

PD-AMY-222

REPORT ON THE SCIENTIFIC PROGRAM REVIEW
OF THE
INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH
IN DHAKA, BANGLADESH

Submitted to: Health Office
Science and Technology Division
United States Agency for International Development
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Submitted by: Applied Diarrheal Disease Research Project
Harvard Institute for International Development
1737 Cambridge Street
Cambridge, Massachusetts 02138

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EXECUTIVE SUMMARY
OF THE APPLIED DIARRHEAL DISEASE RESEARCH PROJECT'S
SCIENTIFIC PROGRAM REVIEW
OF THE INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH
IN DHAKA, BANGLADESH

May and June, 1986

INTRODUCTION

This scientific program review by the Applied Diarrheal Disease Research project (ADDR) of the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh (ICDDR,B) was commissioned by the Health Office of the Science and Technology Division of the United States Agency for International Development (S&T/H/AID). The review is in fulfillment of provisions of a cooperative agreement between AID and ICDDR,B that funds ICDDR,B research. These provisions require such a review six months after the signing of the cooperative agreement in order to determine the appropriateness of further funding.

This report includes evaluations by Drs. Robert E. Black, Gerald Keusch, Peter Kunstadter, and Myron Levine. Their conclusions and recommendations are introduced here, and their written reports are appended. The ADDR evaluation, and this report, did not include the scientific program management review of the ICDDR,B by Dr. James Heiby of AID, nor the financial assessment of the centre by Mr. Peter J. Rousselle of Management Sciences for Health, although these evaluations took place at the same time as those by ADDR and contribute to the same purposes within AID.

AID required a rapid response to its request that ADDR coordinate this review. As a consequence, the schedules of the evaluators precluded having the four ADDR evaluators in Dhaka concurrently. To coordinate the evaluation, each reviewer was assigned specific areas of responsibility. The timing of their visits and areas of responsibility were as follows:

Black	June 1-6	epidemiologic studies, with an emphasis on those in Matlab, including the cholera vaccine trial
Keusch	June 3-10	clinical research

Kunstadter	May 30-June 8	health services delivery, operations research, and social sciences research in general, and extension projects
Levine	May 23-29	laboratory activities, including basic laboratory research, laboratory support of epidemiological and of clinical research

The scientific program reviewers were charged with evaluating the performance of ICDDR,B with respect to the following two criteria (See the memorandum in which the evaluation's scope of work was set forth, Appendix I.):

- o appropriateness and quality of research (with emphasis on AID funded activities); and
- o productivity and merit of staff scientists.

In addition, the reviewers were asked to make recommendations in the following four areas:

- o modification extension of project design, management, implementation, budget, or time period;
- o value of the project to international health;
- o role of the project in fulfilling AID's health strategy; and
- o lessons learned for use in follow-up or subsequent activities or projects.

EVALUATION AND RECOMMENDATIONS

This section presents an overall assessment of the ICDDR,B by three of the four AIDR evaluators. It is drawn from a summary telex by Drs. Feusch and Kunstadter (Appendix VI), which reflects collaboration by Drs. Black, Feusch, and Kunstadter, whose time in Dhaka overlapped. Dr. Levine had already left Dhaka when the telex was written.

Overall Assessment

ICDDR,B serves an essential role in advancing AID health strategy and should receive continued direct support. ICDDR,B is a unique institution with a mandate that is relevant to AID's health strategy. Some of its research is clearly excellent, although there is a wide range of quality. ICDDR,B's director, Dr. R. Eeckels, needs and deserves AID's full support.

Among ICDDR,B's observations are the following items:

Scientific Research

- o Microbiology and immunology facilities are much improved;
- o The Matlab vaccine field trial has been well executed;
- o The Matlab population appears fatigued;
- o The focus on pathogenesis and immune response to shigella, environmental reservoirs of Vibrio cholerae, and other laboratory activities seems appropriate;
- o Research is of uneven quality because of the research review process and too few international level staff;
- o Much research is of a descriptive nature; and
- o The Urban Volunteers Program has been very successful in integrating research and services delivery;

Management

- o There tend to be lags in implementation of ICDDR,B Board recommendations;
- o Administrative staff, such as personnel, finance, and resource development staff, are perceived by many scientific staff as functioning autonomously with inadequate concern or understanding for the scientific agenda of the centre;
- o Donor intervention in ICDDR,B has induced a splintered research agenda and management difficulties;

- o A two tier salary scale and the application of UN staffing rules has created serious financial problems and personnel issues, forcing a choice between qualified spouses; and
- o Budget uncertainties have led to great difficulties for the conduct of research.

Recommendations include:

Scientific Research

- o A research program needs to be developed for the centre, with attention paid to applied research appropriate to the Bangladeshi context;
- o The Urban Volunteers Program should be continued and expanded;
- o Passive surveillance on the cholera vaccine trial needs to be continued;
- o Biochemistry facilities need to be improved;
- o Hospital services, metabolic ward, and clinical study unit each need international level supervision;
- o The centre needs to develop long-term collaboration with developed country research institutions to guarantee international level research;
- o More rapid epidemiological, demographic, and social science data analysis, and follow-up of epidemiological implications are needed, including better integration of medical and social sciences focused on problems of morbidity and mortality; and
- o ICDDR,B should restrict training activities to practical clinical, field, and laboratory skills for Bangladeshi and foreign health workers;

Management

- o Administrative staff, such as personnel, finance, and resource development staff, should be reorganized to promote responsiveness to the scientific agenda of the centre;

- o A new streamlined research review process needs to be developed to encourage scientific dialogue;
- o A new ICDDR,B salary structure with regulations appropriate to the local context needs to be developed; in particular, ICDDR,B should permit the hiring of qualified spouses;
- o Donors need to coordinate efforts more closely; and
- o ICDDR,B should discontinue publications except for the bibliographic series.

Appendices

- I. Memorandum of 7 May 1986 by Dr. Carl Kendall to Dr. Kenneth J. Bart, Dr. Roxanne van Dusen, and Ms. Anne Tinker, on the Scope of the ICDDR,B Review
- II. Dr. Robert E. Black's Evaluation*
- III. Dr. Gerald Keusch's Evaluation*
- IV. Dr. Peter Kunstadter's Evaluation*
- V. Dr. Myron Levine's Evaluation*
- VI. Summary Telex by Drs. Keusch and Kunstadter

*Appendices II-V have been edited to avoid repetition of information that has been consolidated in the executive summary, such as the timing of visits and the purpose of the evaluation.

APPENDIX I

MEMORANDUM

TO: S&T/H, Dr. Kenneth J. Bart
S&T/H, Dr. Roxanne van Dusen
S&T/H, Ms. Anne Tinker

FROM: S&T/H, Dr. Carl Kendall

SUBJECT: Objectives and Scope of Work for an Evaluation of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) by AID

1. Background:

In 1979, the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) was established on the institutional foundation developed by the Cholera Research Laboratory (CRL) under an international charter with the Government of Bangladesh and the assistance of AID and UNDP. Numerous donors help to support ICDDR, B, including USAID, Australia/ADAB, Bangladesh, Switzerland, UK/ODA, CIDA, Japan, IDRC (Canada), Ford Foundation, UNDP, UNICEF, and WHO. The Director of the Centre is Dr. Roger Eckels, appointed June 1985 to succeed Dr. William B. Greenough. The Centre is managed by a Board of Trustees. The total number of people employed by ICDDR,B is at present approximately 1,500.

The two main objectives of ICDDR,B as stated in its charter are:

1. to undertake and promote study, research, and dissemination of knowledge of diarrheal diseases and directly related subjects of nutrition and fertility with a view to developing improved methods of health care and for the prevention and control of diarrheal diseases and improvement of public health programs with special relevance to developing countries.
2. to provide facilities for training Bangladeshi and other nationals in areas of the Centre's competence in collaboration with national and international institutions.

These objective are accomplished by:

1. conducting clinical, laboratory, and field research with the objectives of developing practical technologies for disease prevention and health care along with methods for the application of these technologies.
2. conducting research and applied training programs for scientists, administrators, technicians, and other persons.
3. developing collaborative research and training efforts with national and international institutions, particularly in the developing countries to strengthen local initiatives and capabilities.
4. sponsoring technical and educational seminars.
5. publishing information on new technology.
6. consulting with governments and other agencies on effective application of health interventions.

Under the terms of the reorganization of ICDDR,B in 1979, AID provided \$10 million to the centre for five years of support. A site visit to Bangladesh by AID in late 1984 identified several problems at the centre. At that time, AID expressed to ICDDR,B its concern with issues of monitoring of centre activities, salary levels, unprecedented staff growth, use of US funds, earmarking of AID project support, and the quality and utility of research. Since then, the administration of the centre has taken steps to respond to these concerns.

Thus, in late 1985, after extensive consultation between AID and ICDDR,B, a new Cooperative Agreement in support of a project entitled Diarrheal Disease Research (DDR) (No. DPE-5928-A-00-6002-00) was signed. The purpose of the Cooperative Agreement was to provide support to ICDDR,B to field test important new vaccines, diagnostic techniques, and other preventive and case management strategies through agreement allows substantial involvement by AID in the program of the centre and is meant to guarantee both close coordination of research and high research quality. Currently AID/W is supporting a trial of two oral cholera vaccines. Ultimately AID hopes to support a range of diarrheal disease research activities. Technical resources of the US Centers for Disease Control (CDC), in the form of

epidemiologists who will serve as long-term consultants, will also be provided to ICDDR,B for the purpose of assisting and monitoring its program of research, general technical assistance, and dissemination of findings.

The total estimated amount to this cooperative agreement is \$9 million for 4 years (through December 31, 1989), of which \$1.8 million is obligated. Approximately \$5 million will be for targeted research, \$800,000 for consulting epidemiologists, and \$1.9 million for project development. In addition, a minimum of \$250,000 per year will be provided for unrestricted core support. For the first year, AID will provide an additional \$250,000 for core costs. Additional funds up to \$7.2 million may be obligated subject to availability of funds and satisfactory performance.

2. Objectives and Scope of Work:

We propose to carry out an independent evaluation of ICDDR,B. The activity will involve both a financial review and a scientific program review. The financial review will take place during the months of April and May. The scope of work for that evaluation is only discussed briefly in this document. The review of the scientific program will be conducted by a multidisciplinary team from May 24 to June 3, 1986, in order to provide a report to AID and the centre for its June 26, 1986 Board Meeting and Review. The multidisciplinary team will consist of five persons, 1 member from AID (Jim Heiby, S&T/H) and 4 external consultants specialized in the fields of: epidemiology, microbiology, pediatrics, and medical social science (Black, Levine, Feuch, and Kunstader).

The focus of the evaluation will be on the quality and utility of scientific activities of the center. The cooperative agreement requires AID to evaluate the activities of ICDDR,B within six months of the signing of the cooperative agreement. Subsequent funding will be dependent on successful performance as evaluated by the criteria below:

Financial and management component:

1. adequacy of recipient resources, including budget and steps taken by ICDDR,B to improve its financial status.
2. adequacy of recipient performances, management, and implementation.
3. implementation of ICDDR,B Board of Trustees Meeting (November, 1985 and subsequent) recommendations.
4. appropriateness and quality of recipient research (with emphasis on A.I.D. funded activities).
5. productivity and merit of staff scientists.

In addition, the evaluators will provide AID recommendations concerning the following issues:

6. modification or extension of project design, management, implementation, budget, or time period.
7. value of the project to international health.
8. role of the project in fulfilling A.I.D.'s health strategy.
9. lessons learned for use in follow-up or subsequent activities and projects.

3. Schedules and Procedures:

Appointments of consultants, preparations of travel schedules and a plan of work should be completed by April 30, 1986. The criteria for the financial review will be determined with the help of Mr. Peter Rousselle, Management Sciences for Health, when he returns from a consultation at ICDDR,B in March. The evaluation team will have the following members: Jim Helby, S&T/H; Dr. Robert Black, Chairman, Department of International Health, Johns Hopkins School of Hygiene and Public Health; Dr. Michael Levine, Professor of Medicine, University of Maryland School of Medicine; Dr. Gerald Feusch, Professor of Medicine, Chief, Geographic Medicine, Tufts University School of Medicine; and Dr. Peter Funstadter, Research Institute for Health Sciences, Chiang Mai University, Thailand.

In May, the team members will receive briefing materials, including the Cooperative Agreement, the 1981 Evaluation of ICDDR,B, S&T/H 1984 Trip Report and attachments, the January 1986 ICDDR,B Report to A.I.D., the November 1985 Board Recommendations and other relevant documents by mail. These documents should be reviewed in advance of the field visit to Bangladesh.

The field visit is scheduled for the two week period between May 24 and June 7 due to scheduling conflicts of the consultants. Two members of the evaluation team (Helby, Levine) will arrive in Bangladesh on May 24 to begin the evaluation of the center.

The others (Black, Feusch, Funstadter) will begin the evaluation the following week. A short briefing by AID and the staff of the Center will take place upon arrival of the team members and the remainder of the time will be spent by the evaluation team reviewing the facilities, meeting with the administrators and staff, and continuing with their own specific inquiries, interview, reading and assessment of projects and activities. The final report of the AID Evaluation Team will be submitted to

the Agency Director for Health by June 16, 1986 so that it can be made available for review by the Board of Directors Meeting at ICDDR, B scheduled for the end of June.

4. Major Area to be Addressed in the Scientific program component:

1. Areas of research. Has the centre selected the most appropriate research topics given its location and resources, both human and physical? Is this research the most appropriate for the centre in the long term?
2. Quality of research. Each evaluator will be responsible for a number of projects for intensive review. Examples of the questions which might be asked in such a review: Are the protocols well prepared? Is the project well documented? Is the project well executed? Is there systematic reliability checking? Are the results published in peer reviewed journals? Of what quality are the results?
3. Research review process. How are institutional research priorities set? How are proposals adopted and decisions made about utilization of resources?

On the basis of its assessment, the evaluation team will prepare a report for A.I.D. outlining its recommendations for modifications and future support for ICDDR,B. The final document will be divided into three sections:

1. Research review. Each team member will be responsible for a specific area of research. Dr. Black will be responsible for an evaluation of the activities taking place at the Matlab Field Station and recommendations for future activities, including an evaluation of the oral cholera vaccine field trials. Dr. Levine will be responsible for the review of laboratory activities undertaken in Dhaka, including research in immunology and vaccine development. Dr. Keusch will be responsible for the review of the clinical research program, including cereal-based ORS research. Dr. Kunstadter will be responsible for an evaluation of health services delivery and operations research, including the Community Research Division and the Urban Volunteers Program.

2. Implementation of Board of Trustees recommendations. The AID member of the evaluation team will be responsible for this section, as well as for an evaluation of donor coordination and the impact of targeted research.
3. Recommendations to AID on specific research to be supported.

Appendix II

Dr. Robert E. Black's Evaluation

I. Introduction

An initial interview was held with Dr. Roger Eeckels, Director of ICDDR,B. Subsequent discussions were held with the heads of the Disease Transmission Working Group, the Community Services Working Group, and the Host Defenses Working Group. Further discussions were held with investigators and senior staff members of ICDDR,B.

An extensive set of documents was provided by the working group leaders and investigators, including statements of objectives of the working groups, annual reports, study protocols, and reprints of recent publications. These were carefully reviewed in Dhaka and subsequently.

A visit was made to the Matlab Field Station for discussions on the cholera vaccine field trial and other studies in progress or planned. Brief visits were also made to the Microbiology and Immunology Laboratories and Computer facilities in Dhaka.

II. Scope of Current or Proposed Research

A. Matlab

1. Cholera Vaccine Field Trial.

Parenteral vaccination against cholera has provided insufficient protection; however, a new generation of oral vaccines, which stimulate intestinal immunity, are now available for testing. Oral vaccines consisting of killed *Vibrio cholerae*, either with or without the B subunit of cholera toxin, have yielded promising results in stimulating an appropriate immune response and in protecting North American volunteers against disease. These vaccines, which are completely non-reactogenic, were considered appropriate for a vaccine efficacy trial in Matlab.

In preparation for the efficacy trial, the Matlab census was updated in the latter half of 1984. A vaccine pretest in September to December, 1984, demonstrated that the vaccine and placebo lots prepared for the field trial were both immunogenic. Approximately 1200 subjects (males and females aged 2-15 years and females over 15 years) participated in the study.

The major project in Matlab during 1985 began in January with the cholera efficacy study. The two vaccines evaluated consisted of killed V. cholerae in combination with the B subunit of cholera toxin and killed V. cholerae alone without the B subunit. These vaccines were studied in a randomized placebo-controlled (killed K12 Escherichia coli) trial in which vaccines or placebo were given at 6-week intervals. Of 124,000 persons eligible to participate (males and females aged 2-15 years and females over 15 years residing in the Matlab surveillance area), approximately 90,000 took at least one dose. Of these individuals, approximately 65,000 completed all three doses of their assigned vaccine or placebo. Vaccine efficacy is being evaluated both by passive surveillance for cholera at the Matlab treatment centers and by active surveillance by means of family studies in neighborhoods of at least one known case of cholera.

The efficacy of the vaccines has been assessed to date for the first 6 months after vaccination using the passive surveillance data. For this period it was determined that the combination killed vibrio-B subunit vaccine had an 85% protective efficacy and the killed vibrio-alone vaccine had a 58% efficacy.

The vaccine efficacy trial appears to have been well planned and executed. Particular attention was paid to preparations in Matlab, to methods of randomization of the vaccines, and to careful administration of the vaccines in the village. Appropriate attention is now being paid to the passive and active surveillance activities which will be necessary to evaluate vaccine efficacy.

The investigators and the experienced staff of Matlab are to be commended on the planning and execution of the field trial. It may be a landmark study, not only for the results that it yields, but also for the careful methodology applied. The trial was not without its problems, however. It has been for 1985 and much of 1986 a massive undertaking, placing extensive demands on the personnel resources of Matlab and of ICDDR,B. As a result, few other epidemiologic or health services research studies were possible during this time period. The trial also faced serious political problems, both in Matlab and in Dhaka. Although there appears to be no question that the trial was ethically conducted, questions were raised that caused serious, but transient problems. There is also no question that relations with the population of the Matlab field surveillance area have been strained by the vaccine trial. ICDDR,B will need to be cautious in regard to initiating new large-scale vaccine field trials in this area for at least the next several years. At the moment, it does not appear that the relations have been so strained as to jeopardize the completion of the field trial or of other ongoing or planned projects in Matlab.

The field trial will also address a number of other related questions. First, the efficacy of the vaccine against a number of other diarrheal agents will be evaluated. Using passive and active (family studies) surveillance, the efficacy of the two vaccines against enterotoxigenic E. coli will be determined. Using passive surveillance, the efficacy against non-cholera Vibrionaceae diarrhea will be determined, as will the total impact of the vaccines on hospitalizable diarrhea and mortality in the field area. Furthermore, vaccine efficacy via passive transfer of breastmilk containing antibodies against V. cholerae and enterotoxigenic E. coli will be determined in breastfed children. Numerous other analyses in regard to immune and non-immune risk factors for vaccine failures are anticipated.

The field trial also provides an opportunity to conduct numerous other descriptive studies of the epidemiology of diarrheal diseases. These studies can evaluate the role of risk factors, such as ABO blood group, breastfeeding, pregnancy, nutritional status, and immune correlates of protection. Many of these studies are important and it was appropriate to take the opportunity of the vaccine trial to carry them out. On the other hand, all of these studies are purely descriptive and it will be necessary to think of ways in which these results can be used to intervene to prevent diarrheal morbidity or mortality.

2. Mortality Studies.

The Matlab Demographic Surveillance System (DSS) has been operating for twenty years. Currently, monitoring of demographic events is under way in a population of approximately 195,000. Although it is not my task to review in detail the DSS, it is appropriate to mention some aspects related to mortality. Accurate mortality and cause of death information for Matlab is highly desirable, since it would then be possible to evaluate the effect of health services or other epidemiologic interventions on child survival.

The DSS has continued to provide reasonably accurate information on total and age-specific mortalities. However, until recently the "cause of death" information collected by DSS was almost entirely useless. Some recent attempts have been made to improve this aspect of data collection and the registration forms for death have been modified. A comparison was recently performed of the DSS cause of death information vs. a more detailed "verbal autopsy" done on infants who died in the last two years. Although the "verbal autopsy" approach provided more plausible information on the causes of death of infants than DSS, this study was questionable in that information was sought on deaths that occurred approximately 2 years prior to the interview. Current attempts to collect more detailed and open-ended information on the events preceding death and to classify

the cause of death by a panel of physicians may partially correct the flaws associated with this aspect of data collection in the DSS. However, it will be necessary to move quickly to more systematic questioning and to the development of algorithms and definitions of appropriate causes of death. Furthermore, it would be preferred if the classification of cause of death were done by individuals who are not part of the delivery of health services in Matlab. The determination of cause of death by individuals may be unavoidably biased by their intimate involvement with service delivery.

A review of trends in mortality in Matlab reveals interesting, if disturbing aspects. First, since 1982 the post-neonatal and childhood (1-4 years) mortality rates have been increasing. Second, it appears that a substantial number of childhood deaths are still associated with diarrhea of some kind. Neither of these observations are the focus of current study, although both would seem high priority topics for research.

3. Measles Immunization

A study was undertaken to assess the impact of measles immunization on diarrheal morbidity and growth in Matlab. The study has now been completed but could not be reviewed in detail, since the principal investigator is currently on study-leave outside of Bangladesh.

4. Environmental Microbiology

There is an approved proposal to study the seasonal distribution of zooplankton and phytoplankton and the physical and chemical parameters of water in regard to the survival and transmission of *V. cholerae*. The area is worthy of study; however, the research proposal is not well put together. It has a number of specific aims which are entirely descriptive and does not really propose to test any specific hypothesis. Without proposing hypotheses, it is difficult to discern if the methodology is adequate to test it. In this case the investigator appears to be well trained and highly motivated and may be in need of some assistance to appropriately design a study that can critically evaluate a specific hypothesis.

B. Dhaka

1. Dhaka Hospital Treatment Centre Surveillance.

A systematic 41 sample of all patients coming to the Dhaka Treatment Centre continues to serve as an etiologic and epidemiologic surveillance system. Although this surveillance system has been used effectively in the past for descriptive clinical epidemiological studies, it appears now to be under-

utilized for descriptive or more innovative uses. An exception to this is a recent study evaluating the determinants of the severity of shigellosis which was methodologically extremely well done and provided useful information on an important cause of severe diarrhea and death.

2. Clostridium difficile

I was provided with an approved research protocol for a study which is awaiting funding. The study plans to determine the frequency of isolation of C. difficile in diarrheal specimens, the toxigenicity of the isolates and the presence of antibody to C. difficile toxin in serum. This proposal seems to be reasonably well put together; however, the priority appears to be low. There have been previous evaluations of the importance of C. difficile in Bangladesh and the organism does not appear to be a major contributor to morbidity or mortality.

3. Vitamin A

A study has recently been initiated to evaluate the impact of vitamin A supplementation on diarrheal and respiratory morbidity, nutrition and skin infection. It is planned that 50 children, each between the ages of 1-6 months of age, will be randomized to one of three groups. In one group the child will receive vitamin A supplementation and in the second group the child and the lactating mother will receive vitamin A. The third group will receive a placebo. Although the interaction of vitamin A and infectious disease morbidity is a priority area for research, this study seems to be flawed to the point that it is questionable that useful information will be derived. One would question in particular the age group of the study participants, the size of the sample, the inability to evaluate severity within specific etiologies of diarrhea, and the inability to control for multiple confounding variables in the analysis.

4. Village Volunteerism Program (VVP)

The VVP is a neighborhood service delivery system in which female volunteers provide basic childhood interventions. The volunteers are trained and visited weekly by a paid supervisor. Services are currently directed toward diarrheal treatment, immunizations, vitamin A, and family planning. The VVP has provided the setting for several primary health care research projects. Although a service program, the research aspect is innovative and important. Indeed, many would say the most relevant research questions come from attempts to deal with disease problems and to deliver health services.

The research output of the VVP has been high. Furthermore, the approach taken in the VVP seems to be unique at ICDDR,B and may well serve as a model for future research activities more

broadly. The research strategy is characterized by pursuing an entire continuum of epidemiologic and operational studies until a useful intervention or service can be implemented. The ability of the UVP investigators to progress from simple observations to quantified descriptions to evaluations of innovative interventions to application of this knowledge in the delivery of services is commendable. The fact that this could be done in the space of little more than one year is truly remarkable. It is a common and unfortunate observation that many other important findings at ICDDR,B have been dropped before it is understood how they can be or should be implemented.

C. Other

1. Epidemic Control Preparedness Programme

The Epidemic Control Preparedness Programme has the responsibility of investigating and coordinating assistance to areas of epidemics or natural disasters. It is not entirely clear why this activity is within ICDDR,B when it would appear to be more appropriate to be housed in the Ministry of Health. There is clearly value to Bangladesh from systematic investigations and efforts to provide appropriate treatment and other relief services. There may be value as well in regard to what could be learned from a good epidemiologic investigation of the situations. Unfortunately, at this point the investigations lack sufficient understanding of epidemiologic methods and study design to make them scientifically or even practically of much use. In the long term, it would seem preferable if this activity were within the Ministry of Health with specific epidemiologic consultation provided by ICDDR,B.

III. REVIEW OF SCIENTIFIC PROGRAMME

A. Areas of Research

In the past ICDDR,B has had five scientific working groups, each of which set its own priorities. The resulting research was across a very broad range and lacked focus even within working groups. To date, the research agenda of ICDDR,B has been largely the summation of the interests of individual investigators. Since many of these investigators come to Bangladesh for only a short period, the research has suffered from a lack of continuity and focus. Even more important, many of the significant findings have not been pursued to a logical conclusion.

If one looks at appropriate research for ICDDR,B as a continuum going from the most descriptive etiologic and epidemiologic studies to development and testing of specific hypotheses or interventions to operations research related to implementation of those interventions or services, we would characterize the research agenda of ICDDR,B as having fallen far short of success. The bulk of work at the centre has been in the initial descriptive phases. Even in situations in which specific interventions have been evaluated and demonstrated to be efficacious (e.g., hand washing to reduce diarrhea or feeding during diarrhea to reduce malnutrition), these interventions are rarely studied further in the context of service delivery programs.

A great volume of descriptive epidemiologic studies have been completed in Bangladesh. The challenge at this point is to collect and synthesize that information and to formulate interventions. These interventions must be rigorously evaluated in field studies and, when successful, incorporated into service delivery programs to determine their ultimate role. Important areas for future research, building on the base of already existing information, would be the following:

- impact of improved weaning foods on diarrhea morbidity and mortality and on the growth of children;
- implementation of personal and domestic hygiene education in the primary health care program;
- effect of low birth weight on diarrheal morbidity and mortality;
- effect of feeding during diarrhea on diarrheal severity, growth and mortality (in community-based studies);
- the determinants of life-threatening diarrhea, including both watery and invasive diarrheas;
- the determinants and prevention of persistent diarrhea (in community-based studies).

B. Quality of Research

The quality of research at ICDDR,B is highly variable. The major epidemiologic studies, including the cholera vaccine trial and studies within the Urban Volunteers Programme, appear to be of excellent quality. However, other areas, such as studies of the determinants of mortality in Matlab and of vitamin A appear to be of questionable quality.

C. Research Review Process

The current working groups have not served their intended purpose. It would appear necessary to establish an alternative structure which facilitated, rather than inhibited, scientific dialogue, and permitted more rational establishment of focussed research priorities.

D. Research Selection Process

In the last several years the research agenda of ICDDR,B has been diffuse and of marginal priority. It is clear that the Research Review Committee and Board of Trustees must share the blame with the scientific program heads and investigators. Better scientific leadership and guidance will be needed to establish a more productive research agenda.

VI. RECOMMENDATIONS FOR AID FUNDING

A. Cholera Vaccine Trial

It is clear that continued passive surveillance to determine longer term efficacy of the cholera vaccines will be justified under almost any circumstances. In addition, a great deal can be gained from continued laboratory testing of specimens derived from the field trial and of analyses of field trial related data. At the same time, this component of the research must not continue to dominate the epidemiologic studies, thereby providing resources so that the Centre is able to initiate an important new research agenda.

B. Causes and Determinants of Remaining Diarrhea-Associated Deaths

It is clear that diarrhea continues to play a role in malnutrition and in mortality in Matlab. The reasons for this are unclear and are in urgent need of further study. Of particular interest here may be the so-called prolonged diarrhea. These episodes, which appear to begin as acute watery or dysenteric diarrheal episodes, persist for unusually long times and appear to be associated with a substantial effect on growth

and mortality. The underlying risk factors and determinants of these illnesses and of the resultant mortality must be more clearly understood. A component of these prolonged diarrheas, but also perhaps important in its own right, is invasive diarrhea. The most important etiologic agent of invasive diarrhea is *Shigella* and recent epidemics of antibiotic resistant *S. dysenteriae* type 1 have posed particular problems. Epidemiologic studies of *Shigella* could focus on transmission and means of control. Related health services research questions might address a simple means of identifying episodes requiring antibiotic treatment and the use of such interventions by community health workers.

C. Environmental Microbiology

Additional work would appear justified on the possible role of environmental reservoirs of *V. cholerae* and the factors influencing transmission of the organism. Although probably not requiring a great amount of resources, these studies should be accorded priority due to their possibility for providing new insights into cholera in endemic and epidemic settings.

D. Other

Other suggestions by ICDDR,B investigators of possible priority areas for AID funding included the development of rapid diagnostic tests and the epidemiology of newly recognized agents of diarrhea. Each of these areas may, in a specific instance, be of sufficient importance to merit study. However, these topics are not of such high priority to merit a comprehensive and long-term research program. It would be anticipated that these areas might be studied in regard to priority research areas mentioned above.

LIST OF PERSONS INTERVIEWED

ICDDR,B

R. Eeckels
M.R. Bashir
M.G.M. Rowland
K.M.S. Aziz
D.A. Sack
I. Ciznar

M. Bennis
Q.S. Ahmed
S.Q. Akhter
J.D. Clemens
A. Huq
M.U. Khan
K.A. Monsur
M.S. Huda
J. Chakraborty
B. Stanton
B. Wojtyniak
Md. Yunus
J. Harris
A. Briand
B. Wroot
B. Kay

Shishu Hospital

M.S. Akbar
H.Z. Khan

Appendix III

Dr. Gerald Keusch's Evaluation

I. Summary of Evaluation and Recommendations

A. Summary of Evaluation

1. Changes in actual functioning of ICDDR,B in response to prior evaluations, recommendations, and resolutions of the Board of Trustees appear to be inadequate in speed and scope.

2. The quality of clinical investigation at ICDDR,B varies considerably from modest and derivative to creative and interesting.

3. Improved performance depends upon recruitment of new key personnel at two levels: (1) experienced and scientific leaders, and (2) proven young "hands-on" investigators.

4. The director of ICDDR,B cannot address problems effectively because of hiring freeze (financial crisis) and issues arising from dual personnel structure (international and national level positions).

5. Lack of discretionary funds for Director's use for institutional development paralyzes action.

6. The scientific working group structure is not suited to current scientific needs of centre.

7. Administration and management (e.g. personnel, finance, resource development) are perceived by many scientific staff as functioning autonomously with inadequate concern/understanding for scientific agenda of the centre.

B. Recommendations

1. Prepare a summary of prior external evaluations and resolutions of Board of Trustees with resume of action taken and impact to date.

2. Address issues of personnel structure resulting from dual track system. A single track with flexible salary range for each level may be possible and more effective in practice.

3. Assure that administration functions to support scientific goals of centre. Improved communication between scientists and administrative personnel is needed.

4. Develop procedural rules appropriate to the centre and its activities. The use of WHO regulations in some situations appears to be inconsistent with ICDDR,B needs.

5. With respect to clinical research, there are three separate clinical functions, each of which requires an individual leader. These are: hospital services, metabolic ward, and clinical study unit. Three qualified candidates are presently at the centre, however unless the centre can act quickly it may not retain the services of some of these individuals.

6. Clearly describe the research goals of the centre in both general and specific terms, using outside assistance as necessary, and insure that the scientific staff understands these goals and can describe them to visitors, evaluators, potential donor agencies.

7. Unfreeze hiring in order to recruit new personnel to carry out the research deemed appropriate to fulfill the research goals of ICDDR,B as defined.

8. Streamline research protocol development system. This should be a responsibility of the individual Principal Investigator and the leader of the research area in which the PI works. The current Research Review Committee should be unnecessary and probably contributes to fragmented protocols.

9. Establish a system of direct submission of projects to potential funding agencies to the greatest extent possible. Resource Development should identify potential sources of support and be the interface to bring the scientists in contact with the donor agencies. Resource Development is not qualified to present the science or attempt to "sell" it.

10. Recruit an editor to assist in the preparation of proposals, with adequate Word Processing equipment to insure the quality of the presentation.

11. Review Ethical Review Committee in the context of its composition, definitions of ethical principles and guidelines for review of proposals. This committee would appear to need additional clinical expertise in order to function adequately to deal with the complex protocols necessary if the centre is to make

progress in understanding mechanisms and treatment of the severe and often fatal invasive and chronic diarrheas. The committee needs balanced representation of nationals and expatriates.

II. Introduction

ICDDR,B is an internationally recognized research centre. However, past external evaluations have consistently highlighted the lack of a clearly stated and implemented research strategy, as evidenced by the inability of the scientific staff to describe this strategy in detail. In addition, such reviews generally note the variable quality of the research, at least during the recent period of great expansion of budget, personnel and scope of work. For the past two years, and particularly since November 1985, the centre has been under extreme stress due to the recognition of the financial plight of the institution and the measures taken to address this problem. As a result of the action of the Board of Trustees in late 1985, the newly appointed Director, Prof. Eeckels, has had little opportunity and even less resources to address the above criticisms of the ICDDR,B.

The decision not to renew the contracts of a number of senior Bangladeshi personnel has virtually abolished the national presence at the higher scientific levels of the centre. This has had major political repercussions in the community at large. Although neither the necessity for these actions nor their legitimacy is being questioned by the reviewer (indeed, these are well beyond the scope of the review requested), they do impact on the actual conduct of research at the ICDDR,B and cannot be dismissed. These issues will need to be addressed and successfully overcome if scientific progress is to be made.

It should be noted that the organization of the hospital service and the quality of care provided has improved since the August 1984 report. The microbiology laboratory has been extensively reorganized and upgraded. The ability of the laboratory to provide accurate results with a shortened turn around time is to be praised. The centre has also made important links with the Dhaka Shishu Hospital, which is providing pediatric consultation and training to ICDDR,B Medical Officers. Prof. Eeckels is to be praised for his efforts to accomplish this. In a negative sense, the promising pathology laboratory established by PTMG under Dr. Butler has not survived and the current efforts to revive this service will clearly need a trained clinical pathologist.

III. Evaluation

A. Areas of Research

ICDDR,B is slowly moving its priority areas of clinical research to topics repeatedly suggested by previous external evaluators and by some scientific staff members, eg invasive diarrheas (especially shigellosis) and chronic diarrhea. A review of the protocols of the centre reveals three categories of relevant clinical investigations as follows:

1. Microbial virulence attributes - largely in vitro and/or animal model experiments;

- a) Immunogenicity of oral B subunit/whole cell cholera vaccine (Ciznar)
- b) Characterization of the *V. parahaemolyticus* isolated from clinical cases and environment (Huq);
- c) Evaluation of the use of phage pattern as an identification marker to followup *E. coli* cases (Monsur);
- d) Plasmid profile analysis of epidemic *Shigella dysenteriae* type 1 strains (Haider);
- e) Isolation of temperature-sensitive mutants of *Shigella dysenteriae* 1 and evaluation of their colonization and protective potential in adult rabbits (Ahmed);
- f) Antigenic composition of outer membrane components of *Shigella dysenteriae* (Haider);

2. Evaluation of etiology, host status, or complications - descriptive and/or mechanistic studies in patients

- a) Magnesium breath-hydrogen test for the estimation of gastric acid production in adult Bangladeshi volunteers (Rabbani);
- b) Studies on the incidence of an anaerobic bacterium, *Clostridium difficile* causing diarrhea in Bangladesh (Akhtar);
- c) Rapid diagnosis of shigellosis by coagglutination technique by detecting *Shigella* O antigen in stool in suspected shigellosis (Rahman);
- d) The role of prostacycline in the development of hemolytic-uremic syndrome in acute shigellosis (Alam);
- e) Biochemical basis of hypoglycemic syndrome with high mortality associated diarrhea (Alam, Akbar);

- f) Role of endogenous prostaglandins in secretory diarrhea (van Loon);
- g) Evaluation of Chlamydia trachomatis as a possible diarrheal pathogen (Bennish);
- h) Typhoid fever: determination of cAMP and prostaglandin production during diarrhea and comparative field trial with chloramphenicol and ceftriaxone (Khanam);
- i) Hyponatremia in shigella infections (van Loon);
- j) Role of endogenous prostaglandins in E. coli secretory diarrhea (van Loon);
- k) Gastric emptying of a rice-powder electrolyte solution and sucrose electrolyte solution in adult patients with acute diarrhea (Molla);
- l) Pathological studies of fatal complication of childhood diarrheal disease (Eeckels);
- m) Enteric protein loss in childhood diarrhea (Alam);
- n) Prevalence and mechanism of hypoglycemia in association with diarrhoea (Bennish); and

3. Evaluation of therapeutic interventions - outcome studies of either ORS or antimicrobial agents

- a) Efficacy of different cereal based ORS in the treatment of acute diarrhoea (Molla);
- b) Clinical trial of plantain-based ORS in the treatment of acute diarrhoea in children (Molla);
- c) Comparison of efficacy and digestibility of plantain-salt and rice-salt as home made fluid with standard glucose ORS (Molla);
- d) Oral rehydration therapy with alanine-glucose ORS: A controlled clinical trial (Patra);
- e) Single dose furazolidone in cholera (Islam/Rabbani);
- f) Double blind controlled clinical trial with Bioflorin in management of acute diarrhoea in Bangladesh (Mitra);
- g) Double blind randomized trial of naladixic acid and ampicillin in the treatment of childhood shigellosis (Salas);
- h) Single dose doxycycline in the treatment of cholera (Alam); and
- i) Double blind randomized trial of ciprofloxacin and ampicillin in the treatment of shigellosis (Salas).

Thus, only 9 out of 29 protocols are directly or primarily concerned with shigella infections, and none are targeted to chronic diarrhea. Not all of these studies are active: some never got underway, some are sluggishly moving along, and some are quite

active. In discussions with various investigators, it is clear that several additional protocols are in the development stage and should be mentioned. These include the assay of shigella toxin in clinical specimens using an ELISA method (initial pilot studies are underway), risk predictions and mechanisms of HUS, cause and management of toxic megacolon in shigellosis, and CNS complications of shigellosis. The preliminary steps in the development of these protocols are evidence that the clinical investigators of the ICDDR,B are beginning to address new priority areas for research. Indeed, one may state that the identification of clinical issues for study based on clinical observations is the most fundamental requirement for clinical investigation. It means that the clinical group is doing its job well in this regard.

An emphasis on clinical studies at ICDDR,B is appropriate, since this centre sees an enormous number of patients with diverse etiology of illness. This is not simply academic, for patients are often severely ill and there is a continuing associated mortality. The slow increase in the number of protocols dealing with shigellosis represents a step in the right direction, but it is legitimate to question why it has taken so long to accomplish this and why there is still a lack of protocols to investigate chronic diarrhea etiology, mechanism and consequences. To this reviewer, these findings are indicative of organizational deficits at ICDDR,B. There has not been a well functioning mechanism to plan clinical studies for at least two years, a situation that was evident during the review of the Pathogenesis and Therapy Working Group (PTWG) in August 1984. With the subsequent departure of Dr. Butler, head of the PTWG, no new initiative has been taken to correct the situation. In particular, there seems to be no organized way for the clinical investigators to meet to define critical questions and methods appropriate to answer these questions. They are thus left to act in an individual fashion, and it is no wonder that there is no clearly thought out program of research, as well as a multiplicity of sometimes duplicative protocols. There is no doubt that the dual priority of invasive and chronic diarrhea for quantitative and mechanistic studies of individual patients is a proper decision, and a decision of major importance to future field and intervention activities of the ICDDR,B. There is so little known at this time about mechanisms of and host responses in invasive and chronic diarrhea that it is not possible to define rational interventions for clinical trial. The ability to observe the diseases at first hand, to construct hypotheses, and to conduct clinical studies is a major and laudable strength of ICDDR,B.

B. Quality of Research

Despite some steady productivity, the quality of the overall research effort described above is not satisfactory. This may be discerned from the publication citations, which do not include the most respected and demanding clinical and scientific journals,

for example, the Journal of Clinical Investigation, New England Journal of Medicine, Journal of Experimental Medicine, Science, Nature etc. To be fair, as noted above, the present group of clinical investigators has identified subjects for study of immense importance. They have not yet had the ability, however, to ask penetrating questions or to design studies that may provide new insights. The group needs additional specialized expertise to do this, for example, in renal physiology and electrolyte balance to address the problems of the HUS and the hyponatremia of shigellosis, hematology, and, in particular, the regulation of granulocytogenesis to study the leukemoid reaction, and neurophysiology and appropriate evaluation methodologies to study the central nervous system complications of shigellosis. The ICDDR,B either needs expert consultants or additional staff in these areas, and probably both, to make significant progress in the near future. Similar comments can be made about the problem of chronic diarrhea, where the research priority is high but the ideas are not obvious.

Protocols are flawed. They are not clear expositions of the background leading to the logical generation of a testable hypothesis, and as a result, the questions to be investigated are not clearly defined. Of major importance, the possible results and the implications of each possibility for advancing the research are almost never considered. There is no thought of where the answer to the narrow question being asked will lead to. The protocols are then battered about by a research committee that makes a variety of demands that often do not make sense but are generally acted upon by insertion of additions to the original. It is no wonder that by the time the protocol passes to the Ethical Review Committee, it may be a disjointed, incoherent shadow of the original idea of the investigator.

Although the reviewer did not have an opportunity to evaluate the functioning of the Ethical Review Committee, the investigators convey the impression that this committee meddles in the science, and that their ethical judgements do not consider the relevance of the study in the context of the magnitude of the problem. In particular, the Committee appears invariably to equate "invasive" methods with unethical methods. In part, this may be due to the lack of clarity of the written protocol and the failure to make a case for the question being posed or the method to be employed. In part, it appears to be an inherent problem of the committee, and for this reason, the reviewer has suggested that the Ethical Review Committee guidelines be reviewed, however it is also obvious that the quality of the proposals themselves needs to be improved.

The involvement of various investigators in approved and funded studies differs with the investigator and the demands of the protocol. Under the system initiated at the hospital by Dr. Alam, patients are now selected by medical officers according to

predetermined criteria and are entered into the studies actively underway. In some protocols, the study is carried out directly by the PI, while in other situations, the medical officers are involved. Fortunately, the latter group, in particular the senior medical officers, appear to be competent, careful, and involved. Monitoring the data for completeness and reliability is the responsibility of the PI. There is no systematic way to monitor this. Data analysis is also the individual responsibility of the PI. While data may be sent over to the Computer Branch for analysis, increasing use of PC's for data storage and analysis is a good trend at the ICDDR,B. The PI thus has direct control over the information and can obtain timely analysis during the course of a project.

C. Research Review Process

There appear to be several ways in which protocols are developed among the clinical investigators. In some notable instances, ideas have been generated by direct patient observation and the realization that a real clinical phenomenon was occurring. In other circumstances, discussions within the group or perhaps more commonly with visitors have spawned new research ideas. Some of the protocols in operation have been "commissioned" by outside agencies, are derivatives of previous studies of some value but minimal new creativity, or are minor alterations in drug selection, dosage or delivery. There does not, however, seem to be a systematic way to consider clinical problems in a fashion conducive to generating new ideas.

The comment is repeatedly heard that the fora for scientific discussions among the clinical investigators are inadequate. This was true of the PTWG 2 years ago, and it remains true today, although it must be stated that the clinical conferences are being held on a regular basis and with ample discussion. But there is at present no division head for clinical investigation, as the PTWG and NWG (Nutrition Working Group) are both without a director. Certain members of the Board have attempted to stimulate research activities. None of these members are clinicians, however, and their view of important clinical research is therefore somewhat limited. One is left with the impression that a critical thinking mass could be obtained with a few new clinical appointments and a better organization of present talents.

The review process has been commented upon above. It should be noted that the generation of protocols at ICDDR,B is commonly seen as a primary process, an end in itself, instead of the natural result of the generation of testable hypotheses. The internal review progresses from formal reviews within the working groups to a formal ICDDR,B Research Committee. Protocols appear to be patched to conform to the various suggestions that are made, resulting in some awkwardly written proposals.

It is the opinion of the reviewer that this process is not functioning well. The working group structure, in particular, does not foster the needed interactions among the clinical investigators to develop creditable proposals. The clinical investigators need to be in better contact with one another, perhaps by reorganizing a clinical investigation unit, possibly subdivided by subject of interest (eg invasive diarrhea). By organizing the clinical services to deal interactively with both clinical care and clinical investigation, new and important ideas may be generated and translated into grant proposals.

The final form and scientific content of the protocol, however, should be the judgement of the investigator and the program head, subject to the approval of the ethics committee. A committee cannot be expected to write a creditable proposal. In the end, scientific quality will be judged by the review process of the donor. It is for this reason that the presentation of research ideas to funding agencies without scientific review processes of their own requires that ICDDR,B scientists make the presentation within a well conceived framework of scientific goals and specific steps for their achievement.

D. Research Selection Process

Relevant comments have already been made above. There has not been a systematic mechanism to do this. Conflicting inputs have come from outside visitors to ICDDR,B, the Board of Trustees, local outside scientists, and most importantly, donor agencies. The shift to targeted funding has not yet had a salutary effect on the process, indeed it may be inimical to the necessary progress. As emphasized above, ICDDR,B must develop its own carefully crafted agenda of research goals and present a set of integrated specific research studies designed to reach these goals.

In some sense, if the system is working, the donors will be asked to pick from the menu to suit their particular tastes. Thus it is clear that the donors must find a way to work together. In the case of AID, and the suggestion that ICDDR,B needs institutional collaborators, a major improvement in the quality of the work in Dhaka and its relevance to AID health strategy will follow when such support is provided. For the centre, this would best be in the form of direct secondment of personnel from a U.S. institution, particularly when the specific talents of the individual are targeted to a specific research question of relevance to the overall scientific strategy of the ICDDR,B.

IV. Conclusions

As long as diarrhoeal diseases remain a leading cause of morbidity and mortality in the third world AID will need the kind of information that can be provided by ICDDR-B to shape AID's

health policy. ICDDR-B maintains within a single institution a range of expertise and the capability to carry out diverse investigations from laboratory to patient to population. It is axiomatic that such an environment increases the likelihood of productive and relevant research. Therefore, not only is it of value for AID to support ICDDR-B, it is also imperative to insure that it functions well.

There are deficits in the ICDDR-B, however, that limit its utility. Some are at an institutional level, including managerial issues, and some are at the scientific level. These deficits are not fatal flaws -- they are correctable. The new director, Prof. Roger Eckels, appears to grasp the nature of the problems. With necessary outside assistance and minimal outside interference, he should be able to move the institute in a better direction. He demonstrates a strong but understanding character, and an ability to maintain a course while under heavy fire. He deserves the committed support of AID and the opportunity to use his discretion to effect the desired changes.

V. Recommendations

A. Clarification of Research Goals

It is now more widely acknowledged by ICDDR-B that the old cholera lab days are over -- in this case meaning that invasive and chronic diarrheas have become critical research issues. This is appropriate, given the unresolved clinical problems being seen in the hospital and field. The ICDDR-B must now clearly define these goals by expanding the statement with short descriptions of the specific research questions to be given emphasis.

These should be formulated by ICDDR-B personnel, in some cases with expert consultant help. An organized program to attack these questions is essential, with fewer protocols and more focused collaborative research among centre staff. The formulation of the specific work program will highlight identification of skills required and thus direct recruitment. This recommendation has been made before without adequate response and should be considered to be of the highest priority.

B. Reorganization of Structure

The international vs. national level scale has only served to divide the ICDDR-B and has not improved the quality of work. A new organization scheme is needed that will attract international investigators and keep local scientists at the centre. Salary levels should be set by many factors, including salary history, special needs (e.g. expenses due to temporary relocations), and responsibility of the job.

The needs for flexibility may be met by many mechanisms. One suggestion is to create a wide salary range for every category of position and remove the multiple steps within academic rank. Thus 2 individuals with the same academic rank can receive different salaries without broadcasting by detailed ranking. Such a system is used in many US universities where salary is set by the Department Chairman. This problem needs much thought but quick action, and the above suggestion is simply one model successfully used in some situations where the Director has sufficient authority.

A second category of problem results from adoption of other WHO practices as well. For example, the rule against husband-wife employment may be counterproductive and is certainly archaic in concept. It is very common now for married couples to be professionals working in related fields. No longer can the career of one spouse be ignored in consideration of the other's. To recruit the outside talent it needs, ICDDR-B will often need to face this problem. It may well be that a husband-wife team are qualified for positions at the centre. The rules should not preclude this. Neither should ICDDR-B create jobs for convenience -- if there is a position and the spouse qualifies, they should not be disqualified. The need is for flexibility and appropriate action.

A third area for reorganization is the scientific structure. This reviewer has not changed his opinion of two years ago that the working groups are not working. The ICDDR-B should be urged to reconsider how it functions and to make necessary changes. Only the clinical activities will be considered here, given this reviewer's assignment. The centre must do high quality clinical research because the mortality rate actually represents individuals who are dying with problems that cannot be defined at the population level. The ICDDR-B must maintain a hospital service to keep the flow of patients high enough to be able to select the problems for study.

To maintain the quality of general patient care and to improve the quality of the clinical research will need some redefinition of leadership and responsibility. The responsibility is broad enough to separate into three areas, each of which deserves a separate chief. The first is clearly the head of the clinical services of Dhaka hospital, with responsibility for functioning of both inpatient and outpatient services. The person filling the comparable job at Matlab should probably be responsible to the Dhaka chief.

Given the size and patient load, administrative support is warranted and should be provided in adequate fashion to permit the clinical director to attend to the clinical needs. The clinical research can be divided into two areas. The first is metabolic studies that require the use of a specialized metabolic ward.

This is a full time occupation and should have its own head. A separate clinical study unit is needed for other studies, including therapeutic trials and pathogenesis studies, and it deserves undivided attention and guidance. These three section heads could and should work together administratively and jointly be responsible and report directly to the ICDDR-B Director.

Incidentally, it should be noted for the record that the new hospital suffers from major functional deficits and structural problems that affect patient care and research. That this is the case is not only unfortunate, but is an indication of gross incompetency in its planning. While this is not the subject of this review, corrective physical alterations are clearly indicated, with major cost repercussions. It is not being suggested that AID necessarily take on this problem but that AID should consider renovations when needed for specific research programs or provision of adequate care.

C. Recruitment of Personnel

New people with specific skills and training will be needed to implement many of the defined research activities. At the outset, program leaders of high reputation and research productivity are critical to help attract younger people, and to guide them and to insure that they have an opportunity to flourish scientifically. The ICDDR-B must be perceived to be a helpful, supportive, and creative place to work if it is to be attractive. Although not without problems, institutional cooperative agreements with US sites may be the best way for AID to help provide the leadership talent necessary. There are no doubt many mechanisms to establish such linkages; it is important for AID that the centre needs the help that such linkages can provide to improve its research productivity.

D. Revise the Protocol Generation/Approval System

If the centre formulates its research goals clearly, reorganizes itself to foster the interaction of scientists of high quality, and is able to recruit such individuals, the responsibility for scientific validity of the proposal can easily become a responsibility of the investigator himself. Protocols reviewed and accepted by the program head can be sent directly for evaluation by an ethical review committee and approved protocols can be submitted for funding directly.

The current Research Review Committee system should be dropped because it wastes time, is counterproductive, and should be unnecessary in fact. However, it appears that the Ethical Review Process needs more attention. In particular, the ERC should rethink how it functions and clearly define the principles of ethics it upholds. To do this, the ERC needs more clinical

input, more balanced representation, and a concerted effort in insure that ethics and not politics guides its activity.

The goal must be to protect the individual and still promote research designed to improve individual and/or societal health. The line between ethical and unethical is not always clearly defined, and is often a matter of judgement. In these situations, the nature of the problem, its severity in mortality and sequelae must be considered, as well as urgency and availability and validity of alternative methods. Thus whether or not the composition of the LRC represents the necessary areas to judge these issues becomes of considerable importance to its ability to function.

VI. Evaluation Activities (chronological)

- 3 June: Arrival. Initial meeting with Prof. Eckels.
- 4 June: Visit to Matlab Station.
- 5 June: Visit to Shikha Hospital. Meeting with Dr. Akbar, Nalla Khan and staff. Interviews with ICDDR,B staff, including Drs. Alan, Bennis, Ballant, Harder, Van Loon, Fay.
- 6 June: Meeting of evaluation team (Black, Feusch, Kunstadter). Interviews with Drs. Howland and Sack.
- 7 June: Interviews with Drs. Molla, Van Loon, Bennis. Visit to Dhaka Station Hospital and ward rounds with Dr. Alan, Arad, Nath, and Bardhan. Debriefing session with Dr. Eckels and Dr. Kunstadter.
- 8 June: Interviews with Drs. Patra, Monsur, Akhter, Ehsan, Salam, Arad. Presentation of research seminar and discussion with staff. Debriefing session with Dr. Eckels.
- 9 June: Interview with Dr. Molla. Preparation of draft report.
- 10 June: Preparation of final report. Departure.

Appendix IV

Dr. Peter Kunstadter's Evaluation

I. Introduction

In carrying out this evaluation, I talked to a large number of people and read numerous reports and papers. I visited the Matlab Treatment Centre, with a brief trip to one of the community health stations, and visited four communities in the Urban Volunteer programme in Dhaka. Because of time constraints I was unable to visit areas covered by the MCH-FP Extension project.

II. General Comments and Recommendations

The following comments and recommendations refer to ICDDR,B in general. ICDDR,B is an important institution which has made important contributions to scientific knowledge and to the successful implementation of major interventions consistent with AID's health policy, e.g., in the areas of treatment of acute watery diarrheal diseases, testing cholera vaccines, developing and evaluating methods of providing low cost maternal and child health and family planning services, and development, testing, and implementation of appropriate health and family planning interventions in a community based service system. ICDDR,B provides a unique setting in a developing country with a longitudinally well documented high fertility and high mortality population. ICDDR,B has resources for further research and implementation in terms of its scientific staff, its large number of well trained, well organized, highly motivated, well supervised fieldworkers, and access to well documented study sites. These are resources which are highly relevant to studying and solving problems of high fertility and high mortality, and would be very expensive and time consuming to duplicate.

For these reasons AID should continue its support of ICDDR,B.

III. Lack of Clear Overall Plan or Strategy

Many ICDDR,B scientific staff members, including its current Director, Dr. Roger Leckels, have clear research agendas and a clear idea of where their plans fit into a larger picture of health, nutrition, and population problems in Bangladesh and in the developing world. Unfortunately, ICDDR,B as an institution appears to lack a clear plan or strategy, either in terms of its own development as an institution, or in terms of plans for scientific research. Apparently the lack of an institutional agenda was perceived by AID, and the recent switch from "core" funding to "targeted research" funding was an attempt to give some direction and to assure that the necessary resources for carrying

out specific tasks would be preserved. In general the topics selected by AID for support have been appropriate both to AID's health strategy and to the mandate of ICDDR,B, but this has not led to a systematic solution of ICDDR,B's institutional problems.

ICDDR,B is now suffering from a series of institutional problems and constraints many of which are symbolized but by no means confined to a financial crisis and the way in which it has been handled. These problems include:

1. Multiplicity of programmatic and administrative demands imposed by donor agencies in an uncoordinated fashion. These demands have led to intervention in personnel and program decisions which have weakened the ability of ICDDR,B to define its scientific and institutional goals during a time when funding patterns have changed and new basic personnel policies were introduced in association with financial conditions which have led, at least for the moment, to a major curtailment of funds.

2. Heavy dependence on short term expatriate personnel whose loyalties, careers, and interests are not necessarily congruent with the institutional needs of ICDDR,B. Such personnel have often been highly productive, but selection and recruitment have not always contributed to development of a coherent program of scientific research and implementation.

3. ICDDR,B is both an international and, in many sense (location, personnel, problem orientation, etc.), a Bangladeshi institution. No plan seems to exist concerning the way in which ICDDR,B should be developed within its Bangladesh setting. Only recently, and laudably, have specific efforts been made to collaborate with other research institutions in Bangladesh. Failure to arrive at some plan is associated with failure to develop plans regarding such essential matters as career paths for Bangladeshi staff.

4. Conflicts between basic science, applied research, and service.

In supporting ICDDR,B, AID and other donors should recognize and, to the extent possible, attempt to assist in alleviating these strains and constraints. Dr. Feckels has earned and deserves the support of AID and other donors in his attempts to cope with these problems.

IV. Institutional Linkages and Personnel Recruitment

Recruitment of highly qualified, strongly motivated personnel, and acquisition of appropriate scientific review and advice is a major institutional problem for ICDDR,B. In collaboration with other donors, AID should assist in the development of a series of linkages with centers of scientific excellence in fields relevant to ICDDR,B's areas of interest. Such linkages should be based on mutual interests and understanding, and should lead to the secondment of qualified staff to ICDDR,B. This system will greatly facilitate recruitment of needed personnel and will circumvent some of the problems the dual salary scale which now plagues ICDDR,B in many ways. Secondment agreements should also provide for periodic visits between the senior staff of ICDDR,B and the collaborating institutions and will result in an increase in informal training and in constructive scientific monitoring of ICDDR,B program.

V. Criteria for Evaluation of Specific Activities

A few remarks are necessary concerning the criteria I have used in reaching my judgments. By "appropriateness" I have taken to mean a consideration of need as defined by the volume of the problem in relation to other problems in Bangladesh and the developing world, the state of the art of intervention or of the available knowledge bearing on the topic and the special resources of the institution, including personnel and access to study populations, and the degree to which research appeared to cumulative.

The memorandum defining scope of work for this evaluation suggested publication in peer-reviewed internationally recognized journals as a measure of productivity. Clearly this is important as a measure of some kinds of scientific productivity, but it is not necessarily the only, or the most important criterion for other activities at ICDDR,B. The products of some activities of the Community Services Research Working Group (CSRWG), for example, are health care services delivered to various populations, and these should be judged according to standards of health care and demographic impact. Some essential products of the MCH-FP extension projects are in the form of development of methods for generating and processing data to manage MCH-FP services and measure their effectiveness - these data systems are themselves valuable products; other products include recommendations to the Government of Bangladesh; the Demographic Surveillance System (DSS) and the Sample Registration System (SRS) produce data in usable form, and one criterion to judge them is the extent to which those data are actually used.

Criteria used by AID in evaluating ICDDR,B and AID-supported projects at ICDDR,B should be appropriate to the tasks performed, and the setting within which they are performed. The process of project evaluation should begin when the project is proposed. Criteria which are to be used in evaluation should be stated and agreed upon when proposals are accepted by AID for support.

Criteria for judging the quality and productivity of AID funded project at ICDDR,B should include (though not necessarily simultaneously or for any single project): excellence and quantity of scientific research, as measured by publication in internationally recognized peer-reviewed journals or in peer-reviewed books; effective communication with scholars and policy makers concerned with the "applied" problems to which the project is addressed; influence on policies and practices related to the subject of the project; relevance to diseases or conditions of mandated interest to ICDDR,B (diarrheal diseases, nutrition, high fertility); relevance to diseases or processes of particular importance to AID's health strategy (including child survival, MCH and FP, use of appropriate technology in community based programs, widespread extension of services and benefit of research to economically disadvantaged populations), demonstrable beneficial effects on personal well-being and on relevant demographic measures in the population to which the project is addressed, relevance to the health and family planning interests of the Government of Bangladesh; strengthening of ICDDR,B as an institution.

V2. Coordination of Efforts of ICDDR,B and with Other Donor Agencies

AID should assist in the organization of regular meetings of donors. The donors should request from ICDDR,B a coherent plan of action, and should consider this as a package. Donors should consider that support for specific projects often implies strong "service" departments within ICDDR,B and that ICDDR,B needs stability and continuity of funding in order to implement a coherent plan and to function effectively.

AID should support the development of long lasting institutional collaborations of mutual benefit to ICDDR,B and to the collaborating institution. Collaborating institutions should be selected on the basis of their scientific excellence and their understanding of and sympathy with the long term goals of ICDDR,B. Collaborative relationships should include the supply of appropriate scientific personnel to ICDDR,B by secondment. Such personnel should be selected both on their scientific merit, and on the relevance of their skills and interests to long term goals of ICDDR,B. Mutual agreement on the goals should help to insure that adequate support services will be available for short term visiting scientists, that these scientists will contribute to the

overall program of ICDDR,B, and that their contributions will be appropriately valued by their home institutions.

VII. Comments and Recommendations with Respect to the Urban Volunteers Programme

The Urban Volunteers Programme (UVP) is a good example of the combination of the rapid design, implementation, and verification of effective health interventions for a large population living in dispersed settlements. UVP should serve as a model for other initiatives in this area. Outstanding features include the following:

1. Using general knowledge of the population and its health problems to frame hypotheses and design appropriate epidemiological research.
2. Using techniques of censusing and record keeping similar to those developed by other ICDDR,B projects to conduct the research and manage interventions, and testing for reliability and validity of alternative techniques for measuring variables of special interest (e.g., KAP vs. diaries vs. direct observation of hygienic behavior).
3. Rapid processing of study results and interpretation in terms of potential interventions.
4. Directly observing the population at risk to design specific features of interventions which are appropriate in their socio-environmental setting.
5. Implementation using well-trained and well-supervised community members.
6. Verifying and evaluating the effectiveness of the implementation, including both service statistics and biological and/or demographic measures of impact of the effectiveness of the intervention.
7. Adding interventions incrementally by repeating the processes mentioned above, and retraining to increase to the skills of the urban volunteer health workers.

Aside from services, innovative aspects of the programme include the development, testing, and introduction of record-keeping systems which can be used by illiterate mothers, and verification of this method of record keeping by independent observations. Many of the essential features of the UVP represent "extensions" of the lessons learned from years of painstaking work

by ICDDR,B at Matlab and elsewhere, carefully tailored to urban conditions.

Overall the UVP seems to have been very carefully conducted, with full documentation at each step, and with careful attention to the methods employed for collecting data and to the quality of the data.

Scientific and managerial leadership appears to have been excellent.

The number of publications in international journals from this project is still small, as many of the research reports have not yet been published, but documentation has been very good.

AID should support the continuation of this project at least through its proposed expansion phases in Dhaka, Khulna, etc. future plans should include a strategy and timetable for making programme activities organizationally self-sustaining, as well as for extending activities throughout very low income urban areas in Bangladesh. During the pilot project stage, AID should consider funding a portion of the costs of the Dhaka Hospital, with which the UVP interfaces, and upon which it depends for numerous diagnostic and treatment services.

The UVP is ideally set up for a series of intensive, clearly focused social science studies directly related to its objectives, and AID should support such studies. There is a recognized need, for example, for a demographically trained social scientist to investigate patterns of migration and the apparent rapid adaptation of community standards in intervention communities by new migrants. This information is of interest to UVP because of its implications for the spread of behavioral modification throughout a service area in which there is a great deal of migration. It is also of fundamental scientific interest as regards demographic and behavioral adaptation of migrants to their new surroundings, a common feature of developing countries. AID should support such research.

VIII. Comments and Recommendations Regarding the MCH-FP Extension Project and Associated Operations Research

The Extension MCH-FP Project is an AID-supported activity with a large health services operations research component. The challenge of this project is to transfer what was learned about the introduction of MCH-FP services through intensive work at the ICDDR,B's rural research site at Matlab to sites which are staffed by regular Government of Bangladesh (GoB) personnel in other parts of the country. The Matlab work on MCH-FP service delivery has been criticized by some as irrelevant to national needs because the intensity and expense of the effort at Matlab required

resources far beyond those available nationwide from the GoB. The Extension Project responds to the mandate of the ICDDR,B and the request of the GoB to extend the intervention model developed in the intensive research area at Matlab to large rural test areas in Sirajganj and Abhoynagar using GoB's MCH-FP personnel with a level of support commensurate with GoB resources.

This project required demonstration that the Matlab activities actually had demographic impact which could be attributed to project activities. This was done through use of data from the Demographic Surveillance System.

Operations research described what was done at Matlab, and the Extension Project designed a modification of the Matlab system for other areas. Modifications have included the development, implementation, and testing of a Sample Registration System (SRS), designed to give information essential to manage the routine operations of the large scale MCH-FP activities, and to collect data necessary to evaluate the demographic impact of the project. This system appears to have been well thought through in terms of contents which allows it to serve many purposes simultaneously, and method of operation. Use of microcomputers allows rapid response time, allows records to be updated in the field, and allows quick extraction of data in a useful form for monitoring operations and assessing their effect. The system should have research and operational applications far beyond the limits of this project, and probably will be used elsewhere (with appropriate local modifications) as a research and management tool. The system appears to be considerably less expensive per person in the service area than is the DSS at Matlab, and considerably faster than the DSS System on which it was based. It apparently requires a major investment in personnel to tailor it to the needs of the project in which it will be used, and detailed anticipation of all the uses which will be made of its data.

The fact that Matlab personnel were used in the training phase of this project suggests that it will be replicable elsewhere in Bangladesh. A number of the innovations of the Matlab project have now been accepted by the GoB as the basis for national programs. In sum, the Project appears to have been successful to date in modifying a program based on Matlab experience, training the appropriate GoB personnel, convincing GoB policy makers of the utility of the interventions and management systems, and putting the systems in place. The ultimate test of this project will be in terms of its spread beyond the original implementation areas, demonstration of its demographic effects, special studies to demonstrate health effects, and its ability to respond to varying and changing conditions.

The project activities are well documented. Documentation appears to be of high quality, but to date most of the results are

in the form of briefing documents, conference papers, etc. Published results are focused primarily on family planning issues.

AID should continue to support the MCH-FP Extension Project. Future activities should include the documentation of project activities in formal publications addressed to health policy makers as well as to those interested in family planning and demography. The health research component of the project should be strengthened to balance the already strong demographic component which focuses on fertility.

Data from Matlab suggest that although the service statistics are encouraging, the use of modern contraception is up and fertility is down, mortality, especially for young children, is still very high. Serious thought should be given to developing and testing effective interventions to reduce infant and child mortality to more acceptable levels.

IX. Comments and Recommendations on Social Risk Factor Research

Data from ICDDR,B studies indicate that social risk factors rival biomedical risk factors in correlations with morbidity and mortality. Although there are some important exceptions (as in the Urban Volunteer Programme), for the most part there has been poor integration of social and medical sciences in a setting in which such integration should have been strongly encouraged. Representatives of either discipline have often viewed members of the other as too narrowly focused. In part this may be a result of selection of staff with particular disciplinary interests, and in part a result of requirements of "project" research which is necessarily narrowly focused, to the detriment of attention to the overall picture. Periodic review of the relation of ICDDR,B's research activities with respect to the overall goal of lowering morbidity and mortality should be high on the agenda of researchers, administrators and funders.

Demographers, for example, have focused on family planning and fertility issues; their efforts at understanding mortality issues have been limited and mechanistic, based on correlational analytical models which are unacceptably non-biomedical. Results of biomedical research have not been turned quickly into hypotheses for social science investigation (and vice versa). These points are best illustrated by some recent attempts in this direction as related to cause of death and demonstrated sex differences in death rates of young children.

Documentation of death has been carried out since the earliest days of the DSS, but only within the past few years has an attempt been made to use the data systematically, and to examine their quality. Once examined, it became apparent that the data were of unsatisfactory quality with a wide variety of

systematic biases and errors. For example, it appears that far too many deaths are being attributed to tetanus. If these data are used as the basis for evaluating the current intervention trials (tetanus immunization of pregnant women) the results will be meaningless or misleading.

Attempts are now being made to improve the defects in the DSS cause of death data collection methods. In my view these attempts would be helped by getting the medical personnel into the houses to observe interviews in which the cause of death data are collected, by making systematic attempts to document and understand local diagnostic categories, and by using both relatively unstructured and highly structure questions in an attempt to learn the events leading to death. It has recently become apparent that local Bangli terminology for diarrheal stools approximates valid clinical categories, yet this information has not been used systematically to classify or grade diarrheal cases.

AID should encourage and support integrated social and medical science research on methods for collection of cause of death and morbidity data in populations where deaths and illnesses are poorly documented by medically qualified professionals. ICDDR,B's field sites are ideal locations for such research because of the baseline demographic data, the relevance of such data to ongoing projects, and the excellent entree afforded to research populations. The methodologies for these tasks are poorly developed to date. The aim should be to develop a general descriptive and algorithmic method which allows medically untrained personnel to collect the data which can be reliably and validly classified. Such information is essential for identification of leading causes of mortality and morbidity, for planning rational interventions, and for evaluating the effects of these interventions. Research leading to the development of a valid and reliable lay reporting system will require intensive village based fieldwork on such topics as local terminologies of symptoms, and local classifications of diseases. AID should encourage and support such research.

Recent research using the DSS data has documented a major sex difference in mortality at early ages. Similar sex differences have been reported elsewhere, and have often been "explained" by reference to low status of women. This is inadequate as a guide to remedial action, and is possibly untrue. Recent information from the Urban Volunteers studies suggests that death of young children is associated not just with sex of the decedent, but also with presence or absence of siblings of the same or opposite sex. This suggests that sex preference, if operating, is not absolute. We still do not know what behavioral differences are linked to excess female mortality, and thus have no clue as to appropriate interventions. This calls for direct observation in a selected sample of households, not (at least initially) KAP or other more quantitative methods. Because of the demographic data files,

ICDDR,B is an ideal place for the design of such studies, but they are yet to be designed and carried out.

AID should encourage and support design and implementation of research directed at understanding behavioral differences related to sex differences in mortality in young children. This research will require close collaboration between social and medical sciences, and ultimately should aim at development and testing of interventions to improve chances of survival of young girls.

Research on social risk factors has depended too heavily on analysis of aggregate quantitative data which have been gathered with survey techniques. Too little effort has been made on the fine-grained fieldwork which could increase the validity of the data and the ease with which they are collected, and which would provide insights into linkages between proxy measures of "socioeconomic stats" (e.g., education and occupation) and biomedically meaningful behavior. For example, if education is found to be associated with lower incidence or severity of diarrheal disease, how does education affect parental behavior? Does it make mothers more likely to wash their hands before food preparation? More likely to keep cooking and eating utensils clean? More likely to recognize and respond to symptoms of illness faster than their sisters with less education?

Information of this type is essential both to design and implement effective behavioral interventions, and in order to improve our understanding of the general pattern of association between socioeconomic development and decline in death rates. Answers to such questions (properly phrased in terms of the needs of health service systems) often require detailed fieldwork by trained investigators living in villages and observing the details of village life.

AID should encourage and support integrated social-medical science research designed to document biomedically relevant behavioral differences which distinguish high and low risk parents. The objective of such research is to design, implement, and test interventions to reduce the risks without requiring full scale economic development, or, at a minimum, point to those elements of socioeconomic development which have the greatest impact, and the specific associated behavioral changes which lead to reduction of risk.

This evaluation was not designed for, nor did it allow, a thorough investigation of the needs and potentials for social science research associated with projects of ICDDR,B. I have suggested several areas where it is apparent that social sciences could be more usefully employed.

AID should support a thorough review of what has already been done, and of research opportunities existing in the ICDDR,B data

sets and field sites in which closer collaboration of social and medical scientists would have immediate applicability. The purposes of this survey would be to draw up a list of priority areas, and to establish the requirements for conducting such research and implementing its results. It is likely that additional personnel will be required by ICDDR,B to carry out such a program of research. AID and other donors should consider the secondment of qualified social scientists of appropriate types, and should also consider systematic attempts to strengthen the capabilities of ICDDR,B through additional training, either by bringing experts to ICDDR,B or by sending selected staff members to academic institutions where such training is available.

Systematic attention to the overall data management system at ICDDR,B should be a crucial part of this survey. Biomedical, demographic, and social data have been collected for a number of years, but have not been used as well or as broadly as they might. The DSS is now being computerized (with Canadian support), and the SRS was established (with US support) in order to take advantage of modern computer technology, but the two systems are not well coordinated, either with each other or with various major activities at ICDDR,B. For example, the recent cholera vaccine trial apparently relied on the DSS only as a baseline from which to conduct a new population survey. Apparently the updated information was not fed back and entered in the DSS. This suggests that until access time is improved the DSS is primarily of historical interest, not a readily used tool for real time research. The UVP apparently used the outline of the SRS for data collection, but data were not collected in a compatible way, and so cannot be analyzed with SRS programs. This suggests that there are at least four not-quite-compatible population-based biomedical-demographic-social record keeping systems (DSS, cholera vaccine trial, SRS, UVP) now being maintained at ICDDR,B on a longitudinal basis for large populations. Researchers indicate that the DSS data are not really accessible for regular use in a timely fashion, and the SRS is not readily transferrable to other projects without extensive reprogramming for special purposes.

These conditions jeopardize the integrity and utility of the large longitudinal biomedical, demographic and social data base which is one of the unique features and competitive advantages of ICDDR,B. Solution of "core service" problems of data base accessibility, timeliness, and cross-compatibility is essential if ICDDR,B is to continue as the premier longitudinal population-based laboratory setting in a high mortality country in the developing world. This will require coordination among and between donors, administrators, ICDDR,B researchers and potential users elsewhere with interests in interdisciplinary studies of biomedical and behavioral determinants of mortality and fertility.

Appendix V

Dr. Myron Levine's Evaluation

I. Introduction

As part of this evaluation, the consultant surveyed the physical plant and the availability of fundamental and specialized laboratory equipment; he attempted to ascertain the areas of research at the ICDDR,B that are considered of high priority; he compared the titles and topics of current research protocols with the stated areas of priority; he reviewed the scientific publications stemming from the research. A series of research protocols were selected for detailed review.

II. Prioritization of Laboratory Research Activities

The consultant learned that several broad areas of scientific research have been selected as having a high priority in the laboratory research program of the ICDDR,B. These include studies of the pathogenesis of and immune response to *Shigella* infections (particularly *S. dysenteriae* 1), studies of the ecology of *Vibrio cholerae* O1 (part of a project to assess whether there exists an environmental reservoir of toxigenic *V. cholerae* O1), studies of the extent and magnitude of the immune response to clinical cholera infection and to killed whole cell oral cholera vaccine. As part of the recent field trial of the B subunit/killed whole cell cholera vaccine in Matlab Bazaar, considerable emphasis has been placed on carrying out adjunct studies related to the cholera vaccine trial. These adjunct studies include an assessment of the effect of the B subunit/whole cell cholera vaccine in protecting against diarrhea due to LT-producing *Escherichia coli*, and other Vibrionaceae (non-O1 *V. cholerae*, *Aeromonas*, and *Plesiomonas*).

To this consultant, these priorities appear very appropriate. Currently in Bangladesh (as well as in India, Burma and southern China) there is occurring a pandemic of severe dysentery due to multiply antibiotic-resistant strains of *S. dysenteriae* 1. Case fatality rates have been high in many areas, complications are frequent, and the infection is spreading rapidly due to compromised hygiene and lack of sanitation and potable water. Thus there is considerable interest in these countries, including Bangladesh, in the progress of development of candidate vaccines that might successfully prevent *Shigella* infections. A prerequisite to the development of optimal vaccines is a sound knowledge of the immune response to the various antigens and virulence properties expressed by *Shigella* in the course of natural infection. The ICDDR,B is in an ideal position to try and accomplish this.

Central Bangladesh is the ancestral home of cholera. It is here, in the Gangetic delta of Bangladesh, where cholera is maintained between pandemics, when it is absent or rarely found in other parts of the world. The reasons for the endemicity of cholera in Bangladesh are not known. Recently attention has been drawn to the fact that a focus of cholera (extending for several hundred miles along the Gulf of Mexico coast) has apparently been maintained in the marine environment along the Gulf. It is appropriate to ask whether the environment in certain regions of Bangladesh also serves to maintain an environmental reservoir of pathogenic *V. cholerae* O1. Such studies can be pursued in few places other than Bangladesh and in none with greater epidemiologic relevance.

The large-scale field trial of the B subunit/whole cell combination cholera vaccine provided an opportunity to carry out several related research protocols. This represents an opportunity to amplify the activities of the field trial per se and should be regarded as an opportunistic and wise decision.

III. Physical Plant and Equipment Available for Laboratory Research

A. Physical Plant Facilities

One of the most impressive favorable changes noted by this reviewer on this visit to the ICDDR,B, in comparison with his trip as an AID reviewer in December, 1982, is the extraordinary improvement and reorganization of the facilities of the microbiology and immunology laboratories on the second floor of the ICDDR,B. The improvement is simply astounding and appropriate praise should be extended to all those individuals who played a role in accomplishing it. This modification will reap benefits in morale and work-flow productivity and will also be highly cost-effective. For example, in years past the -70C freezers that maintain and preserve critical reagents and bacterial isolates were kept in the non-temperature-controlled hallway where the ambient temperature in hot season was often 37-40C. As the freezers' compressors previously worked furiously to maintain the ultra-low temperature, they generated and discharged further heat. Under these conditions that were previously present, the freezers prematurely burned out their compressors and required frequent, costly repairs. At a relatively modest expenditure, the hallway has now been closed off and air-conditioned; various labs have also been equipped with a tailored air-conditioning system. As a consequence, the ultra-low temperature freezers, which are a fundamental necessity for a sophisticated laboratory, are no longer in danger of premature compressor burn-out.

A large walk-in cold room has also been installed in the microbiology area, providing impressive space for cold storage and

for procedures (e.g. some chromatography and dialysis) that require a low temperature work area.

The bacteriologic media preparation and autoclaving rooms have been isolated and improved. Within the laboratories themselves, bench space for research has been impressively up-graded. The laboratory activities that support the hospital, such as routine enteric diagnostic microbiology, have been moved out of the research area and into the hospital. This represents an improvement in work-flow, separates the laboratory research from routine clinical microbiology and greatly decreases crowding. These improvements are largely the result of efforts on the part of Dr. Bradley Kay, who is the mastermind behind the reorganization of the laboratories.

Unfortunately, the laboratories on the third floor of the research building of the ICDDR,B are largely unchanged and are located in inadequate physical plant. There is an urgent need to remodel the third floor laboratories as was done on the second floor.

The consultant also visited the laboratories in the treatment center at Matlab Bazaar that support the epidemiological and clinical studies. Here too, Dr. Kay and others have accomplished a notable improvement in the laboratory facilities.

B. Laboratory Equipment

The microbiology, immunology, biochemistry and nutrition laboratories of the ICDDR,B have a fairly impressive array of modern basic and sophisticated equipment to allow credible research to proceed. The support system including autoclaves is adequate; stills exist to supply distilled water. Specialized equipment includes that for gel electrophoresis, chromatography, ELISA, tissue culture, epifluorescence, scintillation counting, etc.

In general, the consultant was quite impressed with the equipment available at the ICDDR,B. Some major (and very expensive) pieces of equipment within the biochemistry area are in fact not presently in use because no investigators are presently at the center who require that equipment for their research.

C. Animal facility

A very impressive animal facility is maintained by the ICDDR,B, a short distance from the main laboratories. In these animal facilities are housed strains of mice, rats, guinea pigs, sheep, goats, a few Rhesus monkeys, and rabbits, as well as some other species of animals.

IV. Quality of Laboratory Research Protocols

The reviewer selected a series of laboratory research protocols on the immune response to cholera infection and cholera vaccination, analysis of plasmids in *S. dysenteriae* 1, outer membrane proteins of *S. dysenteriae* 1, development of attenuated strains of *S. dysenteriae* 1, ecology of *V. cholerae* O1 in the environment in Bangladesh, and Vibrionaceae (other than *V. cholerae* O1) isolated from cases and controls. Short summaries of these reviews are enclosed as Appendix A. One of the protocols was innovative and applied modern techniques of biotechnology to answer critical and relevant questions. However, in general, a disappointing pattern was evident. While it is clear that many techniques of modern biotechnology are available and are being used at ICDDR,B, (such as plasmid analysis, polyacrylamide gel electrophoresis of proteins in the presence of sodium dodecyl sulfate, Western blotting), the scientific questions to which these techniques are being applied are lacking in originality, innovativeness or relevance.

There appears to be an insufficient "critical mass" of experienced, international level investigators to create the environment where such research can flourish. The reviewer regards this as one of the most glaring deficiencies of the ICDDR,B at present, that prevents it from realizing its full potential. There is little doubt in this reviewer's mind that if such a "critical mass" of investigators could be recruited to Dhaka and if close scientific collaborations could be maintained with a few institutions elsewhere that are carrying out state-of-the-art research in related fields, the quality of laboratory research at ICDDR,B could be notably improved, expanded and enhanced. A specific example of such collaboration that can be cited is the relationship between the University of Gothenberg and the ICDDR,B. Drs. Jan Holmgren and Ann-Mari Svennerholm carried out many collaborative research projects with the ICDDR,B, introduced several immunologic techniques, provided reagents that are still in use, trained technical and professional staff. The collaborative research that they fostered has led to the publication in international peer-reviewed journals of several manuscripts on immunologic aspects of cholera and enterotoxigenic *Escherichia coli* infections.

V. Some General Points

In interviews, several expatriate investigators pointed to administrative procedures that they believe are inhibitory to realization of maximal productivity. In the areas of procurement of supplies and personnel, in particular, these investigators have the perception that the infrastructure of the ICDDR,B is inadequate, unsupportive, and, in some instances, less than fully competent. The reviewer cannot comment on the validity of these

complaints made by several scientists, other than to pass them on in this report.

A major and severe morale problem has been created among both the expatriate and Bangladeshi scientific staff by the recent decision by the Board of Trustees that the ICDDR,B cannot simultaneously contract both husband and wife, even though each represents a credible and productive scientist or physician. In recent years some of the most productive scientists at the ICDDR,B have been husband and wife teams. These have include the Mollas, Roger Glass and Barbara Stoll, John Clemens and Bonita Stanton, and Jeffrey Harris and Judith Wasserheit. The AID mission in Dhaka considers this decision by the Technical Advisory Committee to be counter-productive. This consultant also believes that the Board of Trustees should reconsider their decision.

Dr. Roger Eeckels, the new Director, is doing an excellent job. He is diligent, devoted to the ICDDR,B, a good manager, and an excellent pediatrician. His leadership should be supported by AID Washington as well as by all other relevant donors and parties.

VI. Some Suggestions to Increase the Quality and Quantity of Scientific Productivity at the ICDDR,B

This consultant believes that the quality of laboratory research conducted at the ICDDR,B can be increased if a few mature consultants can be identified to come to Dhaka approximately twice each year for at least two years to provide stimulation and guidance. These consultants would serve as visiting professors. They would: provide several lectures and seminars; advise ICDDR,B researchers on protocol design and execution; review manuscripts; teach techniques. If the consultants can serve for at least one and preferably two years, a considerable degree of continuity should be provided.

Some scientific institutional links should be considered as an additional method of providing scientific support and stimulation and to diminish the perception by ICDDR,B scientists of being isolated and out of the scientific "mainstream".

The same sort of structural changes as were carried out on the second floor of the ICDDR,B should be initiated on the third floor to upgrade, at modest cost, the Biochemistry and related laboratories. Consideration might also be given to moving the offices currently on the third floor to another site.

Very high priority should be given to the recruitment of mature, established scientists, as well as promising less-established scientists from the industrialized countries (particularly the U.S.A.) to spend one or more years at the

ICDDR,B. This is necessary in order to establish the "critical scientific mass" that is a prerequisite for productive research units. Means should be explored to accomplish this. Among the impediments are career fears by the individual, with respect to assuring that they will have a position in their parent institution upon their return and the fact that salaries at the ICDDR,B represent a pay-cut for most established U.S. investigators. One possible solution to this problem might be to establish AID senior fellowships whereby scientists from U.S. universities or other research institutions would be funded to spend one to three years at the ICDDR,B while being paid by their own institution at their regular salary. To accomplish this, AID would pay the parent institution to continue the scientist's salary and other benefits, while he/she is working in Bangladesh. Innovative methods must be found to attract mature, established scientists to the ICDDR,B, while preserving their positions in their parent institutions. If enough such scientists can be recruited, the experience at ICDDR,B could become very attractive and rewarding. The extraordinary availability of clinical, bacteriologic and immunologic material at the ICDDR,B will always serve as a basic attraction for scientists and the material is virtually without peer elsewhere in the world.

APPENDIX A

REVIEW OF SELECTED RESEARCH PROTOCOLS

Protocol - PR 85-17 "Mortality Following Shigellosis in Matlab."
Dr. N. Huda, Dr. J. Harris, et al.

Although all retrospective studies are subject to potential biases, this is an excellent protocol of its type. It addresses two cogent specific questions:

- 1) Is the mortality following Shigella dysenteriae 1 greater than that following other Shigella serotypes?
- 2) Is the mortality following Shigella greater than that following diarrhea of other etiologies?

If Shigella is associated with increased mortality compared with other etiologies, a search for risk factors will be undertaken. The discussion of how to identify risk factors and to assess what risk factors might lead to improved survival is a little weak. Surprisingly, the excellent retrospective review of M. Gurwith et al was not cited from the experience of severity of diarrhea in relation to etiology in hospitalized children in Manitoba. In that Journal of Infectious Diseases study Shigella was identified as the etiology causing the most severe illness (mainly judged by duration of hospital stay).

PR 85-14 "Rapid Diagnosis of Shigellosis by Co-Agglutination Technique by Detecting Shigella O Antigen in Stool of Shigellosis Patients." Drs. M. Rahman, K. Aram, et al.

This proposal intends to evaluate the Staphylococcus Co-Agglutination Technique with Group-Specific Shigella Antisera as a method of differentiating S. dysenteriae from S. flexneri infections. This is a worthy project, appropriately performed at ICDDR,B, where there is much S. flexneri as well as S. dysenteriae infection. However, the consultant cannot readily agree that the rationale for differentiating between the serogroups of Shigella is to serve as a guide to antibiotic therapy. Antibiotic resistance of Shigella is notorious for its' rapidity of change. Thus, by the time this study is completed, the pattern of sensitivity of S. flexneri may very likely show a much higher prevalence of resistance to trimethoprim/sulfamethoxazole. Rather, this consultant thinks this assay, if it works, will serve two purposes:

- 1) To rapidly identify Shiga dysentery patients, thereby alerting clinicians that these patients are at high risk of complications.
- 2) To rapidly identify Shiga dysentery patients so that they can be entered into treatment intervention studies

(e.g. a double-blind study of the effect of steroids on the role of complications and fatality of Shiga dysentery).

The introduction is rambling, verbose, and poorly referenced (too many book chapters are cited where original reports are more appropriate if a reference is at all required). The investigators propose plunging right into testing of the clinical samples. No description is given whether they intend to standardize the assay first by reconstruction experiments. In such experiments known inocula of *S. dysenteriae* 1 and *S. flexneri* would be inoculated alone or together into feces shown by culture to lack these pathogens. Mixtures containing 10^4 , 10^6 , 10^8 and 10^{10} *Shigella* per gm feces, should be tried. In this way the investigators could have a preliminary determination of the value of the test with respect to its sensitivity and specificity and could work out any unforeseen technical problems that might arise.

The investigators propose to evaluate 50 suspected cases of Shigellosis. They don't explain how the sample size was derived.

"Assessment of Antitoxic Immunity Conferred by the Oral Whole Cell B Subunit Cholera Vaccine against Non-O1 Vibrionaceae." Dr. Brad Kay et al.

This is basically a very good proposal and it is laudable and appropriate for it to be an "off-shoot" study of the large cholera vaccine trial.

The investigators describe *Aeromonas* species and *Plesiomonas shigelloides* as if it were clearly established and inarguable that these organisms are enteric pathogens. In fact, this is a hotly debated subject. I believe that a qualifying sentence or two should be added to the protocol to point this out. Were there to be a significant difference in the isolation rate of *Aeromonas* and *Plesiomonas* between vaccinees and controls, this might add some evidence to the contention that they are indeed pathogens.

On p.9 it notes in the methods that suspect strains will be grown at 30°C in sycase broth and aerated during incubation. On p.7 it says that strains will be grown in either sycase or caseino acid yeast extract. The culture conditions here (temperature and shaking or resting) are not indicated. Nor is it written when sycase and when CAYE will be used. Since the culture conditions optimal for toxin production are not known, it would seem prudent, at least initially, to use both media and both resting and shaken cultures. On p.8, under preparation of antisera, the immunization schedule using whole cells will favor antibodies to LPS over protein antigens. Why is cholera toxin given IV?

The methods and purpose of the Y-1 adrenal and Gml-ELISA techniques are clear. The rationale, objectives and methods of the crossed immunoelectrophoresis (XIE) are not at all clear to this reviewer.

It would seem that the highest priority of this protocol, and its starting point, should be a determination of the rate of isolation of non-O1 Vibrionaceae from vaccinees versus controls. (This reviewer presumes that this is possible since the code was broken to determine O1 isolations in the three groups.) Then a sample of strains from vaccinees and controls should be examined for CT and other toxins.

Since there is some relatedness among the Vibrionacea, it is theoretically possible that partial protection could be conveyed by the vaccine against non-O1 organisms on the basis of non-toxoid components of the vaccine (i.e. bacterial cell antigens). The XIE could certainly help decipher this but it would probably be worth the effort only if such cross-protection were indeed shown.

Protocol PR 86-04 "Study of the Antigenic Composition of Outer Membrane Components of *Shigella dysenteriae* 1 type 1 Strains in Relation to their Plasmid Profile." Drs. K. Haider and Ivan Ciznar.

The principal investigator has "obtained 6 strains of *S. dysenteriae* 1 with altered plasmid make-up, by using different chemical and physical treatments." She proposes to analyze the lipopolysaccharide O antigens and outer membrane proteins of the strains to assess their pathogenicity (by guinea pig keratoconjunctivitis test and Hela cell invasiveness) and to relate this to the plasmid profile. This protocol shows no innovativeness or originality. It proposes to repeat the experiments of Hale et al that show that the 140 md plasmid of *Shigella* encodes certain outer membrane proteins, the expression of which is correlated with invasion, and the experiments of Watanabe et al who showed that a 6 mdal plasmid is necessary for expression of the O antigen of *S. dysenteriae* 1.

Protocol 85-019 "Isolation of Temperature-Sensitive Mutants of *Shigella dysenteriae* 1 and Evaluation of their Colonizing and Protective Potential in Adult Rabbit". Dr. Zia Ahmed.

The investigator proposes to develop temperature-sensitive mutants of *S. dysenteriae* 1 to be evaluated in the adult rabbit model of *Shigella* infection developed at the ICDDR,B by Sack and co-workers. Both "tight" and "coasting" mutants would be included in testing. Pathogenicity would be assessed by Sereny test. No mention is made of invasiveness-associated outer membrane proteins. No discussion is given as to the desirable

characteristics of a vaccine strain. For example, should it have the property of epithelial cell invasiveness?

Protocol 85-040 "Isolation of Attenuated Strains of *Shigella Dysenteriae* 1 Susceptible to Bacteriolysis as a Consequence of Induced Genetic Block and Evaluation of their Potential in a Rabbit Model". Dr. Zia Ahmed.

The investigator proposes to induce the genetic lesions by mutagenesis with nitrosoguanidine. This represents the use of unsatisfactory out-dated technology that has been superceded by recombinant DNA technology and transposon mutagenesis. Nitrosoguanidine mutagenesis is unsatisfactory for two main reasons in preparing strains either for use as vaccine candidates or for studying pathogenesis. First, it introduces point mutations which are notoriously subject to reversion. Second, it non-specifically induces multiple genetic lesions in the genome, in addition to the mutation that is sought. Thus, although one selects for a particular mutation after treatment of the bacteria with nitrosoguanidine, if one carefully evaluates the daughter bacteria, one almost always finds additional undesired mutations. Unfortunately, not all the inadvertent mutations are readily identifiable. Thus one cannot draw conclusions about pathogenesis using nitrosoguanidine-mutagenized strains. Transposon mutagenesis and recombinant DNA techniques have overcome these drawbacks. For example, the genes encoding specific virulence properties (e.g. toxins or fimbriae) can be cloned and expressed in *E. coli* to assess their effect in isolation. Alternatively, by transposon inactivation or site-directed mutagenesis, genes encoding specific virulence properties can be specifically inactivated or deleted from bacteria and the effect of this deletion on pathogenicity assessed.

Protocol 84-033. "Immunochemical Analysis of *V. cholerae* Antigens with Emphasis on Phenotypic Variations in Carbohydrate Antigens: Implications for Vaccine Development". Dr. Ivan Cisar.

This protocol uses crossed immunoelectrophoresis (XIE) to examine the patterns observed when post-vaccination sera from persons immunized with the B subunit/whole cell cholera vaccine or sera from convalescent cholera patients are reacted against lysates of *V. cholerae* freshly-isolated from patients or against a lysate prepared from the vaccine. This is a very critical study that addresses an important topic in cholera research. The innovative aspect of the study involves the use of XIE, in addition to Western blotting. Several other groups are carrying out similar studies using Western blotting. However, the use of XIE allows the detection and characterization of intact proteins and carbohydrate antigens. In contrast, Western blotting involves antibody directed against denatured protein. This protocol could

provide important information about the number and character of antigens present in the inactivated vaccine vibrios versus fresh clinical isolates and of the immunologic response to the various antigens. This protocol is an example of modern biotechnology being employed as a tool to answer cogent scientific questions.

Appendix VI

Summary Telex by Dr. Keusch & Dr. Kunstadter

Following is brief summary of ICDDR,B evaluation by Black Keusch and Kunstadter. Information not available from Levine or Heiby. Please forward as appropriate to USAID.

1. ICDDR,B serves essential role in advancing USAID Health strategy and should receive continued direct support. ICDDR,B is unique institution with relevant mandate and activities at laboratory, individual patient, pilot field test and large scale implementation level in well documented urban and rural populations with high mortality and fertility.
2. Current scientific and implementation activities of variable quality with some clear excellence. Limitations include number and in some cases qualifications of personnel and institutional administrative constraints. Management of current fiscal crisis precludes rapid reorganization. USAID can play critical role in providing continued support, but multiplicity of donor demands regarding topics of interest and personnel decisions is a complicating factor.
3. Present scope of activities too broad for effective work in some areas and too narrowly conceived in others. Recommend restriction of training activities to practical clinical, field and laboratory skills for Bangladeshi and foreign health workers. Didactic training is provided by WHO. Publications from ICDDR,B except for bibliographic series are not of sufficient quality to continue and represent diversion of effort.
4. High praise for Urban Volunteers Programme as successful example of field research with rapid generation and testing of hypotheses leading to quickly evaluated interventions and widespread implementation. Programme has developed, tested and introduced new interventions with important health impact in less than one year. Similar use of this and other ICDDR,B field areas should be encouraged and supported by USAID.
5. Given additional mature and creative scientific input, ICDDR,B can develop and implement cohesive and critical research program. Current problems exacerbated by conflicting influence of various donor agency interests. USAID can help by targeting resources for development of ICDDR,B program in collaboration with other donors, and with attention to the needs for institutional planning

and development which should attend to problems of overall scientific direction, and appropriate plans for identification of priority research areas and personnel recruitment.

6. In addition to evaluation teams, support for academic institutional linkages will provide needed high level scientists by secondment, and incidentally will provide much needed informal training and constructive scientific monitoring of ICDDR,B programs.
7. USAID should assist donor consortium to act collectively within the perspective of overall research priorities set by ICDDR,B scientists.
8. USAID should work with other donors to insure support for essential service functions for research, patient care and preventive health services and extension, including Dhaka Hospital, Matlab Treatment Centre, computer, demographic surveillance and sample registration systems, laboratories, library, etc.
9. We believe Professor Eckels needs and deserves full support of USAID in addressing problems of ICDDR,B. These can only be resolved by a strong director with authority and resources to act. Present situation has too many masters and too few finances.
10. Reports on specific areas of evaluation will be sent separately by individual team members.

Keusch/Kunstatter