

## EIGHTH ANNUAL REPORT TO CONGRESS

(In accordance with Sec. 5 (h) of Public Law 86-610, the International Health Research Act of 1960)

## United States-Japan Cooperative Medical Science Program

History of the Program

In January 1965, the President of the United States and the Prime Minister of Japan met in Washington, D.C., to discuss many matters concerning the two nations. It was during this meeting that the two heads of state agreed to undertake a greatly expanded, joint cooperative research effort in biomedical sciences, concentrating on health problems of recognized importance in Asia. The new bilateral program was named the United States-Japan Cooperative Medical Science Program (U.S.-Japan CMSP). To implement this agreement, they convened a conference of prominent medical scientists from the United States and Japan to plan and define program objectives and goals. Thus, the two groups of delegates, the United States Delegation and the Japanese Delegation, formed the nucleus of what ultimately became the U.S.-Japan CMSP Joint Committee. This Committee has met annually since 1965 to review jointly the Program's objectives, operations and research accomplishments, and to recommend policy procedures for continued Program growth and development. The last annual meeting was held in Tokyo, Japan on 8-9 August 1974. The next meeting will be held at the National Institutes of Health in Bethesda, Maryland, 2-3 October 1975.

The Scope of the U.S.-Japan CMSP

The Program is concerned with the diseases of substantial health importance in Asian countries. The diseases or categories of diseases are: 1. cholera, 2. leprosy, 3. malnutrition, 4. parasitic diseases (schistosomiasis and filariasis), 5. tuberculosis, 6. viral diseases (rabies, dengue-hemorrhagic fever and other selected arboviral diseases), 7. selected health effects of environmental pollutants.

The U.S.-Japan CMSP operates within a bilateral government framework. Nevertheless, it may involve scientists and facilities in third countries, and/or collaboration with international or other organizations. Joint third country activities are approved in advance by the U.S. and Japanese Delegations.

The relevant regions in Asia, although not specifically defined, are generally understood to include the Republic of Korea on the north, India and Pakistan to the west, and other adjacent nations in the broad Pacific basin.

Organization

The United States and Japanese governments have appointed biomedical scientists to constitute a U.S.-Japan Cooperative Medical Science Program Committee. The United States Delegation to this Committee is appointed by the Secretary of State. This Delegation, in addition to representing the

United States at meetings of the Joint Committee, advises the Secretary of State on the scope, direction and other broad aspects of the Program, and develops review procedures to assure fulfillment of the purposes for which the Program was established. Jointly the United States and Japanese Delegations have designated the seven areas of research which fall within the scope of the overall Program, and they have established separate Panels for each disease category to guide the relevant scientific activities.

In the United States the operational aspects of the Program have been delegated to the National Institutes of Health, Department of Health, Education and Welfare. In Japan the Program activities are the responsibility of the Ministry of Health and Welfare and the Ministry of Education. The United States and Japan maintain separate secretariats.

For each of the disease categories selected for study, ten-member joint Panels, consisting of five scientists from each nation, were established to outline more specifically areas for mutual cooperation and to carry on Program activities. Briefly summarized, these activities may be grouped into the following three categories: support of research, joint scientific conferences, and exchange of persons. In addition, each Panel prepares an annual report of progress for review by their respective Delegation and for the joint Committee. The meetings of the Joint Panels and the Joint Committee alternate annually between locations in the United States and Japan.

#### Financial Support of the Program

The United States and Japan each support the cost of their own scientific projects and meetings. Research by U.S. scientists is funded by the United States and that of Japanese scientists by Japan. Exchange of scientists between the two countries is encouraged as a matter of principle and is supported by official or unofficial agencies of either country. The U.S. does not fund research in Japan nor grant fellowships to Japanese scientists under this Program, nor does Japan fund U.S. research or fellowships for Americans as a component of their Program sponsored activities.

The National Institutes of Health, based upon a delegation of Presidential authority under Public Law 86-610 and on the availability of funds, provides:

- support of scientific projects;
- organization, funding and conduct of scientific meetings held in the United States;
- financial support to the United States Panel members and consultants attending meetings related to the program; and
- staff and operating costs of the U.S. Secretariat.

The Japanese Ministries of Health and Welfare and of Education assume a similar responsibility for their counterpart activities, i.e. research projects, meetings held in Japan, Japanese Panel members and consultants, and for the Japanese secretariat.

#### Joint Committee Report for Calendar Year 1974

The Tenth Meeting of the Joint United States-Japan Cooperative Medical Science Committee was held at the Ministry of Foreign Affairs, Tokyo, Japan on 8-9 August 1974. Welcoming and opening remarks were made on behalf of

the United States Government by the Ambassador to Japan, Mr. James D. Hodgson, and on behalf of the Government of Japan by Mr. Kunikichio Saito, Minister of Health and Welfare. Additional welcoming statements were made by Dr. Ivan L. Bennett, Jr., Chairman of the United States Delegation and Dr. Toshio Kurokawa, Chairman of the Japanese Delegation. The Joint Committee meeting was jointly chaired by the two Delegation Chairmen.

Individual annual reports covering cooperative research activities to improve the health of the people of Asia were presented to the Committee by the seven panel chairmen or their designated representatives. Separate comprehensive scientific reviews of the Joint Malnutrition Panels and the Joint Viral Diseases Panels were completed during the current year and the findings and recommendations of the review groups were accepted by the Committee. This completes the review of the six panels which have been in operation at least five years. The seventh and last, the Panel on Methods for Evaluating Environmental Mutagenesis and Carcinogenesis, usually referred to as the Environmental Panel, was added in 1972 and will not be scheduled for formal review before 1977.

Also, a schedule submitted by the Subcommittee on Program Review and Planning for the preparation of a Second Five Year Report was accepted by the Joint Committee. According to the schedule a final draft of the report will be ready for consideration by the Joint Committee at its October 1975 meeting. Publication of this document should follow shortly thereafter.

A decision was made to initiate the next cycle of panel reviews in 1975. As was done previously, two panels will be formally reviewed annually. Since the Leprosy and Parasitic Diseases Panels initiated the first cycle of reviews, they were chosen again to lead-off the second round of reviews.

Plans were formulated for the next meeting of the Joint Subcommittee on Program Review and Planning to be held early in 1975.

## Research Highlights of the Past Year

### Cholera

During the past several years one of the major efforts of the Cholera Panel has been to provide support and guidance in the development of a cholera toxoid. This has culminated in the production and preliminary testing in man of a sufficient amount of a highly purified toxoid to conduct a controlled field trial in about 90,000 persons in Bangladesh in the autumn of 1974. This toxoid was inactivated with glutaraldehyde and is capable of producing circulating antitoxin levels similar in magnitude and duration to that seen in naturally occurring cholera.

The trial in Bangladesh has been designed to answer the question: Can antitoxic immunity induced by the parenteral route provide significant protection against cholera at natural exposure levels in an endemic area? The results of this first trial will provide the basis for future studies aimed at developing the most effective and long-lasting immunogen against cholera. Continuing studies on antibacterial immunity suggest that the optimum vaccine will contain both bacterial cell and toxoid components.

The effects of cholera enterotoxin on adrenal tumor and Chinese hamster ovary cells in culture have provided additional models for the study of the

mode of action of the toxin at the molecular and cellular level, as well as practical tools for the measurement of toxin and antitoxin.

Studies on local immunity in dogs have indicated that both local and systemic administration of toxoid may play specific and significant roles in evoking resistance to cholera, and point to the need for study of the response to orally administered toxoid in man.

The enterotoxins of *Escherichia coli* have received increasing attention and it is clear that the heat-labile toxin is very similar both pharmacologically and immunologically to cholera enterotoxin. Accumulating data suggest that enterotoxinogenic strains of *E. coli* may play a greater role in provoking acute diarrheal disease than previously realized. Methods for detection and measurement of *E. coli* enterotoxins are less satisfactory than are those used for cholera enterotoxin, but a rabbit skin assay similar to that used for cholera enterotoxin was developed during the past year and this assay holds promise of simplifying the work of the future. The role of heat-stable enterotoxin in human disease is still unclear. To enhance our understanding in this area, epidemiologic studies have been initiated to determine the frequency and significance of diarrheal disease associated with enterotoxinogenic *E. coli* in two selected communities in the United States.

Panel on Methods for Evaluating Environmental Mutagenesis  
and Carcinogenesis (Environmental Panel)

This year the Environmental Program initiated a substantive research effort to develop and to validate selected bioassay systems. A systematic study is being made of the dominant lethal method and of the tests for the induction of chromosomal damage to determine if these methods are really diagnostic for detecting transmissible genetic damage in the form of gene mutations and viable translocations. Dominant lethal mutations consist in part of open chromosome breaks and in part of a symmetrical exchange. In *Drosophila*, where both of these types of damage can be measured as well as heritable translocations and gene mutations, the frequencies with which different categories of genetic damage are induced in a variety of germ cell stages by representative chemical mutagens are being compared. The outcome of these investigations will be of value in determining whether the results of the dominant lethal test have more general validity.

Research is underway to develop a new mouse strain to maximize the sensitivity of a point mutation assay. The sensitivity of a point mutational assay system is directly related to the number of loci that can be tested in each individual. In the present experimental mouse strains (DBA/2J or C57BL/6J) nine loci, which control the electrophoretic mobility of various enzymes, can be sampled. In other mouse strains which have been studied, 13 additional electrophoretic variants have been identified. Initial crosses of these mutants to the C57BL/6J have been studied with the ultimate aim of developing a new strain homozygous with C57BL/6J.

Another research effort is directed toward developing a system to detect recessive lethal mutations in mice. The object is to develop strains of mice carrying inversions which can be used to assay for gene mutations in the chromosome regions which they cover.

To assist in monitoring the human population, three assay systems are being developed: (1) a simple assay on human red blood cells to detect fetal hemoglobin believed to be the result of mutation; (2) adaptation of the Tradescantia test system to chemical and environmental studies; (3) the utilization of diploid human fibroblasts in tissue culture to assay for gene mutations at the HGPRT and AGPRT loci.

The Environmental Mutagen Information Center continues to review the current literature and all published reports on tests for chemical mutagenesis and incorporates pertinent information in its bibliographic files. Keywording with respect to agent, test organism and test object and a summary table of the data are included in the data bank.

In collaboration with the Parasitic Diseases Panel, research results on the mutagenic activity of hycanthone and lucanthone and structurally related derivatives in diploid yeast were discussed at the Joint Workshop on "Long-term Toxicity of Antischistosomal Agents." Preliminary studies provide confirmation that some of the structural analogs of hycanthone have high anti-schistosomal activity but lower mutagenic activity. It is anticipated that these encouraging results will lend support and additional impetus to expanding the development and testing of this class of analogs for control of schistosomiasis.

In December 1974, an important workshop on the Mutagenicity of Chemical Carcinogens was held jointly with Japanese and American scientists. Data from different laboratories were compared and recommendations regarding the various pre-screen tests were made. From the data made available at this workshop, summary tables were compiled of the combined mutagenicity screens with Salmonella, Yeast, and Pol A(-) E. coli. These were made available to investigators in the field.

#### Leprosy

During the past year, U.S. leprosy scientists attended the Ninth International Leprosy Congress in Bergen, Norway, which marked the Centennial of Dr. Hansen's discovery of the causative agent of leprosy, Mycobacterium leprae. This important scientific meeting provided the basis for leading scientists in the field to exchange new information on a variety of research topics including cultivation, immunology, pharmacology, chemotherapy and epidemiologic control measures. In addition, this international conference provided a stimulus for dedicated worldwide investigators to apply new research techniques for conquering this serious infectious disease.

Investigators at Carville, La. have reported on a pilot study with Transfer Factor (TF), prepared from  $7 \times 10^9$  lymphocytes. Three lepromatous patients were treated with 36 divided doses over a 12-week period with no apparent harmful side-effects. The bacteriologic index and clinical condition appeared to improve for each patient during the period of therapy. Following these promising results, the U.S. Leprosy Panel has formulated plans to expand this type of clinical trial with pooled Transfer Factor prepared from donors who demonstrate a positive skin test to M. leprae antigens.

Immunologic studies have confirmed that many lepromatous patients have generalized depression of T-cell function. Preliminary evidence suggests,

however, that the deficit in T-cell function is not primary in origin but instead may be secondary to the disease process itself and associated with the heavy antigenic load chronically present. This is clearly a relationship that requires further investigation.

Based on the experience in a long-term chemotherapy trial in New Guinea, it now appears that acedapsone therapy (approximately five injections per year) is adequate for paucibacillary leprosy infection, and that acedapsone therapy plus 90 days of daily treatment with rifampin will be adequate for multibacillary leprosy.

Investigations continue with experimental leprosy in the armadillo animal model. Recently, young armadillos less than 1 1/2 years old have been inoculated with *M. leprae* and 15 of 24 (62%) found positive for acid-fast bacilli 14 months after inoculation. It is anticipated that the intravenous inoculation of young armadillos will result in a high proportion of heavy infections.

### Malnutrition

Among the various highlights of the past year was the contract support for a scientific conference January 1974, at Guatemala City entitled, "The Latent Effects of Malnutrition and Infection During Pregnancy as Determinant of Growth and Development of the Child." Participants focused attention on malnutrition during pregnancy with discussions of placental function with emphasis on dietary intake, types of dietary supplements and the optimal time for supplementation of the mother so that effective transplacental transfer mechanisms could effect the optimal response. In addition, the biochemical, metabolic and physiologic consequences of cell damage by microorganisms were discussed. The difficulties and methods of diagnosing intrauterine infection were also stressed. Consideration was also given to the significance of asymptomatic bacterial infections during pregnancy which influence low birth weight. Attention was also given to the long lasting implications of low birth weight in respect to survival and growth of the child as well as to psychomotor development. Final edited material from this conference will be prepared for publication and disseminated to the scientific community.

During the past year, the "Food Composition Table For Use in East Asia" was completed and published. This comprehensive reference provides valuable information concerning numerous studies on the subject and will be extremely useful in the evaluation of Asian dietary consumption and in the assessment of the nutritional status of the population in the various countries of East Asia.

Investigators at Ramathibodi Hospital, Bangkok, Thailand, have demonstrated bladder stone disease in children is a major health problem. In Thailand, the prevalence rate is 12 per 1000 population in rural areas of the North and Northeast regions.

Evidence accumulated in Thailand over the past several years supports the concept of a nutritional etiology of bladder stone disease. It appears that phosphate deficiency, high oxalate intake, protein malnutrition and possibly other factors are important in stone formation. Infants and children in endemic stone areas show very low levels of phosphate excretion, somewhat

high levels of urinary oxalate and also oxalocrystalluria. Administration of orthophosphate salts to these subjects dramatically reduces the occurrence of oxalocrystalluria.

In a collaborative study conducted at Chiang Mai, Thailand, the importance of infection in the morbidity and mortality associated with protein-calorie malnutrition has been well established. In 200 children, 1 to 4 years of age, with second and third degree malnutrition, 69 per cent were discovered to have potentially life threatening infections which included diarrheas of bacterial and viral origin, pneumonia, otitis media, gastrointestinal infections, and skin infections. Thirty percent had sepsis, mostly of gram negative origin associated with detectable amounts of endotoxin in the plasma. It was discovered, furthermore, that children with severe protein-calorie malnutrition have an enhanced incidence of hepatitis-associated antigen (HAA) which suggested a defect in cell-mediated immunity. Skin testing with nitrofluorobenzene, monilia and streptokinase-antigens also revealed a defect in cell-mediated immunity in these children which was corrected by improved nutrition. It was also found that blast cell transformation of lymphocytes stimulated with phytohemagglutinin and thymidine uptake was also reduced as additional evidence of alterations in the T-cell system in these children.

### Parasitic Diseases

#### Schistosomiasis

A cell line of the snail host of S. mansoni was developed and by the end of 1974, was in the 47th serial subculture. The conditions for maintaining these cultures have been defined and are currently being described for publication. Preliminary use of this cell line in the culture of schistosome parasites has begun.

Studies on the mechanism of immune response have been expanded during the past year. It was shown that T- lymphocyte depletion prevented the development of anti-schistosomal egg antigen (SEA) cell-mediated immune response and anti-SEA reaginic antibody. Other studies have been initiated to help elucidate the function of the eosinophil in the destruction and elimination of schistosomal eggs from the body.

Suppression of schistosome granuloma formation was brought about experimentally by cholera toxin, by diabetes and by toxoplasmosis.

A series of studies on the effects of a nitrovinylfuran compound on Schistosoma japonicum in chimpanzees showed that treatment with this drug had a pronounced effect on diminishing the extent of colonic lesions and on lessening the degree of schistosomal nephropathy.

#### Filariasis

Work on experimental models of human filariasis continue to corroborate the finding that the gerbil is the most useful rodent host for studies with lymphatic-dwelling filarial worms. Basic data have been obtained on the factors underlying the susceptibility of male gerbils to infection. For the first time, W. bancrofti, the human filarial parasite, has been introduced into primates with the production of microfilariae.

Biochemical studies have included a comparison of the metabolism of L. carinii, D. witei and B. pahangi. D. witei and B. pahangi survive anaerobically for extended periods of time, whereas, L. carinii loses motility rapidly in the absence of air. This may explain the ineffectiveness of cyanines in human infection. It has also been found that stibophen inhibits phosphofructokinase of all three species of filarids, but not that of the host. Incubation of microfilarial in immune serum with radioactive diethylcarbamazine resulted in a three-fold increase in drug uptake.

Immunization of dogs with a single subcutaneous dose of gamma-irradiated infective third-stage larval of Brugia pahangi resulted in a substantial degree of protective immunity against homologous challenge infections.

Ninety carefully selected compounds were tested for chemotherapeutic and/or chemoprophylactic activity against filariae infection. The Brugia pahangi - gerbil system seems promising as a small animal model for evaluating filariasis chemotherapy.

### Tuberculosis

The research sponsored this year by the Tuberculosis Program was again focused on the immunological aspects of tuberculosis. Through several service contracts, highly characterized and standardized mycobacterial materials were made available to qualified scientists in tuberculosis and related fields. The materials included reference strains and antisera for 24 serotypes of the M. avium-intracellulare-scrofulaceum complex, 159 mycobacterial cultures, PPD, and a standard immunoelectrophoretic reference system.

An unheated mycobacterial culture filtrate preparation was fractionated by gradient acrylamide gel electrophoresis (GAGE) and by ion exchange and molecular exclusion chromatography. The isolated antigenic fractions obtained by these two methods are now being studied by in vivo and in vitro test systems to determine the immunologically important and biologically reactive fractions. It is planned that the experience and information gained from this study will be utilized subsequently for a contractual effort to isolate and characterize bacillary antigens in the cell extract preparation.

Because of the great demand for the immunoelectrophoretic reference system for antigens of Mycobacterium tuberculosis, the original supply of antigen and antiserum were depleted. A new supply was produced this year and the relationship of the new materials to the original system was established. The reference kits are again available for distribution.

Research was initiated to systematically study mycobacterial antigens obtained using various cell disruption techniques. Virulent human tubercle bacilli were disrupted by several sonication and pressure cell regimens and the protoplasmic constituents of these preparations were compared. The result of the chemical, physiocochemical, and biological comparisons of the cell extracts prepared by sonic or pressure-cell disruption indicated that sonication for 15 minutes was the most suitable method when judged on the basis of antigen yield and ease of preparation.

The monkey model for studying aerosol BCG vaccination with aerosol challenge was investigated further. It was shown that the protection of aerosol BCG vaccination is dose dependent; i.e.,  $10^5$  organisms gave a greater degree of protection than either  $10^3$  or  $10^4$  organisms. There was some concern that repeated vaccination via the aerosol route might elicit a type of hypersensitivity reaction in the host. Therefore, guinea pigs, an excellent model for exploring such a response, were sensitized and vaccinated with aerosolized BCG organisms. No adverse effects were observed even in animals highly reactive to PPD.

An association between the lymphokines of delayed hypersensitivity and cell mediated immunity has been indicated *in vivo*. Immunization of mice with a lipid (P3) and a protein (PPD) from *M. bovis* strain BCG produces lymphokines, such as migration inhibition factor (M.I.F.) and type II interferon, and cell-mediated immunity to aerosol challenge with the virulent strain H37Rv. Only those components of BCG cells that induce lymphokines simultaneously induce cell-mediated immunity to tuberculosis, and those routes of inoculation of vaccine that produce maximum quantities of lymphokines also produce protection against infection and also prevent the growth of mouse sarcoma. These developments and newer concepts in lymphokine research were discussed at a special workshop conducted in November 1974. Priority areas for future research were outlined at this very successful and productive workshop.

Advances in the basic immunology of the mycobacterioses were seen. Improved methods of studying the blastogenic response of human leukocytes has made it possible to determine qualitatively and quantitatively the immunologic status of individuals. The role in cellular immunity of macrophages, B and T lymphocytes, soluble mediators, surface antigens, and a battery of enzymes are being clarified by continuing research.

## Viral Diseases

### Rabies

Work has continued on the isolation and characterization of the protective antigens of rabies virus. Guanidine extraction has been shown to result in products of low immunogenicity. In contrast, Triton, a non-ionic detergent, has been found to yield a high titer product. The results demonstrated that dissociation of virus particles did not inactivate the protective antigen and that the solubilized antigen was an effective immunogen.

Also being developed are improved methods for the inactivation of rabies virus without significant loss of immunogenicity. Twelve consecutive 10 liter lots of rabies virus have now been inactivated by betapropiolactone at a concentration of 0.025%. No residual live virus has been found in any of these lots as measured by the sensitive rabies virus amplification procedure.

An *in vitro* test for the evaluation of the potency of rabies vaccines by the stimulation of sensitized lymphocytes was elaborated. Several vaccine preparations of tissue culture origin were tested and compared with several preparations of the standard NIH vaccine. Results indicate that a reasonable degree of correlation can be obtained between the potency measured in experimental animals and that measured by *in vitro* procedures.

### Dengue

Studies are being directed at determining whether susceptibility of mosquitoes to dengue viruses is genetically controlled. The infection in the mosquito is also being studied quantitatively. Of 11 different geographical strains of *Aedes albopictus* which have been screened for susceptibility to dengue viruses, 2 consistently showed lower infection rates and 1 strain showed a higher rate than the others.

In a study of the ecology of dengue viruses in Malaysia, an area of undisturbed primary rain forest was chosen as the site of investigation. Serological conversions for dengue were detected in three leaf monkeys in the high canopy at about 75 feet above ground. The results have established that enzootic dengue occurs in the high canopy of the study area. A search continues for the proven forest vector.

Attempts are being made to develop temperature-sensitive mutants of dengue viruses as potential seed material for live attenuated vaccines for human use. Of several hundred clones (after ten passages) analyzed, 8 were found to be temperature sensitive.

Pathological studies of dengue infections have involved the development of quantitative techniques for the detection of viremia, techniques for purification of type-specific viral antigens and antibodies for specificity studies, and the physico-chemical characterization of viral antibody complexes.

### U.S. DELEGATION

- Dr. Ivan L. Bennett, Jr., Chairman (1972--), Member 1967-1972),  
Provost of the Medical Center, Dean of the Medical School,  
New York University Medical Center, New York, New York 10016
- Dr. William R. Barclay (1974--), Assistant Executive Vice President,  
American Medical Association, 535 N. Dearborn Street,  
Chicago, Illinois 60610
- Dr. Charles C.J. Carpenter, Jr. (1972--), Chief of Medicine,  
University Hospitals of Cleveland, Cleveland, Ohio 44106
- Dr. Leighton E. Cluff (1971--), Professor and Chairman, Department  
of Medicine, University of Florida, School of Medicine,  
Gainesville, Florida 32601
- Dr. Edwin H. Lennette (1970--), Chief, Biomedical Laboratories,  
California Department of Health, 2151 Berkeley Way,  
Berkeley, California 94704
- Dr. James V. Neel (1971--), Lee R. Dice University Professor and  
Chairman, Department of Genetics, University of Michigan, School  
of Medicine, Ann Arbor, Michigan 48104
- Dr. Nevin S. Scrimshaw (1974--), Professor and Head, Department  
of Nutrition and Food Science, Massachusetts Institute of  
Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139
- Dr. Robert S. Stone (1973--), Director, National Institutes of Health,  
Bethesda, Maryland 20014

Dr. Theodore E. Woodward (1965--), Professor and Chairman,  
Department of Medicine, University of Maryland, School of Medicine,  
Baltimore, Maryland 21201  
U.S. Secretariat--Dr. Mark S. Beaubien (1973--), Science Officer,  
Bureau of International Scientific and Technological Affairs,  
Department of State, Washington, D.C. 20520

#### MEMBERS WHO RESIGNED IN 1974

Dr. Gustave J. Dammin (1972-1974), Friedman Professor of Pathology  
and Pathologist-in-Chief, Harvard Medical School-Peter Bent  
Brigham Hospital, Boston, Massachusetts 02115  
Mr. Herman Pollack (1965-1974), Director, Bureau of International  
Scientific and Technological Affairs, Department of State,  
Washington, D.C. 20520

#### JAPANESE DELEGATION

Dr. Toshio Kurokawa, Chairman (1965--), Director, Cancer Institute  
Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan  
Dr. Tatsuro Iwasaki (1965--), Director, Research Institute, Japan  
Anti-Tuberculosis Association, Tokyo, Japan  
Dr. Shunichi Kakurai (1972--), Director-General, Public Health  
Bureau, Ministry of Health and Welfare, Tokyo, Japan  
Mr. Saburo Kasagi (1974--), Counselor, Bureau of Higher Education  
and Science Bureau, Ministry of Education, Tokyo, Japan  
Dr. Yasugi Katsuki (1974--), Professor Emeritus, Tokyo Medical  
and Dental University, Tokyo, Japan  
Mr. Yoshio Ogawara (1974--), American Affairs Bureau, Ministry  
of Foreign Affairs, Tokyo, Japan  
Dr. Manabu Sasa (1974--), Director, Institute of Medical Science,  
University of Tokyo, Tokyo, Japan  
Dr. Takemune Soda (1968--), Advisor, Institute of Public Health,  
Tokyo, Japan  
Dr. Norio Suwa (1974--), Director of Medical Department of  
Tohoku University, Sendai, Japan  
Dr. Ken Yanagisawa (1971--), Director, National Institute of Health,  
Tokyo, Japan

#### RETIRING MEMBERS

Dr. Shuji Hasegawa (1965-1974), Professor Emeritus, University of  
Tokyo, Tokyo, Japan  
Dr. Ko Hirasawa (1968-1974), Professor Emeritus, Kyoto University,  
Kyoto, Japan  
Mr. Tadashi Inumaru (1971-1974), Councilor, Higher Education and  
Science Bureau, Ministry of Education, Tokyo, Japan  
Dr. Shigeo Okinaka (1968-1974), Director, Toranomon Hospital,  
Tokyo, Japan

U.S. SECRETARIAT

National Institute of Allergy and Infectious Diseases (NIAID);  
National Institutes of Health (NIH)

- Director, NIAID: Dorland J. Davis, M.D.  
Associate Director, NIAID: Howard A. Minners, M.D.  
Chief, Geographic Medicine Branch and  
Head, U.S.-Japan Program: Earl S. Beck, Ph.D.  
Administrative Officer: Mrs. Marilyn M. Page  
Administrative Assistant: Mrs. Beatrice B. Benson
- I. Secretariat for the U.S. Cholera, Leprosy, Parasitic  
Diseases, Tuberculosis and Viral Diseases Panels:  
Cholera Program Officer: Carl E. Miller, D.V.M.  
Leprosy Program Officer: Richard E. Horton, M.D., M.P.H.  
Parasitic Diseases Program Officer: Kenneth O. Phifer, Sc.D.  
Tuberculosis Program Officer: Paul D. Lambert, V.M.D., Ph.D.  
Viral Diseases Program Officer: Kenneth O. Phifer, Sc.D.
- II. Secretariat for the Malnutrition Panel:  
Director, National Institute of Arthritis, Metabolism  
and Digestive Diseases (NIAMDD): G. Donald Whedon, M.D.  
Associate Director for Program Analysis and  
Scientific Communication (NIAMDD): Benjamin T. Burton, Ph.D.  
Malnutrition Program Officer (NIAMDD): Karl E. Mason, Ph.D.  
Assistant Malnutrition Program Officer (NIAID):  
Richard E. Horton, M.D., M.P.H.
- III. Secretariat for the U.S. Environmental Panel:  
Director, National Institute of Environmental Health  
Sciences (NIEHS): David P. Rall, M.D., Ph.D.  
Environmental Diseases Program Officer:  
Paul D. Lambert, V.M.D., Ph.D., (NIAID)

PANEL MEMBERS

U.S. Cholera Panel

- Dr. John Craig, Chairman (1972--), Member (1970-1972), Professor of  
Microbiology and Immunology, State University of New York,  
Brooklyn, New York 11203  
Dr. Abram S. Benenson (1973--), Chairman, Department of Community  
Medicine, University of Kentucky, College of Medicine,  
Lexington, Kentucky 40506  
Dr. M. Carolyn Hardegree (1974--), Director, Bacterial Toxin Branch,  
Food and Drug Administration, Bethesda, Maryland 20014  
Dr. Nathaniel F. Pierce (1972--), Associate Professor of Medicine,  
Baltimore City Hospital, Baltimore, Maryland 21224

#### Members Whose Term Expired in 1974

- Dr. Sherwood L. Gorbach (1971-1974), Chief, Department of Infectious Diseases, Sepulveda Veterans' Administration Hospital, Sepulveda, California 91343
- Dr. Stephen H. Richardson (1969-1974), Professor, Department of Microbiology, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103

#### Japanese Cholera Panel

- Dr. Hideo Fukumi, Chairman (1965--), Director, Department of Bacteriology, National Institute of Health, Tokyo, Japan
- Dr. Osam Kitamoto (1965--), Professor, University of Tokyo, Tokyo, Japan
- Dr. Shogo Kuwahara (1965--), Professor of Microbiology, Toho University Medical School, Tokyo, Japan
- Dr. Shogo Sasaki (1970--), Professor of Bacteriology, Keio University Medical School, Tokyo, Japan
- Dr. Kenji Takeya (1965--), Professor of Bacteriology, Kyushu University Medical School, Fukuoka, Japan

#### U.S. Environmental Panel

- Dr. Frederick J. deSerres, Chairman (1972--), Chief, Mutagenesis Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709
- Dr. Harry V. Gelboin (1974--), Chief, Chemistry Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014
- Dr. Robert W. Miller (1972--), Chief, Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014
- Dr. Arno Motulsky (1972--), Professor of Medicine and Genetics, Division of Medical Genetics, University of Washington, School of Medicine, Seattle, Washington 98105
- Dr. Norton Nelson (1972--), Professor and Chairman, Institute of Environmental Medicine, New York University Medical Center, New York, New York 10016

#### Member Whose Term Expired in 1974

- Dr. Warren W. Nichols (1972-1974), Head, Department of Cytogenetics, Institute for Medical Research, Camden, New Jersey 08103

#### Japanese Environmental Panel

- Dr. Tadashi Yamamoto, Chairman (1972--), Department of Oncology, The Institute of Medical Science, University of Tokyo, Tokyo, Japan

- Dr. Takashi Fuji (1972--), Faculty of Science, Shizuoka University,  
Shizuoka-ken, Japan  
Dr. Takashi Sugimura (1972--), National Cancer Center Research  
Institute, Tokyo, Japan  
Dr. Takeo Suzuki (1972--), Director, Division of Occupational  
Health, National Institute of Public Health, Tokyo, Japan  
Dr. Yataro Tazima (1972--), National Institute of Genetics,  
Yata, Misima, Sizuoka-ken, Japan

#### U.S. Leprosy Panel

- Dr. Charles C. Shepard, Chairman (1965--), Chief, Leprosy and  
Rickettsial Diseases Unit, Center for Disease Control,  
Atlanta, Georgia 30333  
Dr. Ward E. Bullock (1972--), Associate Professor and Director,  
Division of Infectious Diseases, University of Kentucky,  
Lexington, Kentucky 40506  
Dr. Robert R. Jacobson (1973--), Chief, Medical Department, U.S.  
Public Health Service Hospital, Carville, Louisiana 70721  
Dr. Norman E. Morrison (1974--), Associate Professor of Pathobiology,  
Leprosy Research Laboratory, Johns Hopkins-Leonard Wood Memorial,  
Baltimore, Maryland 21205  
Dr. Russell S. Weiser (1971--), Professor of Immunology, Department  
of Microbiology, University of Washington, Seattle, Washington 98105

#### Member Whose Term Expired in 1974

- Dr. Louis Levy (1970-1974), Chief, Leprosy Research Unit,  
U.S.P.H.S. Hospital, San Francisco, California 94118

#### Japanese Leprosy Panel

- Dr. Masahi Namba, Chairman, (1974--, Member 1965-1974), Chief,  
Medical Affairs Department, National Leprosarium, Tokyo, Japan  
Dr. Masahide Abe (1970--), Director, Second Research Unit, National  
Institute for Leprosy Research, Tokyo, Japan  
Dr. Tonetaro Ito (1974--), Professor, Department of Leprology,  
Research Institute for Microbial Diseases, Osaka University,  
Osaka, Japan  
Dr. Masahiro Nakamura (1973--), Professor of Bacteriology,  
Kurume University, School of Medicine, Asahi-cho,  
Kurume-shi, Japan  
Dr. Mitsugu Nishiura (1965--), Director, Special Dermatological  
Laboratory, Kyoto University, Kyoto, Japan

#### Member Whose Term Expired in 1974

- Dr. Yoshio Yoshie, Chairman (1965-1974), Director, Tama National  
Institute of Leprosy Research, Tokyo, Japan

### U.S. Malnutrition Panel

- Dr. David B. Coursin, Chairman (1974-- , Member 1967-1974), Director of Research, St. Joseph Hospital, Lancaster, Pennsylvania 17604  
Dr. Josef F. Brozek (1973--), Professor of Psychology, Lehigh University, Bethlehem, Pennsylvania 18001  
Dr. Sheldon Margen (1971--), Chairman, Department of Nutritional Sciences, University of California, Berkeley, California 94720  
Dr. John F. Mueller (1969--), Chief of Medicine, St. Luke's Hospital, Denver, Colorado 80203  
Dr. Barbara Underwood (1974--), Associate Professor of Nutrition, College of Human Development, The Pennsylvania State University, University Park, Pennsylvania 16802

### Member Whose Term Expired in 1974

- Dr. Nevin S. Scrimshaw, Chairman (1965-1974), Professor and Head, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

### Japanese Malnutrition Panel

- Dr. Norio Shimazono, Chairman (1966--), Professor, Department of Biochemistry, Tokyo Medical College, Tokyo, Japan  
Dr. Masao Arakawa (1966--), Professor, Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan  
Dr. Ichiro Nakagawa (1966--), Chief, Department of Nutrition, Institute of Public Health, Tokyo, Japan  
Dr. Toshio Oiso (1966--), Director, National Institute of Nutrition, Tokyo, Japan  
Dr. Hisato Yoshimura (1966--), Professor, Kyoto Prefectural University of Medicine, Kyoto, Japan

### U.S. Parasitic Diseases Panel

- Dr. Franz von Lichtenberg, Chairman (1973-- , Member, 1971-1973), Professor of Pathology, Peter Bent Brigham Hospital, Boston, Massachusetts 02995  
Dr. Lawrence R. Ash (1972--), Associate Professor, Division of Infectious and Tropical Diseases, University of California, Los Angeles, California 90024  
Dr. Paul F. Basch (1974--), Associate Professor, Department of Community and Preventive Medicine, Stanford University, School of Medicine, Stanford, California 94305  
Dr. Julian J. Jaffee (1971--), Professor of Pharmacology, University of Vermont Medical School, Burlington, Vermont 05401  
Dr. Thomas C. Orihel (1974--), Professor and Director, Tropical Medicine and Parasitology, Tulane University Medical Center, New Orleans, Louisiana 70012

Member Deceased in April 1974

Dr. Guillermo Pacheco (1973-1974), Research Zoologist, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20014

Member Whose Term Expired in 1974

Dr. Eli Chernin (1970-1974), Professor, Department of Tropical Public Health, Harvard School of Public Health, Boston, Massachusetts 02115

Japanese Parasitic Diseases Panel

Dr. Muneo Yokogawa, Chairman (1971--), Member 1965-1971), Professor, Department of Parasitic Diseases, Chiba University School of Medicine, Chiba, Japan

Dr. S. Hayashi (1974--), Professor of Parasitology, Yokohama City University, Yokohama, Tokyo, Japan

Dr. Seito Inatomi (1972--), Department of Parasitology, Okayama Medical School, Okayama, Japan

Dr. Tasushi Ishizaki (1968--), Chief, Department of Parasitology, National Institute of Health, Tokyo, Japan

Dr. Daisuke Katamine (1965--), Professor, Institute for Tropical Medicine, Nagasaki University, Nagasaki, Japan

Member Whose Term Expired in 1974

Dr. Manabu Sasa (Chairman 1968-1971, Member 1971-1974), Director, Institute of Medical Science, University of Tokyo, Tokyo, Japan

U.S. Tuberculosis Panel

Dr. Edgar E. Ribic, Chairman (1974--), Member 1965-1973), Chief, Molecular Biology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana 59840

Dr. Bernard W. Janicki (1969--), Assistant Chief, Allergy and Immunology Branch, Extramural Programs, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20014

Dr. John E. Kasik (1970--), Associate Professor of Research, University of Iowa, Iowa City, Iowa 52240

Dr. Emanuel Wolinsky (1969--), Professor of Medicine, Metropolitan General Hospital, Cleveland, Ohio 44109

Dr. Samuel B. Salvin (1973--), Professor of Microbiology and Immunology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

Member Whose Term Expired in 1974

Dr. William R. Barclay, Chairman (1969-1974, Member 1965-1969),  
Assistant Executive Vice President, American Medical Association,  
Chicago, Illinois 60610

Japanese Tuberculosis Panel

Dr. Shigeichi Sunahara, Chairman (1968--), Director, Tokyo  
National Chest Hospital, Tokyo, Japan  
Dr. Toyoho Murohashi (1965--), Chief, Department of Tuberculosis,  
National Institute of Health, Tokyo, Japan  
Dr. Shiro Someya (1969--), Vice-Director, Institute of Public  
Health, Tokyo, Japan  
Dr. Tadao Shimao (1968--), Vice-Director, Research Institute of  
Tuberculosis, Tokyo, Japan  
Dr. Masahiko Kato (1969--), National Sanitorium, Toneyama  
Hospital, Osaka, Japan

U.S. Viral Diseases Panel

Dr. Robert E. Shope, Chairman (1974--, Member 1973-1974), Director,  
Yale Arbovirus Research Unit, Associate Professor of Epidemiology,  
Yale University School of Medicine, New Haven, Connecticut 06510  
Dr. George Baer (1974--), Chief, Laboratory Investigation Unit,  
Center for Disease Control, Lawrenceville, Georgia 30245  
Dr. Thomas Monath (1974--), Chief, Vector Borne Diseases Division,  
Center for Disease Control, Fort Collins, Colorado 80521  
Dr. William F. Scherer (1974--), Professor and Chairman, Department  
of Microbiology, Cornell University Medical College, New York,  
New York 10021  
Dr. Alexis Shelokov (1971--), Chairman, Department of Microbiology,  
University of Texas Medical School, San Antonio, Texas 78229

Members Whose Term Expired in 1974

Dr. Fred M. Davenport, Chairman (1969-1974), Chairman, Department  
of Epidemiology, University of Michigan, Ann Arbor, Michigan 48104  
Dr. Gordon Meiklejohn (1970-1974), Head, Department of Medicine,  
University of Colorado, Medical Center, Denver, Colorado 80220  
Dr. Leon Rosen (1969-1974), Head, Pacific Research Section, NIAID,  
National Institutes of Health, Honolulu, Hawaii 96813

Japanese Viral Diseases Panel

Dr. Minoru Matsumoto, Chairman (1974--, Member 1972-1974), Professor,  
The Institute of Medical Science, Tokyo University, Tokyo, Japan

Dr. Nakao Ishida (1967--), Professor, Department of Bacteriology,  
Tohoku University, School of Medicine, Tohoku, Japan

Dr. Juntaro Kamahora (1967--), President, Osaka University,  
Osaka, Japan

Dr. Reisaku Kono (1971--), Director, Central Virus Diagnostic  
Laboratory, National Institute of Health, Tokyo, Japan

Dr. Toshiomi O'Kuno (1974--), Professor, Research Institute for  
Microbial Diseases, Osaka University, Osaka, Japan

Member Whose Term Expired in 1974,

Dr. Masatsugi Kanamitsu, Chairman (1970-1974), Professor, Department  
of Hygiene and Epidemiology, Sapporo Medical College, Sapporo, Japan

CALENDAR YEAR 1974

<u>Date</u>	<u>Research Conferences and Workshops</u>	<u>Delegation &amp; Committee Meetings</u>
January 10-12, 1974	Latent Effects of Malnutrition and Infection During Pregnancy, Malnutrition Panel, Guatemala City, Guatemala	
January 24-25, 1974		Joint Subcommittee Meeting on Program Review and Planning, Honolulu, Hawaii
May 1-3, 1974	Long-Term Toxicity of Antischistosomal Drugs, Joint Environmental and Parasitic Diseases Panels, Bethesda, Maryland	
June 19, 1974		U.S. Delegation Meeting, Washington, D.C.
August 5-7, 1974	Joint Viral Diseases Panel Conference, Tokyo, Japan	
August 6-7, 1974	Joint Environmental Panel Conference, Tokyo, Japan	
August 8-9, 1974		United States-Japan Joint Committee Meeting, Tokyo, Japan
August 17-19, 1974	Joint Parasitic Diseases Panel Conference, Unzen, Japan	
September 25-27, 1974	Joint Tuberculosis Panel Conference, Kyoto, Japan	
October 14-16, 1974	Joint Cholera Panel Conference, Kyoto, Japan	
October 16-18, 1974	Joint Leprosy Panel Conference, Kyoto, Japan	

<u>Date</u>	<u>Research Conferences and Workshops</u>	<u>Delegation &amp; Committee Meetings</u>
October 28-30, 1974	Joint Malnutrition Panel Conference, Mt. Fuji, Japan	
) November 14-15, 1974	The Role of Lymphokine Mediators in Immunity to Tuberculosis and Related Diseases, Bethesda, Maryland	
December 4, 1974	Rabies Workshop, Bethesda, Maryland	
December 9-11, 1974	Joint Workshop on the Mutagenicity of Chemical Carcinogens, Honolulu, Hawaii	