sarker  
Delowara Begum  
Devi Sarker  
Dipali Rani Das  
Fatema Begum  
Fazilater Nessa  
Ferdaushi Hossain  
Gita Rani Das (Dalal)  
Golencoor Rashid  
Hashina Begum  
Hasina Akter  
Hasina Zahir  
Jahanara Begum  
Jahanara Begum  
Jobeda Begum  
Joystna Begum  
Khorsheda Begum  
Kibria Akter  
Lutfa Begum  
Lutfun Nessa  
Lutfun Nessa  
Mafia Begum  
Mahfuza Akter  
Mahmuda Akter (Maksuda)  
Malina Rani Roy  
Mamtaz Begum  
Mazeda Khatun  
Milon Nessa  
Minoara

Female Village Workers Contd.

Monju Rani Das  
Monowara Akter  
Monowara Begum  
Monowara Begum  
Namita Rani Das  
Nazma Begum  
Nurjahan Begum  
Peera Begum (Patul)  
Pervin Akter  
Prodhen Mahmuda Akter  
Puspa Rani Majumder  
Rabeya Khatun  
Rabeya Khatun  
Razia Khatun  
Rakha Rani Roy  
Rokeya Begum  
Rokeya Begum  
Rokeya Begum  
Rokeya Begum  
Roushan Akter  
Roushan Ara Akter  
Roushan Ara Begum  
Rumi Begum  
Runia Begum  
Salima Akter  
Sanjali Rani Saha  
Sarju Bala Das  
Selina Akter  
Shahida Akter  
Shahida Khanoom  
Shahida Khatun  
Shanaka Rani Das  
Shamsun Saher  
Sufia Khatun  
Suraiya Begum  
Tafura Begum  
Usha Rani Sarker  
Wahida Hoq.

MATLAB ADMINISTRATIVE BRANCH

A.K.M. Abdul Matin, Head

Administrative Assistant

S.M. Abdus Sattar

Clerk/Typist

Nasrullah

Speedboat Driver/Despatcher

Abdur Razzak I

Speedboat Driver/Mechanic

Abdus Salam II

Morshed Khan

Speedboat Driver

Abdul Barez

Abdur Razzak II

Abdur Rob

Abdus Salam I

Abdus Sobhan

Abul Hashem

Akram Khan

Amir Hamza

Bazlur Rahman

Jalal Ahmed

Joynal Abedin I

Joynal Abedin II

Lal Miah

Mohiuddin

Monu Miah

Naderuzzaman

Nazimuddin

Osiur Rahman

Sadu Miah

Showkat Ali

Car Driver

Abdul Matin

Monsur/Ahmed Chowdhury

Security Foreman

Rampresh Rajbher

Security Guard

Abdul Bari

Abdul Jattir

Abdus Samad

Abu Bakar

Ali Arshad

Ali Hossain

Security Guard Contd.

Didar Bux

Dulal Miah

Faiz Ahmed Bhuiyan

Fazar Ali

Fazlul Huq

Joynal Abedin III

Kalat Bepari

Minnat Ali

Mohor Ali Molla

Noor Mohammad

Nurul Huq Molla

Rahim Bux Fafozi

Cook

Nuru Miah

Cook Helper

Ali Reza

Delwar Hossain

Siddiqur Rahman

House Cleaner

Akka Ali

Safar Ali

Maintenance Personnel under

Supervision of Matlab

Administrative Branch.

Abul Kalam

K. Shamsuddin Ahmed

Shafiullah

MATLAB HOSPITAL BRANCH

A.S.M. Mizanur Rahman, Chief Physician  
Md. Yunus, Deputy Chief Physician

Physician

A.S.G. Faruque

S.K. Roy

Ward Master

E.U. Majumder

Assistant Staff Nurse \*

Nur Hussain

Sharifuddin Ahmed

Aid Nurse

Aminul Islam Mia

Asit Baran Saha

Laboratory Technicians\*

Habibur Rahman

Ward Attendant

Abu Saleh

Amir Ali Khan

Jainal Abedin

Johanara Khair

Meherunnessa Dolly

Mustaz Begum

Rafiqul Islam

Urmila Sundari Majumder

\* Position vacant for 1 person.

Card  Study No.   
Village  Name of New Born  Identification

Day  Month  Year

Size : (15)  Single  Twin  Triple

Sex  Result

Miscarriage induced ( < 7 m )  1 Miscarriage induced ( < 7 m )

Miscarriage-spontaneous ( < 7 m )  2 Miscarriage-spontaneous ( < 7 m )

Still birth  3 Still birth

Live birth  4 Live birth

Census No. '74

Information on Mother :

Age  M-In  Date M-In   
Census No. '74

Information on Father :

Age  M-In  Date M-In   
Census No. '74

of previous pregnancy to mother  ( Exclude this birth )

of living children total  Sons

of children born alive now dead total  Sons

of children born dead total

of birth  Village  P. O.  Thana  Code

Residence of Mother  P.O.  Thana  Code

ks :   
ted by :

entered : Field  Matlab

**DEATH REPORT**  
**CRL/Matlab**

(1)

Card

2

(2-)

Village

Study No.

of deceased :

Identification

(9-10)

(11-12)

(13-14)

of death : Day

Months

Year

(15-16)

(17-18)

(19-20)

Years

Months

Days

Sex

M

F

M-In

Date of M-In

Date of Birth

(22-30)

o. : '68/'70

Census No. '74

c's VTS No. '68/'70

Census No. '74

(if any)

~~space for future use~~

of death

1 Residence

Village

P.O.

Thana

Code

e of death

Village

P.O.

Thana

Code

arks

orted by

Date

entered, in field census vol

Matlab

Date entered in Matlab Census vol.

Date entered in

MIGRATION IN REPORT  
 CRL/Matlab

Village  Card  Study No.  Identification   
 f movement : Day  Month  Year  Event : Moved In

| <u>VTS No</u><br>1968/1970 | <u>Census No.</u><br>1974 or after | <u>Name</u> | <u>Age</u> | <u>Sex</u> | <u>Marital Status</u> | <u>Remarks</u><br>(Type of age) |
|----------------------------|------------------------------------|-------------|------------|------------|-----------------------|---------------------------------|
|                            |                                    |             |            |            |                       |                                 |

for movement :

From: Vill/Thana HQ/Sub-Divn./Dt. Town/City P.O. Thana District

6:

ed by: \_\_\_\_\_ Date \_\_\_\_\_

Created: Field  Matlab

DISCONTINUED OUT REPORT  
CRL/Matlab

Card

Study no.

Ident: 1102.00

f' movement: Day

Month

Year

Event : Moved Out

| VTS No.<br>1968/1970 | Census No.<br>1974 or after | Name | Age | Sex | Remarks<br>(Type of age) |
|----------------------|-----------------------------|------|-----|-----|--------------------------|
|                      |                             |      |     |     |                          |

for movement:

20:

Vill/Thane Hq/Sub-Divn/Dt. Town/City

P.O.

Thank,

District

ed by:

Varia

zeros:

Field

## h2tlab

MARITAL STATUS REGISTRATION FORM  
CRL/Matlab

Village  Event  Study No.   
Day  Month  Year

ion (Male Partner)

V.T.S.No '68/'70  Census No. '74   
 M-In  Date M-In

idence. (Male Partner)

P.O.  Dist.  Code  H.F.No. of Current

ion (Female Partner)

V.T.S.No. '68/'70  Census No. '74   
 M-In  Date M-In

of current residence

of female partner prior to this event

P.O.  Dist.  Code

By  Date

CAL/Matlab.

~~no change~~

De: [redacted]

Total families reviewed in field

demands by  
F. A.

29 3

ation out :

of VIII. To :

Will From :

## Age & Divorce

coverage & date of last visit by S. I.

Date of last visit by F. A.

Signature of S. I.

Signature of F. A.

DEMAND SLIP FOR CENSUS NUMBER  
ORI/Matlab

Sl. No.  Village

To : \_\_\_\_\_

This is to inform you that.....Father/Husband  
..... of village.....has come/har come  
To/From.....bairi near.....part of village  
.....on.....

His/her census No.  Age  Sex

He/she is staying under H/F.....

Sender : \_\_\_\_\_

Date : \_\_\_\_\_

TEKNAF FIELD RESEARCH STATION

Cholera Research Laboratory

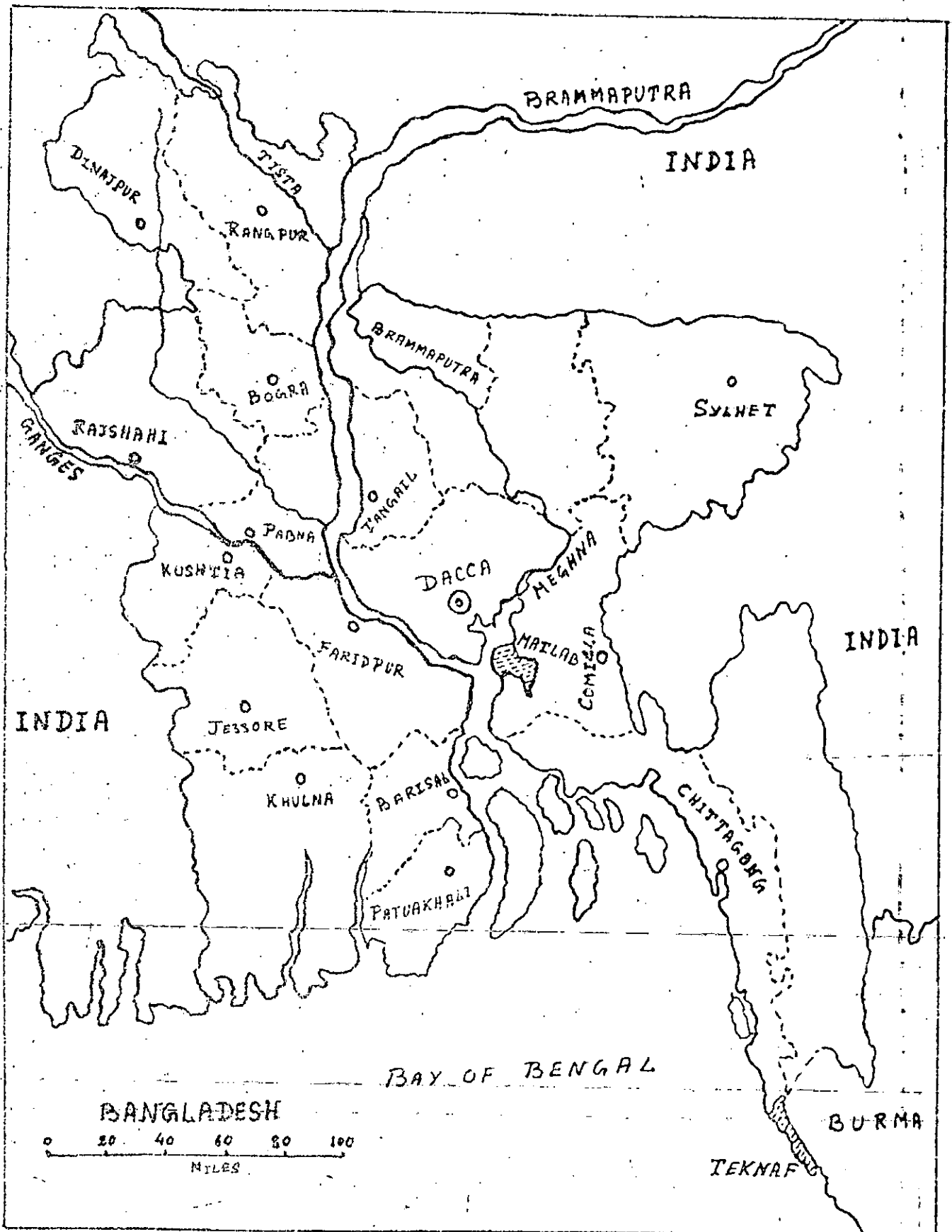
December 1977

## Introduction

Since its establishment in 1960, the Cholera Research Laboratory (CRL) has operated several rural field stations as part of its scientific program. The first and largest rural field research station was established in 1963 in Matlab thana (county), Comilla District. Matlab is situated 45 km southeast of Dacca, the capital of Bangladesh (see Map 1). In 1974 a second research station was established in Teknaf thana, Chittagong District. Teknaf is situated 160 km from Chittagong at the southeastern tip of Bangladesh, bordering Burma to the east and the Bay of Bengal to the west. These two field stations form the basis of most CRL field research in diarrheal disease, nutrition, and population. In addition to these field sites, other rural areas (Pirur, Sylhet, Chittagong Districts) and urban areas (Dacca and Chittagong Cities) have also served as temporary sites for field research.

The permanent field stations were established to support the research and training functions of the CRL. Field research, linked to basic science and clinical facilities, is crucial to a better understanding to the pattern, causes and consequences of diarrheal disease, malnutrition, and high fertility. Elucidation of effective interventions against these problems also relies heavily on field research. The linkage of field work with health services in a population where specific health problems are highly prevalent also provides a relevant environment for the training of a variety of health professionals and paraprofessionals.

MAP - I



Why Teknaf?

The Teknaf field station was set up mainly to study the problem of dysentery in an hyperendemic area. It started functioning from September 1974 with the opening of a simple treatment unit supported by a bacteriological diagnostic laboratory. To begin the Teknaf field program, an initial grant was provided by UNICEF, Dacca; subsequent, longer-range support was provided through a grant from the International Development Research Centre (IDRC) Canada.

Beginning in April 1972 an unprecedented number of severe shigellosis cases were observed reporting for treatment at the hospital of the Cholera Research Laboratory (CRL) in Dacca. The majority of the positive isolates were Shigella dysenteriae type 1 which were resistant to tetracycline, streptomycin and chloramphenicol, the strain being sensitive only to ampicillin. The incidence of complications like extreme hypoproteinaemia, leucocytosis, severe electrolytes imbalances, partial or complete kidney failure were also noticed in a high proportion of cases (15%). These were responsible for an overall mortality in excess of 10% in contrast to less than 0.5% among cholera cases. Epidemics of severe shigellosis were also reported from many other parts of the country throughout 1972 and 1973.

During the monsoon season of 1973 a particularly severe epidemic of dysentery hit the offshore island of St. Martin in the Bay of Bengal. Very high levels of morbidity and mortality were reported. Consequently CRL was invited by the Ministry of Health to investigate the epidemic and to provide necessary medical assistance. Following this epidemic in St. Martin's island it was noticed that the adjacent mainland area of nearby Teknaf had also been severely hit by shigellosis. With the assistance of UNICEF, CRL established a small research and treatment centre to study the problem of shigellosis in Teknaf.

A listing of the current CRL Teknaf staff is shown in Appendix II.

### Population and Geography of Teknaf:

Teknaf is situated in the South-eastern tip of Bangladesh in the Cox's Bazaar sub-division of Chittagong district. It is a narrow peninsula. Its eastern side is bound by the Naf river bordering Burma, and its western side is circumscribed by the Bay of Bengal. The thana is about 25 miles long and 4 miles wide. Until recently it was relatively isolated from the rest of Bangladesh. In 1974, a motorable road between Teknaf and Cox's Bazaar, the nearest sub-divisional headquarter with an airport some 55 miles away, was opened.

Teknaf thana has a population of over 80,000 and is sub-divided into four Union Councils. St. Martin's island situated on a coral reef some 15 miles into the Bay of Bengal belongs to the southern most Teknaf union, Shahpuridwip Union. Almost two-thirds of Teknaf is hilly, being a part of the Reju Teknaf range of reserve forest and having many species of wild-life like elephants, deers and bears. No human inhabitation is allowed to encroach on these forests. The only exceptions are a small number of hill-tribes, who had settled in the forests before it was declared a reserve forest.

Most of the population of Teknaf are Bengali Muslims, although there is a sizable number of tribals who speak their own dialects. A small population consists of Buddhists. Most of the population are very conservative in their outlook. Women are rarely seen outside their homes and the system of "purdah" or seclusion of women is strictly adhered to by the population.

The principal occupation of the inhabitants of Teknaf is fishing and agriculture. Most of the fishing is done in the

Naf river and the Bay of Bengal during the dry season of the year i.e. from October to March. Surplus fish caught by using locally crafted unmechanized boats are sun-dried and transported for commercial sale in other parts of Bangladesh. Mechanized fishing boats are fewer in number, although there is plenty of opportunity for developing a highly profitable fishing industry. Agriculture consists of a single crop of rice, grown during the monsoon. Production of cereals is inadequate to meet the local needs. Supplementary food therefore needs to be imported into Teknaf, paid for by surplus fish. A second crop of rice may be grown in a small proportion of arable land by damming up local rivulets during the dry season and using the water for irrigation. A large proportion of the population are landless labourers and either work in fishing boats or in the fields. Many of them, particularly women and children, collect firewood from the jungles and sell these in the local markets. Considerable acreage is devoted to the production of betel nuts or arache nuts and betel leaves. These commercial crops grow particularly abundantly in Teknaf.

#### TEKNAF VS. MATLAB

Teknaf is distinctly different from Matlab in several respects. Whereas Matlab is situated in the plains and is riverine criss-crossed with canals, Teknaf is hilly, dry except in monsoon, and almost devoid of rivers except the Naf river which is actually a tidal creek or fjord. Although the majority of the population is Bengali Muslim in both areas, there are distinct differences in life style and culture. For example, houses are built on stilts in Teknaf, not unlike the rest of the rural south-eastern Asia. Availability of seafish in Teknaf is likely to be a factor in the low prevalence of vitamin A deficiency of children, in sharp contrast to Matlab. Multiple marriages are far more common in Teknaf, even amongst the poor section of the community. Broken marriages are also more frequent in Teknaf which results in a large number of children who are living with their divorced mothers, stepmothers

or stepfathers. Sources of water are very few in Teknaf compared to Matlab. Sinking of handpumps is laborious, expensive, and sometimes impossible in many areas of Teknaf due to a layer of volcanic rock or boulders several feet below the surface. The population in general therefore depends on hand-dug ditches which are dug frequently during the dry season to obtain potable water. During the long dry spell of the pre-monsoon period, there are reported episodes of fights over wells as neighbours try to "steal" each others' water supply. Under these circumstances the population in general likes tubewell water in contrast to those from Matlab who tend to complain about its taste and colour.

#### Teknaf vs. Matlab: Incidence of various diseases:

It is interesting to note that dysentery is far more common in Teknaf than in Matlab with an annual attack rate of over 100 per 1,000 in Teknaf versus less than 10 in Matlab in 1976. Watery diarrheas on the other hand, are relatively less common in Teknaf. Cholera, fortunately, is seen but rarely in Teknaf.

Fever on the other hand is probably the most serious illness in Teknaf. The exact etiology of the "fever syndrome" is not known, but a large bulk of the fevers are probably due to malaria. Teknaf is recognized as one of the hyperendemic malaria zones which surround the hilly northern and eastern borders of Bangladesh. It is probable that chloroquine resistant malaria may be found in Teknaf as its presence has been documented in Burma. Past censuses and the longitudinal surveillance systems have also established that fever is one of the most important causes of death. In Matlab, however, fever does not occupy such a high position amongst the causes of mortality.

#### A summary of present activities in Teknaf is discussed below:

1. Treatment Centers: The first center was established in Teknaf on September 15, 1974 with the assistance of the

the staff of the Government Thana Dispensary who also ran it for approximately six months. The centre was located very close to the Government Dispensary. At that time the load of diarrheal patients was also relatively low. As the attendance of patients increased, new staff has been recruited. This includes a full-time male nurse-paramedic who operates the centre. Although a physician has been employed as the leader of the Teknaf field station, the bulk of the patient care activity is provided by paraprofessionals.

From the beginning of 1976, another Treatment Centre was opened in Shahpuridwip managed by personnel from the local community. Two educated young men from Shahpuridwip were selected to undergo training at the Teknaf Treatment Centre. The objective of this training was to learn the skill for diagnosing dysentery and diarrhea, to assess their severity, and to provide therapy by oral hydration and, where necessary, by the intravenous route. They were also instructed to use antibiotics like tetracycline and ampicillin in selected cases.

2. Diagnostic Laboratory: The laboratory was established to make bacteriological diagnosis of the organisms causing dysentery. Stool microscopy and collection of blood for haemoglobin is also part of the laboratory activity. For the first year it was managed by technicians from the Dacca CRL who were sent periodically to the field station. All media were also carried regularly from Dacca by airfreight. The Teknaf Project now employs full-time technicians residing in Teknaf to prepare media as well as carry out bacteriological investigations including biochemical and serological tests without depending on Dacca. Sensitivity tests against antibiotics are carried out in Teknaf. The bacteriological quality of water is also assessed in Teknaf. This laboratory is equipped with one incubator and two refrigerators, both

run by kerosene. Only dehydrated media are sent from the Dacca laboratory.

3. Census: One of the first objectives of the Teknaf Project was to carry out a comprehensive census of Teknaf using the personnel of the local health administration. This activity was started in the latter half of 1974 and completed by March 1975 at a modest cost to the project. The census not only enumerated the population but also gathered additional information like socioeconomic status, family size, sources of bathing, washing and drinking water, places of defaecation, and the types of dwellings as well as crowding pattern. Each individual residing in Teknaf thana (80,000 population) was given a unique number so that an event occurring in the family or to any individual could be located with ease by computer. All of the relevant information have now been punched on IBM cards and transferred to computer tape.

4. Morbidity Surveillance: Soon after the census was completed, regular surveillance for the diarrheal diseases was instituted weekly. At the beginning this surveillance was limited to a small area near the treatment centre, but presently it covers over 40,000 or half of the population of Teknaf. The main objectives of the surveillance are to detect outbreaks of diarrhoeal illness, to report on episodes of dysentery and diarrhea on standard reporting forms, and to collect rectal swabs for diagnosing the bacteria responsible for shigellosis.

Episodes of major illnesses like fever, measles, pneumonia etc. are also recorded in the family card provided to each of the households under surveillance.

5. Demographic Surveillance: Field staff in Teknaf are required to report all births, deaths and migrations occurring in the families in standard forms. Although the protocol followed in Teknaf is the same as in Matlab, the reporting forms have been modified to meet the specific research needs of the Teknaf Project.

6. Nutrition Studies: One of the objectives of the Project was to establish the relationship between dysentery/diarrhea and nutrition. A group of 370 children below 3 years of age are being followed longitudinally for episodes of diarrhea, dysentery and other morbidities with periodic measurement of their height, weight and feeding pattern. A smaller group is being subjected to measurement of dietary intake during illness and again after recovery. It is expected that this study may be able to identify the reason for failure of weight gain in children with diarrhea and dysentery. The study may also show a higher frequency of various morbidities including diarrhea and dysentery in malnourished children.

7. Causes of Death in Teknaf: The pattern of illness and morbidity in Teknaf is considerably different from other areas of Bangladesh, like Matlab and Companiganj. It was considered worthwhile to engage a physician to interview the immediate relations of the deceased to arrive at the probable cause of death through "verbal autopsy". An area of Teknaf comprising a population of 17,000 is being subjected to this study. The objective is to establish relative importance of dysentery and diarrhea as a cause of death vis-a-vis other causes, like fever and pneumonia.

8. Water and Sanitary Intervention Programme: Due to low availability of water in Teknaf and low levels of health consciousness and education, it was decided that Teknaf might be a suitable site for a study to determine the effects of intervention measures like augmented water supply by hand-pumps, sanitary latrines, and health education on the incidence

of diarrhea, dysentery and skin infections. With these objectives in view, a proposal has been formulated to carry out an intervention study on selected areas in Teknaf where one or multiple intervention measures will be instituted. Since the base-line incidences of various types of diarrhea and dysentery have already been collected for the last two years, the plan is to observe the effects of these measures on a longitudinal basis.

Cholera Research Laboratory  
Teknaf Dysentery Project  
Staff Roster - December 1977

Project Office

Dr. M.H. Munshi, Manager  
Dr. S.M.N. Nawab Hossain  
Public Health Consultant

Clinical Staff

Mr. Md. Yakub  
Mrs. Renu Bala Dey  
Mr. Bacha Mia  
Mr. Nazir Hossain  
Mr. Zamir Hossain  
Mr. Shafique Ullah  
Mr. Nurul Islam

Laboratory Staff

Mr. Abdul Huq  
Mr. Meshbahaiddin  
Mr. G. Gomes  
Mr. A. Monaf  
Mr. Mir Kashem  
Mr. A. Kashem

Statistical Office

Mr. Mizanur Rahman  
Mrs. Marjina Begum  
Miss Saleha Begum  
Miss H. Ara

Field Programme Staff

Mr. Yakub Patwari  
Incharge, Field Activities

Research Assistant

Miss Shankari Kar

Field Surveillance Assistant

Mr. S.A. Choudhury  
Mr. A.Q. Mandal  
Mr. D.B. Chakma  
Mr. M. Amanullah  
Mr. Md. Umra

Field Assistants

Mr. Tofazzal Hossain  
Mr. Abushama  
Mr. Nirmal Ch. Mali  
Mr. Anisur Rahman  
Mr. M.A. Rashid  
Mr. Saidul Haque  
Mr. Jashim Uddin  
Mr. Azmal Haque  
Mr. Mustaque Ahmed  
Mr. Nur Bakhta  
Mr. Salim Ullah  
Mr. Kyathen  
Mr. Fazlul Kader  
Mr. Dulal Kanti Dey

Female Village Workers

Mrs. Ava Rani  
Mrs. Alo Rani  
Mrs. Mahmuda Begum  
Miss Anju Pal  
Miss K. Mukherjee  
Mrs. Hani Bibi  
Mrs. Nabin Sona  
Mrs. Banu Bibi  
Mrs. Amina Begum  
Mrs. Ayesha Khatoon  
Mrs. Hazera Khatoon  
Mrs. Lakshmi Rani

Administrative Clerk

Mr. Azizul Islam

Store Assistant

Mr. Nazibur Rahman

Security Guard

Mr. Jabbar Malluk

Mr. Abdul Latif

Engine Boat Driver

Mr. Kabir Ahmed

Mr. Lal Mohd.

Driver/Mechanic

Mr. Hasan Ali

Cook

Mr. Milan Kanti Barua

A visit to

The Cholera Research Laboratory Facilities

located at

Mohakhali, Dacca, Bangladesh

## SOME CURRENT GOALS OF CRL DACCA

In the 17 years since the dedication of CRL Dacca the facilities have been developed and expanded to support a broadened and more intensive program. People have been trained for the support of diverse field and laboratory activities. The following lists some of the current goals of CRL:

1. To train health workers in the available simple effective and inexpensive methods for treating diarrhea.
2. To explore ways to put the responsibility for simple care of diarrhea to the communities from which our patients come.
3. To investigate the different causes of diarrhea in the Dacca area and define the ways they spread.
4. To devise and test ways of preventing spread of disease and protecting individuals who may be at risk.
5. To evaluate interactions between different causes of diarrhea and nutrition.
6. To carry out studies which define the relative importance and interactions of the local and systemic immune defenses, and test methods for safely enhancing such defenses.
7. To carry out studies which define the roles of non immune defenses such as gastric acid and normal gut microflora.
8. To make observations on any unusual manifestations of diseases that are commonly seen at CRL, and define their importance as indicators of problems in the community.
9. To devise relevant training programs with collaborating institutions both within and outside of Bangladesh.
10. To become part of a network of regional laboratories which are involved in the study of morbidity, mortality and fertility in South Asia. This would include establishing CRL as a reference laboratory for reagents and training where we possess special expertise.
11. To investigate the linkages between malnutrition and diarrhea.

## HOW THE PEOPLE OF CRL APPROACH ITS GOALS

The Dacca facilities are central resource for all activities. In addition to being a base for the research that goes on in Dacca there are also people and materials required to support the field stations in Matlab and Teknaf and any temporary activities that arise during epidemics or short term studies. In addition to a clinical facility and laboratories there are a scientific library, statistical unit, administrative services, animal resources, and a complete maintenance shop. The scientific programs are defined and priorities set by several working groups. Each group focuses on a problem and members of the groups determine priorities and initiate the research. A list of currently ongoing or just completed work in Dacca may be seen in table 1.

Table 1

| <u>WORKING GROUP</u>  | <u>PROJECTS</u>                                                                                          | <u>GOALS</u><br>(see page 1) |
|-----------------------|----------------------------------------------------------------------------------------------------------|------------------------------|
| DIARRHEA TREATMENT    | 1. Comparisons at Sucrose versus glucose based oral replacement solutions                                | 2                            |
|                       | 2. Gastric acid in diarrhea                                                                              | 7                            |
|                       | 3. Single dose ampicillin in Shigellosis                                                                 | 2                            |
|                       | 4. Factors determining severe colitis in E.histolytica disease                                           | 6, 7                         |
|                       | 5. F.buski infection                                                                                     | 3                            |
|                       | 6. Hypoglycemia in diarrhea                                                                              | 8                            |
|                       | 7. Treatment center as a model for care in diarrhea.                                                     | 1, 2                         |
| HOST DEFENSE          | 1. Antibody response to cholera in breast milk.                                                          | 7                            |
|                       | 2. Local immunity in cholera                                                                             | 7                            |
| DIARRHEA TRANSMISSION | 1. Causes of diarrhea in Dacca<br>a) Rotavirus studies<br>b) Enterotoxigenic E.coli<br>c) V.cholerae NAG | 3, 4                         |
|                       | 2. Comparison of media for isolation of Vibrios                                                          | 3, 4                         |
| NUTRITION             | 1. Infection absorption and nutrition studies.                                                           | 10                           |
|                       | 2. Effect of maternal nutrition on volume and quality of breastmilk                                      | 10                           |
|                       | 3. Protein loss in diarrhea                                                                              | 10                           |
|                       | 4. Hydrogen breath test as a measure of malabsorption                                                    | 10                           |
|                       | 5. Level of nutrition and gastric acid                                                                   | 6, 10                        |
|                       | 6. Nutrition and immune defenses                                                                         | 5, 10                        |
| POPULATION            | 1. The analysis of data and theoretical base is in Dacca but detailed listing is under Matlab            |                              |
| TRAINING              | 1. Health workers                                                                                        | 8, 9                         |
|                       | 2. Laboratory workers                                                                                    | 8, 9                         |
|                       | 3. Field workers                                                                                         | 8, 9                         |
|                       | 4. Biometricians and epidemiologists                                                                     | 8, 9                         |

In reviewing the list of research projects one may ask are some not rather academic. The best answer to this question and justification for a sophisticated laboratory based clinical research effort can be seen by reviewing the development of one of the major contributions of the laboratory. What is now accepted by many as a home care method for the effective treatment of diarrhea began as a very esoteric curiosity of the Harvard Biophysics laboratory late in the 1950's. It was discovered that certain sugars and amino acids facilitated the transport of sodium ion on which the absorption of fluid from the intestine depends. Physicians who were aware of this sort of basic biological discovery began to make careful observations on cholera patients. After defining the basic physiology of cholera it was shown by meticulous balance studies in a few patients that glucose did indeed facilitate the absorption of salt and water. Differently composed solutions were tested and finally one that was successful under carefully controlled conditions was tested in a few patients in the field. Now this is proven therapy that is being simplified and the most urgent issue is how to more rapidly disseminate this form of treatment to mothers and the home. Thus from an esoteric basic biological phenomena through a series of careful clinical investigations has come a generally applicable simple and effective home treatment of diarrhea. This story suggests an important and delicate linkage between practical field observations and the discoveries in the root sciences on which advances in health are founded.

#### A TOUR OF THE FACILITIES

##### 1. The Clinical Research Center

On the ground floor is an area that is used for the study of patients with different diarrheal diseases. In addition to the wards themselves which are staffed by highly skilled nurses and technicians there is an X-ray unit, pharmacy, and clinical pathology laboratory. Physicians and nurses attend this unit on a twenty-four hour basis. The most experienced of the physicians are principal investigators for the research protocols. Patients are admitted to this unit only if they are entering a research study or if they represent complex problems in health care that cannot be referred elsewhere. Admissions to these wards average about 10 patients a day.

##### 2. The Treatment Center

This unit is run by two senior nurses but the patient care is carried out by unregistered health workers all of whom have been taught the skills needed to judge the degree of dehydration and consequent fluid needs of the patients. Physicians are always on call to help with complex cases and they walk through the center several times on each shift to assist in picking up complicated patients. This unit was opened on October 1, 1977 and in the first month treated over 10,000 patients in the midst of a cholera epidemic. The results were comparable with those obtained when patients were formerly admitted to the main hospital area and attended by physicians. No laboratory work, or bacteriology are done in this unit.

since these are not needed for the successful treatment of diarrhea patients. No distinction is made between in and out patients. Patients are held until it is seen that they are able to keep up with their fluid losses. They are then sent home with packets of oral electrolyte salts to be made up and used at home. The current staff per annual patient visit ratio is one staff member per 4,000 patients. In terms of those actually giving care directly it is one staff member per 10,000 patients per year. This means that each health worker cares for more than 30 patients each day many of them arriving with no pulse or blood pressure. The growth of use of CRL as a source of care by the community may be seen in figure 1.

### 3. The Microbiology Laboratory

On the floor directly over the Clinical Research Center is one of the busiest laboratories. This is the microbiology laboratory which backs up all field studies as well as all the clinical studies. It is one of the most experienced laboratories in the world in the isolation of vibrios. It is also very good at isolating all intestinal bacterial pathogens and has the capacity to do essential bacteriology for non-intestinal organisms. When new methods become available and applicable to problems in the CRL populations they are readily set up. This laboratory does the most sophisticated tissue culture tests for enterotoxins and has recently started a new method for the direct detection of rotavirus in patients. The total samples processed last year by this laboratory were 40,804.

### 4. The Immunology Laboratory

On the same floor and corridor there are several laboratories where immunologic research is done. In addition to doing a great deal of routine serology in connection with measuring antibody responses of the local population to vaccines methods are developed by which the local immune responses of the gut may be observed. It is now thought that such local responses may be the crucial determinants of long standing immunity against enteric diseases. Methods such as tissue culture, Enzyme Linked Immune Sorbent Assay (ELISA), fluorescent antibody, and hemolytic plaque assays are some of the tools being used to dissect the responses to natural and vaccine antigens.

### 5. Community Studies

On the same corridor is an area used by the community studies group who carry out epidemiologic investigations on problems in the Dacca community. Index cases are usually picked up from the hospital population as part of an ongoing study. This permits using the population coming to us from many parts of Dacca district to serve as a "window" on what is going on

in the surrounding communities. Communities with special problems with diarrhea can be identified and studied.

#### 6. The Biochemistry Laboratory

On the top floor of the building directly over the Microbiology Laboratory is the Biochemistry Laboratory. This laboratory serves as a clinical chemistry unit for the Clinical Research Center. It also is capable of setting up sophisticated assays involving the use of radio-isotopes for measuring hormonal responses involved in fertility and reproduction. Abnormalities of body chemistry in states of malnutrition and disease may also be measured here. Assays for different nutrients or substances which are used to test for the efficiency of absorption are done. This unit is able to set up almost any test that may be needed to carry the research conceived of by the CRL scientists. When necessary it can also innovate to adapt methods to problems encountered locally.

#### 7. The Director's Office

On the same corridor is a group of offices which include several devoted to population research, several for the Scientific Directors and the Director's office. This grouping of those responsible for different areas of research encourages frequent informal contact and discussion between scientists from different disciplines.

#### 8. The Administrative Offices

In the adjacent wing on the top floor one finds a group of offices which house the Controller, Administrator and most of the administrative services including a Personnel Manager. Nearby is a room which provides duplicating services for copies of articles, letters or other documents.

#### 9. The Library

One floor directly below the Administrative Offices is the Library. It houses 10798 volumes. A total of 198 journals are subscribed to and many of them have back volumes to 1963 or before. There is also a publication unit located in the library which produces and circulates CRL publications and working papers in the form of monographs. The library is also the site for seminars and most working groups currently use the smaller conference room for their meetings.

#### 10. The Statistics Unit

Just opposite to the library there is a corridor and the statistical unit is one of the first doors off this corridor. Here is a data coding and keypunching operation to put studies into format for computer analysis. This is also an area where original research in sampling methods and other innovations in measurement and analysis are going on. All data from Teknaf, Matlab, and the Dacca area studies is processed here. In another area of the Institute of Public Health is the Medical Records Room which is the repository of all records pertaining to hospital and Dacca patient statistics.

#### 11. The Animal Resources Unit

Several hundred yards to the east of the main building there is a separate structure which houses all the animals used in research by the CRL. Since most assays for the diseases being studied require animal tests this is a very active area. Mice, rats, guinea pigs, rabbits, chickens, sheep and if needed other animals large or small may be accommodated. The colonies are self sustaining with breeding stock for all animals in regular use. This is the only such facility in Bangladesh. CRL from this unit also supplies animals as needed for other medical or public health research in Bangladesh. The most active user outside of CRL is the Institute of Public Health.

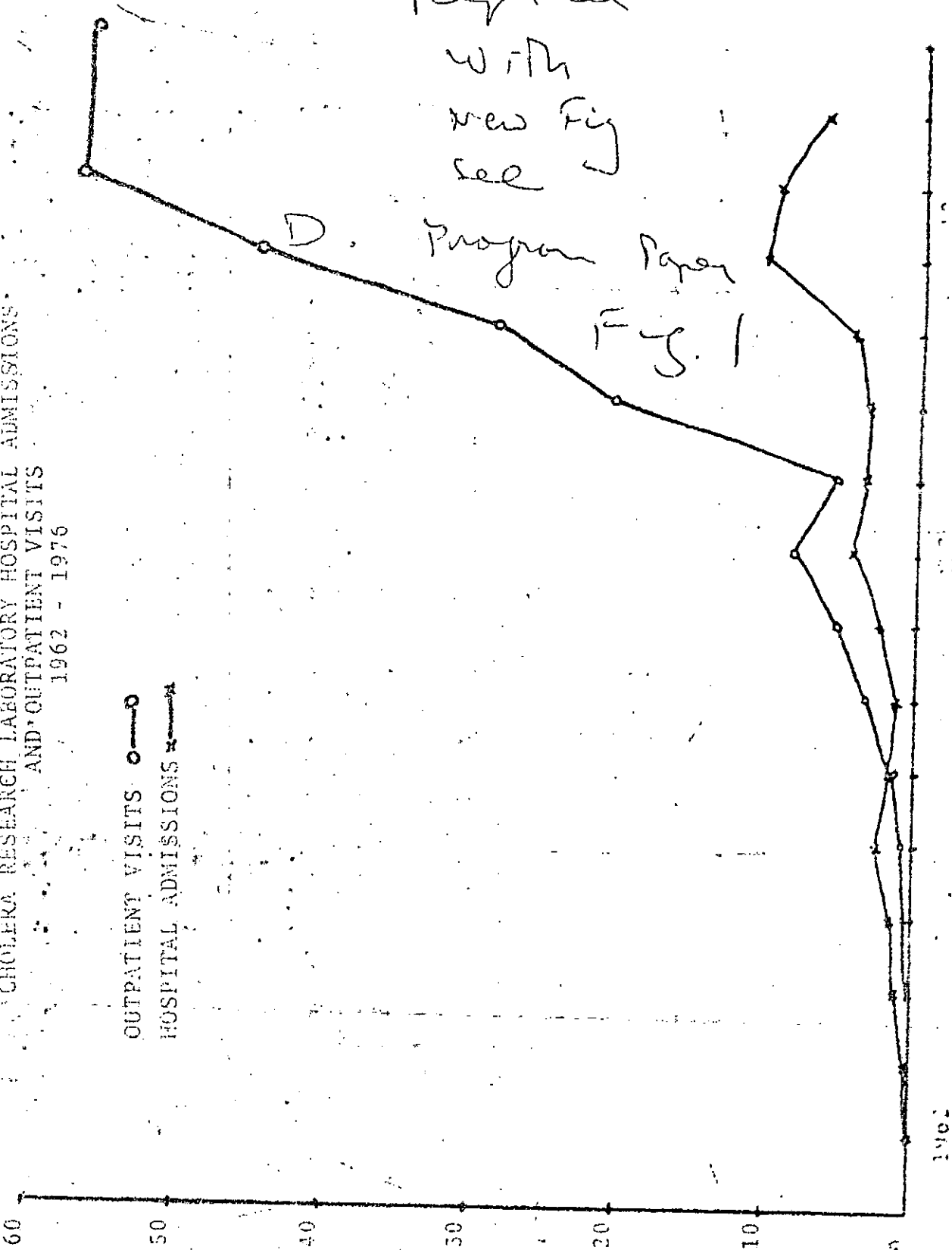
#### SUMMARY

This brief guide provides an introduction to CRL Dacca. The real CRL is however primarily the individuals who comprise the staff. Most of the accomplishments have been achieved through a great deal of dedicated hard work often under great adversity. Visitors are encouraged to talk to individual employees and become acquainted with their work.

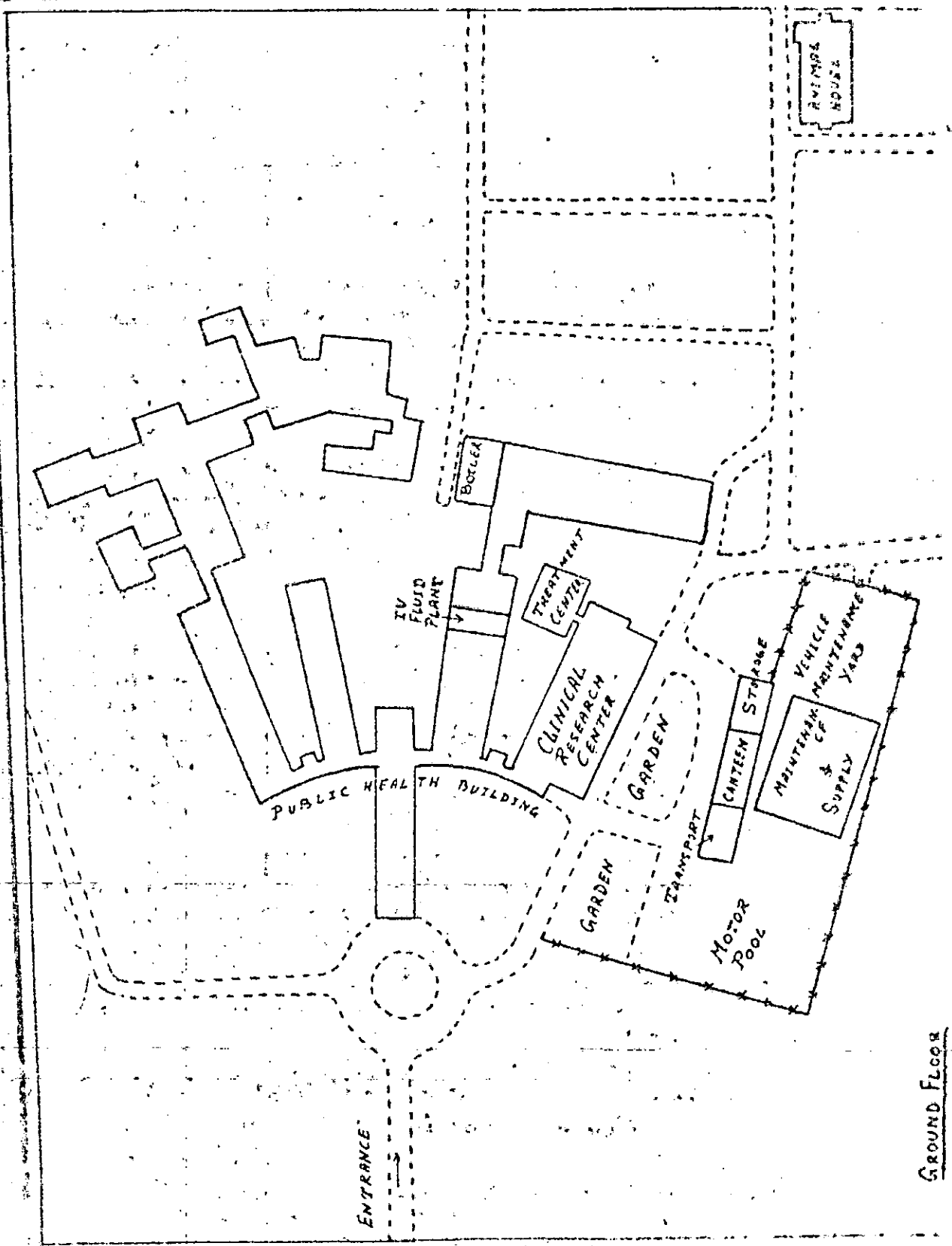
CHOLERA RESEARCH LABORATORY HOSPITAL ADMISSIONS  
AND OUTPATIENT VISITS  
1962 - 1976

OUTPATIENT VISITS ○—○  
HOSPITAL ADMISSIONS ×—×

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Fig. 1

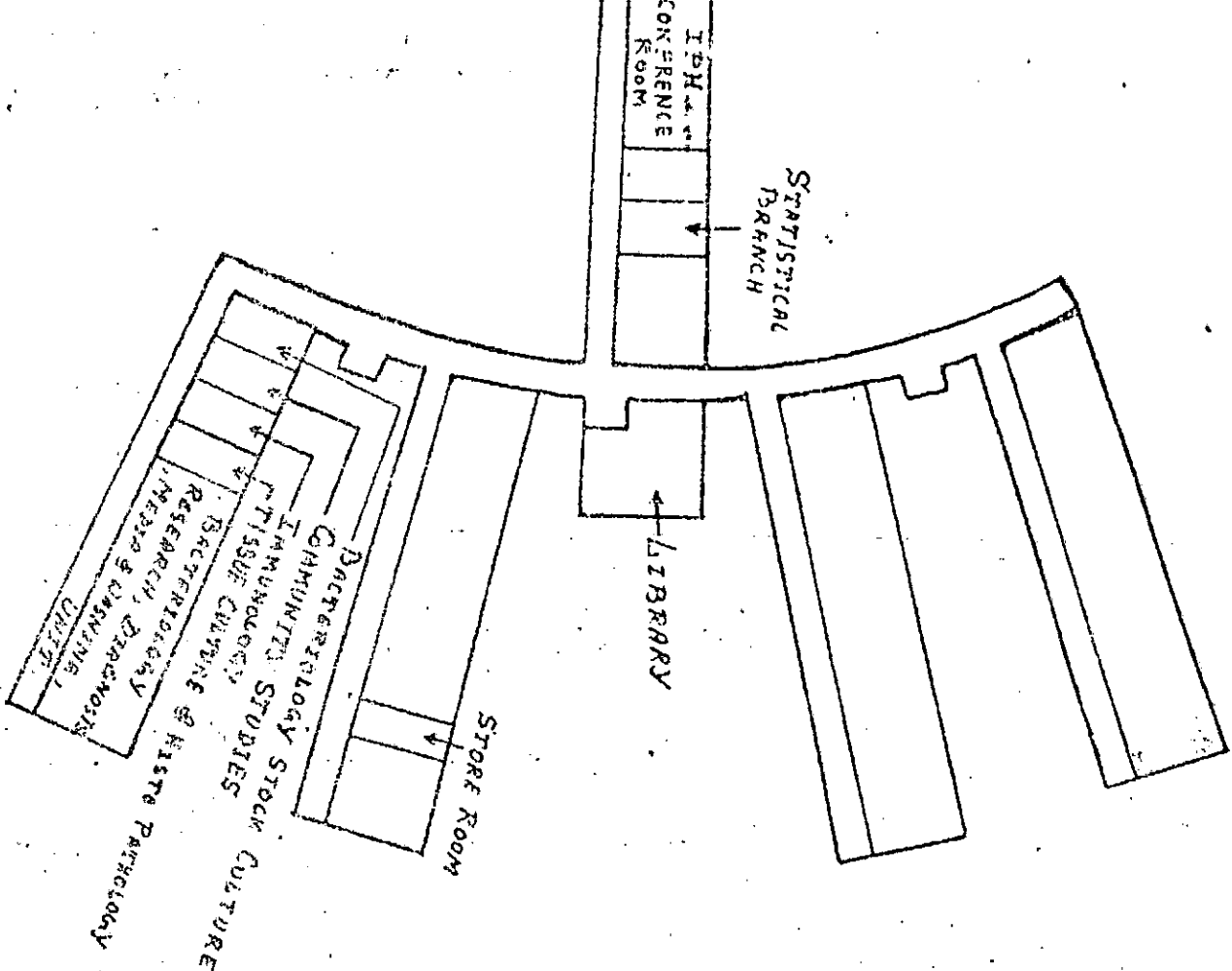


Years Jan 1 - Dec 31

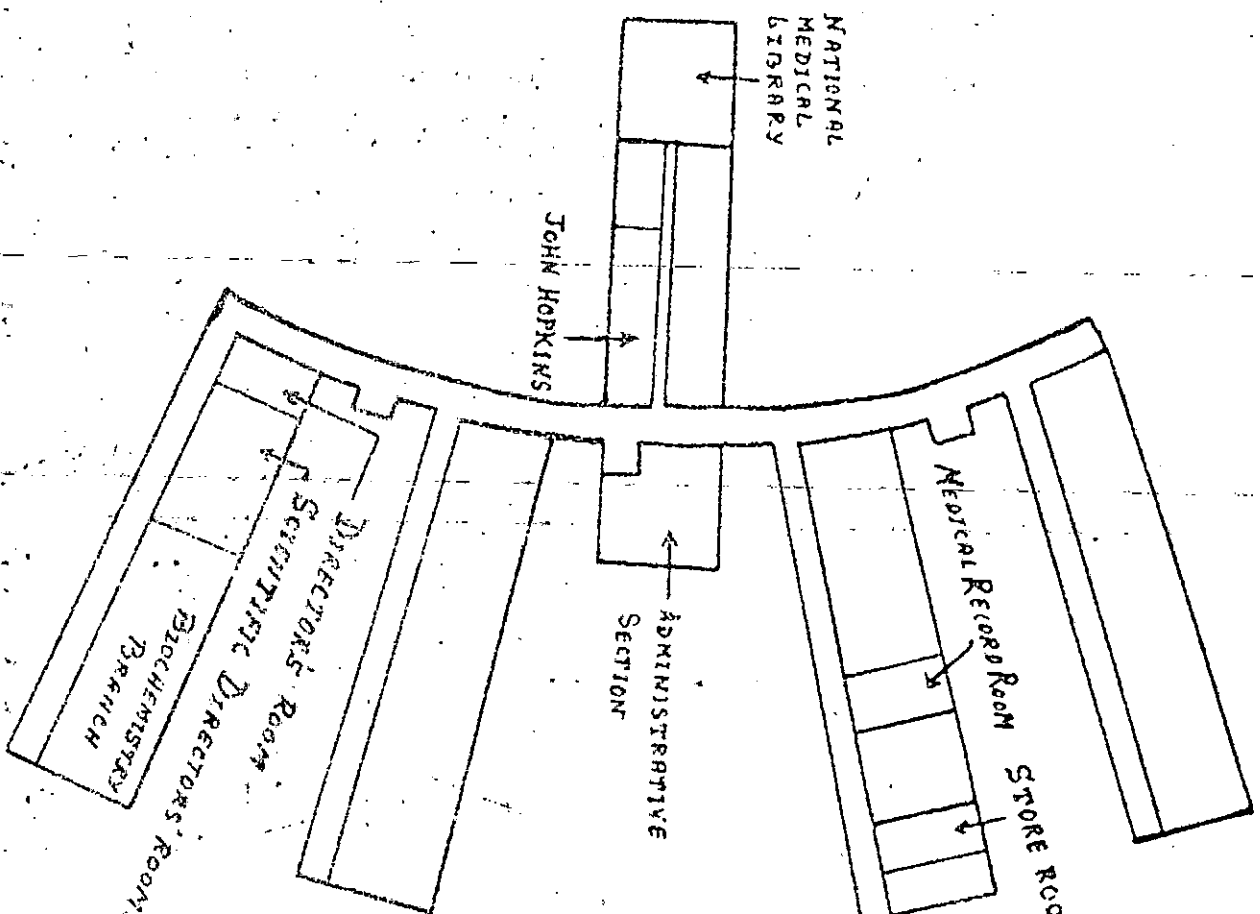


GROUND FLOOR

# FIRST FLOOR



# SECOND FLOOR



BACKGROUND PAPER FOR  
INTERNATIONAL SCIENTIFIC REVIEW MEETING  
FEBRUARY 6 - 14, 1978

HEALTH AND HEALTH SERVICE DELIVERY IN BANGLADESH

Colin McCord  
Cholera Research Laboratory  
Dacca, Bangladesh

The population of Bangladesh at the end of 1977 has been estimated at 82 million. This projection from the 1974 census is probably high by 1 or 2 million because of high mortality and low fertility which prevailed during the famine years of 1974 and 1975. Population density is the highest in the world for a major country - 560 persons per square kilometer. Only 8% of the population lives in an urban center, with "urban" defined as population over 5,000 persons. 60% of gross domestic product is direct agricultural production and 65% of income from industrial production is derived from processing of agricultural products. Per capita income is 1,600 takas annually (107 dollars). The distribution of income is seriously skewed, since 20% of the predominantly rural population have no land at all and more than 50% do not have enough land to maintain a family.

About 50% of the country's area has the possibility of daily access to urban centers, but this access is difficult for financial reasons and because road and river transport facilities are slow and crowded. At least one-third of the population lives in areas which are quite remote and have very little contact with urban areas. Medical facilities are concentrated to a heavy degree in urban areas and rural medical facilities generally are in locations where transport to urban areas is relatively easy.

These important transport problems are, nevertheless, not a major impediment to the development of a decentralized health service because of the high density of population in rural areas. Even in remote rural areas union level health centers will have a population of more than 12,000 within a radius of 3 km.

CAUSES OF DEATH

The major causes of death are those found in all poor countries. Malnutrition and malnutrition related disease predominate and 50% of deaths are deaths of children less than five years of age. In addition to deaths from outright malnutrition; diarrheal disease, respiratory infections,

complications of pregnancy and infectious diseases are the most common causes. Table 1 presents the results of a survey carried out in a rural area in 1975 and 1976. 1975 was a famine year so that both malnutrition and malnutrition related disease were higher in this year than in subsequent years.

Estimates from the 1974 census have produced a calculation of a crude death rate of 19.0 per thousand for the nation as a whole. Accurate age specific death rates are available only for specific project areas. These areas are thought to be typical, and in them the infant mortality rate has been 125 per thousand livebirths in recent normal years - it rises with famine and war, of course. The mortality rate for children aged 1-4 in normal times has been 25 per thousand and the maternal mortality rate has been about 6 per thousand livebirths. The birth rate has generally been about 45 per thousand population, but fell to below 40 in the war years of 1970 and 1971 and the famine year of 1974 and 1975.

#### MAJOR DISEASES

Surveys in government and private clinics throughout the country have consistently reported the following conditions as the major disease problems encountered.

- Malnutrition
- Diarrhea and Dysentery
- Respiratory tract infections
- Tetanus, particularly tetanus neonatorum. (this is not a problem in clinics, but is known to be a major health problem).
- Pulmonary tuberculosis
- Peptic ulcer syndrome
- Worm infestations, in children particularly
- Fever of various etiologies
- Ear and Eye infections
- Skin disease, particularly scabies
- Anemia, usually due to iron deficiency and hookworm infestation. (Folic acid deficiency is probably also a significant problem, but research is needed on this point.)

Chronic disease is frequently encountered and results

generally from chronic nutritional deficiency and infectious disease. Protein calorie malnutrition is widespread in early childhood. Several surveys have reported prevalence of "third degree malnutrition" to be 10 to 20% of children less than 5 years of age (third degree malnutrition in this instance is defined as weight less than 60% of the expected weight for age in the Harvard standard growth curve). Vitamin A deficiency is widespread and is a common cause of blindness. Iron and folic acid deficiency have already been mentioned as major causes of anemia. Riboflavin is the only one of the B vitamins which has been shown to be deficient in a large proportion of the population. Goitre, due to iodine deficiency, is common in certain areas of the country.

The malaria program in the 1960's was quite successful, but endemic areas persist in the Chittagong Hill Tracts and certain border areas particularly those adjacent to Assam. There has been a dramatic increase in malaria in Chittagong district and Chittagong Town with a high incidence of resistant *Falciparum* strains.

Filariasis is very common in Rajshahi and Dinajpur districts, with a high incidence of elephantiasis and other complications.

There are estimated to be 200,000 cases of leprosy in the country and 7 active cases of tuberculosis (sputum positive) per 1000 population.

Mental disease is relatively common and for the most part is remarkably well managed within the village community structure. It does not appear to be any more common than in western countries.

Cardiac disease is rare, but there are a fair number of patients with rheumatic heart disease and in the upper income groups there are patients with coronary artery disease. Stroke, on the other hand, is very common and is more common in poorer parts of the population. Hypertension is also widespread and also more common among the poor.

Table 2 shows the proportion of rural and urban households with nutrient intakes below an "acceptable" level.

#### GOVERNMENT AND PRIVATE EXPENDITURES ON HEALTH SERVICES AND PUBLIC HEALTH

Government expenditures for health are divided into a revenue budget (Takas 274,878,000 for 1976-77) and a development budget (Takas 377,500,000 for 1976-77). In general, recurring expenditures appear in the revenue budget, but this is a bit misleading because important ongoing programs such as malaria eradication are carried in the development budget. Tables 3 and 4 present the distribution

of funds in the revenue and development budget. Table 4 shows that the revenue budget for medical and public health services has risen steadily in the last ten years, but remains at the same percentage of the total revenue expenditure. Any increases in the proportion of expenditure on health which have occurred have been derived from aid funds and have been largely confined to the development budget.

If both the revenue budget and the development budget are taken together, the total for the health division for 76-77 becomes Tk. 652,000,000. Per capita health expenditure by government in this year was about Tk. 8, or a little more than 50 U.S. cents. Estimates of private expenditure on health are not available, but in other countries at a comparable level of development it has been found to be at least 2% of personal income - about Tk. 24 per capita. Preliminary results from surveys conducted in one rural area (Companiganj, Noakhali) suggest that per capita private expenditure is at least equal to government spending.

In addition to the health budget, there is 294 million takas within the development budget allocated to population control and family planning. The population budget is provided entirely within the development budget and is financed almost entirely through foreign aid. The present government plan calls for development of maternal child care services within the population division (see below). In 1977 a large grant became available from the world bank which will make it possible to construct union level health centers in each of the 4,500 unions in the country. The plan is to staff the union health centers partly with family planning and maternal child care personnel from the population division and partly with medical personnel from the health division (see below).

#### HEALTH MANPOWER

The situation with respect to health manpower statistics is best summarized by quoting from the "country health profile" prepared by WHO and the Government of Bangladesh, April 1977 (Section 18, page 2):

"Health manpower statistics in this country are highly deficient. In the government services, sanctioned posts for various categories of personnel are available but these figures are merely expressions of intention to meet planned requirements....."

Data on health manpower is available at the institutional level where additions to or separations from service at the institutions are more closely followed up. At the national level, this becomes more difficult because the management system is weak and does not readily permit

the flow of information. Statistics on health manpower outside of government service are more deficient than inside. The total number of doctors in the country can only be guessed at.....

The medical registration council is inadequate, lacks legal force and so cannot provide accurate data."

It is usually estimated that there are about 7 thousand doctors in the country. 5 thousand were registered in 1974, 4,800 of these in government service. In addition to these MBBS physicians, there are probably another 1000 "licentiate" practitioners who were trained in a 3 year course discontinued about ten years ago. Many of those originally trained in this short course have been upgraded by an examination procedure and are now considered fully qualified physicians. In 1976 there were 1063 registered nurses, 856 registered midwives and 413 registered lady health visitors.

Annual production of medical personnel is greater than might be expected from these very low figures: 1078 physicians are graduated annually from medical schools. Nursing schools of various types produce 620 basic nurses, 200 registered nurses, 100 Lady Health Visitors and 170 midwives each year. The population division has established 8 schools for "Family Welfare Visitors" who will receive essentially the same training as a lady health visitor in addition to Family Planning instruction. These are producing about 300 "FWV's" per year, and expansion of these schools is planned, since FWV's will be key personnel in the proposed new rural health system.

There has, in fact, been considerable expansion of manpower production from all of these schools in the last 10 years, but losses (of physicians, particularly) to foreign countries, have more than compensated for the increase. Most observers believe that this is a temporary phenomenon since the route to Britain and the U.S. is now closed and the market in Arab countries is a limited one which should be saturated soon. In any event, new personnel for rural health services will not be exportable since there are no FWV's in other countries, and the physician will be largely replaced by a "medical assistant" who will be trained specifically for delivery of primary care in rural areas.

Four schools for medical assistants have been set up, and the first class will complete the two year course next year. Production of about 400 per year is planned.

There are 10,300 registered homeopathic practitioners and 4,000 Ayurvedic and Unani practitioners. Surveys conducted in rural areas (see below) have consistently shown that the traditional practitioners are in the minority and that most indigenous practitioners are unregistered individuals who have acquired experience informally.

A survey of private practitioners in rural areas was conducted in 1969 covering a population of 570,000. The results are summarized in Table 5. It is clear that a vast majority of these private practitioners are untrained dais, dispensers and others. Of the estimated 7,000 physicians in the country, only 1,000 are believed to be practicing in the rural areas where 92% of the population resides.

A large proportion of sick people in rural areas receive no care at all. Most of the rest go to unregistered local practitioners. Only a small fraction are seen by a physician or make use of the government health facilities, which are very limited at present although there are plans for a tremendous expansion and funds have been allocated for this.

### FACILITIES

The government operates a total of 84 hospitals with 8,712 beds. In addition, there are 2,148 specialized hospital beds for police personnel, railroad personnel and in jails. There are 33 private hospitals with 2,439 beds and there is a large medical establishment providing services to military personnel. All these hospital facilities are located in urban areas. In rural areas there are 1,500 beds in rural health centers and 900 beds in dispensaries, but many of these are presently not functioning. In total, there are 15,700 hospital beds or 19.6 per 100,000 population. In rural areas, however, there are only 2,400 beds sanctioned so that if all these beds were functioning there would be only 3.2 beds per 100,000 population.

### THE RURAL HEALTH PROGRAM

In rural areas there are 356 "thanas" or counties, each with a population of about 200,000. Government plans call for a rural health center in each of these, but only 150 have been built to date. These centers have out-patient clinics which are fairly active, but they provide very little hospital service. In addition, there are 366 sub-centers and 922 dispensaries. Services provided by sub-centers and dispensaries up to the present have been very limited, but government plans call for construction of a sub-center in each union in the country which will be the base for provision of health services in a greatly expanded rural system. Funds for these sub-centers have been granted by the World Bank and construction has begun. When it is completed there will be a sub-center for each 20,000 population - a total of 4,500 in the country. The population division of the Health Ministry will provide a lady health visitor with 18 months training in maternal child care and family planning for each of these centers and the health division will provide a "medical assistant". Four schools have been established to train these medical assistants who will have two years training in provision of basic medical care. The first class of medical assistants will

graduate next year and it is expected that about 400 new graduates will be produced each year thereafter. In addition to these trained medical personnel, each sub-center will have 8 or 10 supporting staff including a compounder and a laboratory technician.

The sub-centers will relate to a large staff of government field workers which is already in place. On the health side there are 16,000 "Family Welfare Workers (FWW's)" - 1 per 5,000 population - who are re-trained malaria workers and sanitary inspectors. They are continuing the malaria program and, now that smallpox has been eradicated, they have begun a campaign to give BCG vaccine to all children. It is proposed that they will vaccinate all women against tetanus as a measure to control neo-natal tetanus. These workers are expected to visit every house in the country once a month, and there is obvious potential for many programs which could be conducted through them.

On the population side there are 3 female workers and 1 male worker for every union - a ratio of one worker per 5,000 population. This is a new program, and hiring has just been completed. At present, their work is confined to provision of family planning supplies but it is proposed to train them in maternal-child care work and to coordinate their activities with the work of the family welfare visitor in the sub-center.

As a part of its maternal child care program, the population division also proposes to train indigenous midwives in order to coordinate their activities with those of the sub-center, ensure that all pregnant women are immunized against tetanus, improve the nutrition of pregnant women and care for certain complications of pregnancy. Most people inside and outside the government who have worked in rural areas in this country feel that these efforts to coordinate government activities with indigenous practitioners and with other self-generated activity within the community must be greatly expanded if the program is to succeed.

Table 1

## CAUSES OF DEATH - ALL AGES

|                                                                         | 1975   |                   | 1976   |                  |
|-------------------------------------------------------------------------|--------|-------------------|--------|------------------|
|                                                                         | Deaths | Rate per 100,000. | Deaths | Rate per 100,000 |
| Chronic Diarrheal Disease<br>(76% had recorded associated malnutrition) | 48     | 442               | 22     | 206              |
| Acute Diarrheal Disease                                                 | 21     | 194               | 22     | 206              |
| Malnutrition                                                            | 49     | 452               | 9      | 84               |
| Pneumonia                                                               | 8      | 74                | 30     | 282              |
| Birth Injury, Neonatal<br>Asphyxia, & Prematurity                       | 8      | 74                | 12     | 113              |
| Congenital Anomaly                                                      | 1      | 9                 | 0      | -                |
| Tuberculosis                                                            | 11     | 101               | 5      | 47               |
| Fever                                                                   | 9      | 83                | 7      | 66               |
| Tetanus                                                                 | 3      | 28                | 9      | 84               |
| Measles                                                                 | 5      | 46                | 14     | 131              |
| Whooping Cough                                                          | 1      | 9                 | 3      | 28               |
| Diphtheria                                                              | 1      | 9                 | 1      | 9                |
| Chicken Pox                                                             | 2      | 18                | 0      | -                |
| Meningitis                                                              | 1      | 9                 | 1      | 9                |
| Skin infection                                                          | 1      | 9                 | 2      | 19               |
| Anemia                                                                  | 4      | 37                | 0      | -                |
| Acute Abdomen                                                           | 6      | 55                | 3      | 28               |
| Acute Nephritis                                                         | 1      | 9                 | 0      | -                |
| Rheumatic Fever                                                         | 1      | 9                 | 0      | -                |
| Sore Mouth                                                              | 1      | 9                 | 0      | -                |
| Heart Failure                                                           | 6      | 55                | 2      | 19               |
| Cancer                                                                  | 2      | 18                | 0      | -                |
| Stroke                                                                  | 7      | 65                | 8      | 75               |
| Senility                                                                | 23     | 212               | 6      | 56               |
| Maternal Death                                                          | 1      | 9                 | 5      | 47               |
| Injury                                                                  | 3      | 28                | 2      | 19               |
| Drowning                                                                | 9      | 83                | 5      | 47               |
| Suicide                                                                 | 1      | 9                 | 3      | 28               |
| Homicide                                                                | 0      | -                 | 0      | -                |
| Cirrhosis                                                               | 2      | 18                | 2      | 19               |
| Other                                                                   | 19     | 175               | 18     | 169              |
| Unknown                                                                 | 8      | 74                | 19     | 178              |

TABLE 2

\*Percentage of households with nutrient intakes  
below acceptable level

|            | <u>Rural</u> | <u>Urban</u> |
|------------|--------------|--------------|
| Calories   | 45.7         | 76.4         |
| Protein    | 60.8         | 77.2         |
| Calcium    | 85.8         | 93.9         |
| Iron       | 67.9         | 93.9         |
| Vitamin A  | 83.8         | 80.3         |
| Thiamine   | 15.5         | 39.1         |
| Riboflavin | 86.6         | 80.3         |
| Niacin     | 7.8          | 37.9         |
| Vitamin C  | 60.1         | 59.3         |

\*Source: Bangladesh Country Health Programming  
Exercise, 1973

TABLES 3 AND 4

REVENUE BUDGET

| <u>Fiscal year</u> | <u>Total Revenue Expenditure</u> | <u>Medical &amp; Public Health</u> | <u>Percentage</u> |
|--------------------|----------------------------------|------------------------------------|-------------------|
| 1966-67            | 1166                             | 50.5                               | 4.33              |
| 1967-68            | 1367.4                           | 61.8                               | 4.52              |
| 1968-69            | 1679.8                           | 65.9                               | 3.92              |
| 1969-70            | 2010.1                           | 82.1                               | 4.08              |
| 1970-71            | 2482.9                           | 83.4                               | 3.36              |
| 1971-72            | 2686.8                           | 101.9                              | 3.79              |
| 1972-73            | 2131.1                           | 118.8                              | 5.57              |
| 1973-74            | 3643.9                           | 144.7                              | 3.97              |
| 1974-75            | 4702.9                           | 196.4                              | 4.17              |

For the year 1976-77, the Revenue Budget (the budgeted expenditure for Health Division alone is Taka 274,878 million. The breakdown in thousands of takas is as follows:

|                                              |               |              |
|----------------------------------------------|---------------|--------------|
| Rural Health Services                        | 46401         | (16.88)      |
| Hospitals                                    | 119490        | (43.47)      |
| Training & Education                         | 31279         | (11.38)      |
| Health Establishment                         | 5511          | ( 2.80)      |
| Preventive Health Services                   | 39641         | (14.42)      |
| Grant                                        | 6289          | ( 2.29)      |
| Cyclone                                      | 411           | ( 0.15)      |
| Additional Expenditure for Development Works | 25856         | ( 9.41)      |
| <b>Total:</b>                                | <b>274878</b> | <b>(100)</b> |

TABLE 5  
DEVELOPMENT BUDGET FOR HEALTH

| Components<br>(Both on-going & new schemes) | Provisions for<br>1976-77 takas<br>in millions | Percentage |
|---------------------------------------------|------------------------------------------------|------------|
| Rural Health                                | 159,689                                        | 42.30      |
| Health Manpower Development                 | 115,800                                        | 30.68      |
| Malaria Eradication                         | 45,000                                         | 11.92      |
| Hospitals & Clinics                         | 17,500                                         | 4.64       |
| Miscellaneous                               | 10,211                                         | 2.70       |
| Stores & Supplies of Drugs                  | 2,800                                          | 0.74       |
| Reconstruction                              | 2,300                                          | 0.61       |
| Public Health Services                      | 1,700                                          | 0.45       |
| Military Health Projects                    | 22,500                                         | 5.96       |

TABLE 6

Healers in Private Practice in Rural Bangladesh 1969

(Total Population of Surveyed Unions : 567,961)

Source : From Awan, A.H., 1969

| Type                                   | Number per<br>Survey<br>Population | % of<br>Total | Health/Pop<br>ulation Ratio |
|----------------------------------------|------------------------------------|---------------|-----------------------------|
| <u>Adequately Trained</u>              |                                    |               |                             |
| Qualified Doctors                      | 10                                 |               | 1: 57,000                   |
| Nurses                                 | 1                                  |               | 1: 570,000                  |
| Lady Health Visitors                   | 1                                  | 6             | 1: 570,000                  |
| Health Technician                      | 0                                  |               |                             |
| Trained Dais                           | 4                                  |               | 1: 142,500                  |
| <u>Poorly Trained or<br/>Untrained</u> |                                    |               |                             |
| Untrained Dais                         | 101                                |               |                             |
| Dispensers                             | 30                                 | 49            | 1: 4,400                    |
| <u>Non-Scientific</u>                  |                                    |               |                             |
| Homoeopath                             | 44                                 |               |                             |
| Hakims                                 | 11                                 | 45            | 1: 4,800                    |
| Faith Healers & others                 | 64                                 |               |                             |
|                                        | 266                                | 100           |                             |

CURRICULUM VITAE

Name: Dr. Ansaruddin Ahmed

Professional Training:

| a) | <u>Degree</u> | <u>Place</u>              | <u>Year</u> |
|----|---------------|---------------------------|-------------|
|    | M.B.B.S.      | Medical College, Calcutta | 1955        |

| b) | <u>Type</u> | <u>Place</u> | <u>Year</u> |
|----|-------------|--------------|-------------|
|----|-------------|--------------|-------------|

Professional Employment:

| <u>Major Position</u>                  | <u>Place</u> | <u>Dates</u>        |
|----------------------------------------|--------------|---------------------|
| Clinical Bacteriologist, Bact. Section | CRL          | Feb-June 1966       |
| Research Associate, Epid. Section      | CRL          | July 1966-June 1970 |
| Head, Immunology Branch                | CRL          | July 1970-till date |

## CURRICULUM VITAE

Name: Dr. A.K.M. Jamiul Alam

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>          | <u>Year</u> |
|----|---------------|-----------------------|-------------|
|    | B.Sc.         | Rajshahi University   | 1955        |
|    | M.B.B.S.      | Dacca Medical College | 1961        |

| b) | <u>Type</u>                                                | <u>Place</u>                                                                | <u>Year</u> |
|----|------------------------------------------------------------|-----------------------------------------------------------------------------|-------------|
|    | Full time Postgraduate Teaching Course in General Medicine | Whittington Hospital, London & Edgware General Hospital, Middlesex, England | 1966        |
|    | Training in Gastrointestinal Diseases                      | Birmingham General Hospital, Birmingham, U.K.                               | 1966-1968   |

### Professional Employment:

| <u>Major Position</u>           | <u>Place</u>               | <u>Dates</u>   |
|---------------------------------|----------------------------|----------------|
| House Surgeon & House Physician | Mirzapur Hospital, Tangail | 1962           |
| Physician                       | CRL Dacca Hospital         | 1963-1969      |
| Resident Physician              | CRL Dacca Hospital         | 1969-1972      |
| Chief Physician                 | CRL Dacca Hospital         | 1973-till date |

## CURRICULUM VITAE

Name: Susan F. Alamgir

### Professional Training:

| a) | <u>Degree</u>           | <u>Place</u>                              | <u>Year</u> |
|----|-------------------------|-------------------------------------------|-------------|
|    | M.S. in Library Science | Simmons Collège,<br>Boston, Mass., U.S.A. | 1971        |

| b) | <u>Type</u> | <u>Place</u> | <u>Year</u> |
|----|-------------|--------------|-------------|
|----|-------------|--------------|-------------|

### Professional Employment:

| <u>Major Position</u> | <u>Place</u> | <u>Dates</u>         |
|-----------------------|--------------|----------------------|
| Head Librarian        | CRL, Dacca   | Feb. 1976-till date. |

## CURRICULUM VITAE

Name: Dr. K.A. Al-Mahmud

### Professional Training:

| a) | <u>Degree</u>   | <u>Place</u>                                                             | <u>Year</u> |
|----|-----------------|--------------------------------------------------------------------------|-------------|
|    | B.Sc. (A.H.)    | E.P. College of Veterinary<br>Science & Animal Husbandary,<br>Mymensingh | 1961        |
|    | M.Sc. (Vet.Sc.) | Bangladesh Agricultural University,<br>Mymensingh                        | 1967        |
| b) | <u>Type</u>     | <u>Place</u>                                                             | <u>Year</u> |
|    |                 |                                                                          |             |

### Professional Employment:

| <u>Major Position</u>         | <u>Place</u> | <u>Dates</u>      |
|-------------------------------|--------------|-------------------|
| Veterinarian                  | CRL          | 1962 - 1965       |
| Research Veterinarian         | CRL          | 1967 - 1974       |
| Head, Animal Resources Branch | CRL          | 1974 - till date. |

## CURRICULUM VITAE

Nama: Mr. K.M. Ashraful Aziz

### Professional Training:

| a) | <u>Degree</u>                           | <u>Place</u>                   | <u>Year</u> |
|----|-----------------------------------------|--------------------------------|-------------|
|    | B.A. (Hons.)                            | Dacca University               | 1960        |
|    | M.A.                                    | Dacca University               | 1961        |
|    | M.Phil                                  | Rajshahi University            | 1976        |
| b) | <u>Type</u>                             | <u>Place</u>                   | <u>Year</u> |
|    | Specialization in Cultural Anthropology | University of Hawaii, Honolulu | 1962-1964   |

### Professional Employment:

| <u>Major Position</u>             | <u>Place</u> | <u>Dates</u>    |
|-----------------------------------|--------------|-----------------|
| Sociologist                       | CRL, Dacca   | 1961 - 1962     |
| Field Supervisor                  | CRL, Matlab  | 1964 - 1966     |
| Field Surveillance Supervisor     | CRL, Matlab  | 1966 - 1968     |
| Section Chief, Field Surveillance | CRL, Matlab  | 1968 - 1969     |
| Head, Field Surveillance Branch   | CRL, Matlab  | 1969 - 1977     |
| Investigator                      | CRL          | 1977-till date. |

## CURRICULUM VITAE

Name: Dr. K.M. Sultanul Aziz

### Professional Training:

| a) | <u>Degree</u>                                                                                             | <u>Place</u>              | <u>Year</u> |
|----|-----------------------------------------------------------------------------------------------------------|---------------------------|-------------|
|    | B.Sc. (Hons.)                                                                                             | Dacca University          | 1956        |
|    | M.Sc.                                                                                                     | Dacca University          | 1957        |
|    | Ph.D.                                                                                                     | Duke University, U.S.A.   | 1965        |
| b) | <u>Type</u>                                                                                               | <u>Place</u>              | <u>Year</u> |
|    | Certificate in Liberal Arts                                                                               | Yale University, U.S.A.   | 1959        |
|    | Certificate in Marine Biology                                                                             | Oregon University, U.S.A. | 1963        |
|    | SEATO Medical Research Laboratory                                                                         | Bangkok                   | 1966        |
|    | U.S. Naval Medical Research Unit No.2                                                                     | Taipei                    | 1966        |
|    | National Institute of Animal Health<br>Institute of Infectious Diseases<br>and Primate Research Institute | Tokyo                     | 1966        |
|    | Certificate in Data Processing                                                                            | Dacca University          | 1975        |
|    | Certificate in Arabic Language                                                                            | Islamic Foundation, Dacca | 1976        |

### Professional Employment:

| <u>Major Position</u>           | <u>Place</u>                    | <u>Dates</u>        |
|---------------------------------|---------------------------------|---------------------|
| Associate Professor of Biology  | N.C. Central University, U.S.A. | 1964-1965           |
| Guest Investigator              | CRL                             | 1966-1967           |
| Chief, Animal Resources Section | CRL                             | 1967-1969           |
| Senior Investigator             | CRL                             | 1969-1975           |
| Head, Laboratory Division       | CRL                             | 1975-1977           |
| Scientific Director             | CRL                             | 1977-<br>till date. |

CURRICULUM VITAE

Name: Dr. Stanley R. Becker

Professional Training:

| a) | <u>Degree</u> | <u>Place</u>             | <u>Year</u> |
|----|---------------|--------------------------|-------------|
|    | B.A.          | University of Chicago    | 1972        |
|    | M.A.          | University of Chicago    | 1973        |
|    | Ph.D.         | Johns Hopkins University | 1977        |

| b) | <u>Type</u> | <u>Place</u> | <u>Year</u> |
|----|-------------|--------------|-------------|
|    |             |              |             |

Professional Employment:

| <u>Major Position</u> | <u>Place</u>                | <u>Year</u> |
|-----------------------|-----------------------------|-------------|
| Post-doctoral Fellow  | Cholera Research Laboratory | Jan. 1978-  |

## CURRICULUM VITAE

Name: Dr. Shushum Bhatia

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                                      | <u>Year</u> |
|----|---------------|---------------------------------------------------|-------------|
|    | M.B.B.S.      | Delhi University                                  | 1970        |
|    | M.P.H.        | Johns Hopkins School of Hygiene and Public Health | 1974        |

| b) | <u>Type</u>                                               | <u>Place</u>           | <u>Year</u> |
|----|-----------------------------------------------------------|------------------------|-------------|
|    | Diploma OB-GYN                                            | Delhi University       | 1970        |
|    | Certificate in Advance Technique for Fertility Management | Johns Hopkins Hospital | 1974        |

### Professional Employment:

| <u>Major Position</u> | <u>Place</u>                                                    | <u>Dates</u>             |
|-----------------------|-----------------------------------------------------------------|--------------------------|
| Research Officer      | Rural Health and Research Centre, Narangwal, Ludhiana, Punjab   | June 1971-<br>Sept. 1973 |
| Consultant            | Companiganj Health Project, Bangladesh                          | April-Aug. 1975          |
| Director              | Rural Community Health Program, Faridpur, Barcilly, U.P., India | Jan. 1976-Apr. 1977      |
| Investigator          | CRL                                                             | Aug. 1977-Present        |

# CURRICULUM VITAE

Name: Dr. Robert E. Black

## Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                                                     | <u>Year</u> |
|----|---------------|------------------------------------------------------------------|-------------|
|    | M.D.          | Hahnemaun Medical College,<br>Philadelphia, Pennsylvania, U.S.A. | 1971        |

|  |        |                                  |      |
|--|--------|----------------------------------|------|
|  | M.P.H. | University of California, U.S.A. | 1976 |
|--|--------|----------------------------------|------|

| b) | <u>Type</u>                        | <u>Place</u>             | <u>Year</u> |
|----|------------------------------------|--------------------------|-------------|
|    | Medical Intern                     | University of California | 1971 - 1972 |
|    | Medical Resident                   | University of California | 1972 - 1974 |
|    | Fellow in Infectious<br>Diseases   | University of California | 1974 - 1975 |
|    | Resident in Preventive<br>Medicine | University of California | 1976        |

## Professional Employment:

| <u>Major Position</u> | <u>Place</u>                                    | <u>Dates</u>      |
|-----------------------|-------------------------------------------------|-------------------|
| E.I.S. Officer        | Center for Disease Control,<br>Atlanta, Georgia | 1975 - 1977       |
| Epidemiologist        | CRL                                             | June 1977-Present |

# CURRICULUM VITAE

Name: Dr. Lincoln C. Chen

## Professional Training:

| a) | <u>Degree</u>                              | <u>Place</u>                          | <u>Year</u> |
|----|--------------------------------------------|---------------------------------------|-------------|
|    | B.A.                                       | Princeton University, New Jersey      | 1964        |
|    | M.D.                                       | Harvard Medical School, Massachusetts | 1968        |
|    | M.P.H.                                     | Johns Hopkins University              | 1973        |
| b) | <u>Type</u>                                | <u>Place</u>                          | <u>Year</u> |
|    | Intern in Internal Medicine                | Massachusetts General Hospital        | 1968 - 1969 |
|    | Assistant Resident in<br>Internal Medicine | Massachusetts General Hospital        | 1969 - 1970 |
|    | Clinical Fellow in Medicine                | Harvard University                    | 1969 - 1970 |

## Professional Employment:

| <u>Major Position</u>                                    | <u>Place</u>                                                        | <u>Dates</u>          |
|----------------------------------------------------------|---------------------------------------------------------------------|-----------------------|
| Clinical Research Associate                              | National Institute of Allergy &<br>Infectious Disease               | 1970 - 1971           |
| Research Physician                                       | Cholera Research Laboratory                                         | 1970 - 1971           |
| Assigned to the Digestive &<br>Hereditary Disease Branch | National Institute of Arthritis<br>and Metabolic Diseases, Bethesda | 1971 - 1972           |
| Staff Associate                                          | International Division, Population<br>Council, New York             | 1973 - 1977           |
| Program Officer                                          | Ford Foundation, Dacca                                              | 1973 - 1975           |
| Acting Representative                                    | Ford Foundation, Dacca                                              | 1976 - 1977           |
| Scientific Director                                      | Cholera Research Laboratory                                         | May 1977 -<br>Present |

## CURRICULUM VITAE

Name: Mr. A.K.M. Alauddin Chowdhury

### Professional Training:

| a) | <u>Degree</u>        | <u>Place</u>             | <u>Year</u> |
|----|----------------------|--------------------------|-------------|
|    | B.Sc.                | Dacca University         | 1957        |
|    | M.Sc.                | Johns Hopkins University | 1974        |
| b) | <u>Type</u>          | <u>Place</u>             | <u>Year</u> |
|    | Computer Programming | -                        | -           |

### Professional Employment:

| <u>Major Position</u>                         | <u>Place</u>                                      | <u>Dates</u> |
|-----------------------------------------------|---------------------------------------------------|--------------|
| Assistant Statistician                        | Department of Agriculture<br>Govt. of E. Pakistan | 1960-1961    |
| Assistant Statistical Officer                 | WAPDA, Dacca                                      | 1961-1963    |
| Statistician                                  | Dept. of Co-operatives<br>Govt. of E. Pakistan    | 1963-1964    |
| Research Assistant                            | ISRT, Dacca University                            | 1964-1967    |
| Head, Statistics Branch                       | Cholera Research Laboratory                       | 1967-1972    |
| Jr. Investigator & Head,<br>Statistics Branch | Cholera Research Laboratory                       | 1974-Present |

## CURRICULUM VITAE

Name: Dr. William B. Greenough III

### Professional Training:

| a) | <u>Degree</u>                                  | <u>Place</u>                             | <u>Year</u> |
|----|------------------------------------------------|------------------------------------------|-------------|
|    | B.A.                                           | Amherst College, Amherst, Mass.          | 1953        |
|    | M.D.                                           | Harvard Medical School, Cambridge, Mass. | 1957        |
| b) | <u>Type</u>                                    | <u>Place</u>                             | <u>Year</u> |
|    | Internship and Assistant Residency in Medicine | Presbyterian Hospital, New York          | 1957 - 1959 |

### Professional Employment:

| <u>Major Position</u>                                                         | <u>Place</u>                          | <u>Dates</u>      |
|-------------------------------------------------------------------------------|---------------------------------------|-------------------|
| Senior Surgeon, USPHS                                                         | -                                     | 1964              |
| Research Associate                                                            | Pak-SEATO Cholera Research Laboratory | 1962-1965         |
| Staff Associate                                                               | National Heart Institute, Bethesda    | 1965-1967         |
| Assistant Chief of Medicine                                                   | Baltimore City Hospitals              | 1967-1977         |
| Associate Professor of Medicine & Microbiology                                | Johns Hopkins University              | 1970-Present      |
| Chief, Infectious Diseases Division                                           | Johns Hopkins Hospital                | 1970-1976         |
| Associate Professor of Emergency Medicine                                     | Johns Hopkins University              | 1974-Present      |
| Director, The Clinical Scholars Program of the Robert Wood Johnson Foundation | Johns Hopkins University              | 1974-1977         |
| Chairman, The Bacteriology & Mycology Study Section of NIH                    | NIH, Bethesda, Maryland               | 1974-1976         |
| Hospital Epidemiologist                                                       | Johns Hopkins Hospital                | 1974-1977         |
| Scientific Director                                                           | Cholera Research Laboratory           | July 1977-Present |

## CURRICULUM VITAE

Name: Mr. Md. Imdadul Huq,

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                                         | <u>Year</u> |
|----|---------------|------------------------------------------------------|-------------|
|    | B.Sc.         | Dacca University                                     | 1956        |
|    | M.Sc.         | Dacca University                                     | 1958        |
| b) | <u>Type</u>   | <u>Place</u>                                         | <u>Year</u> |
|    | Dip. Bact.    | London School of Hygiene & Trop.<br>Medicine, London | 1956        |

### Professional Employment:

| <u>Major Position</u>            | <u>Place</u>             | <u>Dates</u> |
|----------------------------------|--------------------------|--------------|
| Chief Chemist-cum-Bacteriologist | EDRUC, Pabna, Bangladesh | 1960-1962    |
| Bacteriologist                   | Parson's Corp., Dacca    | 1959-1960    |
| Head, Microbiology Branch        | CRL                      | 1962-Present |

# CURRICULUM VITAE

Name: Dr. Md. Rafiqul Islam

## Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                                | <u>Year</u> |
|----|---------------|---------------------------------------------|-------------|
|    | B.Sc.         | Murari Chand Govt. College,<br>Sylhet       | 1955        |
|    | M.B.B.S.      | Dacca Medical College                       | 1961        |
| b) | <u>Type</u>   | <u>Place</u>                                | <u>Year</u> |
|    | D.T.M. & H.   | London School of Tropical Med. &<br>Hygiene | 1967        |

## Professional Employment:

| <u>Major Position</u>  | <u>Place</u>                        | <u>Dates</u>            |
|------------------------|-------------------------------------|-------------------------|
| Medical Officer        | Dacca Medical College Hospital      | Aug. 1961-Feb. 63       |
| Physician              | CRL                                 | 1963-1964               |
| Senior Physician       | CRL                                 | 1964-1965               |
| Senior House Officer   | Royal Victoria Hospital,<br>Belfast | Sep. 1966-<br>Feb. 1967 |
| Chief Resident         | CRL                                 | 1965-69                 |
| Deputy Chief Physician | CRL                                 | 1969-Present            |

## CURRICULUM VITAE

Name: Dr. Moslemuddin Khan

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                                       | <u>Year</u> |
|----|---------------|----------------------------------------------------|-------------|
|    | M.B.B.S.      | Dacca Medical College                              | 1956        |
| b) | <u>Type</u>   | <u>Place</u>                                       | <u>Year</u> |
|    | D.P.H.        | Institute of Preventive Medicine & Hygiene, Lahore | 1962        |
|    | E.I.S.        | Center for Disease Control, Atlanta, U.S.A.        | 1974        |

### Professional Employment:

| <u>Major Position</u>                         | <u>Place</u> | <u>Dates</u>         |
|-----------------------------------------------|--------------|----------------------|
| District Health Officer                       | Rangpur      | 1961-1964            |
| Deputy Asst. Chief Epidemiology Section       | CRL          | April 1964-Oct. 64   |
| Asst. Chief, Epidemiology Section             | CRL          | Oct. 1964-June 1966  |
| Deputy Chief, Epidemiology Section            | CRL          | July 1966-Sept. 1969 |
| Head, Community Studies Branch                | CRL          | Sept. 1969-Feb. 1974 |
| Investigator & Head, Community Studies Branch | CRL          | Feb. 1974-Present    |

## CURRICULUM VITAE

Name: Dr. Colin W. McCord

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                       | <u>Year</u> |
|----|---------------|------------------------------------|-------------|
|    | B.A.          | Williams College, Massachusetts    | 1949        |
|    | M.D.          | Columbia University, New York City | 1953        |

| b) | <u>Type</u>                   | <u>Place</u>                                             | <u>Year</u> |
|----|-------------------------------|----------------------------------------------------------|-------------|
|    | Fellow-ship, Dept. of Surgery | New York Hospital                                        | 1954-1955   |
|    | Assistant Resident, Surgery   | Hospital of University of Pennsylvania                   | 1955-1956   |
|    | Assistant Resident, Surgery   | Presbyterian Hospital, New York                          | 1956-1957   |
|    | Assistant Resident, Surgery   | 1st Division, Bellevue Hospital New York                 | 1957        |
|    | Resident, General Surgery     | 1st Division, Bellevue & Presbyterian Hospital, New York | 1958        |
|    | Resident, Chest Surgery       | Bellevue & Presbyterian Hospital, New York               | 1959-1961   |

### Professional Employment:

| <u>Major Position</u>                         | <u>Place</u>                                              | <u>Dates</u>         |
|-----------------------------------------------|-----------------------------------------------------------|----------------------|
| Chief, Thoracic Surgery                       | U.S. Veterans Admin. Hospital Portland, Oregon            | 1961-1965            |
| Instructor, Department of Surgery             | University of Oregon Medical School, Portland, Oregon     | 1961-1964            |
| Associate in Cardiopulmonary Surgery          | Oregon Medical School                                     | 1963-1964            |
| Assistant Professor, Cardio-pulmonary Surgery | University of Oregon                                      | 1964-1965            |
| Director, Cardiac Surgery                     | St. Luke's Hospital, New York                             | 1965-1971            |
| Director, Surgical Research Department        | St. Luke's Hospital, New York                             | 1969-1971            |
| Assistant Clinical Professor of Surgery       | Columbia University                                       | 1965-1970            |
| Associate Clinical Professor of Surgery       | Columbia University                                       | 1970-1971            |
| Resident Administrator                        | Johns Hopkins Rural Health Research Center, Punjab, India | <del>1971-1972</del> |
| Director                                      | Companiganj Health Project, Bangladesh                    | 1973-1975            |
| Investigator                                  | Cholera Research Laboratory                               | 1977-Present         |

## CURRICULUM VITAE

Name: Dr. Michael H. Merson

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                                    | <u>Year</u> |
|----|---------------|-------------------------------------------------|-------------|
|    | M.D.          | Downstate Medical Center, Brooklyn,<br>New York | 1970        |

| b) | <u>Type</u>                          | <u>Place</u>                                    | <u>Year</u>   |
|----|--------------------------------------|-------------------------------------------------|---------------|
|    | Straight Medical Internship          | Johns Hopkins Hospital                          | 1970-71       |
|    | Assistant Medical Resident           | Johns Hopkins Hospital                          | 1971-72       |
|    | Supervised Medical Ward              | Aboard hospital ship - SS Hope                  | May-June 1977 |
|    | Training in epidemiologic<br>methods | Center for Disease Control,<br>Atlanta, Georgia | July 1972     |

### Professional Employment:

| <u>Major Position</u>                                                                 | <u>Place</u>                                    | <u>Dates</u>          |
|---------------------------------------------------------------------------------------|-------------------------------------------------|-----------------------|
| Commissioned Officer, U.S. Public<br>Health Service                                   | EIS Center for Disease Control                  | 1972-1974             |
| Chief, Enteric Disease Branch<br>Bacterial Disease Division<br>Bureau of Epidemiology | Center for Disease Control,<br>Atlanta, Georgia | 1974-1975             |
| Resident in Preventive Medicine                                                       | Center for Disease Control                      | 1974-1975             |
| Instructor, Physical Diagnosis<br>Course                                              | Emory Medical School                            | 1975                  |
| Scientific Director                                                                   | CRL                                             | Aug. 1977-<br>Present |

## CURRICULUM VITAE

Name: Dr. W. Henry Mosley

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                              | <u>Year</u> |
|----|---------------|-------------------------------------------|-------------|
|    | B.A.          | Southwestern at Memphis                   | 1955        |
|    | M.D.          | University of Oklahoma School of Medicine | 1959        |
|    | M.P.H.        | Johns Hopkins School of Public Health     | 1965        |

| b) | <u>Type</u> | <u>Place</u>           | <u>Year</u> |
|----|-------------|------------------------|-------------|
|    | Intern      | Johns Hopkins Hospital | 1959-1960   |
|    | Residency   | Johns Hopkins Hospital | 1960-1961   |
|    | Residency   | Johns Hopkins Hospital | 1963-1964   |

### Professional Employment:

| <u>Major Position</u>                                           | <u>Place:</u>                                                      | <u>Dates</u> |
|-----------------------------------------------------------------|--------------------------------------------------------------------|--------------|
| Epidemic Intelligence Service,<br>U.S.P.H.S.                    | U.S.P.H.S.                                                         | 1961 - 1963  |
| Head, Epidemiology Division                                     | Pakistan-SEATO Cholera<br>Research Laboratory, Dacca               | 1965 - 1971  |
| Professor and Chairman,<br>Department of Population<br>Dynamics | Johns Hopkins University<br>School of Hygiene and<br>Public Health | 1971 - 1977  |
| Director                                                        | Cholera Research Laboratory<br>Dacca                               | 1977-to date |

## CURRICULUM VITAE

Name: Dr. Trinidad S. Osteria

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>             | <u>Year</u> |
|----|---------------|--------------------------|-------------|
|    | B.S.          | Manila                   | 1965        |
|    | M.A.          | Manila                   | 1968        |
|    | D.Sc.         | Johns Hopkins University | 1971        |
| b) | <u>Type</u>   | <u>Place</u>             | <u>Year</u> |

### Professional Employment:

| <u>Major Position</u>  | <u>Place</u>                                            | <u>Dates</u>        |
|------------------------|---------------------------------------------------------|---------------------|
| Assistant Professor I  | Population Institute,<br>University of Philippines      | July 1971-July 72   |
| Assistant Professor IV | Institute of Public Health<br>University of Philippines | Aug. 1972-June 1977 |
| Demographer            | CRL                                                     | July 1977-Present   |

## CURRICULUM VITAE

Name: Dr. M. Mujibur Rahaman

### Professional Training:

| a) | <u>Degree</u>                            | <u>Place</u>                     | <u>Year</u>    |
|----|------------------------------------------|----------------------------------|----------------|
|    | M.B.B.S.                                 | Dacca Medical College            | 1959           |
|    | M.Sc.                                    | Columbia University              | 1962           |
|    | Ph.D.                                    | University of Glasgow            | 1966           |
| b) | <u>Type</u>                              | <u>Place</u>                     | <u>Year</u>    |
|    | Training in Child Health and Paediatrics | Dundee, Scotland                 | 1962-1963      |
|    | Research Associate in Nutrition          | Institute of Physiology, Glasgow | 1963-1966      |
|    | Training in Radioisotopic Investigation  | Northwick Park Hospital, London  | June-July 1972 |

### Professional Employment:

| <u>Major Position</u>                                        | <u>Place</u>                                   | <u>Dates</u>      |
|--------------------------------------------------------------|------------------------------------------------|-------------------|
| Research Associate                                           | Institute of Physiology, University of Glasgow | 1963-1966         |
| Lecturer                                                     | Institute of Post-Graduate Medicine<br>Dacca   | 1968              |
| Senior Investigator                                          | CRL                                            | 1967-1974         |
| Acting Director                                              | CRL                                            | 1972-1973         |
| Head, Clinical Division & Director, Teknaf Dysentery Project | CRL                                            | 1974-1977         |
| Deputy Director                                              | CRL                                            | Oct. 1977-Present |

## CURRICULUM VITAE

Name: Mr. Makhlisur Rahman

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>               | <u>Year</u> |
|----|---------------|----------------------------|-------------|
|    | B.Sc.         | Govt. M.C. College, Sylhet | 1963        |
|    | M.A.          | Rajshahi University        | 1966        |

| b) | <u>Type</u> | <u>Place</u> | <u>Year</u> |
|----|-------------|--------------|-------------|
|----|-------------|--------------|-------------|

### Professional Employment:

| <u>Major Position</u>                               | <u>Place</u>                                                              | <u>Dates</u>          |
|-----------------------------------------------------|---------------------------------------------------------------------------|-----------------------|
| Assistant Director, Research                        | Directorate of Training, Research<br>Evaluation & Communication,<br>Dacca | Aug. 1970-Nov. 75     |
| Project Manager, Contraceptive Distribution Project | CRL, Matlab                                                               | Dec. 1975-July 77     |
| Head, Field Surveillance Activities Branch          | CRL, Matlab                                                               | July 1977-<br>Present |

## CURRICULUM VITAE

Name: Dr. A.S.M. Mizanur-Rahman

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>          | <u>Year</u> |
|----|---------------|-----------------------|-------------|
|    | M.B.B.S.      | Dacca Medical College | 1961        |
| b) | <u>Type</u>   | <u>Place</u>          | <u>Year</u> |
|    | House-job     | Dacca Medical College | 1962        |

### Professional Employment:

| <u>Major Position</u>    | <u>Place</u>         | <u>Dates</u> |
|--------------------------|----------------------|--------------|
| Assistant Epidemiologist | CRL, Dacca           | 1963-1965    |
| Physician                | CRL, Dacca           | 1965-1966    |
| Physician In-charge      | CRL, Matlab Hospital | 1966-1977    |
| Chief Physician          | CRL, Matlab Hospital | 1977-Present |

CURRICULUM VITAE

Name: Dr. David A. Sack

Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                        | <u>Year</u> |
|----|---------------|-------------------------------------|-------------|
|    | B.S.          | Clark College, Oregon               | 1964        |
|    | M.D.          | University of Oregon Medical School | 1968        |

| b) | <u>Type</u>    | <u>Place</u>                    | <u>Year</u> |
|----|----------------|---------------------------------|-------------|
|    | Medical Intern | University Hospitals, Iowa City | 1968-1969   |

Professional Employment:

| <u>Major Position</u>                            | <u>Place</u>                   | <u>Dates</u> |
|--------------------------------------------------|--------------------------------|--------------|
| Resident, Internal Medicine                      | University Hospital, Iowa City | 1971-1973    |
| Instructor, Infectious Disease Division          | Johns Hopkins University       | 1976         |
| Assistant Professor, Infectious Disease Division | Johns Hopkins University       | 1977         |
| Investigator                                     | CRL                            | 1977-Present |

## CURRICULUM VITAE

Name: Dr. Brian Beaton

### Professional Training

| a) | <u>Degree</u> | <u>Place</u>                         | <u>Year</u> |
|----|---------------|--------------------------------------|-------------|
|    | B.A.          | Mansfield College, Oxford University | 1966        |
|    | B.Sc.         | Mansfield College, Oxford University | 1967        |
|    | D.Phil        | Oxford University                    | 1970        |

| b) | <u>Type</u>                                                      | <u>Place</u>                                   | <u>Year</u> |
|----|------------------------------------------------------------------|------------------------------------------------|-------------|
|    | Ford Foundation Research Fellow,<br>Zoological Society of London | London                                         | 1973-1976   |
|    | Research Fellow, MRC<br>Biochemistry of Repro-<br>duction Group  | Strathdyde University,<br>Scotland, U.K.       | 1970-1973   |
|    | Research Assistant                                               | University Laboratory of<br>Physiology, Oxford | 1967-1970   |

### Professional Employment:

| <u>Major Position</u> | <u>Place</u> | <u>Dates</u>       |
|-----------------------|--------------|--------------------|
| Investigator          | CRL          | April 1977-Present |

## CURRICULUM VITAE

Name: Dr. William M. Spira

### Professional Training:

| a) | <u>Degree</u> | <u>Place</u>                     | <u>Year</u> |
|----|---------------|----------------------------------|-------------|
|    | B.S.          | University of Wisconsin, Madison | 1968        |
|    | M.S.          | University of Wisconsin, Madison | 1972        |
|    | Ph.D.         | University of Wisconsin, Madison | 1974        |

| b) | <u>Type</u> | <u>Place</u> | <u>Year</u> |
|----|-------------|--------------|-------------|
|----|-------------|--------------|-------------|

### Professional Employment:

| <u>Major Position</u>                          | <u>Place</u>                                                         | <u>Dates</u>        |
|------------------------------------------------|----------------------------------------------------------------------|---------------------|
| Visiting Scientist (NRC<br>Research Associate) | U.S. Army Natick Research &<br>Development Command,<br>Natick, Mass. | June 1974-June 1976 |

|              |     |                   |
|--------------|-----|-------------------|
| Investigator | CRL | July 1976-Present |
|--------------|-----|-------------------|

CURRICULUM VITAE

Name: Dr. Md. Yunus

Professional Training:

|    |                                       |                       |             |
|----|---------------------------------------|-----------------------|-------------|
| a) | <u>Degree</u>                         | <u>Place</u>          | <u>Year</u> |
|    | M.B.B.S.                              | Dacca Medical College | 1968        |
| b) | <u>Type</u>                           | <u>Place</u>          | <u>Year</u> |
|    | House job in medicine<br>for 4 months | Dacca Medical College | 1968        |

Professional Employment:

|                        |                      |                      |
|------------------------|----------------------|----------------------|
| <u>Major Position</u>  | <u>Place</u>         | <u>Dates</u>         |
| Physician              | CRL, Matlab Hospital | Nov. 1968-Sept. 1976 |
| Deputy Chief Physician | CRL, Matlab Hospital | Nov. 1976-Present    |

## ORGANIZATIONAL CHART

November 1, 1977

