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Library,
Pakistan-SEATO Cholera Research Lab,
Mohakhali, Dacca-12

MEETING OF
NIH CHOLERA ADVISORY COMMITTEE

Building 31, Conference Room 2
National Institutes of Health
Bethesda, Maryland

TENTATIVE AGENDA

Friday, October 22, 1965

- 9:00 Call to Order - Dr. John R. Seal
- Approval of the minutes of the meeting of January 30, 1965 (Tab C)
- Old business: Items 1, 2, 3, 4, 6, 7, 8, 13, 14 of the minutes of January 30, 1965.
- 9:45 Report on current status of the Pakistan-SEATO Cholera Research Laboratory - Dr. A. S. Benenson, Director
- 10:15 Report on U. S. - Japan Cooperative Program Panel Meeting on Cholera - Dr. Charles C. J. Carpenter
- 10:30 Coffee Break
- 10:45 Consideration of 1965-1967 and 1967-1970 program plans for:
1) SEATO Cholera Research Program
2) Pakistan-SEATO Cholera Research Laboratory
- N. B. This item is for the purpose of developing program objectives and plans in accordance with item 11 of the minutes of the meeting of January 30. Subsequent discussions with AID have reinforced the necessity of this action. It will be in preparation for discussions in the afternoon with Dr. Shannon and representatives of the State Department and AID.
- 12:45 Lunch
- 2:00 Meeting with Dr. Shannon, State Department and AID representatives.
- Presentation and discussion of tentative program plans and objectives for period 1965-1967 and 1967-1970. This will include consideration of extension of existing agreements with AID and the Government of Pakistan after June 30, 1967.
- 5:30 Recess

Saturday, October 23, 1965

9:00 Executive Session of Committee

12:00 Adjourn

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Materials distributed with this tentative agenda are for background information and should be brought to the meeting. The most important business of the meeting is the consideration of extension of the agreements for operation of the Program, including the Laboratory. Tab D contains the general "Agreement between the AID and the DHEW." Tab E contains the more specific "Memorandum of Understanding between AID and the NIH." AID requests that a detailed outline of the program and financial requirements be provided prior to making additional funds available for operation to the present termination date of June 30, 1967. They will also desire the same type of information in connection with plans to request extension of the agreements to June 1970.

Members of the Committee are requested to review the attached informational material before the meeting in order that discussion may be expedited.

If members wish to include additional items on the agenda, it is requested that these be forwarded prior to the meeting.

John R. Seal, Chairman
NIH Cholera Advisory Committee
Building 31 room 7-A-52
National Institutes of Health
Bethesda, Maryland 20014

NIH CHOLERA ADVISORY COMMITTEE

Oct. 1965

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National Institutes of Health
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Revised November 1, 1964

Background Information

SEATO CHOLERA RESEARCH PROGRAM

The SEATO Cholera Research Program was established in 1959 by an interchange of diplomatic notes between the Secretary-General of the South-East Asia Treaty Organization (SEATO)* in Bangkok, Thailand, and the U.S. representative to SEATO. Under the terms of this agreement, the Government of the United States agreed to make available the sum of \$400,000

"to finance a cholera research program to be carried out by the National Institutes of Health [NIH] of the United States Department of Health, Education, and Welfare [HEW], through American, Asian and other appropriate institutions and bodies."

These notes also indicated the interest of both the Governments of Pakistan and Thailand in participating in the cholera program and in developing activities in their respective countries.

This program was a direct outgrowth of the epidemic spread of cholera into Bangkok, Thailand, in June 1958. This was the first time in approximately ten years that cholera had occurred in epidemic form in this portion of Asia. Considerable scientific interest was shown by U.S. investigators in working in Thailand, and U.S. teams from both civilian and military institutions offered their assistance to the Thais in studying the epidemic. It was the desire to continue these activities that led to the development of the SEATO Cholera Research Program in 1959.

The National Institutes of Health in January 1959 appointed an Ad Hoc Committee on Cholera, under the leadership of the late Dr. Joseph Smadel, then Associate Director of NIH, to advise the Director of NIH on the extent of NIH participation in this program. As this became a continuing program, the Committee was formalized in December 1959 and became the NIH Cholera Advisory Committee whose function is "to advise the Director of the National Institutes of Health on all phases of the operation of the SEATO Cholera Research Program and assist him in the technical direction of the program." (The present membership of this Committee is noted in appendix I.)

In August 1959, an interagency agreement was signed between the International Cooperation Administration (ICA)** and the Department of Health, Education, and Welfare of the United States Government, asking the National

* The following nations are members of SEATO: Thailand, Philippines, Pakistan, U.S., U.K., France, Australia, and New Zealand.

** ICA was succeeded by the Agency for International Development (AID) in 1961, and all further references are to AID.

Institutes of Health to assume the responsibility for the development of the SEATO Cholera Research Program and allocating the sum of \$400,000 with the following objective:

"A research program consisting of fundamental and applied field and laboratory investigations . . . as a means of increasing knowledge of cholera and as an approach toward more effective control of this disease."

It proposed that a cholera research laboratory be established in an Asian SEATO member country which would serve to initiate studies in three broad areas: (1) epidemiological studies of the disease both in epidemic and non-epidemic periods, (2) bacteriological studies, and (3) studies of other diarrheal diseases in epidemic and non-epidemic periods. It was contemplated that training would play an important part of the program and that the laboratory would be used as a base for field expeditions which would be conducted to study cholera in Asia. (This interagency agreement is still in effect and has been amended to provide funding totaling \$940,000 as of June 1964.)

In August 1959, the NIH sent to various countries in Asia, a cholera research advisory team headed by Dr. Smadel to make a study of the situation in Asia and to make recommendations regarding the development of the SEATO Cholera Research Program. (The members of the advisory team are noted in appendix II.) The team recommended a broad research program including clinical and physiological studies, epidemiological studies on cholera endemicity, the role of carriers, the role of potable water from tube wells, etc., vaccine studies to determine the efficacy of cholera vaccine, and nutritional studies to determine the relationship between nutrition and cholera. They proposed that this work be initially undertaken in Bangkok and that SEATO support a laboratory there for approximately one year, during which time arrangements would be made to develop a permanent SEATO Cholera Research Laboratory in Dacca, East Pakistan. In addition to the basic laboratory, the group also recommended training cholera investigators from the Asian area and holding scientific conferences of cholera workers.

A formal agreement was developed in December 1959 between the Governments of Thailand and the United States for the development of the Thailand-SEATO Cholera Research Laboratory. This laboratory was a logical continuation of the activities of Thai and United States personnel who engaged in the cholera studies in 1958, and furnished them with a base of operations. It was officially located in the Royal Thai Army Institute of Pathology in Bangkok and was financially supported by both the Thai and U.S. Governments. The U.S. Government's contribution came principally from the SEATO Cholera

Research Program, the Walter Reed Army Institute of Research (WRAIR), and the AID program in Thailand. U.S. workers from the U.S. Naval Medical Research Unit No. 2 in Taipei, Taiwan (NAMRU No. 2), Walter Reed, and Jefferson Medical College were involved in this program. Studies on the epidemiology of the outbreak in Thailand, including extensive bacteriological observations, were reported. Physiological studies involving fluid replacement were of particular interest, and pathological studies involving a new technique for making intestinal biopsies on acute cholera cases were made. The latter study was of particular significance because it was the first report that showed that the lining of the intestine tended to remain intact in acute cholera cases, contrary to the classical concept of denudation of the intestinal lining by toxins resulting in heavy fluid loss.

The Bangkok laboratory continued through December 1960 when it was succeeded by the SEATO Medical Research Laboratory, a cooperative endeavor between the Walter Reed Army Institute of Research and the Government of Thailand, completely separate from the SEATO Cholera Research Program. It is a broad-based medical research laboratory interested mainly in problems other than cholera, although it has carried on a few activities in cholera research.

The SEATO Cholera Research Program sponsored the SEATO Conference on Cholera that was held in Dacca, East Pakistan in December 1960. A special publication of the proceedings of this meeting was prepared and distributed by SEATO and NIH, and included extensive reports on (1) management of clinical cholera in established hospitals and in field stations, (2) physiological changes in cholera, (3) pathology and pathogenesis, (4) vaccines and immunity, (5) epidemiology, and (6) laboratory identification of cholera vibrios.

Additional research conferences on cholera are to be sponsored by the Program from time to time in order to facilitate exchange of ideas and knowledge among the scattered investigators actively working in the field. A second conference is scheduled in Honolulu, Hawaii, January 24-29, 1965, under the auspices of the University of Hawaii.

In October of 1960 a formal agreement was signed by the United States Government and the Government of Pakistan which created the Pakistan-SEATO Cholera Research Laboratory (CRL). This agreement was superseded nearly in its entirety by a second agreement dated December 30, 1961, which called for the development of an autonomous international laboratory to be established at the Institute of Public Health in Mohakhali in Dacca, East Pakistan. The broad objective of the CRL was defined as

"the development, evaluation, and demonstration of measures of prevention and eventual eradication of cholera."

The laboratory was to be financed by contributions from the Governments of Pakistan and the United States, but the Governments of other SEATO nations who desired to participate were invited to do so. In 1962, the United Kingdom became a participating nation. The NIH was given the responsibility for the immediate scientific direction of the laboratory under the overall guidance of a Directing Council and the responsibility for appointing the director of the laboratory, who in turn was authorized to direct the activities of the CRL. The Directing Council was to consist of a representative from (1) each of the nations participating in the laboratory program (Pakistan, U.S., and U.K.), (2) the Secretary General of SEATO, and (3) the Director of NIH. (Representation on the Directing Council is noted in appendix III.) In addition to the Directing Council, a Technical Committee appointed by the Director of NIH was provided for, to advise the Director of the laboratory and the Directing Council on the technical aspects of the Dacca laboratory's program development. The Technical Committee consists of three members who are research scientists from the U.S., the U.K., and Pakistan. A Panel of Experts made up of scientific workers from the different SEATO countries, interested in various aspects of the cholera program, is also appointed to provide specialized advice to the Committee. (See appendix IV for members of Technical Committee and Panel of Experts.)

The laboratory was inaugurated at the time of the SEATO Conference in December of 1960 and became operational shortly thereafter. The cholera ward was completed in November 1962 and admitted its first patients November 28, 1962. The laboratory occupies one entire wing of the Institute of Public Health Building and consists of three floors; the first floor is a 20-bed cholera ward with the usual ancillary facilities; the second and third floors are devoted to office space, a library, and laboratories for the clinical, physiological, and bacteriological studies. A separate suite accommodates the Epidemiology Section, and animal facilities are also provided. The total staff as of November 1964 was almost 300, including six Americans, one from the U.K., two from Australia, and the remainder Pakistanis. (A list of the non-Pakistani personnel that have been assigned to the laboratory is attached as appendix V.)

The laboratory is comprised of four scientific sections - Epidemiology, Clinical Research, Bacteriology, and Water Study - supported by Administrative and General Services Sections. The main research emphasis of the Epidemiology Section has centered on studies of the mode of transmission of cholera within the endemic zone, as exemplified by investigations of the pattern of its spread within families, and on field research to evaluate the effectiveness of cholera vaccine. The Section on Clinical Research has carried out studies aimed at simplifying and reducing the cost of cholera

treatment and, using these results, has supported the vaccine field trials by establishing a second cholera treatment center in the study area. Investigations of the pathologic physiology of acute cholera, and a search for host factors that might predispose to cholera infection (the latter in collaboration with the Nutrition Survey of Pakistan) have also been undertaken. The Bacteriology Section offers essential support for both epidemiologic and clinical studies by examining large numbers of specimens for the presence of V. cholerae and/or other pathogenic bacteria. In addition, research studies designed to improve these diagnostic methods, and to study the interactions of the cholera vibrio with specific bacteriophages are being carried out. The Water Study Section collaborates with Epidemiology and Bacteriology in investigating the relationship of contaminated water supplies to local outbreaks of cholera and is also carrying out a long-range study of the ecology of the cholera vibrio in natural waters, as affected by both chemical and biological factors. This includes both field studies, and in vitro experiments in which aquaria containing various waters, fishes, plants, and the like are artificially inoculated with V. cholerae. The results of these investigations have been reported annually to the CRL Technical Committee and have been the subject of publications in appropriate scientific journals. (Appendix VI is a list of publications relating to the SEATO Cholera Research Program, with those originating at the CRL in Dacca marked by an asterisk*.)

The CRL is financed mainly from funds from the United States Government which come from four principal sources: (1) Funds made available to NIH by AID, a portion of which are budgeted for the CRL, as this constitutes the principal activity of the SEATO Cholera Research Program, (2) Pakistan rupees made available from Public Health Service P.L.-480 funds under the terms of a research agreement between NIH and the CRL, (3) direct financial contribution and administrative support from the USAID Program in Pakistan, (4) direct contributions of NIH, particularly in the payment of salaries of the U.S. staff from the National Heart Institute and the Office of International Research. The Government of Pakistan has made available the physical facilities of the Institute of Public Health, including utilities, and an annual contribution, currently 250,000 rupees, to the operating fund of the laboratory. The Government of the United Kingdom has made an annual contribution of 10,000 pounds which has been used for the payment of salaries of U.K. personnel or for the purchase of supplies and equipment. Australia has contributed two vehicles and also the services of an anthropologist team to work with the Epidemiology Section.

The main emphasis of the SEATO Cholera Research Program has been concerned with the base laboratory in Dacca; however, NIH has followed with great interest the various outbreaks of cholera occurring elsewhere in Asia. For instance, in August 1961, when there was a cholera outbreak in Hong Kong, over 130 specimens of Vibrio cholerae from Hong Kong patients were supplied by the Hong Kong Health Department to NIH investigators and their university colleagues who were concerned with the program. In addition, the Jefferson Medical College group in Philadelphia stockpiled special diagnostic antisera and prepared a teaching manual describing new and quick methods for isolating and identifying Vibrio cholerae.

When cholera spread to the Philippines in October 1961, two bacteriologists, one from the NIH and one from the Jefferson Medical College, who had been concerned with these techniques and special sera, were sent to Manila by the SEATO Cholera Program to work with bacteriologists of the Philippine Department of Health. In collaboration with their Manila colleagues, they taught the techniques to other Philippine bacteriologists brought in from outlying areas and supplied them with the new diagnostic materials. In 1962, further studies were carried out by the Program in the Philippines when a group from the Communicable Disease Center of the P.H.S. worked with the Philippine Department of Health in studying the epidemiology of cholera and in attempting to find a suitable location for a field trial of the efficacy of cholera vaccine. After careful evaluation, it was decided that a field trial could not be undertaken profitably at that time. However, the CDC group did contribute significant observations on the method of spread of cholera in the Philippines.

Appendix I

NIH CHOLERA ADVISORY COMMITTEE
(As of November 1964)

Dr. Clifford A. Pease, Jr. (Chairman)
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Mr. Richard C. Parsons
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Captain John R. Seal, MC, USN
Commanding Officer
Naval Medical Research Institute
National Naval Medical Center
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Colonel William D. Tigertt, MC, USA
Director
Walter Reed Army Institute of Research
Walter Reed Army Medical Center
Washington, D. C.

Dr. Theodore E. Woodward
Professor of Medicine
University of Maryland
School of Medicine
Baltimore, Maryland
(Presently: University of Maryland
International Center for Medical
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6 Birdwood Road
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1959 SURVEY TEAM

Dr. John H. Dingle
Professor of Preventive Medicine
Western Reserve University School of Medicine

Dr. Kenneth Goodner
Professor of Microbiology
Jefferson Medical College

Dr. Colin M. MacLeod
Professor of Medicine
New York University School of Medicine
(Now Deputy Director, Office of Science & Technology, Executive
Office of the President)

Colonel Richard P. Mason
Director, Walter Reed Army Institute of Research
Walter Reed Army Medical Center
(Now Vice President for Research, American Cancer Society)

Dr. Joseph E. Smadel (Now deceased)
Associate Director for Intramural Research
National Institutes of Health

Dr. Theodore E. Woodward
Professor of Medicine
University of Maryland School of Medicine

DIRECTING COUNCIL OF THE
PAKISTAN-SEATO CHOLERA RESEARCH LABORATORY

1964

Dr. Ralph E. Knutti (Chairman)
Director
National Heart Institute
Bethesda, Maryland

Representing the Director
of the National Institutes
of Health

Dr. D. J. M. MacKenzie
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Edinburgh, Scotland

Permanent Representative
of the Government of the
United Kingdom

Lt. Col. S. A. Mallick (Vice-Chairman)
Director of Health Services
Government of East Pakistan
Eden Buildings
Dacca, East Pakistan

Representative of the
Government of Pakistan

Mr. D. A. Wraight
Deputy Secretary-General
South-East Asia Treaty Organization
Bangkok, Thailand

Representing the Secretary-
General of SEATO

Dr. Willard Boynton
Senior Public Health Officer
US AID Pakistan
Karachi, West Pakistan

Representative of the
Government of the United
States of America

Dr. Abram S. Benenson (Secretary)
Director
Pakistan-SEATO Cholera Research Laboratory
Dacca, East Pakistan

Director of the Pakistan-
SEATO Cholera Research
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TECHNICAL COMMITTEE
OF THE
PAKISTAN-SEATO CHOLERA RESEARCH LABORATORY
(As of November 1964)

U. S. A.:

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Microbiology, epidemiology

Dr. Jacinto Dizon, Chief
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Infectious disease and
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Water biology

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University of Texas Medical Branch
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Microbiology, ~~immunology~~,
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Clinical disease, general
aspects

Appendix V

List of non-Pakistani personnel who have been assigned
to the Pakistan-SEATO Cholera Research Laboratory
through November 1, 1964

Director:	Dr. Fred L. Soper 1961-62	U. S.
	Dr. Abram S. Benenson 1962-	U. S.
Epidemiology Section:	Dr. Joe L. Stockard 1960-63 (also Deputy Director)	U. S.
	Dr. Robert O. Oseasohn 1963-	U. S.
	Dr. Robert M. Glasse 1963-	Australia
	Mrs. Robert M. Glasse 1963-	Australia
Clinical Research Section:	Dr. Robert S. Gordon 1961-64 (Scientific Director)	U. S.
	Dr. William B. Greenough 1962-	U. S.
	Dr. John Lindenbaum 1963-	U. S.
	Dr. M. L. Reiner 1963-	U. S.
	Miss Dorothy Torrance 1963-	U. K.
	Dr. O. Ross McIntyre 1961-62	U. S.
Bacteriology Section:	Dr. B. I. Davies 1962-63	U. K.
	Mr. John J. Brennan 1963-64	U. K.
Administrative Section:	Mr. Robert S. Townsend 1962-63	U. S.
	Mr. Robert E. Freise 1964-	U. S.

SEATO CHOLERA RESEARCH PROGRAM PUBLICATIONS
(as of November 1964)

- SEATO Conference on Cholera. Papers Presented and Summaries of Discussions. Dacca, East Pakistan, December, 1960. SEATO, Bangkok, 1962, pp. 174.
- Direction of the Wind. SEATO Conference on Cholera. Pub. Health Rep. 76: 323-334, 1961.
- Monsur, K. A.: A highly selective gelatin-taurocholate-tellurite medium for the isolation of Vibrio cholerae. Trans. Roy. Soc. Trop. Med. Hyg., 55: 440-442, 1961.
- Feeley, J. C.: Isolation of cholera vibrios by positive-recognition plating procedures. J. Bact. 84: 866-867, 1962.
- * Ahmed, S. Z.: Water studies in connection with cholera epidemics. East Pakistan Med. J.: 7: 13-15, 1963.
- * Gordon, R. S., Jr., Greenough, W. B. III, Benenson, A. S., Ahmad, K., and Rosenberg, I. H.: Cardiac manifestations of disturbed intermediary metabolism in cholera (abstract). J. Clin. Invest. 42: 937-938, 1963.
- Immunological aspects of cholera. Report of meeting of Technical Committee of Pakistan-SEATO Cholera Research Laboratory. Pub. Health Rep. 78: 699-705, 1963.
- * Gordon, R. S., Jr.: Nutrition and cholera (abstract). Proceedings of the Seventh International Congresses of Tropical Medicine and Malaria. Grafica Olimpica Editora, Rio de Janeiro, Brasil, 1963.
- * Monsur, K. A.: Bacteriologic diagnosis of cholera under field conditions. Bull. W. H. O. 28: 387-389, 1963.
- * Gordon, R. S., Jr.: Nutrition and cholera (abstract). Proceedings of the Sixth International Congress of Nutrition. Edinburgh, E & S Livingstone, Ltd., 1964.
- * Greenough, W. B. III, Gordon, R. S., Jr., Rosenberg, I. H., Davies, B. I., and Benenson, A. S.: Tetracycline in the treatment of cholera. Lancet, 1: 355-357, 1964.
- * Gordon, R. S., Jr., Ahmed, J., Akbar, R., Alam, A.K.M.J., Ali, M. M., Barui, R. K., Greenough, W. B. III, Islam, M. R., Islam, M. A., Khan, A. Q., Lindenbaum, J., Rahman, A.S.M.M., and Zoha, M. S.: Treatment of cholera in 1964. East Pakistan Med. J. 8: 10-19, 1964.
- * Greenough, W. B. III: Cholera. In Current Therapy, 1965. In press.

* Papers originating at the Pakistan-SEATO Cholera Research Laboratory

NIH CHOLERA ADVISORY COMMITTEE

MINUTES OF MEETING

January 30, 1965

The meeting was held at the Waikiki Biltmore Hotel, Honolulu, at 9:00 a.m. on Saturday, January 30, 1965 following the Cholera Research Symposium. Members present were:

Dr. Clifford A. Pease, Jr., OIR, NIH (Presiding)
Dr. John H. Dingle, Western Reserve
Dr. Thomas Francis, Jr., University of Michigan
Col. William Tigerat, MC, WRAIR
Dr. Alexander D. Langmuir, CDC
Mr. Richard C. Parsons, AID
Capt. Robert A. Phillips, MC, USN
Dr. Margaret Pittman, BBS, NIH
Capt. John R. Seal, USN
Dr. Kenneth Gardner, Jefferson
Dr. Theodore E. Woodward, Maryland

Also participating were:

Dr. James A. Shannon, OD, NIH
Dr. Colin M. MacLeod, OST
Dr. Abram S. Benenson, CRL
Dr. Robert S. Gordon, Jr., NIAMD, NIH
Dr. John C. Feeley, BBS, NIH (Rapporteur)

Matters considered by the committee are listed in the order discussed.

1. Should the CRL paper on "Treatment of Cholera in 1964" (East Pak. Med. J. 8: 10-19, 1964) be distributed widely in English-speaking areas in Asia?

After some discussion, it was decided that a distribution of the paper was desirable, and that the matter should be taken up with SEATO to work out a means of disseminating the document.

2. Discussion of treatment manual and preparation of a paper on treatment of cholera and a brochure on laboratory diagnosis.

The above items were discussed together. In the matter of treatment, it was recognized that there is a need for: (1) A practical manual which avoids technical debate, and (2) A sophisticated authoritative publication

(perhaps in the JAMA). It was felt that the Armed Forces TB-Med issuance on cholera could be employed as a model or perhaps used directly, with some modification, for the purpose of evolving a practical manual. Capt. Seal and Col. Tigertt were asked to look into the matter regarding the TB-Med document, the current version of which is two to three years old and in need of revision. Dr. Gordon observed that anything written now will have to be re-edited, especially in regard to chemotherapy and pediatric aspects. Capt. Phillips indicated that they had found the NAMRU-2 Manual inadequate in some respects due to the poor backgrounds of the people writing it, and asked that it be returned to NAMRU #2.

There was discussion of the preparation of a manual on laboratory diagnosis. Dr. Goodner felt that the laboratory aspects of the TB-Med document also needed revision and expressed the view that the laboratory and treatment manuals should be separate. Dr. Francis suggested that the American Journal of Public Health might be a good outlet for publishing an article for covering diagnosis and treatment.

It was decided: (1) that the Committee should encourage the early publication of an article on treatment in the J.A.M.A. (Dr. Gordon and Capt. Phillips were asked to work this out); (2) that the Committee will assume responsibility for preparation of the appropriate manual-type issuance(s) on treatment and laboratory diagnosis.

3. SEATO Training Film Dr. Pease presented a status report on arrangements with the Audiovisual Section of CDC for the preparation of documentary and teaching films. Matters have progressed more rapidly than anticipated, and the photographers were ready to work before the scripts were finalized. It is anticipated that two films will be prepared: (1) a training film for medical and paramedical personnel, and (2) a general purpose documentary film on the SEATO Cholera Research Program. The necessity for preparing scripts was discussed. Dr. Woodward is preparing a typhoid film and offered his material as a guideline. He felt that films were of value as a perpetual record of the disease, although Dr. MacLend questioned their effectiveness in teaching American medical students. Dr. Shannon noted that there might be considerable public relations value in such films, particularly in view of the expenditure of U. S. funds. It was decided that the details should be worked out with CDC, and that USIA and SEATO should be brought into the picture.

4. Staffing Report on CRL Dr. Pease commented on the report which had been circulated to the Committee. He noted that several of the physicians who were to go to the CRL in the future had been brought to the Honolulu Symposium. There was considerable doubt that the Army would make Dr. Miller available. Col. Tigertt was to look into the matter. Dr. Shannon suggested

that he could be assigned to CRL on an Armed Services reimbursable detail. Capt. Phillips stated that some consideration might be given to arranging tri-service representation on a rotating basis at the laboratory.

5. Publication of the Proceedings of the Cholera Research Symposium.
Several items relative to publication were reviewed as follows:

- (1) Need for senior author for library indexing purposes. It was felt that none was needed.
- (2) The proceedings were to be dedicated to the late Dr. Joseph E. Smadel.
- (3) Should Dr. Sabin's address be included? The Committee recommended that it not be included.
- (4) Should color reproduction be used? This was ruled out by the high cost.
- (5) Should the photograph of the Symposium participants be included? This was felt inadvisable due to loss of detail in size reduction.
- (6) Should authors receive galley proof? This was regarded as impractical and would delay publication. It was suggested that chairmen and rapporteurs could read proof.
- (7) How many copies should be printed? Dr. Cummings (Director, NLM) was to be consulted regarding library list before deciding.
- (8) How was discussion of papers to be handled? Rapporteurs were to be sent the transcript of the discussions and they would prepare a summary of the discussions, omitting names, and return this to Hawaii.

6. Report on the Technical Committee meeting. Dr. MacLeod noted that the report had already been distributed, and summarized by saying that the Technical Committee was highly pleased with the majority of developments to date. The main area of concern of the Technical Committee was a weakness in the Bacteriology Section due to the lack of a competent senior directing scientist. Dr. Cruickshank has agreed to attempt to recruit such a person in the U. K. and, through Dr. Howies, has elicited the interest of Dr. Tomlinson, a senior microbiologist in the Public Health Laboratory Service. It was decided that Dr. Tomlinson's curriculum vitae should be obtained. Dr. Goodner stated that Dr. Harry Smith could not be persuaded to accept an assignment in Dacca.

Considerable discussion followed on personnel needs in the microbiological area. Dr. Dingle noted that an adequate microbiology service would require competence in both (1) large volume diagnostic work to support clinical and epidemiologic studies, and (2) research capability in several areas. There was debate on whether one individual could fulfill both functions. It was recognized that some areas of research could best be

done in Dacca, while others could be more profitably pursued elsewhere. Dr. Shannon suggested that the Career Development files should be checked to locate younger workers who could be sent to Dacca for first-hand experience, which hopefully would stimulate interest in problems that could be brought back and pursued in home laboratories.

Dr. Goodner expressed concern that the CRL program was outgrowing existing personnel capabilities and physical space. Dr. Benenson answered that they had prospects of additional space in the Institute, and that they were using the garage for additional patient care space. He noted also the COEP plans for a new Infectious Disease Hospital on the Institute grounds.

The function of the laboratory in the training of Pakistani physicians and scientists was discussed. It was recognized that many Pakistani physicians, if sent to the U. S. for additional training, would find arrangements such as the NIH Clinical Associate Program far over their heads. Dr. Benenson noted that a basic problem was that really good physicians do not become interested in cholera because there is no financial reward.

Dr. Woodward emphasized that, over the long term, younger persons who attain a high degree of competence through training and experience will be at a disadvantage when U. S. contingents pull out. He noted that they have no future because higher jobs in universities and government are controlled by a firmly entrenched "old guard." This problem is widespread in Asia. He recommended the establishment of full time positions for these younger persons who have had excellent training, so that training efforts would not be wasted when they go into clinical practice.

Dr. Langmuir raised the question of his own role and that of CHC. He expressed concern over the scope of the routine epidemiology load that Dr. Mosley will inherit. Dr. Pease noted that CDC had agreed to provide epidemiological support and that this involved CDC's providing the necessary personnel with adequate experience to carry out the responsibilities required at Dacca.

7. Report on the Directing Council meeting, held Jan. 18-19, 1965
In Dr. Knutti's absence, Dr. Benenson summarized the report. He noted that the Council recommended a routine 10% increase in budget in contributions of the U. S., U. K., and Pakistan to the Operating Fund. The Council also recommended that the dollar fund at NIH be used to purchase a reserve supply of intravenous fluids. The Council also noted that the COEP had set aside a fund of Rs. 96,000 which can be made available when AID produces matching funds.

Dr. Benenson noted that Australia was providing wireless equipment and extending support for Mrs. Glasse. The question of representation of Australia and other countries on the Directing Council was raised. At present this is available to any SEATO country on contribution of a certain sum of money. It was noted that the U. S. is currently funding approximately 75% of the operation, and that support from other countries would be welcomed.

Mr. Parsons raised the question of how the CRL could implement all the suggestions for future research which emanated from the Symposium and the Technical Committee. Dr. Pittman observed that all the research problems made evident at the Symposium were not intended just for the CRL. Dr. Shannon suggested that serious thought should be given to determining the feasibility for automating as many routine laboratory procedures as possible. He suggested that the CRL define their requirements so that a program along this line can be developed.

8. Dr. Pease noted that they were considering an agreement with Dr. Stanley Bradley, Professor of Medicine at Columbia P & S in New York, regarding their interest in the work of the CRL. Dr. Goodner suggested that Dr. Code should be brought under such an arrangement, but Dr. Pease noted that arrangements under Dr. Bradley had proceeded so far that we should try and complete them before approaching another institution.

9. Report of visits to the Philippines and Thailand and consideration of Special Training Grant proposals for those countries. Dr. Pease cited the basic authority for such actions in the agreements between HEW and AID. He noted that the Philippines are interested in sending bacteriologists to Dr. Mukerjee's laboratory in Calcutta, and that these are all training grant proposals, and it seems apparent that there is little likelihood of placing any research grants in these countries at this time.

10. Discussion of Dr. Craig's Grant Proposal The question was whether the SEATO Cholera Research Program should provide interim funds to carry on the work on the guinea pig skin permeability factor until it can be funded in the regular way through an NIH grant. The proposal is now being processed for the April Study Section, to be considered by the June Council. If approved, regular NIH grant support would commence Jan. 1, 1966.

Dr. Pittman briefly reviewed the proposal. Reports received from three reviewers were favorable, one approving without reservation, and the others expressing concern that the scope was too broad. Dr. Goodner had not sent in his report, but asked that he be included in the latter category. It was noted that Dr. Craig also has a grant for work on diphtheria toxin project.

There was discussion of what would happen if his grant did not receive regular approval, but this could be considered if and when that happened. There were several suggestions for improving the application and Dr. Craig was to be advised of these. Dr. Shannon suggested that it might be better for Dr. Craig to unify his grants, and he noted that there was a possibility that it might not be given high priority. Even if approved, it might not be funded at the stated time.

The proposal for interim support was approved unanimously by the Committee, and it was recommended that an endorsement be sent to the Study Section.

11. Other Business Mr. Parsons stated that there was a tightening up of various programs and that the AID was concerned about the cholera program. He asked that the following second paragraph of a memo to him from J. M. Blume of NESAs/AID/Washington dated January 22, 1965 be entered in the minutes:

"I propose to initiate more systematic review through a joint NESAs/FE/TCR effort. I think it would be useful for you to inform NIH and the Advisory Committee of our intentions and of the likelihood that we will be requesting from NIH a project plan to cover the project to its termination. This would be similar to the E-1s required on other projects and would recount both achievements to date and time-phased targets for the future."

Dr. Shannon stated that this request for a study plan and a more thorough accounting was reasonable.

12. Dr. Goodner requested that the Committee go on record as expressing its pleasure with the productive efforts of the Director and Staff of the CRL. This was approved unanimously.

13. Dr. Gordon suggested that the Committee should consider supporting the development of a single intravenous fluid to simplify cholera therapy. He suggested that U. S. firms with Affiliates or branches in India or Pakistan be interested in this problem. The necessity for local production was emphasized in view of the high cost of transporting "water."

14. Dr. Francis suggested that there were too many papers crowded into the program for Symposium. Dr. MacLeod felt that the next Symposium should be held in two years.

15. Mr. Parsons expressed his personal concern and that of AID over Dr. Pease's upcoming departure. Dr. Shannon assured that an orderly transition will be made.

16. The Committee voted a unanimous resolution of appreciation to Dr. Pease for his outstanding contributions to the success of the program.

The meeting was adjourned at 1:15 p.m.

The following is a consolidation of the Agreement between the International Cooperation Administration and the Department of Health, Education, and Welfare dated August 15, 1959, Amendment #1 dated July 11, 1962, and Amendment #2 dated June 30, 1964.

SOUTHEAST ASIA TREATY ORGANIZATION CHOLERA RESEARCH PROGRAM

I. General Statement

In furtherance of the support by the Government of the United States of America to the Southeast Asia Treaty Organization (hereinafter "SEATO") and in recognition of the fact that cholera remains a major problem in Asia, the Government of the United States of America by means of an agreement at the diplomatic level with the Secretary General of SEATO which was effective May 29, 1959 agreed to contribute up to \$400,000 to permit American scientists to work with their Asian colleagues on their research on cholera. The agreement between the United States of America and SEATO provides that \$400,000 of the appropriation for the President's Fund for Asian Economic Development (hereinafter "AEDF") will be allocated by the International Cooperation Administration (hereinafter "ICA") to the National Institutes of Health of the United States Public Health Service of the Department of Health, Education, and Welfare (hereinafter "NIH") which in turn makes grants to and/or contracts with American, Asian and other appropriate institutions and bodies, or otherwise finance, research on cholera. The product of the research will be made available to the Free Asian nations. In addition to the original contribution of \$400,000 the Agency for International Development will provide for the same purposes as herein before specified, from appropriate sources, the additional sum of \$150,000 in fiscal year 1962, up to \$200,000 in fiscal 1963 subject to the availability of funds and in subsequent years such additional amounts as are mutually agreed upon by the AID and NIH, subject to the availability of funds. This agreement as amended, is entered into under authority of Section 632(b) of the Foreign Assistance Act.

The International Cooperation Administration (ICA) has been succeeded by the Agency for International Development (AID); therefore, all references to "ICA" will be read as "AID".

II. Cholera Research Project to be Performed by NIH

Objective

A research program consisting of fundamental and applied field and laboratory investigations will be organized as part of the SEATO Cholera Research Program as a means of increasing knowledge of cholera and as an approach toward more effective control of this disease.

Organization

A research laboratory (and as appropriate sub-laboratories) will be established in conjunction with an established institution in an Asian SEATO member country. This laboratory will be closely linked with research laboratories in the United States, as well as other appropriate research institutions in SEATO and other countries.

A. Cholera Research Laboratory

1. Program

(a) Research - Studies will be undertaken in three broad areas (i) epidemiological studies of the disease both in epidemic and non-epidemic periods, (ii) bacteriological studies related to better diagnosis, carrier states antibiotic or other anti-bacterial sensitivity tests, collection and identification of strains, provision of selected strains of organisms and other biological specimens to cooperating research laboratories in the U. S. and elsewhere, (iii) other diarrheal diseases in epidemic and non-epidemic periods. Since cholera must be differentiated from other diarrheal diseases, the studies should be designed to yield information on the type, distribution and prevalence of other such diseases.

(b) Training - An important purpose of the laboratory will be to train selected Asians to become independent investigators in bacteriology, epidemiology and/or diarrheal diseases. Selected individuals will be employed on the project, given training and experience on the job. Those with the most promise will be given one year of additional training and experience in one or more of the cooperating research laboratories. The aim will be to create gradually a trained group that can carry out this type of research program independently.

(c) Base for field expeditions - Periodically, and especially during epidemics, this laboratory will serve as the base of operations for individuals, or teams, from cooperating laboratories in the U. S. or elsewhere. Likewise, it will serve as the base for teams which may go to outlying districts, or to other countries, where the disease may be epidemic. Field studies will be dependent, obviously, on where cholera continues to occur. If possible, a sub-laboratory will be established for use during epidemics and during interim periods as indicated.

2. Staff

The NIH will furnish for the laboratory a staff of approximately five scientists, including a Director and such other personnel as may be mutually agreed upon between the GOP and NIH. The permanent staff will be nationals of SEATO countries.

3. Advisory Committees

(a) The Pakistan-Seato Cholera Research laboratory will have a Directing Council consisting of one member representing each of the nations participating in the CRL, the Secretary-General of SEATO or his representative, and the Director of NIH or his representative. The Director of the CRL shall be a non-voting member ex-officio and serve as Secretary of the Council. The Directing Council will meet at least once a year to consider the CRL Director's scientific, administrative and financial reports; to approve the general program; to review the auditor's reports; and to approve, with the approval of the participating nations, the level of the general operating fund of the CRL for the succeeding year.

NIH shall notify the Department of State 30 days in advance of plans to convene a meeting of the Directing Council, recommend to the Department an individual to represent the U. S., furnish the requisite security clearance of any nominee who is not an officer of another Department or agency of the U. S. Government, and provide the Department a copy of the agenda and recommended U. S. positions on those items which are not purely technical in nature.

(b) A CRL Technical Committee, preferably not more than three to five persons, including at least one member from Pakistan, shall be appointed by the Director of the NIH. This Committee shall visit the CRL at intervals for sufficient periods of time to become familiar with the development and progress of both laboratory and field projects. The CRL Technical Committee shall be responsible for the preparation of a detailed commentary and appraisal of the CRL program which shall be taken into consideration in preparing the annual report and in drafting recommendations to the Directing Council for the ensuing budgetary period.

B. Research Activities in the United States

Selected laboratories in the United States interested and experienced in research on infectious diseases and on certain aspects related particularly to cholera, will undertake the basic research studies which would be impractical in the laboratory in Southeast Asia. Their work will constitute an important part of the total program, and will be closely linked with the work in SEATO countries. They will provide training to selected

individuals from Asia, as well as send their own staff from time to time to assist in specific aspects of the research program, Specific arrangements have been worked out with the following laboratories, others may be included as the program develops:

1. University of Chicago

This project will focus on immune responses to vaccine, and to the disease, in both immunized and non-immunized persons. Assays would be done both on serum and as coproantibody. Antibody would be titrated as vibrio agglutinin, hemagglutinin, antimucinase, and protective antibody. This would require rather extensive research and developmental work on appropriate laboratory methods, as well as systematic study of vibrio antigens. The vibriocidal, vibriolytic, and possibly vibriostatic activity of antibody would be investigated. The studies would also include the effects of endotoxin and other components, and/or products of the vibrios on the permeability of living membranes. Some of these studies would be done in the laboratory, and extended to related studies in patients with the disease.

2. Jefferson Medical College

This project will be focused on fundamental investigations on the cholera organism. It will include study of growth characteristics hydrophobic qualities, significance of granular and motile globular forms, antigenicity of various vaccines, and methods to measure antigenicity, mechanisms of resistance to infections, bacterial antagonisms, rapid laboratory diagnostic procedures, etc.

3. University of Pittsburgh

This project would be focused on viral agents which may be associated with or involved in, susceptibility or resistance to cholera.

C. Program Direction

The U. S. participation in the program will be carried out under the direction of the NIH in coordination with the guidance of the NIH Cholera Advisory Committee. This Committee is appointed by and responsible to the Director, NIH, to assist him in all aspects of NIH's technical direction of the SEATO Cholera Research Program. Projects in any other country will, of course be done with the knowledge, agreement and cooperation of that country.

D. Timing

U. S. participation in the program is to continue in operation until June 30, 1967 unless extended or terminated by further amendment to this agreement.

E. Financing

Activities carried out with American, Asian or other appropriate institutions and bodies for research on cholera will be financed through grants-in-aid, contracts or direct expenditure by the NIH in accordance with NIH procedures. Such grants or contract would include necessary funds for travel, field trips, training and other elements of the program, as well as equipment and supplies necessary for the research.

III. Personal Services, Supplies, or Equipment to be Furnished by NIH

A. Services necessary to carry out the U. S. portion of the project described in II, shall be provided by the NIH with the costs of such services including the costs of the NIH Cholera Advisory Committee, and, if necessary, the cost of U. S. representation on the CRL's Directing Council and Technical Committee, to be financed from the funds provided under this Agreement.

B. NIH agrees to consult with and keep STATE/ICA informed of developments with respect to this program including periodic reports on a quarterly basis to STATE/ICA and SEATO. These reports will be in a form mutually acceptable to the ICA and NIH.

C. NIH agrees to be guided by policy instructions of STATE/ICA particularly with a view to coordinating the work performed by NIH with U. S. objectives in SEATO. This includes the coordination of contacts with governmental institutions in the member countries.

IV. Administrative Arrangements, Services, Supplies, Materials, or Equipment to be Furnished by ICA.

STATE/ICA will provide NIH assistance in carrying out liaison and arrangements with governmental institutions in the countries where activities may be conducted. ICA will extend to NIH such logistic support in the form of local transportation, temporary housing and facilities as the USOM may have available for this purpose.

V. Duration of this Project

This Agreement shall be effective as of the date of transfer of funds and shall extend until such time as the funds transferred hereunder are expended or this Agreement is terminated by mutual consent.

VI. Cost

\$750,000 and up to a maximum of \$190,000 in FY 1964, and in subsequent years, subject to the availability of funds, such additional amounts as are mutually agreed upon by AID and NIH.

VII. Payment

Payment is to made to NIH by: Transfer of funds as soon as possible after the execution of this document from the ICA to the United States Public Health Service, Department of Health, Education and Welfare, Washington 25, D. C., by use of Standard Form 1151.

COMBINED Memorandum of Understanding between the International Cooperation Administration (ICA) and the National Institutes of Health (NIH) dated July 22, 1960 and Amendment #1 dated October 12, 1962.

A - PURPOSE

On August 15, 1959, an Inter-Agency Agreement (hereinafter "the Agreement of August 15, 1959") was signed between the Department of Health, Education and Welfare and the International Cooperation Administration (hereinafter "ICA") providing for the responsibilities of the Department and ICA in carrying out a cholera research program in Southeast Asia. (This is the program agreed to by the United States and the South East Asia Treaty Organization (SEATO) in an exchange of notes dated May 29, 1959.) The Agreement of August 15, 1959, contemplates that the responsibilities of the Department of Health, Education, and Welfare thereunder are to be carried out by the National Institutes of Health of the United States Public Health Service (hereinafter "NIH").

This memorandum sets forth in detail the commitments and responsibilities of NIH and ICA, respectively, the the establishment of a cholera research project in Pakistan, pursuant to the US-SEATO Exchange of notes, the Agreement of August 15, 1959, as amended, and the Agreement between ICA and the GOP provided for herein. The International Cooperation Administration (ICA) has been succeeded by the Agency for International Development (AID), therefore all references to "ICA" will be read as "AID."

B - COMMITMENTS AND RESPONSIBILITIES OF NIH

1. Of the \$400,000 obligated for the program by the exchange of notes of May 29, 1959, and such other amounts as shall be made available by mutual agreement, not less than \$227,500 shall be allocated to this project by NIH subject to terms and conditions as hereinafter specified. A tentative budget for this amount is attached as part of Attachment 1. / Draft of Pakistan-US Agreement. /

2. Subject to the conditions contained in this memorandum, the amount allocated to the project pursuant to paragraph B.1. above may be used by NIH for:

a. Establishment, including design and layout, of a cholera research laboratory, to be known as the Pakistan-SEATO Cholera Research Laboratory (hereinafter "the laboratory"), in Dacca, East Pakistan. It is contemplated that this laboratory will be physically located in the Institute of Public Health;

b. Procurement and delivery to the laboratory of minimum essential scientific equipment, air conditioners and supplies to commence operation of the laboratory. In addition, NIH will procure and deliver to the laboratory such additional imported research supplies and scientific equipment as the laboratory staff shall deem necessary based upon the operating experience of the laboratory. Title to all property provided pursuant to this paragraph shall be in NIH. Disposition of such property upon termination of the project shall be subject to negotiation between the GOP and ICA with the concurrence of NIH;

c. Costs of international travel, including per diem, of the scientific staff of the laboratory as may be determined necessary.

d. Recruitment and assignment to the laboratory, and the costs of international travel, including per diem, of two nonscientific assistants to assist in receiving, transporting within Pakistan and installing the equipment and supplies provided pursuant to paragraph B-2. b. above;

e. Costs of NIH Cholera Advisory Committee and, if necessary, costs of U.S. representation on the laboratory's Directing Council and CRL Technical Committee.

f. Procurement and delivery to the laboratory of vehicles including, but not limited to, two jeep station wagons or equivalent, a truck equipped and suitable for carrying personnel and field equipment, to be furnished to the Director of the laboratory, and a vehicle capable of transporting patients. Title to such vehicles will be in NIH. Disposition of these vehicles upon termination of the project shall be subject to negotiation between GOP and ICA with the concurrence of NIH;

g. To the extent that funds allocated to this project pursuant to paragraph B-1. hereof and set out in the tentative budget attached as part of Attachment 1 are made available from other sources, such additional funds may be rebudgeted for use elsewhere in this project or reallocated for use elsewhere in the overall program.

3. NIH will provide, with United States funds provided for the cholera research program pursuant to the exchange of notes of May 29, 1959, and with such other funds as may be made available, but not included within the \$227,500 allocated to this project, the costs of international travel, including per diem where appropriate, or such specialists, experts or consultants as it shall deem necessary to assign to this project for periods of consultation.

4. NIH will provide, with nonprogram funds, the salaries of the two nonscientific assistants assigned to the project pursuant to paragraph B-2. d. hereof.

5. In addition, NIH will be responsible for:

a. The exercise of general scientific and administrative responsibility for and direction of project activities including field studies in Pakistan;

b. Appointment of a CRL Technical Committee pursuant to Section II.A.3.(c) of Amendment No. 1 to the ICA-DHEW Agreement signed on July 11, 1962.

c. Appointment of an NIH Cholera Advisory Committee to give advice to the Director of NIH on the implementation of the project.

d. The NIH will furnish for the laboratory a staff of approximately five scientists, including a Director and such other personnel as may be mutually agreed upon between the GOP and NIH. The permanent staff will be nationals of SEATO countries.

C - COMMITMENTS AND RESPONSIBILITIES OF ICA

1. ICA will negotiate with the GOP an agreement providing for the respective contributions to the project of the GOP, ICA/NIH, and other SEATO members. A draft of the proposed agreement upon which USOM/Pakistan and the GOP are in substantial accord is appended hereto as Attachment 1. The current agreement between the GOP and USAID/Pakistan dated December 30, 1961 is appended.

2. ICA will provide necessary operational and policy guidance to the project through USOM/Pakistan. The Chief Public Health Advisor, Karachi, will participate in the project and, to the maximum extent possible, regular ICA medical care and public health programs will be coordinated with the project.

3. Subject to the concurrence of the GOP and subject to availability of funds, ICA will provide, from funds contained in the Pakistan Trust Fund, the cost in Pakistan rupees of necessary administrative support to the project. Such support costs will include the provision of living accommodations equal to those provided to ICA personnel of equivalent rank for permanent staff members and dependents, the NIH administrative officer and engineer, and such other United States or non-Pakistani personnel as may be mutually agreed upon, on an individual basis, by USOM and GOP, the cost of travel, including per diem where appropriate, for personnel assigned to the project, allowances payable to United States Government personnel assigned to the project and gasoline, oil and maintenance for the vehicles furnished to the Director of the laboratory as provided in paragraph B-2. f. hereof, and such further costs as ICA shall deem necessary and appropriate.

4. ICA will provide, with Fiscal Year 1960 Pakistan program funds, for a six-month training grant for the Pakistani scientist to be assigned by the GOP as research bacteriologist to the laboratory. This training will be programmed by ICA in conjunction with NIH.

5. United States Government personnel assigned to the project will be accorded equal status to ICA personnel of equivalent rank insofar as it lies within the power of ICA to grant or withhold such status.

D - EFFECTIVE DATES: AMENDMENTS

1. These understandings will take effect as of the effective date of the Agreement between ICA and the GOP providing for this project and will remain in effect until full responsibility for the operation of the laboratory shall have been assumed by the Government of Pakistan (estimated to occur in 1964), or until the Dacca laboratory project shall otherwise have been terminated or extended as provided in the agreement between ICA and the GOP.

2. These understandings may be modified, altered or amended at any time by mutual agreement of ICA and NIH in writing, provided that, where necessary, such modification, alteration or amendment shall first be concurred in by the GOP.

Library,
Pakistan-SEATO Cholera Research Lab,
Mohakhali, Dacca-12

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