

Report of the Tenth Meeting of the Scientific Review
and Technical Advisory Committee of the
Cholera Research Laboratory
Dacca, Bangladesh

February 25 - March 2, 1976

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Agenda and Participants

The Technical Committee and its expert advisors met with Dr. Willard Verwey, Director of the CRL, at the Intercontinental Hotel, Dacca, on Wednesday morning, February 25. Dr. Verwey gave a general review of the administrative organization of the CRL and of the overall scientific program. During the afternoon the committee members were conducted by Dr. Verwey on a tour of the hospital and laboratory facilities in Dacca.

On Thursday and Friday, February 26 and 27, the Committee heard presentations of scientific papers and attended investigator conferences at the CRL in Dacca.

On Friday, February 27, the Committee met in Dacca in Joint Session with the Directing Council of the Cholera Research Laboratory.

On Saturday, February 28, the Committee visited the Vaccine Trial Study Area in Matlab thana, where papers on field studies were presented.

Preceding the meetings, on Sunday and Monday, February 22 and 23, a subcommittee of the Technical Committee, composed of Professor Robert Williams, Chairman, Professor Derrick Rowley, Dr. Philip Brachman and Dr. Carl Miller, visited the Teknaf Dysentery Project Study Area in Teknaf, Chittagong District. Their report is incorporated into the body of this report.

In addition to the members of the CRL Staff, the following persons attended the scientific meetings:

Members of the Technical Committee

Dr. John P. Craig
Professor of Microbiology and Immunology
Downstate Medical Center
State University of New York, Brooklyn, New York, U.S.A.
Chairman of the Technical Committee
Government of the United States of America

Dr. M. A. Latif
Deputy Director
Biological Production Laboratory
Institute of Public Health, Dacca, Bangladesh
Government of Bangladesh

Professor Derrick Rowley
Professor of Microbiology
University of Adelaide
Adelaide, Australia
Government of Australia

Professor R.E.O. Williams
Director, Public Health Laboratory Service, London, England
Government of the United Kingdom

Expert Advisors to the Technical Committee

Dr. Philip S. Brachman
Director, Epidemiology Program
Center for Disease Control
U.S. Department of Health, Education and Welfare
Atlanta, Georgia, U.S.A.

Dr. Edward W. Hook, Jr.
Professor and Chairman
Department of Medicine
University of Virginia School of Medicine
Charlottesville, Virginia, U.S.A.

Dr. Nevin Scrimshaw
Head, Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts, U.S.A.

Dr. John C. Snyder
Center for Population Studies
Harvard University School of Public Health
Boston, Massachusetts, U.S.A.

3.

Observers

Dr. Earl S. Beck
Head, Geographic Medicine Branch
National Institute of Allergy & Infectious Diseases
Bethesda, Maryland, U.S.A.

Dr. Carl E. Miller
Cholera Program Officer
Geographic Medicine Branch
National Institute of Allergy & Infectious Diseases
Bethesda, Maryland, U.S.A.

Dr. Howard A. Minners
Associate Director for Collaborative Medicine
National Institute of Allergy & Infectious Diseases
Bethesda, Maryland, U.S.A.

Dr. R. Bradley Sack
Co-Director, Johns Hopkins University Center for Medical Research
Associate Professor of Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland, U.S.A.

Dr. Wiley H. Mosley
Professor and Chairman
Department of Population Dynamics
The Johns Hopkins University School of Public Health
Baltimore, Maryland, U.S.A.

INTRODUCTION

The Cholera Research Laboratory has continued to make good progress in the reconstruction following the war, and Br. Verwey is greatly to be commended for his part in seeing that the process has been pursued with vigor. In particular, the reorganization of the administrative services including the setting up of the cost-accounting procedures is noteworthy.

The Committee also wishes to express its gratitude to Dr. K. A. Monsur, former Chairman of the Directing Council of the CRL, who last year left Bangladesh for service elsewhere. Dr. Monsur has been a loyal supporter of the CRL since its establishment in the early 1960's. We particularly wish to commend Dr. Monsur for his efforts to keep the CRL functioning during the recent war and the turmoil which followed in its aftermath.

The Committee considers it appropriate that the core program of the CRL continues to center around diarrheal disease. Last year the Committee commended the Laboratory for its initial attempts to broaden its activities to include a greater proportion of studies involving nutrition, immune competence and demography, particularly in areas in which these factors influence diarrheal disease morbidity and mortality in Bangladesh. Equally important are the reverse relationships; namely, the impact of diarrheal disease upon nutritional status, immune responsiveness and population dynamics and attitudes.

The Committee believes that this interdisciplinary thrust is desirable and should be expanded in the future, even though for some

time the major expertise of the laboratory scientists may lie in various aspects of diarrheal disease itself. Last year we recommended that the CRL exercise caution in extending its activities into other fields such as population planning. This was not meant to inhibit the initiation of appropriate population studies, but rather to encourage careful planning and selection of those projects which can utilize the unique resources of the Matlab field study area without jeopardizing ongoing studies related to the core diarrheal disease program. Emphasis should be on those questions which CRL is in a unique position to answer.

The Committee believes that it is appropriate for the CRL to participate in studies in nutrition and population planning provided that they are well designed and executed and that they strengthen the CRL and contribute to its core diarrheal disease program.

Within the CRL there are still clear signs of insufficient planning and discussion before embarking on new projects. Before the start of any research project it is essential to define the objectives and by careful discussion within the institute to design suitable projects.

We were glad to hear of the regular program of seminars and project review meetings and would emphasize our belief that these should be extended to provide opportunities for reviewing incomplete projects at a time when modification is still possible. Moreover, we feel that protocol preparation and review is inadequate and should be strengthened by both internal review and outside consultation. Preview of major protocols might best be presented during the Committee meetings.

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We believe that there should be greater use of consultants at an early stage in each important project and that local expertise should be sought whenever possible. Stronger links should be forged with Dacca University and other local institutions.

During the past three years the CRL has been host to several investigators who are members of the staff of the John Hopkins University Center for Medical Research (JHCMR). The work of these investigators is considered a part of the total CRL effort and is therefore reviewed in this report.

The Technical Committee is grateful for the contributions and interest of our expert advisors. The fine cooperation and assistance of the Director and his staff have made our visit both pleasant and informative.

REVIEW OF SCIENTIFIC ACTIVITIES

I. Clinical Division

A. Clinical Characteristics, Complications and treatment of Shigellosis

Shigellosis continues to be a major public health problem in Bangladesh. In 1975, about 2,700 isolations of shigellae were made at the CRL in Dacca and about 900 patients with shigellosis were admitted to the wards of the CRL. Shigella dysenteriae type 1 accounted for 35% of the total isolates and Shigella flexneri accounted for 52%. The largest number of cases occurred from December to May with the highest peaks in December and January. The overall case fatality rate was 3.5%, although the fatality among patients admitted to the hospital was 10%.

The focus of the research effort has continued to be on the clinical characterization, pathogenesis and therapy of three major complications of shigellosis: (1) neutrophilic leukemoid reactions with leukocyte counts in excess of 50,000 per mm.³; (2) hemolytic anemia with fragmentation of peripheral blood erythrocytes, (3) persistent colitis.

In addition, because of the increasing or existing high proportion of shigella strains resistant to antibiotics, including streptomycin, tetracycline, chloramphenicol, and more recently ampicillin, monitoring of antibiotic sensitivity of shigella isolates and evaluation of newer antimicrobials for effectiveness continue to be important functions of the CRL.

Some progress in all of these areas has been made during the past year. These efforts have been facilitated by the establishment of a Shigellosis Research Unit for study of selected patients within the existing CRL hospital. The times of onset of the leukemoid and hemolytic reactions, not previously well defined, have been determined (median onset of leukemoid reaction on the 6th day of illness and of the hemolytic reaction on the 12th day), and the clinical and laboratory characteristics of both of these "complications" have been elucidated more completely than in the past. Bacteremia occurs in 5% of the patients hospitalized with S. dysenteriae infection and in 2% of patients with S. flexneri infections. No association between bacteremia and hemolysis could be demonstrated, but studies currently in progress appear to indicate a striking relationship between endotoxemia, as detected by the limulus lysate technique on admission, and subsequent

hemolysis. Additional studies have shown that serum complement components are decreased and have identified quite precisely the coagulation defects. Serum has been collected for a assay of immune complexes. It is postulated that endotoxemia initiates a series of immunologic events which serve to activate the clotting mechanism resulting in microangiopathic hemolytic anemia.

Retrospective data comparing ampicillin therapy at two dosage levels appeared to show that the patients receiving the larger dose (100 mg/kg/day orally) had fewer hemolytic episodes than patients receiving the smaller dose (50-80 mg/kg/day orally). From these same studies it was also concluded that the course of illness was abbreviated, both clinically and bacteriologically, by higher dose of ampicillin.

The Committee was concerned about the design of these experiments and the interpretation of these data because it was felt that comparative analysis was not possible in two groups of patients selected by inadequately defined criteria and studied several months apart.

The Committee wishes strongly to support the studies of shigellosis in Bangladesh. Attempts should be made to define the pathogenesis of the hemolytic syndrome and especially to test the hypothesis that this is the result of a massive antigen-antibody reaction. The studies to detect circulating complexes and the immunofluorescent studies of antigen and/or antibody localization in the colonic mucosa also should be given high priority.

The Committee believes the establishment of the Shigella Research Unit was an appropriate move. This unit will permit emphasis on selection of cases appropriate for prospective study of therapeutic

measures and more careful collection of data for comparative purposes than in the past.

The Committee is optimistic regarding the future productivity of the shigellosis program. We urge that in the future careful attention be directed to experimental design and to recurrent critical analyses at all phases of study.

B. Comparative Clinical Trial of Dacca Solution and a WHO Solution

Results of a clinical trial were presented comparing Dacca Solution (DS) containing sodium of 133 mEq/l and no glucose with diarrhea treatment solution (DTS) containing 118 mEq/l of sodium and 0.8% dextrose. The concentrations of other electrolytes were similar. The rationale behind the trial was the concern of WHO that a "universal" solution containing a lesser quantity of sodium could be recommended for use in patients suffering from both cholera and non-cholera diarrhea. The latter group lose considerably less sodium in stool compared to those with cholera. The added glucose in the DTS would also help prevent hypoglycemia in small children.

The study carried out at CRL showed convincingly that there is little difference in the efficacy of the two solutions. The rate of correction of dehydration and acidosis and the levels of serum sodium were similar in both groups. The intake of water by mouth during the first 24 hours was not significantly different--suggesting that 133 mEq/l of sodium in the Dacca Solution was not enough to build up a high concentration of serum sodium and increase thirst. Two patients with hyponatremia were removed from the DTS group as the amount of sodium in DTS was thought to be too little to correct the deficiency.

The most dramatic effect of hydration with either of the solutions was the fall in the levels of glucose during the 4 hours after the beginning of treatment. The amount of dextrose in the DTS was inadequate to prevent this development. However, although hypoglycemia of less than 40 mg/100 ml was noted in two patients in the glucose-free DS group (with none in the DTS group), no patients showed clinical signs of hypoglycemia.

It seems clear that there is little advantage of one solution over the other. DS, being glucose free, is easier to manufacture and has a longer shelf life; DTS, being low in sodium, should be more acceptable to those who think that DS contains sodium in excess of the requirements. The small amount of glucose in DTS did not make much impact on the blood glucose level but may add considerable difficulty in the manufacturing process if special autoclaves are not available. The addition of glucose also demands more careful storage, as contaminants grow much more easily.

From the levels of approximately 100 mEq/l sodium found in stools of cholera in this group of patients, it seems that lowering the concentration of sodium in the DS to the level of DTS may not be harmful. Therefore, a solution with the electrolyte concentration of DTS but containing no glucose should be a more acceptable solution for use in cholera as well as in non-cholera diarrhea.

C. A Comparison of Sucrose and Glucose in Oral Electrolyte Treatment of Severe Diarrhea

The Committee in 1975 recommended a controlled study to compare the effectiveness of sucrose with glucose in the oral electrolyte solution used in the therapy of cholera. The study has been completed;

one hundred and twenty-two patients with a clinical diagnosis of cholera were studied in April, May and June, 1975. Initial rehydration for the first 4 to 6 hours was accomplished with intravenous Dacca Solution and was followed by oral hydration with a coded electrolyte solution which contained either sucrose or glucose. The two groups of patients were similar in all pre-treatment parameters except for a significantly larger number of males in the sucrose group. The overall success rate, with maintenance of hydration without need for reversion to intravenous fluids, was high (85% for sucrose and 88% for glucose). However, if only cholera cases are considered, the success rates were lower, and the differences in success rates between the sucrose and glucose groups are more impressive (68% for sucrose and 81% for glucose), although statistically insignificant. Sucrose-fed patients had a higher volume of purging than glucose-fed patients after onset of oral fluid therapy, although the difference was not statistically significant. Nevertheless, in the patients with cholera, those receiving the sucrose solution showed a total stool rate 27% higher than the patients taking the glucose solution (total stool rates of 46 ml/kg/4 hr in the sucrose group as compared to 36 ml/kg/4 hr in the glucose group).

The number of patients studied was only 122 (69 in the sucrose and 53 in the glucose group). The series contained only 56 patients with bacteriologically confirmed cholera (29 in the sucrose and 27 in the glucose group). Although there are no statistically significant differences between the sucrose and glucose groups, it is possible that a larger number of patients might have shown that the trends observed are significant.

It became apparent during the course of presentation of these studies that an error had been made in the total stool rates and failure rates shown for cholera cases in the written material and verbal presentations for the Technical Committee. Although this error was corrected after much discussion, it inevitably cast doubt and concern on the validity of the observations. Data should be subjected to recurrent → critical analysis from within the CRL before presentation to outside review groups.

In the final analysis, the Committee feels that the evidence shows that sucrose-electrolyte solutions for oral fluid replacement therapy of patients with severe diarrhea are successful in a large proportion of cases. Although glucose solutions may still be preferred because of the possibility of disaccharidase deficiency, sucrose-electrolyte solutions can be utilized as a substitute for glucose-electrolyte solutions with safety and effectiveness. Sucrose solutions have the advantages of lower cost, greater availability and better patient acceptance than glucose solutions.

D. Treatment of Diarrheal Disease by Means of Unsupervised Oral Hydration

Both Oralyte distributed by UNICEF and Bicohydrol produced by a Swiss company are effective in the oral rehydration of children with dehydration due to severe diarrhea conducted under medical or paramedical supervision. There is, however, a need for a mixture which can be locally produced and which has an acceptability for use in the home without immediate supervision. During the past year the Laboratory has put considerable effort into determining a flavor, color and packaging which would meet these needs and has arrived at an orange

colored and flavored product in a glass bottle with a child-proof and tamper-proof seal. They are uncertain as to the need for a preservative to retard bacterial growth after the solution is reconstituted in the home. This project is judged to be appropriate and worthwhile. Attention should now be concentrated on a field trial of the proposed mixture.

→ The matter of a preservative need be explored only if the results of the field trial indicate it to be necessary.

While this development was proceeding, a study was initiated in the cholera hospital OPD patients. They were treated for 4 hours with oral solution and then sent home with OralYTE packets to continue the therapy. In 31 of 39 patients the continued oral hydration at home was judged successful and the OralYTE found to be acceptable for the purpose. In view of these results and the possible lack of familiarity of some rural families with orange flavor, a trial in the Matlab area comparing the acceptability for home rehydration of OralYTE and

→ the CRL preparation as presently developed and packaged is recommended.

E. Teknaf Dysentery Project

Following the observation of an epidemic of dysentery due to Shigella dysenteriae type 1 (shigae) in St. Martin's Island that apparently arose from a focus on the nearby mainland at Teknaf, and the indications of a high prevalence of dysentery in Teknaf, a project was set up to study (1) the epidemiology of dysentery and its control by various intervention methods, (2) the relation of dysentery incidence to nutritional status, and (3) methods for providing treatment facilities at minimal cost. This project is supported by funds from UNICEF and from the Canadian IDCR. A census has been conducted, a treatment

center and a small laboratory established at Teknaf bazar and a surveillance system based on house visits initiated to supplement the monitoring provided by the treatment center.

Teknaf has some striking advantages for these studies. It has a very high dysentery attack rate, about 4 times that in Matlab; it is an isolated community, yet it has a hospital and laboratory; and it has an advantage over the Matlab area in that there are relatively few water sources. One major disadvantage appears to be that all adult women are held in purdah which must make adequate surveillance more difficult.

The minimal treatment study is being conducted in a series of communities along a coastal strip and as set up seems to provide very little opportunity for proper controlled evaluation; surveillance is very difficult, and the drug being used-- sulfaguanidine--is not of proven value. We consider that this study as at present conducted is not capable of yielding useful results. There seem some real dangers in the relatively uncontrolled distribution of sulfaguanidine.

The nutritional status of the children is being monitored by anthropometry, and these measurements are probably required for help in interpreting the epidemiological studies. It seems to us unlikely, however, that they will constitute a useful study of the effect of nutrition on disease without considerable elaboration.

We consider that the available resources should be concentrated on epidemiologic and intervention studies of dysentery in the two main communities. Areas appearing to require extensions in study are: (1) epidemiologic, e.g., patterns of spread in the villages and within

the families, sex-specific attack rates (especially in view of the seclusion of the women), differences associated with socio-economic class, etc., and (2) bacteriologic, including sampling of water in wells, tanks and ditches, foodstuffs, fingers, for E. coli and shigellae, determination of survival of shigellae in various possible reservoirs, including exposed feces, tank water, soil.

The forms of intervention that should be considered include (1) provision of latrines with associated washing facilities, (2) provision of soap, (3) provision of laundry facilities, (4) chlorination of drinking water supplies and (5) oral attenuated vaccine. In all cases there would be a need for associated health education programs.

The epidemiologic studies already in progress should show which of these intervention methods would be the most appropriate and should also show how some 'control' studies could be included.

F. Incidence of E. histolytica in Diarrheal Patients

Vegetative E. histolytica was detected in the stools of 5.6% of the patients with diarrhea who came to the CRL in Dacca in 1974 and 1975. The prevalence of E. histolytica is greater in outpatients (1974: 8.9%; 1975: 11.0%) than in inpatients (1974: 2.5%; 1975: 4.3%). Vegetative forms are found more often in individuals 13 years or more of age than in those under 13 years. E. histolytica had not been recognized previously as occurring so frequently in the stools of patients with diarrhea at the CRL. Studies will be initiated to define the clinical features of amebiasis in Bangladesh, including an evaluation of nutritional status and other host factors on the clinical course and response to therapy. Trials will be conducted to determine the comparative efficacy of several amebicidal drugs.

G. Experience with an Apparently Toxic Lot of Guanimycin

Guanimycin is a proprietary mixture of sulfaguanidine, dihydrostreptomycin and kaolin in an orange-flavored vehicle. The preparation is widely used in the treatment of diarrhea in Bangladesh. Epidemiologic evidence was obtained by physicians at the CRL which linked ingestion of guanimycin with the onset of lethargy, coma and vascular collapse in a patient with diarrhea.

Four additional patients with similar clinical features after guanimycin were discovered; one of these patients died. The CRL study of these apparently toxic reactions led to the withdrawal of the incriminated lot of guanimycin from the market. Study by the CDC in Atlanta revealed that the specific lot of guanimycin contained large amounts of carbon disulfide, an industrial solvent known to produce damage to the nervous system and vascular collapse. The source of the contamination is unknown. No further studies of this problem are contemplated.

Studies of this type represent important contributions of the CRL, not only because of the specific medical care given, but also because of the interaction such experiences provide between the CRL and the community. It is unfortunate that the source of the carbon disulfide has not been detected because such information might serve to prevent a recurrence in the future.

H. Interrelationships Between Nutritional Status, Cell-Mediated Immunity and Infectious Disease

In 250 Matlab children aged 12 months to 8 years, the relationship between nutritional status as measured by weight and height, cell-mediated immune status as judged by skin tests with P.P.D., Candida

and streptococcal antigens, and dinitrochlorobenzene (DNCB) and infectious disease incidence were determined by daily visits to each family. Although only a hand tabulation of part of the data has been completed, it is evident that they will confirm in a definitive manner the preliminary results presented at the time of the last Technical Committee meeting which indicated a significant correlation among these variables. All of the data have been completed and punched on IBM cards and a computer program is being developed for their analysis. While they show diarrheal attacks to be three times more frequent and prolonged in anergic children and anergy to be associated with malnutrition, they leave unanswered the question of the cause of anergy.

To some degree this will be answered by efforts to determine the proportion of anergy associated with specific kinds of infectious disease. It has already been established that shigella infection can be only a minor factor in this phenomenon. The attempt to control for environmental and genetic influences by studying the frequency of infection in allergic siblings of anergic children seems of limited value because they cannot be of the same age, and the effects are strongly influenced by the factors associated with age differences.. One approach would be to determine the direct effect of infection on skin reactivity to antigens.

II. Epidemiology Division

A. Cholera Toxoid Field Trial

The early results of the 1974 field trial of purified glutaraldehyde cholera toxoid were presented in last year's report. The final analyses of the first 365 days' experience were presented at

this year's meeting. The toxoid was given in two injections in July and August of 1974, and it has now been possible to follow the immunized and control groups through two large autumnal epidemics peaking in October 1974 and October 1975, providing an excellent assay of the toxoid's efficacy. There was a total of 92,000 participants in toxoid and placebo groups.

The toxoid afforded only minor (28%) protection during the first 9 weeks after the first injection and no protection whatsoever during the remainder of the one year of observation. A puzzling fact emerging from this trial, however, is the apparent serotype specificity of the protection seen. For Inaba cholera, there was 60% protection in the 5 - 14 age group during the 14 - 97 day interval, a difference that is significant; the protection in the 1 - 4 and 15+ age groups was below the significance level. There was slight (33%) but statistically insignificant protection against Ogawa cholera in 5 - 14 yr. olds at 14 - 97 days and no other protection in any age group at any time period.

It seems likely that this protection was real and due to antitoxic immunity and that it was more marked in Inaba cholera because of the fact that Inaba disease peaked earlier in the season during the earlier part of the 14 - 97 day time period. It is, however, possible that the protection really was serotype-specific and caused by an undetected Inaba antigen in the toxoid (which was made from an Inaba strain). This possibility should be examined by suitable tests using high titer antisera produced against this toxoid antigen. One such test would be the assay for mobility-inhibiting antibody.

The toxoid trial has been well conducted and has made a major contribution to our understanding of the mechanism of immunity of enterotoxin-mediated diarrheas. It has shown that a parenteral toxoid capable of raising quite respectable antitoxin titers afforded only weak and evanescent protection against natural cholera. In the same population several years back, a whole-cell vaccine provided better protection for a longer period of time.

B. Urban Cholera Studies, 1974 and 1975

The past year, 1975, was another 'large cholera year' in Dacca, with 3,370 cholera admissions to the CRL hospital. Epidemiologic studies initiated in 1974 were continued and some additional studies were initiated following suggestions of the Technical Committee. However, the reported analyses of the 1975 data do not clarify the route of transmission so that intervention studies are still not indicated.

There have been changes in urban cholera in Dacca over the past six years both in serotype and biotype of the predominant strains. In 1970, classical Inaba predominated (94% of 2,968 isolates); in 1971, classical Ogawa accounted for 54% and classical Inaba for 39% of the 2,653 isolates. In 1972, classical Ogawa predominated with 85% during a light cholera year (702 isolates). Since 1973, El Tor cholera has essentially been the only biotype identified, with Ogawa the predominant serotype in 1973 (99% of 1,276 isolates) and in 1974 (85% of 5,517 isolates) and Inaba upsurging in 1975 (54%).

The data reported for 1975 show similarities to the data for 1974 in seasonal occurrence, with a spring upsurge (April in 1974 and June in 1975), and a fall-winter epidemic from September to November

(peak in October). A case-control study showed no differences attributable to geographic area, sources of water, or use of latrines.

In 1974, there was a suggestion that eating out and especially eating 'charitable meals' and from 'roadside hawkers' was related to clinical cholera. However, the same differences were not apparent in the 1975 data. In the 1975 investigations, specific food histories were obtained; however, these data did not provide any significant leads as concerns the role of food in the transmission of cholera.

Environmental cultures were obtained in 1975; none of 57 foods was positive; 7 of 57 water specimens were positive. However, this only confirmed previous studies showing that V. cholerae can be isolated from water.

If any epidemiologic advances are to be made, strict attention will have to be made to carefully conceived, well-conducted studies in a well-specified area within Dacca. With knowledge that the CRL hospital can serve to alert the Laboratory to the occurrence of cholera in Dacca, it should be possible to initiate studies early in the season (before April), selecting as the study area one that has a relatively stable, well-defined population, with a limited and well-defined water supply, and an area in which it is reasonable to expect cholera to occur and spread. Each case of confirmed cholera from the study district should be promptly followed up by field investigation including environmental cultures. More information and more water specimens for culture concerning the source of all water used by the family should be regularly collected. All data should be regularly analysed in an attempt to identify any changes that should be made

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in the study protocol as the investigations progress. Careful attention to the spring upsurge may reveal important epidemiologic information.

Data should be obtained on progression of cases through the area on a weekly basis, age-sex specific attack rates for 'index' cases and other family cases, and confirmation as to sources of water used in the home by conductivity studies. It was previously suggested that analysis of all deaths for the past years may uncover risk factors; → These analyses should be conducted. Possibly more intense surveillance could be initiated in the study area to monitor the movement of cholera through the area and to observe water utilization habits.

In 1975, some intervention studies were initiated using tetracycline for family contacts and 'bleach' for household water. The results of these studies did not show any effect of these actions. → They should not be reinitiated unless the epidemiologic data suggest that transmission can be interrupted by these or other specific measures.

C. Epidemiology of E. coli Diarrhea

Since less than 50% of cases of diarrhea can be associated with a known etiology, investigations to delineate further the causes of diarrhea should be conducted. The studies of E. coli diarrhea at CRL should be continued but only if the Laboratory is able to give full support. The brief analyses presented to the Technical Committee revealed some interesting epidemiologic data, such as the increasing severity of disease with increasing age, the decreased incidence in association with the increase in clinical cholera, and the age-specific incidence showing a significant peak for the 1 - 4 year age group in March followed by a peak for the 15 year and older group in May (all women). If the data allow other analyses, these should be conducted

as soon as possible so that further studies can be planned. A full year's data need to be collected and analysed before further studies can be discussed. Serologic surveys of family contacts should be considered.

D. An Epidemic of Diarrhea Due to Vibrio parahaemolyticus

An epidemic of Vibrio parahaemolyticus diarrhea associated with drinking fresh water and not with eating fish was well investigated. Fecal contamination of canal water appeared to be the mode of transmission.

Report ?

E. Impact of the Hand Pump Tubewell on Diarrheal Disease Rates in Rural Bangladesh

The control and prevention of diarrheal disease is related to a microbiologically clean water supply. To this end, UNICEF, Bangladesh, is investing 35 million dollars in a hand pump tubewell program for rural Bangladesh and has accepted CRL's offer to evaluate the effectiveness of this intervention program. The results of these analyses will undoubtedly have a far-reaching effect on the tubewell program and thus they must be conducted with great care, thoroughness and speed.

The very preliminary data presented to the Committee suggest that tubewell water is only used for drinking, but not by all people who have access to it. In several villages there was a reduced diarrheal disease incidence among families who reported that they drank tubewell water; in others, however, there was no such association. The significance of these data has not been determined. Additional analyses of the accumulated data are necessary before any further pronouncements concerning tubewells can be made. It may be necessary to develop

additional studies using more precise methods to ascertain the source of drinking water (including home water conductivity studies) and the occurrence of diarrheal disease before a definitive evaluation can be given.

F. Growth Studies in Meharan

A growth and development study has been undertaken, since 1966 in the village of Meharan, a low-income area consisting primarily of fishermen, cultivators and small businessmen, located on the bank of a canal far way from any urban area and a part of the Matlab surveillance area. Its population in 1974 was 1,934, and over 300 children are now in the study. Every expectant mother is followed, and measurements of the newborns and hemoglobin of mother and child made within 1 - 5 days of birth. The children are then measured monthly for the first year and quarterly thereafter for height and weight, and head and chest circumference. Illness, 'diet' and dentition are recorded during both regular and unscheduled clinic visits and cases of severe disease are referred to the CRL hospital in Matlab.

Meharan children weigh 1 kg less than Boston children at birth and 6 kg less by 5 years of age, and the other measurements show comparable growth lag in the village children, as already indicated by an earlier cross-sectional study in Matlab with 10,000 children. The new contribution here is that of longitudinal growth data and the opportunity of comparing them with morbidity data from the Matlab surveillance program. Morbidity recorded from clinic visits alone is too incomplete to be useful for this purpose. The effect of disease frequency on the rate of change in anthropometric measurements will

be one useful way of analyzing the data. For descriptive purposes, comparison of the Bangladesh 50th percentile with the Boston 3rd percentile will be appropriate.

It will be useful to continue this study for an additional two years to cover the age period of greatest frequency of malnutrition, infection and growth retardation. Clinic observations, however, are not an essential part of the program except for the periodic measurements. Arm circumference might be added to the list of measurements. More importantly, the routine disease surveillance in this village should be modified as necessary to obtain information, which is as reliable as that now obtained for diarrheal disease, on the frequency of all disease in this age group. The baseline data and continuing growth measurements can in the future be utilized for concurrent projects requiring malnutrition-related observations such as the prevalence of energy, tests of intersensory integration or cognitive performance, and supplementary biochemical observations. Eventually they should be the basis for an intervention study designed to decrease morbidity and increase growth velocity during this critical age period.

G. Effect of Large Doses of Vitamin A on the Immune Response

A proposal was presented for a project to investigate the effect of vitamin A on the immune response. There is evidence from laboratory studies in experimental animals that administration of vitamin A at the same time as an antigen may potentiate the humoral antibody response, but this has not yet been confirmed by field studies in human populations. Tetanus toxoid will be administered to children under three years of age. Half will receive a large oral dose of vitamin A at the same

time, and tetanus antitoxin titers will be determined initially and after three weeks employing a neutralization test.

After discussion, it was agreed that it would be wise to determine initial serum vitamin A levels using finger tip blood and a micro-technique already well standardized in the Nutrition Department of the University of Dacca. Two groups will be selected, one with serum vitamin A levels below a specified level and the other above. This is necessary to control for the possible influence of initial vitamin A status on the outcome and to distinguish between a nutritional and an adjuvant effect. If done carefully, 20 - 25 children in each of the four groups (low vitamin A status with and without added oral vitamin A and normal vitamin A status with and without added oral vitamin A) should suffice. Hematocrit or hemoglobin status should also be determined from the initial finger prick blood sample.

This is a well-conceived and defined project which can be completed in the next six months and is well worth pursuing. If negative, the results will provide useful information and, if positive, it will be of potential practical programmatic importance.

III. Laboratory Division

A. Initial Studies of the Toxins of Shigella dysenteriae type 1 and Shigella flexneri

Studies have just begun on the enterotoxin-producing capacity of locally isolated strains of Shigella dysenteriae type 1 (Shiga bacillus) and Shigella flexneri. Crude culture filtrates of 52 strains of S. dysenteriae and 40 strains of S. flexneri have been tested in the rabbit ileal loop model. Seventy-seven per cent of S. dysenteriae strains and 20% of S. flexneri strains produced ileal fluid accumulation

of more than 1.0 ml/cm following inoculation of 5 ml of filtrates. Only two strains of S. dysenteriae and none of the S. flexneri produced this amount of fluid following an inoculum of 2 ml. A concentrate of one filtrate produced HeLa cell degeneration but no delayed increase in vascular permeability in rabbit skin.

These initial steps indicate that enterotoxinogenic strains probably occur here, but none of the essential steps has yet been taken to demonstrate clearly that a real exotoxin is present, nor have attempts been made to determine cultural conditions required for maximal toxin production if it exists. Tests such as reproducibility of the assay, heat sensitivity, effect of dialysis, and neutralizability by known Shigella antitoxin must be carried out. The time-course of toxin production in various media and dose-responses of those preparations yielding maximal toxin are also essential initial steps in characterizing this toxin.

The original bio-assay systems for Shiga neuro-enterotoxin were based on lethality in mice and limb paralysis following parenteral injection in rabbits. These should be done early to determine whether the toxins under investigation are similar to classic Shiga toxin.

The Committee feels that these studies are worthwhile and that it is appropriate for basic studies on toxins produced by local strains to be carried out at the CRL. We would urge that future studies be directed toward better characterization of toxins from one or two selected local strains and comparison of these strains with both an earlier well-characterized strain and with a strain from the recent Central American outbreak of type 1 dysentery.

B. Changing Pattern of Antibiotic Susceptibility Among Shigella Strains in Dacca

Results are now available for antibiotic susceptibility tests on Shigella dysenteriae 1 and S. flexneri from 1971 through 1975. Throughout the period almost all S. dysenteriae strains have been resistant to streptomycin and tetracycline; around one-third are now resistant to chloramphenicol, and there has been an increasing, though still small proportion, resistant to ampicillin. About two-thirds of the S. flexneri strains are resistant to streptomycin and tetracycline and, in 1975, 9% are resistant to ampicillin. These studies are clearly a useful part of the routine activities of the bacteriologic laboratory.

C. Studies on Enterotoxinogenic E. coli

The Chinese hamster ovary (CHO) cell culture assay for heat-labile E. coli enterotoxin has been established at the CRL and seems to be going well. Unfortunately this assay, as well as all assays available at the moment, is tedious and must be conducted on ten separate colonies from each patient before the results can be reliably accepted. None of the available assays is really suited to mass screening work, but until such time as a simple test, such as gel precipitation in the presence of specific antitoxin has been developed, the CRL will need to continue with the present tests. It may be that heat-stable toxin will always need to be assayed by a biologic test, and at the moment its ability to cause fluid accumulation in the suckling mouse intestine appears the most reliable and should also be established at the CRL.

D. Development of Hemagglutination Assay for Antibodies in Shiga Dysentery

A good reproducible test for anti-Shiga antibodies has been developed. It is about four times more sensitive than bacterial agglutination

and uses the well-established principle of coating human red cells of group O with a Shigella dysenteriae type 1 antigen preparation by chromium chloride coupling. The hemagglutination test with these cells can be conducted on a micro scale with finger-prick samples of blood. This method will be useful for studying antibody levels in pre- and post-shigella serum in both Teknaf and Dacca.

E. Vibrios in the Environment

The studies of the ecology of vibrios have recently been initiated and should be supported. Progress has included developing methodology and training personnel. Further technological studies remain, some of which may be accomplished in the Laboratory. The method of transporting the specimens from the field must be evaluated. Attention should be given to the algal content of the water and to any impact of aquatic and terrestrial animals. There will be a need to coordinate the findings from these studies and the clinical studies of the population who use these waters. Data should be collected over a full year.

IV. Population Studies

A. Nutritional and Physiological Determinants of Natural Fertility

A three-year prospective study was initiated in November to investigate the effect of nutrition and infectious disease morbidity on the onset of menarche, waiting time to conception, gestation and pregnancy outcome, lactational post-partum amenorrhea and menopause. This study will also obtain information on the relationship between maternal nutrition and infant mortality and between lactational patterns and post-partum amenorrhea. Only fragmentary early results are available from this important, well designed and well presented study.

They show that the natural rate of population increase in the Matlab surveillance area dropped from 3.1 in 1973-74 to 2.0 in 1974. Whether this was a temporary response to unusually adverse economic conditions and excessive flooding or due to more lasting factors is not yet known. An investigation of the effect of socio-economic and nutritional factors on variable fertility rates is part of the program. Variations in nutritional status indicated by anthropometric measurements, serum albumin and hematocrit are viewed as possible intervening variables.

Data for the first three months of the prospective study confirm the extraordinarily long period of post-partum amenorrhea (an average of 22 months) previously described for this population. They also show hematocrit values which are slightly lower in women with recent pregnancies and slightly higher in Hindus than in Muslims. A major hypothesis of the project is that malnutrition is currently a major factor in the relatively long interval between births in this population due to prolonged post-partum amenorrhea and additional delay in return to fertility thereafter.

This project is not only investigating the hypothesis that malnutrition is responsible for the long birth interval but also that there is something different in the sucking pattern of the way children breast-feed, possibly associated with the pattern of supplementary feeding. The preliminary data show no variation in post-partum amenorrhea by the time of initiation of supplementary feeding, possibly because the quantities given are so small. Moreover, the percentage of children 100% breast-fed at various ages was higher in 1964-71 than in 1975

but the birth interval appeared to be unchanged. The Committee considered these studies an appropriate and valuable use of the Matlab Field Surveillance Area.

B. Contraceptive Distribution Project: Matlab

The Technical Committee at its meeting in February 1975 took the position that the CRL should be cautious in extending its activities to areas outside of infection, immunity and nutrition. Subsequent to that meeting a separately funded project was undertaken by the CRL to measure the effects of saturating a rural area with oral contraceptives. The project proposes to test the hypothesis that 'the rural population desires to limit their fertility' and that 'oral contraceptives made widely available through local distribution mechanisms are an effective way of satisfying this spontaneous demand'. The project description notes that such attempts have been made elsewhere, but that the effects could not be evaluated because of concomitant social changes. For this reason the project specifies that only a single change be introduced, namely, to make oral contraceptives widely available.

Activities began in August 1975. A baseline survey was completed in the treatment area which has 125,000 residents and in the control area of the same size. The survey figures suggest that less than 2% of eligible women in the areas were using contraceptives in September 1975. Of 19,027 women who were offered oral contraceptives, 68.8% took the supplies. Among the side effects that were noted, the most commonly cited was dizziness. By the 13th week after starting the pills, the interview data suggested that approximately 50% of the pill-takers had dropped out. Information is incomplete on the extent to which the

pill-takers can be classified according to the usual definitions as acceptors and continuing users. The proportion of women using the pills correctly and without omissions is not known as yet. The project is scheduled to run until 30 June 1978.

The fact that this project on contraceptives was undertaken means that the CRL has become directly involved in the population field. The population consultant to the Technical Committee recommended that, if the CRL is to continue or extend its population activities, then the CRL should develop as promptly as possible a plan that indicates the nature and extent of its further activities. To accomplish this, consultations should be held between the CRL and the individuals in Bangalee institutions who are concerned with population policies and programs. The consultations should provide for continuing communication and harmony of purpose. They should lead to the formulation of a coordinated program of research and action. The first topics in the consultations might review the currently available information about determinants of population growth and family size in Bangladesh and then assess the relative importance of the principal factors operating in the rural Moslem and Hindu communities. This should be a brief exercise of only a few weeks or months at most. The next phase might be the development of intervention strategies based on existing knowledge and resources and designed to reduce age specific fertility rates. This could take two to four months. The third phase might be the conduct of field trials, primarily by CRL, comparing different strategies. If results of field trials indicated the feasibility and efficacy of one or more strategies then the next steps might be wider application

thereof by the appropriate agencies of the Bangladesh Government, perhaps with the assistance of international organizations.

In regard to the current project itself, two sorts of questions were raised. Does the protocol meet the usual criteria of committees on medical and ethical aspects of experiments on people? Our viewpoint is that, to be acceptable, this project should include more emphasis on providing information to the women about the way to use the pills correctly and safely. There should be some type of checklist similar to the questions asked in Thailand by the field workers in order to screen out the women who might not benefit from, or even be harmed by the pills. The actual manner of use of the pills in the villages should be monitored more thoroughly. Provision should be made for appropriate assistance to those women who encounter difficulties arising from the oral contraceptives.

The second question relates to the dosage of steroids in the pills being distributed by the project. For Asian women, a lower dosage level might be preferable because of their lower body weight. It would be important to take the recommendation of Bangalee gynecologists on this point.

C. Demographic Studies in the Matlab Surveillance Area

Praise is due to those who conceived and organized this extraordinary operation. Its continuation is a necessity. Demographic data of this high quality are rare indeed, yet provide the information essential to the work of scientists, teachers, economists, doctors and health planners, as well as policymakers and other government agencies. By analogy, the demographic studies from Matlab can be thought of as

providing the knowledge of anatomy and physiology that the physicians and surgeons of the political and social institutions require for their efforts on behalf of public welfare.

V. Recommendations

A. Specific Projects

1. Clinical Complications of Shigellosis

The Committee strongly supports continuation of studies on the pathogenesis and therapy of shigellosis. A high priority should be given to studies of the microangiopathic hemolytic anemia observed in severe shigellosis and to the specific causes of death in shigellosis.

2. Teknaf Dysentery Project

The work on shigellosis at Teknaf should concentrate on epidemiological studies directed toward defining patterns of spread and methods of preventive intervention. The 'minimal treatment' studies in the coastal villages should cease.

3. Urban Cholera

Epidemiologic studies of cholera in Dacca should be continued, *Being done?* being directed toward identifying the mode of transmission. The studies should be limited to a well-defined water supply. In addition to case investigations, water specimens should be regularly collected for culture.

4. Tubewell Studies

The evaluation of hand pump tubewells will have a significant impact on the policy for controlling diarrheal disease, not only in Bangladesh but in many developing countries. The data already collected should be analysed as soon as possible.

5. Shigella Toxins

The investigation of shigella enterotoxins should continue with emphasis on characterization of toxin produced by local strains and comparison with other Shigella dysenteriae toxins.

6. Vibrios in the Environment

The investigation of the ecology of vibrios and of the epidemiology of E. coli diarrhea should be fully supported and should proceed at a steady pace.

7. Nutritional Studies

It is evident that the important synergistic relationships between nutrition and infection require a sophisticated integration of nutritional evaluation techniques into the CRL hospital and field programs. Moreover, the capacity to test the relationship between nutrition and infection is an important component of the kind of population studies appropriate to the CRL. Over the past two years the Laboratory has made a commendable start in developing a nutritional component to its diarrheal disease and population studies as described in the present report. It is, however, still far from achieving the professional competence in nutrition which would be desirable. This can be achieved to some degree by collaboration with the Nutrition Institute of the University of Dacca, but this will not be a substitute for the judicious use of consultants in the formulation and evaluation of projects involving nutrition. We recommend the establishment of cooperative studies with suitably qualified foreign investigators and the recruitment or training of CRL staff with a higher degree of sophistication in this field.

8. Population Studies

The Technical Committee recommends that the CRL define as soon as practicable the nature of its involvement in the population field.

The Technical Committee also recommends that projects in the population field in which the CRL participates should be part of a coordinated plan arrived at in consultation with the appropriate institutions in Bangladesh.

B. General

1. Clinical Research Facilities

We recommend that planning begin for the development of a facility for clinical experimentation that will include the capacity to induce cholera in volunteers in order eventually to conduct studies on the protective value of immunizing agents against cholera. A number of studies have been carried out in the United States which have established that with the use of appropriate safeguards and precautions, cholera can be induced in volunteers by the ingestion of living cholera vibrios with virtually no risk whatsoever to the lives of healthy volunteers. It now becomes essential that such studies be carried out in persons who were born and raised in Bangladesh and who therefore have had similar exposure to cholera and other enteric infections to those whom we wish to protect with vaccines. First, we need to know how many vibrios, and under what conditions of exposure, are required to induce reliably experimental disease in natives of Bangladesh. After this has been established it will be possible to test the protective capacity of various vaccines more precisely, safely and economically than by the use of a large field trial involving thousands of subjects.

Candidate vaccines which show promise in small volunteer trials could then be subjected to large field trials with much more assurance.

A Clinical Experimentation Committee of outside physicians and laymen, which is called for in the Project Agreement under which the CRL is authorized, has been nominated by the Director. This committee has been recommended to the Director of the National Institute of Allergy and Infectious Diseases, U.S.A., for his approval. When this has been accomplished the CRL should draw up a protocol for induced infection studies for consideration by the Directing Council of the CRL, the Clinical Experimentation Committee and by the Clinical Investigation Committee of the National Institutes of Health, U.S.A.

Since all planning in this kind of project will be done with utmost caution and the input of large numbers of committees and individuals is both appropriate and required, it is anticipated that it will take some time between the conception of experimental designs and final approval for their execution. Therefore, we urge that specific plans begin as soon as possible.

2. Recruitment

The Committee strongly supports continuation and extension of efforts to recruit qualified professionals to work at the CRL. In looking to the future, the Director is encouraged to contact the members of the Technical Committee and Consultants regarding staff requirements and for suggestions regarding specific persons or groups who might be contacted.

3. Training

We believe that positive steps should be taken to recruit and develop high-quality medical and scientific personnel from local

sources. This obviously involves some liaison with Dacca University and Medical College, the Post-Graduate Medical College, the Institute of Nutrition, etc. Students from these colleges should be given the opportunity to work in CRL on an elective basis; this would make the existence and interests of the Laboratory more widely known.

A few temporary positions should be available to graduates each year with the intention, known to both sides, that the CRL would sponsor any outstanding person from amongst these for further training overseas. Such overseas training might be funded by fellowships awarded by WHO, Colombo Plan, or other bodies with the cooperation of the Government of Bangladesh. The Technical Committee recommends that the Directing Council should discuss this issue with the Government of Bangladesh. In addition, funds from private universities and foundations and the U.N. University should be sought. It is not thought that there would be need for a guaranteed post on return because such outstanding graduates would have no difficulty in obtaining employment, but the clear intention would be that the best students should form the future leaders in the CRL.

The Committee recommends the development during the next year of a specific training program which will include definition of goals, number of trainees and duration of training.

4. Training Goals

We believe that the CRL should plan its recruitment and training programs in such a way that the work of the institute can eventually be prosecuted by well-trained and selected Bengali personnel.

5. Use of Consultants

The Technical Committee recommends a greater use of visiting consultants to assist in the experimental design of new projects and periodically to review areas for which expertise may not exist in the CRL. About four consultant visits per year should be arranged.

6. Need for Diversification and Expansion of Financial Support

Much greater use could be made of the facilities and capabilities of the CRL if additional financial support were obtained for relevant research activities. Moreover, funding from a variety of sources provides increased security. This can be obtained in a number of ways. Project-type funding generated by either CRL or guest investigators should be sought from government agencies and private foundations in the United States, Canada, Great Britain, Germany, Japan, Sweden and other countries in which such support is available. In addition, more effort should be made to bring additional industrialized countries into regular support of the CRL as is now the case for the U.S., U.K., and Australia. Moreover, a special effort should be made to interest selected OPEC countries in contributing to the CRL for the benefits which would accrue to them from research and from the practical training opportunities for their nationals in its programs. The CRL also clearly derives benefits from the participation in its programs of investigators from the Johns Hopkins University ICMR program. Similar mutually beneficial research relationships should be sought with other academic institutions in the industrialized countries on whatever scale is appropriate. This should include single investigators who are able to provide for their support.

7. CRL Library

The library is an important resource not only for CRL but for other medical institutions in the country. Close cooperation with the National Medical Library on the floor above will be essential, as well as the formulation of policies and procedures for controlling the use of the library and its services by persons not associated with the CRL. The staff and resources required will depend on the nature of these policies. As the Laboratory broadens the scope of its research interests, there will also be greater pressure than at present for additional books, journals and space. Now that a new and well-qualified librarian has been hired, the Committee urges a thorough review of library needs, procedures and policies and will look forward to a report and discussion of these at its next meeting.

C. Future Meetings of the Technical Committee

The proceedings of the meeting this year were much improved over last. The members were provided with abstracts of most papers well before the meeting, and full manuscripts were available for a number of papers during the meeting. Time was set aside for a meeting with the Director and a tour of the laboratory in Dacca, and much more time was available for report writing and meetings of the Committee. The days given over to scientific presentations were so full, however, that little time could be found for discussions with individual investigators without missing a scheduled event.

We would suggest the following schedule for future meetings:

First full day (day after arrival in Dacca):

Meetings with Director and Division Heads (separately).

Tour of CRL.

Second and Third Days:

Presentation of individual papers and investigator conferences. Individual presentations may include summaries of division activities by division chief.

Fourth and Fifth Days:

Discussion with individual investigators in their laboratory or at their field project sites. The emphasis would be on one-to-one discussion.

Sixth Day -- Trip to Matlab by all TC members:

No papers presented. All formal presentations will have been completed on the second and third days.


Seventh and Eighth Days:

Write report.

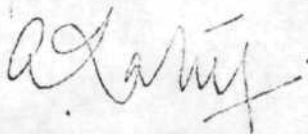
Ninth Day -- Departure

Finally, the members of the Technical Committee and the Expert Advisors wish to express their thanks to the Director of the CRL and to the entire staff for their individual and collective efforts to make our visit to Bangladesh and the CRL a delightful and rewarding experience.

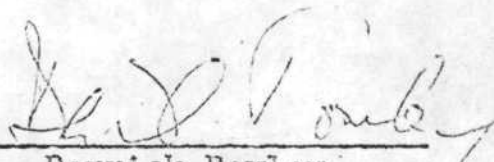
Signed by the members of the Technical Committee:



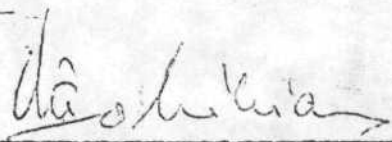
John P. Craig, Chairman
United States Representative



M.A. Latif
Bangladesh Representative



Derrick Rowley
Australian Representative



R.E.O. Williams
United Kingdom Representative