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The Coat of Arms
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Medical Department of the Army

A 1976 etching by Vassil Ekimov of an
original color print that appeared in
The Military Surgeon, Vol XLI, No 2, 1917

A publication of the

Borden Institute

Office of The Surgeon General
Department of the Army, United States of America

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1994

THE ARMED FORCES EPIDEMIOLOGICAL BOARD

The Histories of the Commissions

Theodore E. Woodward, M.D.
Editor

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Published by:
Office of The Surgeon General
Textbook of Military Medicine
Borden Institute
Walter Reed Army Medical Center
Washington, DC 20307-5001

Library of Congress Cataloging-in-Publication Data

Woodward, Theodore E. (Theodore Englar), 1914–
The Armed Forces Epidemiological Board : history of the Commissions / by Theodore E. Woodward.
p. cm.
Includes bibliographical references.
1. United States. Armed Forces Epidemiological Board History.
2 . Epidemiology—Research—United States—History—20th century.
I. Title
UH453.W66. 1994
614.4'0973—dc20

94-37993
CIP

PRINTED IN THE UNITED STATES OF AMERICA

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Foreword

The Armed Forces Epidemiological Board (AFEB) was conceived over 50 years ago as a medical and scientific advisory board to the Department of the Army. After World War II, on advice of The Surgeon General of the Department of the Army, the Secretary of the Army recommended that the AFEB be established as a triservice board. The new charter was formally adopted on 8 October 1953, with the Board serving as a joint agency for the three military departments. Throughout its history, the Board has responded to the needs of the services with dedication, wisdom, and sound advice.

From its inception in 1940 through 1972, the Board developed and used commissions to study specific military medical problems. Commission investigators engaged in basic and field investigations of problems relating to epidemiology and preventive medicine within the military medical community.

Called on during times of war and peace, the Commissions responded willingly to the medical needs of men and women in uniform. Commission accomplishments combined with intramural research benefited the general public health as well as the military and included the development of influenza vaccine and the treatment and prevention of pneumonia, hepatitis, meningococcal meningitis, rheumatic fever, tetanus, and diphtheria.

On behalf of the soldiers, sailors, airmen, and marines who have served over the years to preserve our democracy, we express our gratitude to the unselfish and dedicated members of the Armed Forces Epidemiological Board and its former Commissions.

Lieutenant General Alcide M. LaNoue
The Surgeon General of the U.S. Army

Vice Admiral D. F. Hagen
The Surgeon General of the U.S. Navy

Lieutenant General Edgar R. Anderson, Jr.
The Surgeon General of the U.S. Air Force

September 1994
Washington, DC

Preface

The Armed Forces Epidemiological Board (AFEB) and its system of commissions was conceived by necessity just before entry of the United States into World War II; it was born in 1940. Without question, the tenacity, advice, leadership qualities, and wisdom of Drs. Simmons, Bayne-Jones, Blake, and MacLeod during the early and later stages of the AFEB's inception made the unique enterprise possible. The innovative program is a refreshing demonstration of how two entirely separate professional groups, military and academic, could crystallize perceived goals and interests and reach a common conclusion aimed at maintaining the highest standards of prevention and control of disease of military importance. This system has never been surpassed and seldom equalled. Indeed, the AFEB-commission enterprise is a model of its kind frequently used by other nations and duplicated to advantage by our own nation.

Some "first" scientific contribution of the AFEB of military and public health significance are listed below:

- Developed vaccines and use of immune serum for influenza, measles, pertussis, the viral encephalitides, poliomyelitis, pneumococcal infections, and others.
- Experimentally reproduced hepatitis and demonstrated existence of several strains and that gamma globulin will prevent hepatitis.
- Identified the transmissible agent of primary atypical pneumonia and developed live oral vaccines for adenoviruses and use of mineral oil as an adjuvant.
- Clarified the pathogenesis and method of spread of coccioidal infections.
- Demonstrated that penicillin and tetracyclines prevent rheumatic fever and that sulfadiazine prevents meningococcal infections.
- Clarified methods of controlled air-borne infections and showed that streptococci are spread by personal contact.
- Demonstrated the first specific cures for the rickettsioses and typhoid fever and active chemoprophylaxis for scrub typhus with antibiotics.
- Developed strain E attenuated epidemic typhus vaccine and use of inactivated and living vaccines for typhoid fever.
- Proved that automobile seat belts prevent serious injury and that defective door locks cause injury.
- Clarified the role of atabrine as effective chemoprophylaxis for malaria.
- Introduced tetanus-diphtheria toxoid for military use, showed that small doses of diphtheria toxoid recalls established immunity, and developed purified toxoids.

- Greatly advanced knowledge of the importance of cellular immunity, fluorescent labeling of antibodies, and importance of properdin—the forerunner of complement.
- Developed new knowledge of dengue strains, protective vaccines for dengue infections, and clarification of the dengue-shock syndrome.
- Performed classic work on plague, plague vaccines, and oral antibiotic treatment.

This second book of the Textbook of Military Medicine series describes in detail the work of eleven former commissions of the AFEB. Without the devoted persistence of former AFEB and commission members, the valuable information contained in these writings would have been buried in the cobwebs of time.

Too much wholehearted praise and thanks cannot be given to Bill Jordan, who prepared four commission reports (Commissions on Acute Respiratory Diseases, Meningococcal Meningitis, Air-Borne Infections, and Pneumonia); Gordon Meiklejohn (Commission on Influenza); Floyd Denny and Harold Houser (Commission on Streptococcal and Staphylococcal Infections); Paul Beaver (Commission on Parasitic Diseases); Dan Crozier (Commission on Epidemiological Survey); and Dick Hornick (Commission on Enteric Diseases).

The reader can reflect with pride on these historic accomplishments, which truly are milestone contributions of immeasurable value not only for the military services but the public.

Grateful appreciation is expressed to authorities of the Department of Army, Navy, and Air Force who made necessary resources available without which this volume could not have been printed. Jean Ward, administrative assistant of the AFEB expertly retyped edited copies of the original manuscripts. The illustration department of Walter Reed Army Institute of Research prepared the necessary photographs that effectively embellish this book. Further editorial and technical arrangements were made by the Borden Institute. Special appreciation is expressed to the following persons for their help in securing fiscal support for this book: Lieutenant General Alexander M. Sloan, USAF, MC; The Surgeon General, Captain S. William Berg, USN, MC; Major General Thomas R. Temple, USA, DC; and Colonel Frederick J. Erdtmann, USA, MC.

I feel a sense of pride and gratitude for those special persons whose contributions have ensured that these important records have reached fulfillment and are now a part of our history.

—Theodore E. Woodward, M.D.

September 1994
Baltimore, Maryland

SECTION 1

Commission on Acute Respiratory Diseases

Incorporating Three Other Commissions: Commission on Air-Borne Infections Commission on Meningococcal Meningitis Commission on Pneumonia

This history is dedicated with grateful appreciation to Drs. John H. Dingle and Colin M. MacLeod. Dingle's pioneering work was highly instrumental in ensuring success of the Commission on Acute Respiratory Diseases. MacLeod, his friend and associate, directed the first Commission on Pneumonia and made lasting contributions not only to a number of commissions, but to the Armed Forces Epidemiological Board. It is not possible to measure the impact of each of these two remarkable medical scientists in the whole field of preventive medicine.

Foreword

The annals of military preventive medicine provides a remarkable record of achievement extending from Beaumont to Billings to Sternberg, Reed, Strong, Siler, Simmons, and so many more. Their work was a culmination of intelligent thought and scientific innovation all aimed at solving problems that arose from those social forces and political upheavals that involve society as a whole. So often, there has been productive interaction between military and civilian scientists. Their combined opinions and collective funds of knowledge have helped determine just what should be done and how it might be accomplished, all with the aim to better maintain the highest standards of health in military personnel.

William S. Jordan, Jr., has carefully evaluated and addressed these principles in preparation of his history of four commissions of the Armed Forces Epidemiological Board (AFEB). Each commission, in its own unique way, was involved in vital issues that required identity of cause, clarification of pathogenesis, and how best to prevent specific illness in the individual and throughout the military population.

Throughout the AFEB's illustrious history, no one has been more devoted and contributed more to the cause of prevention and control of infectious diseases in the U.S. military services than Dr. Jordan. He was in an admirable position to prepare this account of the activities of the Commission on Acute Respiratory Diseases (CARD) and three related, short-lived Commissions, having knowledge of them almost from their beginnings. John Dingle, first director of the CARD, was one of Jordan's attendings in 1940 and 1941, when he was a medical student serving as a substitute intern on the Harvard Medical Service at Boston City Hospital (BCH). After graduation in 1942, he interned at BCH with such mentors as Drs. Chester Keefer and Maxwell Finland before active duty as a Naval Medical Officer. When home on leave in his hometown of Fayetteville, North Carolina, in the summer of 1944, he visited Dr. Dingle and the CARD laboratory at Fort Bragg. After World War II and more training at BCH, he joined Dr. Dingle's new Department of Preventive Medicine at Western Reserve University, working there during the years that Dr. Dingle continued as director of the CARD and later as president of the AFEB. Dr. Jordan then moved to the University of Virginia School of Medicine in Charlottesville to create his own Department of Preventive Medicine and to serve for 6 years as the CARD director. Subsequently, as dean of the College of Medicine at the University of Kentucky in Lexington, and as director of the Microbiology and Infectious Diseases Program at the National Institute of Allergy and Infectious Diseases, he continued to participate in the activities of the AFEB.

Never have I known Bill to shirk a difficult assignment because of being "too busy." Furthermore, the ultimate product always came as close to the best solution as possible. Although technically retired, he continues as an involved public servant performing with his characteristic alert, vigorous, and wise approach to problem solving.

—Theodore E. Woodward, M.D.

History of the Commission on Acute Respiratory Diseases, Commission on Air-Borne Infections, Commission on Meningococcal Meningitis, and Commission on Pneumonia

William S. Jordan, Jr., M.D.

INTRODUCTION

Five of the first seven commissions formed at the first meeting (6 February 1941) of the Board for Investigation and Control of Influenza and Other Epidemic Diseases in the Army dealt with respiratory pathogens: Commissions on Influenza, Measles, Meningitis, Pneumonia, and Streptococcal Infections. At its third meeting 5 months later, the Board formed the Commission on Cross Infections in Hospitals, which was renamed the Commission on Air-Borne Infections shortly thereafter because the sterilization of air was a common problem for all groups seeking to prevent disease by limiting the dissemination of airborne organisms. Within 1 year, the Commissions on Acute Respiratory Diseases (CARD) and Neurotropic Viruses began. Thus, 7 of the first 10 commissions were concerned with airborne bacteria and viruses that cause respiratory infections.

As the Board gained experience with the commissions and as new problems were identified, new commissions were formed and existing ones merged or terminated. The Commission on Measles soon added Mumps to its title and eventually joined the Commission on Neurotropic Viruses to become the Commission on Viral and Rickettsial Diseases. The Commission on Hemolytic Streptococcal Infections was folded into the CARD in 1946 but was revived in 1949. The other three respiratory pathogen-related commissions were incorporated into the CARD after World War II,: Pneumonia in December, 1945, and Air-Borne Infections and Meningococcal Meningitis in April, 1946. These and subsequent administrative actions are listed in chronological order in Appendix 1. The research projects undertaken and observations made by the last four above-named commissions are listed in approximate order in Appendix 2.

As far as possible, study results are dated when they were reported to the Board or to the Commissions, rather than when they were published, to illustrate better the evolution of the problems explored, information gained, and control measures tested. Except for the items in Appendices I and II, the material related to streptococcal infections has been incorporated in the account of the Commission on Streptococcal and Staphylococcal Diseases (CSSD).

The following sections discuss the origins and organization of these four commissions, with emphasis on the longer-lived CARD. The scientific contributions made during their periods of service are then summarized, along with information as to the current knowledge of the etiology, epidemiology, prevention, and control of the diseases of concern to them. Lists of the publications of the Commissions are appended and will not be referenced here. Those interested in learning of the details of a particular study can do so by matching Appendix 2 with the list of publications and by consulting the supplemental references that cite the relevant and subsequent reports of others.

ADMINISTRATION

Acute Respiratory Diseases

The specter of a repeat of the influenza pandemic of 1918 and 1919 and its attendant high mortality from pneumonia accounted for the inclusion of influenza as the only specific disease mentioned in the title of the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army. The structure of the Board and its commissions was similarly shaped by the experience in these years. In World War I, the Pneumonia Commission of 1917 had supplemented undermanned military staffs with civilian physicians, and the Pneumonia Board of 1918 had organized specialist groups on short notice to investigate pneumonia whenever the need arose.

Among the commissions formed by the Board at its first meeting 10 months before the attack on Pearl Harbor were those for Influenza and Pneumonia. The minutes of this meeting note that the Influenza Commission is to include "related acute respiratory diseases," although a mission statement prepared after the third meeting of the Board just a few months later makes no mention of this fact.

One year later, at the fifth meeting of the Board in May, 1942, John H. Dingle, M.D. presented the report of a group appointed to investigate primary atypical pneumonia at Camp Claiborne, Louisiana. In addition to discussion of that disease, the minutes emphasize the difficulty in characterizing respiratory disease, noting that "advance requires a major effort in etiology and serology." There was prolonged and detailed discussion of the proposal, first outlined by Dr. Dingle in response to an informal suggestion by Colonel James Stevens (Steve) Simmons, that a permanent commission or group be established to study respiratory diseases. The Board recommended to The Surgeon General that provision be made for a permanent year-round study of respiratory disease by a specially selected group of investigators, provided details could be worked out satisfactorily. Such was the genesis of the CARD, a commission that differed from all others in that it was "organized on a full-time or permanent basis for the purpose of making a continuing study of various types of acute diseases of the respiratory tract, particularly those of undetermined etiology."

The report that Dr. Dingle presented to the Board summarized studies of the Commission for the Investigation of Atypical Pneumonia and Other Respiratory Diseases at Camp Claiborne, the forerunner of the CARD. Dr. Dingle had been studying this recently described syndrome with Dr. Maxwell Finland at the Boston City Hospital and had earlier led a team of Harvard scientists to investigate simultaneous outbreaks of diphtheria, meningococcal meningitis, and scarlet fever at Halifax, Nova Scotia, an important wartime port for the British Commonwealth. He was already a member of the Influenza Commission. Drs. Dingle and W. Barry Wood, Jr. (Associate, Department of Medicine, The Johns Hopkins Medical School, Baltimore, Maryland), a member of the Commission on Pneumonia, were dispatched by the Board to Camp Claiborne to investigate an outbreak of an unusual "acute pneumonitis." When the scope of the problem became obvious, the group of investigators was expanded by the addition of Drs. G. John Buddingh (Associate Professor of Bacteriology, Vanderbilt University School of Medicine, Nashville, Tennessee) and Alto E. Feller (Associate, Department of Internal Medicine, State University of Iowa, Ames, Iowa) of the Commission on Influenza, Drs. Theodore J. Abernethy (Associate Professor of Medicine, George Washington University, School of Medicine, Washington, D.C.) and James M. Ruegsegger (Chief, Pneumonia Service, Cincinnati General Hospital) of the Commission on Pneumonia, and consultants in biostatistics, Dr. George F. Badger (Associate in Biostatistics, School of Hygiene and Public Health, The Johns Hopkins University) and epidemiology, and Dr. Alexander Langmuir (Deputy Commissioner, Westchester County Health Department, New York). An Army staff member assigned to assist was Captain Norman L. Cressy of the Fourth Corps Area Laboratory.

The initial field team of Drs. Dingle (laboratorian) and Wood (clinician) was selected by Dr. Colin MacLeod (Professor of Bacteriology, New York University, New York, New York), Director of the Com-



Commission for the Investigation of Atypical Pneumonia and Other Respiratory Diseases at Camp Claiborne, Louisiana, 1942.

Front row, left to right: Captain Norman L. Cressy, Dr. G. John Buddingh, Dr. James M. Ruegsegger, Dr. Theodore Abernethy, Dr. John H. Dingle, Dr. W. Barry Wood, Jr., and Captain Rappoport (Base pathologist).

Back row, left to right: Dr. Edward Weiss, Dr. Alexander D. Langmuir, and Dr. George F. Badger.

mission on Pneumonia, at the request of Dr. Francis Blake (Professor of Medicine, Yale University, School of Medicine, New Haven, Connecticut), President of the Board; the team was supposed to include Dr. Langmuir, as recommended by Dr. Dingle. The members of the team were to be released on leave with pay by their respective institutions and paid as "Consultants to the Secretary of War" at the rate of $10.00 per day; however, Langmuir's superior refused to recommend him for leave with pay. Dr. Blake then persuaded the National Academy of Sciences to fund Dr. Langmuir's salary and travel, and he reported 2 months after Drs. Dingle and Wood to Camp Claiborne, where he and the others stayed for 3 months.

When CARD was activated on 1 August 1942, with Dr. Dingle as Director, all members of the Claiborne Commission, with the exception of Drs. Buddingh and Wood, including Captain Cressy, became members of this permanent group. They were joined within the year by Drs. Elias Strauss (Research Associate in Epidemiology, College of Physicians and Surgeons, Columbia University, New York), Charles H. Rammelkamp (Instructor of Medicine, Boston University School of Medicine), and Hugh Tatlock, a National Research Council Fellow.

The CARD, like the Board, was a creature of the Boston-to-Baltimore axis, with a few extensions to the middle west, reflecting the dominance of the eastern medical schools in the early 1940s. Drs. Dingle and Badger were graduate students at The Johns Hopkins School of Hygiene and Public Health at the same time. Dr. Dingle then went to Harvard Medical School, Boston, Massachusetts, and met Dr. Wood when the latter was a fellow in bacteriology. Ten years earlier, Dr. Ruegsegger had done work on the pneumococcus with Dr. Finland at the Thorndike Memorial Laboratory of the Boston City Hospital before joining the Department of Medicine at the University of Cincinnati. Dr. Dingle knew Drs. Rammelkamp and Strauss at the Boston City Hospital, Dr. Langmuir at both that hospital and at Johns Hopkins, and Dr. Feller at Harvard before Feller joined Dr. MacLeod's department at New York University. Dr. Abernethy had entered practice in Washington, D.C., after a residency with Dr. William S. Tillett at Johns Hopkins (before Tillett moved to New York University) and after 3 years at the Rockefeller Institute, New York, New York, where he met Dr. A. R. Dochez, a member of the Board. The youngest member to join the group in November 1943 was Dr. Irving Gordon, who had done work on the influenza virus with Dr. Frank Horsfall at the Rockefeller Institute before spending 1942 at Trudeau Sanatorium with tuberculosis. After leaving Trudeau, Dr. Gordon worked in the laboratories of the New York State Health Department in Albany, where he met Dr. Langmuir, who was then Deputy Health Commissioner of Westchester County. All of these relationships were of great value, for these friends and acquaintances became an extremely effective, productive, and congenial group of investigators.

In the interval between Camp Claiborne and Fort Bragg, North Carolina, the initial CARD members worked on the report of the Camp Claiborne studies at Johns Hopkins, accommodated through the kindness of Dr. Lowell Reed, while awaiting construction of facilities at the station hospital at Fort Bragg. A W-1 ward building at Fort Bragg was remodeled to serve as a laboratory, and an animal house was constructed as an addition to the hospital morgue. The staff reported on 19 October and lived for about 6 weeks in a nurses' barracks, while seeking housing in nearby Fayetteville. The rooms in the barracks were retained in subsequent years as on-call sleeping quarters. As the work expanded, a ward adjacent to the CARD's laboratory was made available, and a new nine-room air-conditioned animal house constructed.

Additional facilities were obtained to house volunteers during attempts to transmit primary atypical pneumonia and other respiratory illnesses to them. A preliminary study was conducted at a Civilian Public Service Camp in the Great Smoky National Park near Gatlinburg, Tennessee in buildings formerly used by the Civilian Conservation Corps. Subsequent experiments were conducted in the Holly Inn in nearby Pinehurst, North Carolina, a hotel with facilities adequate for the isolation of volunteers in individual rooms equipped with a private bath. Volunteers were recruited from a group of conscientious objectors identified with the assistance of Selective Service, the National Service Board for Religious Objectors, and the American Friends Service Committee.

When the establishment of a commission to be located on a military base was discussed at the fifth meeting of the Board, the Chief of Personnel Service, Colonel George F. Lull "was of the opinion that it



Staff of the Commission on Acute Respiratory Diseases (CARD) Laboratory at Fort Bragg, North Carolina, May, 1943.

Kneeling, left to right: T/4 R. L. Robinson, Private G. O. Whitaker, T/4 L. P. Godifer, Private First Class R. W. Mott.

Standing, second row, left to right: Captain H. L. Cressy, M.C., Dr. G. F. Badger, Dr. E. Strauss, Dr. J. M. Ruegsegger, B. A. Mulliken, M. Buckingham, E. E. Searles, Dr. J. H. Dingle, Dr. A. E. Feller.

Third row, left to right: Dr. A. D. Langmuir, A. Keogh, A. M. Galligan, M. E. Corcoran, L. W. Powell, Dr. C. H. Rammelkamp, Jr., Dr. T. J. Abernethy, 2nd Lieutenant A. Ignatow, M.A.C.

Fourth row, left to right: T. J. Oliver, W. A. Mickle, D. D. Graham, Sergeant H. E. Duke.

Back row, left to right: Private L. M. Ragland, Private First Class E. J. Noal, Private J. E. Stanfield, Private First Class C. E. Owens.

would be possible to hold together a group of commissioned medical officers for this purpose." It was noted that a "waiver of disability could be applied to any member of such a group for limited service." As it happened, the professional members and associates of the CARD remained primarily a civilian group for the first 18 months. About this time, Ruegsegger left to accept a commission in the Navy because, "I didn't think I was contributing much to the war effort" looking for unknown agents. During his 3 years as a Naval Preventive Medicine Officer, he helped make the diagnosis of pneumococcal endocarditis in President Franklin Roosevelt and to obtain penicillin for the President's treatment. By the spring of 1944, the majority of the physicians were commissioned in the Army of the United States. Despite a limp attributed to poliomyelitis in childhood, Dr. Dingle was commissioned Major, as were Drs. Abernethy, Badger, and Langmuir. Dr. Tatlock was made a Captain; Dr. Cressy advanced from Captain to Major, and Dr. Strauss, from 1st Lieutenant to Captain. Despite the prior waiver statement, Drs. Feller, Gordon, and Rammelkamp were not commissioned because of their medical histories. The group did manage to stay together, although Dr. Langmuir received orders for detached duty (never executed) shortly before all were decommissioned and returned to civilian status. Dr. Dingle received a terminal commission as Lieutenant Colonel.

Funds for the CARD budget were provided through a War Department contract with Yale University. The budget approved by the Board for the year beginning 1 July 1943 was $4,000 short of the $100,000 requested by Dr. Dingle, as follows:

CARD Budget for Year Beginning 1 July 1943

Professional salaries	$40,000
Secretarial and technical salaries	15,000
Equipment, supplies, and travel	41,000
Total	$96,000

The major source of financial support was obtained from private foundations, presumably through the combined efforts of Commission Director Dingle and Board President Blake. Contributions to the Board on behalf of CARD were as follows:

Private Financial Support for CARD

Rockefeller Foundation	$25,000
W. K. Kellogg Foundation	20,000
Commonwealth Fund	15,000
John & Mary R. Markle Foundation	10,000
Total	$70,000

By November 1945, the budget for the Central Board and 10 commissions totaled $570,544, with the largest budget, $86,200, being that for the CARD. The available records do not make clear how the foundation funds were melded into the total or why the CARD budget appeared to decrease by $10,000 in 2 years. One possible explanation is that the fiscal year 1946 Board budget included an additional $14,330 for civil service employees at the CARD laboratory and $6,000 for supplies. The field laboratory closed 8 months later, at which time the CARD budget consisted of all research contracts and CARD with its investigators and their institutions.

Such a contract was awarded to Western Reserve University in Cleveland, Ohio, on behalf of Dr. Dingle, to continue studies on acute respiratory diseases. Although the war was over, the military decided that it still needed the advice of the Army Epidemiological Board and the expertise of certain of its commissions. Dr. Dingle, who continued as CARD Director until 1955, and his colleagues at Fort Bragg, conceived the idea of applying the epidemiological and laboratory methods used to study recruits to the study of a civilian population. Dr. Dingle and three other members of the CARD, Drs. Badger, Feller, and Rammelkamp, were persuaded by Dr. Joseph T. Wearn, then Dean of the School of Medicine at Western Reserve, to come to Cleveland to undertake such studies using as a base a new Department of Preven-



Staff of The Commission Acute Respiratory Diseases (CARD) Laboratory, November, 1944.

Kneeling, left to right: Dr. C. H. Rammelkamp, Jr., Dr. A. E. Feller, Dr. I. Gordan, Private W. Park, Private E. Oliver, T/5 D. Foltz, Staff Sergeant E. Gold, Sergeant C. Hoover.

Standing, second row, left to right: J. P. Neeley, D. C. Mickle, M. J. Croker, R. Chase, I. A. Salamandra, Private A. Adler, Private F. Sullivan, Corporal M. H. Kaplan, Sergeant H. E. Duke, Corporal W. W. Skatrud, Private First Class V. Culver.

Third row, left to right: B. Smith, S. Harlam, S. Taylor, R. M. Kierman, I. Weissinger, Technical Sergeant L. P. Codifer, Corporal G. J. Leuty.

Fourth row, left to right: Major J. H. Dingle, MC , C. Kaldus, 2nd Lieutenant W. A. Mickle, SnC, B. A. Mulliken, 1st Lieutenant H. M. Lemon, MC, M. Pate, Frank David, H. H. Bobbitt.

Fifth row, left to right: 1st Lieutenant T. J. Oliver, SnC, Major T. J. Abernethy, MC, Captain Straus, MC, 1st Lieutenant H. Tatlock, MC, 1st Lieutenant R. L. Robinson, SnC, Captain C. G. Loosli, MC, 1st Lieutnant A. Ignatow, MAC.

Back row, left to right: Captain A. D. Langmuir, MC, Captain G. F. Badger, MC, Major N. Plummer, MC, Major N. L. Cressy, MC.

Sergeant E. Gold (front row, second from right), a technician, later followed CARD members to the School of Medicine at Western Reserve University as a medical student and became Professor and Chairman of the Department of Pediatrics at the University of California, Davis.



Physician Members and Associates of the Commission on Acute Respiratory Diseases (CARD), November, 1944.

Front row, left to right: Major T. J. Abernethy, MC, Major J. H. Dingle, MC, Captain A. D. Langmuir, MC.

Second row, left to right: 1st Lieutenant H. Tatlock, MC, Dr. A. E. Feller, Captain C. G. Loosli, MC (Commission on Air-Borne Infections), Dr. I. Gordon.

Third row, left to right: Major N. Plummer, MC (Commission on Influenza), Captain E. Strauss, MC, Captain G. F. Badger, MC.

Back row, left to right: 1st Lieutenant H. M. Lemon, MC (Commission on Air-Borne Infections), Major N. L. Cressy, MC, Dr. C. H. Rammelkamp, Jr.

tive Medicine, of which Dr. Dingle was to be Chairman. They were joined at the outset by Dr. Richard G. Hodges, a pediatrician, who had conducted the studies of pneumococcal vaccine at the Army Air Base Technical School in Sioux Falls, South Dakota, with Dr. MacLeod of the Commission on Pneumonia. This nuclear group was joined later by William S. Jordan, Jr., who had known Dr. Dingle at the Boston City Hospital, Harold S. Ginsberg, also trained at Boston City and formerly Chief of the Medical Service at the Station Hospital at Fort Bragg; Floyd W. Denny, Jr., once assigned as a young medical officer to the Department for training before a tour of duty at the Streptococcal Diseases Laboratory at Warren Air Force Base, Cheyenne, Wyoming; Harold B. Houser, who served as Field Director of the Laboratory on Housing and Illness, Robert Oseasohn, and others. When Dr. Dingle became President of the Board, Drs. Feller, Jordan, and Denny, in turn, became Director of CARD.

Dr. Dingle served as Chairman of the Department of Preventive Medicine at Western Reserve until 1969. Despite a progressive disability, he maintained an interest in education and research until his death in 1973. Dr. Badger became Chairman of the Department of Biostatistics before retiring in 1972 to a community southeast of Cleveland, where he died on 30 November 1991 of a heart attack. Dr. Feller became Chairman of the Department of Microbiology at the University of Virginia School of Medicine, Charlottesville, Virginia, but unfortunately died at an early age of coronary heart disease in 1946 while vacationing at Nag's Head, North Carolina. Dr. Hodges died in Cleveland of myocardial infarction at an even earlier age. Dr. Rammelkamp, as Professor of Medicine, became Director of the Department of Medicine at the Cleveland City Hospital and played a major role in transforming it into the Metropolitan General Hospital of Cuyahoga County. He died in 1981 of a ruptured abdominal aortic aneurysm. Dr. Denny served as Chairman of the Department of Pediatrics at the University of North Carolina for 17 years and continued as a professor there in 1992. Dr. Ginsberg served sequentially as Chairman of the Departments of Microbiology at the University of Pennsylvania and the College of Physicians and Surgeons of Columbia University, retiring in 1993 to Bethesda, Maryland, where he continued studies of adenoviruses in the Laboratory of Infectious Diseases of the National Institutes of Health (NIH). Dr. Houser became Chairman of the Department of Epidemiology and Biostatistics at Case Western Reserve, the eventual successor of Dr. Dingle's Department of Preventive Medicine, retiring in 1992 to Sun Lakes, Arizona. Dr. Jordan became, in succession, Chairman of the Department of Preventive Medicine and Professor of Medicine at the University of Virginia, Dean of the College of Medicine at the University of Kentucky, Lexington, Kentucky, and Director of the Microbiology and Infectious Diseases Program at the National Institute of Allergy and Infectious Diseases (NIAID), NIH. Dr. Jordan retired in 1987, continuing as a member of the AFEB until 1992 and as a consultant to the National Vaccine Program Office in 1994. Dr. Oseasohn served sequentially as Chairman of the Department of Epidemiology and Community Medicine and Professor of Medicine at the University of New Mexico, Albuquerque, New Mexico; Professor of Epidemiology and Associate Dean, University of Texas School of Public Health, Houston; Chairman, Department of Epidemiology and Health, McGill University, Montreal, Quebec; Professor of Epidemiology; and Associate Dean, University of Texas School of Public Health, Master of Public Health Program at San Antonio. In 1992, his wife having died the previous year, he retired to a nursing home suffering from Alzheimer's disease. He died on June 7, 1994.

Worthy of note is Dr. Eli Gold. He was a Sergeant in the laboratory at Fort Bragg and followed the senior staff from there to Western Reserve to enroll as a medical student. After graduation, he was an intern and resident of the Children's Medical Center in Boston, before returning to Cleveland as Dr. Frederick Robbins' Chief Resident in Pediatrics at the City Hospital. He advanced through the academic ranks to become Chairman of the Department of Pediatrics at the University of California, Davis, Medical Center at Sacramento. He retired in 1987 to Mercer Island, Washington, from where he recalled the occasion of Dr. Dingle's marriage to Doris Brown in June of 1946, when the 6 x 6 truck used to transport the enlisted men got mired in the mud on the grounds of her parents' house. The new Mrs. Dingle, a native of Fayetteville, which was also Dr. Jordan's hometown, had worked as a secretary for CARD at Fort Bragg, and followed her husband's activities with the CARD and the AFEB for many years.

The other original CARD members' careers continued as follows. Dr. Abernethy returned to private practice in Washington, D.C., retiring after over 40 years to Baltimore, where he died on 4 January

DIRECTORS OF THE CARD



ALTO E. FELLER, M.D.

1955 to 1959



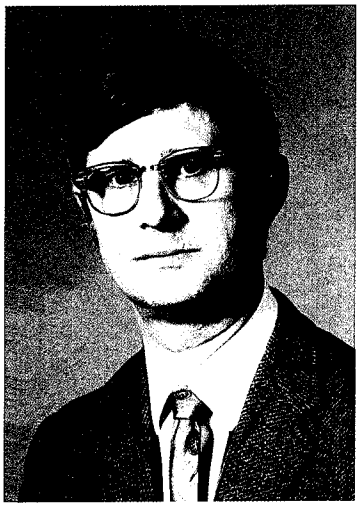
WILLIAM S. JORDAN, JR., M.D.

1959 to 1967



JOHN H. DINGLE, M.S., M.D.

1942 to 1955
President AFEB
1955 to 1958



FLOYD W. DENNY, JR., M.D.

1967 to 1972



GEORGE G. JACKSON, M.D.

Acting Director
September 1971 to September 1972

1992 after a stroke. Dr. Ruegsegger joined Lederle Laboratories. Dr. Strauss maintained an active practice in Texas until his death in 1988. Dr. Tatlock ended his Army career as Chief of Infectious Diseases at Walter Reed General Hospital and then spent 35 years in the practice of internal medicine in Northhampton, Massachusetts, becoming Chief of Medicine at Cooley Dickinson Hospital before retiring in 1981 to devote himself full time to photography. Dr. Gordon returned to the New York State Department of Health in Albany to head its virology laboratory before moving to California as Chairman of the Department of Microbiology at the University of Southern California, where he continued to teach in 1993, even after retiring. Dr. Langmuir returned to Johns Hopkins as Associate Professor of Epidemiology before moving in 1949 to the Centers for Disease Control (CDC) in Atlanta, where he founded the Epidemic Intelligence Service and from which he retired in 1970 to teach at The Johns Hopkins School of Hygiene and Public Health until his death from kidney cancer on 22 November 1993 at age 83.

During the postwar life of CARD, the major investigators and their associates supported by the AFEB, in addition to Dr. Dingle at Western Reserve, included Drs. Harry F. Dowling and George G. Jackson at the University of Illinois, Chicago; J. Thomas Grayston, Hjordis M. Foy, and E. Russell Alexander, University of Washington, Seattle; Floyd W. Denny, Wallace A. Clyde, and Gerald W. Fernald, University of North Carolina at Chapel Hill; Carl G. Harford, Washington University, St. Louis; Harry A. Feldman, State University of New York (SUNY)-Syracuse; Lewis Thomas, New York University; Charles E. Smith, initially at the School of Medicine of Stanford University in San Francisco, then later at the University of California at Berkeley with Demosthenes Pappagianis; Alto E. Feller, William S. Jordan, Jack M. Gwaltney, and Owen Hendley, University of Virginia, Charlottesville; Harold S. Ginsberg, University of Pennsylvania, Philadelphia. An important group of investigators supported by another source of federal funds was housed at the NIH Laboratory of Infectious Diseases under the leadership of Dr. Robert M. Chanock, an associate member of the CARD.

Among the members of this group not previously mentioned, Dr. Dowling retired to Northern Virginia to author a book, *City Hospitals*, to add to his earlier ones, *The Acute Bacterial Diseases* and *Medicines for Man*. Dr. Jackson served with distinction as Editor of the *Journal of Infectious Diseases* , moved to England to become Director of Virology at the London Hospital Medical Center, and then retired to his home state of Utah. Dr. Grayston became, in succession, Chairman of the Department of Preventive Medicine, School of Medicine; Dean of the School of Public Health; Vice President for Health Science, all at the University of Washington Medical Center before returning to research in 1984 as Professor of Epidemiology. Dr. Harford remained active at Washington University after his official retirement, but 1992 found him in a nursing home suffering from Alzheimer's disease. Dr. Foy continued at the University of Washington; Dr. Alexander moved to the University of Arizona and then to the CDC, before returning to Washington; both were still active in 1993. Dr. Feldman served for many years as Chairman of the Department of Preventive Medicine at SUNY-Syracuse and as President of both the American Epidemiological Society and the Infectious Diseases Society of America, each of which established awards in his name after his death in 1985. Dr. Thomas authored delightful and insightful notes as an observer of biology and medicine (*The Lives of a Cell, The Medusa and the Snail, The Youngest Science*), while en route from medical school deanships at NYU and Yale to the Chancellorship of Memorial Sloan-Kettering Cancer Center, retiring to continue as Scholar-in-Residence at Cornell University Medical College. Thomas died of Waldenstrom's disease on 3 November 1993, at age 80. Smith continued to work on coccidioidomycosis while serving as Dean of the School of Public Health at Berkeley. After Dr. Smith's death in 1967, Dr. Pappagianis moved these studies to the University of California at Davis when he became Chairman of the Department of Microbiology at its medical school.

Among noncontractor members who made significant contributions were Drs. Robert Austrian, Professor of Medicine, University of New York, Downstate Medical Center, who became Professor of Research Medicine at University of Pennsylvania, where he continued to study the pneumococcus in 1994; Theodore E. Eickhoff, who was at the CDC when recruited to serve on the Committee on Meningococcal Infections, and was to become Professor of Medicine at the University of Colorado School of Medicine and Chief of Medicine at Presbyterian/St. Luke's Medical Center in Denver, continuing there in 1994; and Jay P. Sanford, initially at the University of Texas Southwestern Medical School, who

served as Dean and Vice President of the Uniformed Services University of the Health Sciences before returning to Texas. Worthy of special mention is another noncontractor and loyal associate member, Dr. Finland, who consistently refused to become a member because he didn't want to participate in contract reviews. Dr. Finland trained many CARD investigators on the wards of the Harvard Medical Service or in the laboratories of the Thorndike Memorial Laboratory at the Boston City Hospital during his 50 years at that institution. He died in 1987 at the age of 85.

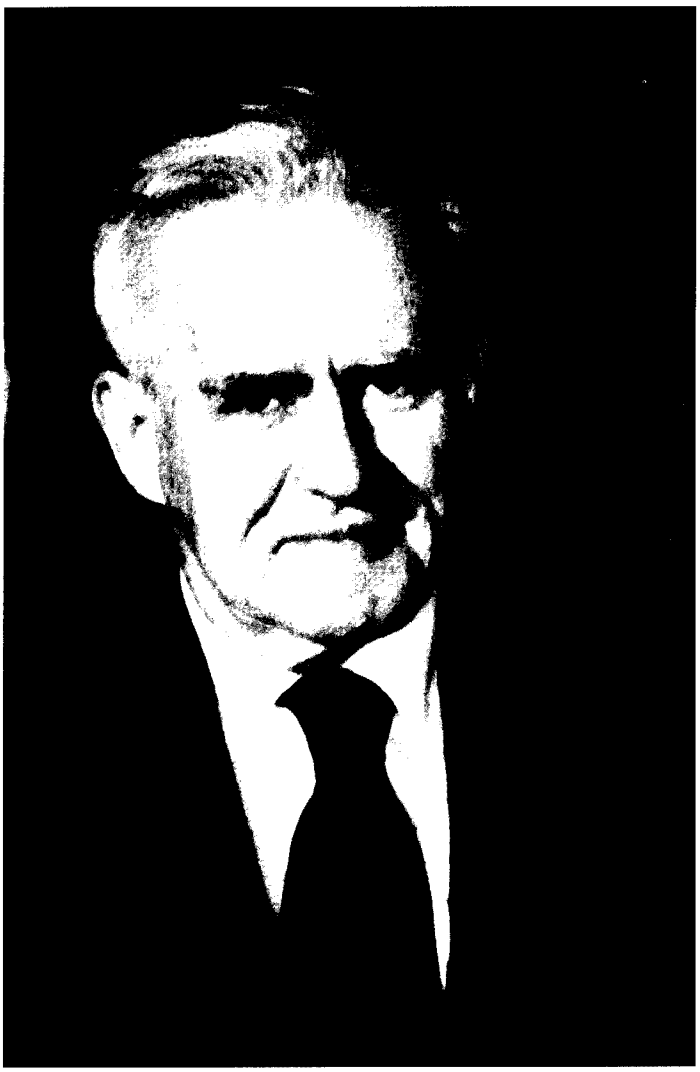
An outstanding feature of the structure and function of the AFEB and its commissions was the interchange that occurred when these investigators met periodically, along with those from military laboratories, to review work in progress and to learn of current problems in the armed forces. Between meetings, commission members and associates could respond to calls for assistance more effectively than might otherwise have been the case because of their knowledge of each other and of three military services. The major annual CARD meeting was held in the spring, usually in tandem with the Commission on Streptococcal and Staphylococcal Diseases (CSSD), so that the two groups could share an overlapping agenda for a day. In the fall, CARD and the Commission on Influenza took advantage of the meeting of the Central Society for Clinical Research in Chicago to meet for 1 day before the Society meeting. Drs. Dowling and Jackson often arranged a dinner for the attendees at a convenient university facility. At the 1959 fall meeting, Dr. Thomas Francis labeled the challenge resulting from the explosive identification of new viruses as "viral smog," and the suggestion was made that CARD sponsor the preparation of a laboratory guide for the isolation and characterization of the new respiratory viruses. Dr. Jackson enlisted the help of Drs. Chanock, Karl Johnson, and Robert Muldoon to produce a loose-leaf *Manual of New Viruses Causing Respiratory Illnesses in Man*. The first 100 copies of this manual, prepared at a cost of $377.66, exclusive of the authors' time and effort, were distributed in June 1961. The publication was widely acclaimed, with requests for copies coming from the World Health Organization, and laboratories in many countries.

Concurrently, the use of cell cultures had resulted in the discovery of a host of enteric viruses "in search of disease" or "orphan viruses." Investigators who sought to relate these enteroviruses to clinical syndromes and to distinguish them from polioviruses needed appropriate antisera and antigens. Because this was also true of those working with respiratory viruses, the AFEB sought the support of the NIAID, which, like the National Foundation for Infantile Paralysis, also had recognized the need for standardized reference reagents. NIAID had created an adenovirus committee for this purpose. The committee was initially chaired by Dr. Jerome Syverton, Chairman of the Department of Microbiology, University of Minnesota, with Drs. Ginsberg and Jordan of CARD and Dr. Edwin Lennette of the Commission on Influenza among the members. Dr. Syverton died of a heart attack in a New York taxi on his way to another meeting, after an early meeting of the adenovirus committee. He was succeeded as chairman by Dr. Jordan.

At a meeting at NIAID on 16 February 1960, representatives of the Public Health Service (PHS) and AFEB agreed to seek mechanisms to expand the scope of the adenovirus committee. Those in attendance were Drs. Dorland Davis, Scientific Director (subsequently Director), Paul Peterson, Associate Director, and Robert Huebner, Chief, Laboratory of Infectious Diseases, all of NIAID; Dr. Francis, President, AFEB; Dr. Fred Davenport, Commission on Influenza; Dr. William Hammon, Commission on Virus Diseases; Dr. Ralph Hogan, Chief, Laboratory of Virology, CDC; Dr. Harvey Scudder, Division of Research Grants, NIH; and Dr. E. H. Arnold, affiliation not recorded. Out of this meeting grew the Reference Reagents Program of NIAID that was to provide high quality antigens and antisera to investigators for many years before its repository and distribution functions were transferred to the American Type Culture Collection in the 1980s. The contributions made by CARD investigators and others to the dispersal of the etiologic smog are summarized in the research section.

Air-Borne Infections

The Commission on Air-borne Infections (CABI) began life in June 1941 as the Commission on Cross Infections in Hospitals. The investigations required by The Surgeon General, at that time, were to "carry on work pertaining to the prevention of cross-infections in Army Hospitals. Cross-infections



MAXWELL FINLAND, M.D.

As a Professor of Medicine at Harvard Medical School and Chief of Infectious Diseases at the Thorndike Memorial Laboratory at Boston City Hospital, Dr. Maxwell Finland, long a student of pneumonia, conducted pioneering studies of the sulfonamides and penicillin. He trained many members of CARD and served it faithfully as a Associate Member for over 12 years.

have been an important problem for many years and it is now believed that their control can be brought about through the installation of air filters on sterilizing lamps. These studies will involve the purchase of extensive equipment and very close observation by highly-trained specialists and technicians over extended periods of time."

Dr. Oswald H. Robertson, Professor of Medicine at the University of Chicago and already a member of the Commission on Influenza, was named Director. He had just published the results of studies of the effectiveness of propylene glycol vapor as an aerosol against a number of organisms, including influenza A virus. Three other members also represented liaison with other Commissions: Drs. C. Philip Miller, also a Professor of Medicine at the University of Chicago (Meningococcal Meningitis); Wilson G. Smillie, another former research fellow at the Rockefeller Institute, Chairman of the Department of Public Health, Cornell Medical College (Influenza); and Joseph Stokes, Jr., Professor of Pediatrics, University of Pennsylvania (Measles and Mumps). Two other physician members were Drs. Clayton G. Loosli, who had done research with Dr. Robertson and had advanced to Assistant Professor of Medicine at the University of Chicago, and Dr. Francis F. Schwentker, Staff Member, International Health Division, Rockefeller Foundation (Director, Commission on Hemolytic Streptococcal Infections). Undoubtedly at the suggestion of Dr. Stokes, Mr. William F. Wells, Associate Professor in Air-Borne Infection, an expert from the University of Pennsylvania, completed the roster. This group, with the exception of Dr. Schwentker who was added later, met in Chicago the following October to plan how to exploit air sterilization methods to reduce the number of pathogenic bacteria and viruses in operating rooms, hospital wards, and barracks. A field study was initiated at the Station Hospital at Chanute Field, Illinois, and research with animals begun in laboratories at the University of Chicago and the University of Pennsylvania. During the following year, the CABI program was designed to include the following:

(1) Study of the effects of ultraviolet light, under varied conditions of radiation, for its bactericidal action on air-borne microorganisms and for the prevention of spread of bacteria from patient to patient.

(2) Investigation of the pharmacological effects of propylene glycol vapor on animals and the ability of this vapor to destroy pathogenic microorganisms and viruses.

(3) When satisfactory evidence is obtained showing that propylene glycol vapor is not toxic, study of the activity of the vapor in the same manner in which ultraviolet light is being investigated.

(4) Study of the comparative effectiveness of both ultraviolet radiation and propylene glycol vapor on dust-borne bacteria.

(5) Investigation of the bactericidal and viricidal properties of other glycols.

(6) When deemed appropriate, the application of these measures for the control of air-borne infection to relatively isolated and fairly large non-hospitalized groups.

The first budget found in the records is for $53,705.00 in fiscal year 1946, by which time two other members had been added to the commission: Morton Hamburger, Jr., M.D., and Theodore T. Puck, Ph.D., both members of the Department of Medicine, University of Chicago. Hamburger, who had worked in Robertson's laboratory in 1938, was named Field Director. In addition, Captain Henry M. Lemon participated in CABI studies as they were transferred to Camp Carson, Colorado, and later to Fort Lewis, Washington. After development of an apparatus for dispensing glycol vapor, its use was tested at the Harriet Lane Home, The Johns Hopkins Hospital, and laundry methods were sought for the application of an oil emulsion to bedding.

Increasing attention was being paid to the physical aspects of housing prompted by the decision of the Commanding General, Services of Supply, in October 1942, to reduce the space allowance for troop housing to 40 square feet per man. At the request of The Surgeon General, 10 members of the AFEB and its commissions visited 19 Army posts and camps during December to consider the current and expected incidence of acute respiratory disease in troops. The survey called particular attention to inadequate provisions for proper ventilation and recommended that steps be taken to ensure that ventilation of 1,800 cubic feet per man hour be provided in barracks at night. Members of the AFEB were critical of the overcrowding that existed but did not consider double bunking undesirable because it created more floor space and air space and less actual contact of men while sleeping.



DR. OSWALD H. ROBERTSON, M.D.

Dr. Oswald H. Robertson served as Professor of Medicine, University of Chicago, and Director of the Commission on Air-Borne Infections from 1942 to 1946. He was one of the first to study the effectiveness of propylene glycol vapor as an aerosol against influenza virus.

Dr. Kenneth F. Maxcy, in his report on Fort George G. Meade, Maryland, noted that

> Attention is particularly directed to defects in design and operation of the heating systems installed in standard two-story barracks (Plans 700-1165 and 800-443). From the point of view of comfort and spread of infection improvement could and should be made. This is a very practical and important problem which might receive more extended attention from Dr. O. H. Robertson and his Commission on Cross Infections in Hospitals.

At a special meeting on 29 January 1943, the AFEB transmitted the following resolution to the Surgeon General:

> In view of the increasing incidence of acute respiratory diseases and meningococcal meningitis during December 1942 and January 1943 and based upon an inspection of camps by members of the Board and its Commissions, the Board desires to go on record as emphasizing the influence of crowding in barracks, mess halls, and recreation halls on the spread of meningitis, acute respiratory and other epidemic diseases. Crowding is only one factor in this situation but a highly important one. In general terms it can be positively stated that the greater the crowding the greater is the risk of an epidemic of serious proportions. The order reducing the minimum floor space per man in barracks from sixty (60) square feet to forty (40) square feet, while a military necessity, is in an undesirable direction from the standpoint of maintenance of health. The effect of this provision not only results in overcrowding in barracks but also an equally undesirable overcrowding in mess halls, wash rooms, latrines, post exchanges, etc., and overloads all existing facilities. The Board especially emphasizes the greater susceptibility of recruits to acute respiratory and other epidemic diseases and the greater risks of epidemics during the winter months (December through March), particularly under conditions of crowding.

In May 1943, the name of the Commission was changed from Cross Infections in Hospitals to Air-Borne Infections in keeping with the emphasis on housing and the search for methods to limit the spread of respiratory pathogens in barracks. The CABI and CARD addressed these problems for the next 3 years, in collaboration with the Commission on Hemolytic Streptococcal Infections. A report in 1945 noted that significantly lower rates were observed during an epidemic of acute respiratory disease among men living in barracks with double bunks than in control barracks. At the same meeting of the AFEB on 15 April 1946, at which the CABI was terminated, the AFEB reaffirmed its position of being opposed to the use of double bunking unless overcrowding is avoided.

> It is recommended that double bunking is justified in barracks, but should not be used to accommodate more than one man per sixty square feet of floor space (i.e., per one hundred and twenty square feet of floor space for each double bunk).

The notes of this meeting called for the Commission on Environmental Hygiene to continue the studies of the CABI. In truth, that Commission focused on occupational health and toxicology, studying the adaptation of a human to his environment, the medical aspects of clothing, cold, heat, ventilation, and the disposal of waste. Yet, a need existed for additional studies of the effect of housing on the occurrence of disease, both infectious and neuropsychiatric. An ad hoc committee of CARD on space allocation in troop housing recommended that a Laboratory on Housing and Illness be established at Sampson Air Force Base, New York.

At the time of organization of this Laboratory in January 1954, Sampson Air Force Base had been a recruit training center for about 3 years. The Air Force had established the Epidemiological Detachment, 1141st Medical Service Squadron of the 1070th Medical Activity Group at Sampson in 1951 to study streptococcal infections and methods of prophylaxis. In addition, the Epidemiological Detachment was cooperating with the Commission on Influenza in influenza vaccine trials. The stated ap-

proach of the new laboratory was fundamental study of the problem of military housing on a long-term basis, rather than simple determination of the ideal number of square or cubic feet per man. The work of the Epidemiological Detachment was to be coordinated with and under the direction of the director of the housing studies. Initial support of the Laboratory was by contract with the School of Aviation Medicine. Drs. Feldman (SUNY-Syracuse) and Houser (on assignment from Western Reserve University) were the responsible investigators, with Dr. Houser designated as Field Director. Planning and conduct of the studies were under the aegis of CARD. From 1 August 1955, the laboratory was supported through Department of Army contracts, with Dr. Houser as the responsible investigator.

Field, laboratory, and clinical studies were well underway by February 1954. The deficiencies of the original laboratory space for virological work and the increased volume of bacteriologic and other laboratory procedures necessitated remodeling of the laboratory; this remodeling was completed in September 1955. In December 1955, input of recruits to Sampson was markedly reduced and the decision to close the base was announced. In June 1956, the base officially closed. Dr. Houser transferred records and selected biological specimens to the Upstate Medical Center at Syracuse. There, a new laboratory was completed and in operation by late fall of 1956. Work continued at Syracuse on the collected material and specimens until June 1958 when the contract and certain materials were transferred to Western Reserve University, where work on the contract continued until 31 July 1960.

The subsequent careers of Drs. Feldman and Houser have been recorded earlier. Of the original CABI members, Dr. Robertson retired to California in 1949 to devote himself to the study of the endocrinology of salmon and trout; he died in 1966. Dr. Miller became Professor Emeritus in 1960; he died in 1985. Dr. Smillie continued as head of the Department of Pubic Health at Cornell until 1955, during which time he coauthored a textbook on preventive medicine with Dr. Edwin D. Kilbourne, then a member of his department and a long-time member of the Commission on Influenza. Dr. Smillie died in 1971. Dr. Stokes died in 1972 after a distinguished career in academic pediatrics. Dr. Loosli moved from Chicago to Los Angeles to become Dean of the School of Medicine of the University of Southern California; he died in 1976. Dr. Schwentker, the first Director of the CSSD, had been the first to report, along with coauthors Drs. Sidney Gelman and Perrin H. Long in 1937, that sulfanilamide was effective in the treatment of meningococcal meningitis. Suicide shortly after the commissions were formed ended Dr. Schwentker's promising career.

Dr. Hamburger became Professor of Medicine at the University of Cincinnati and was a continuing contributor to the CSSD, until he drowned in 1970 while fishing in the Snake River in Wyoming. Dr. Puck, who had received his doctorate only 1 year before joining CABI, remained at the University of Chicago until 1947, spent 1 year at the California Institute of Technology, Pasadena, and then became Professor of Biophysics and Chairman of the Department at the School of Medicine of the University of Colorado, Boulder. A recipient of many awards for his work in genetics and immunology, he retired as department chairman in 1967, but continued as Director of the Eleanor Roosevelt Institute of Cancer Research. In 1972, he authored *The Mammalian Cell as a Microorganism: Genetic and Biochemical Studies In Vitro*. Although his contribution to the control of airborne infections is not evident, of interest is the fact that he listed his brief CABI membership in *Who's Who*.

Meningococcal Meningitis

The Commission on Meningococcal Meningitis was the seventh of the eight commissions created by the Board in March 1941. The Surgeon General "determined" that:

> The Meningitis Commission will study the incidence, treatment and prevention of cerebrospinal meningitis. In the control of meningitis, it is necessary to determine the type of germ causing the disease. For this purpose, typing laboratories will be set up and a more efficient means of typing will be studied. Through work with small groups of individuals, an attempt will be made to develop effective administrative methods for the control of meningitis carriers. Such carriers are apparently normal individuals who harbor the germ in the nose or throat and who disseminate the infection through their secretions during contact, or in sneezing or coughing.



HAROLD B. HOUSER, M.D.

Dr. Harold B. Houser is shown here (in lab coat) in 1955 with USAF (MSC) Officers at Sampson Air Force Base, where he served as Field Director of the Laboratory on Housing and Illness from 1954 to 1960. Left to right: Captain James Murphy, Houser, Captain Norbert Schalet, 2nd Lieutenant Kenneth W. Sprague. Dr. Houser also served as Field Director of the Influenza Study Group in Santiago, Chile, in 1957.

Dr. Long, who, like many others, had trained for 2 years at the Rockefeller Institute before becoming Professor of Preventive Medicine of the School of Medicine, The Johns Hopkins University, was named Director. An organizational meeting held in Washington on 19 March brought together Dr. Mary C. Kirkbride, Associate Director, Division of Laboratories and Research, New York State Department of Health; Dr. Miller, Professor of Medicine, School of Medicine, University of Chicago; Lieutenant Colonel Arthur P. Hitchens, U.S. Army, retired, Professor of Public Health and Preventive Medicine, School of Medicine, University of Pennsylvania; and Dr. John J. Phair, Associate in Epidemiology, School of Hygiene and Public Health, The Johns Hopkins University. Drs. Long and Miller were charged with reviewing the therapy of the disease, Lieutenant Colonel Hitchens and Dr. Phair were to act as epidemiological consultants, and Drs. Miller and Kirkbride were to set standards for bacteriologic and immunologic studies.

A tentative program for study and control of meningococcal meningitis was formulated and submitted to the AFEB on 26 April. A recommendation was made that a central laboratory be established at The Johns Hopkins School of Hygiene and Public Health to act as a focal center for interim laboratory studies, preparation and distribution of meningococcal typing sera, and analysis of case data for correlation with strain characteristics. An investigative team was planned to carry on the necessary field studies and to evaluate therapeutic and prophylactic measures. In addition, the importance of a specialized consultation service for the Office of The Surgeon General, Commanding Officers of Army posts, and medical laboratories was recognized and provided.

The organization and these plans were approved at the third meeting of the AFEB held on 19 June. After this action, the laboratory and personnel of the Department of Epidemiology of the School of Hygiene and Public Health, The Johns Hopkins University, under the direction of Dr. Phair, were made available through the courtesy of Dr. Maxcy, Professor of Epidemiology. Additional personnel and funds were provided by Dr. Long's Department of Preventive Medicine. The work of the central laboratory was begun late in May 1941 under the supervision of Dr. Phair.

A contract between the Army and The Johns Hopkins University, effective 22 November 1941, and totaling $25,000 in 1942, provided support for the Central Laboratory. In addition to the work of the central laboratory, two other studies were financed from November 1941 through June 1943 by contracts, one at the University of Chicago, under the direction of Dr. Miller, the other at Columbia University, under the supervision of Dr. Elvin A. Kabat.

Anticipating an increasing demand for consultation, the personnel of the CARD were augmented in August 1942 by the addition of Drs. Robert W. Graves, Assistant Professor of Neurology, Duke University School of Medicine; Lowell Rantz, Assistant Professor of Medicine, Stanford University School of Medicine; Smith, Professor of Public Health and Preventive Medicine, Stanford University School of Medicine, also a member of the Commission on Epidemiological Survey (CES); and Wood, Professor of Medicine, Washington University School of Medicine, also a member of the Commission on Pneumonia. On 31 August 1942, Dr. Long resigned to accept a commission in the Medical Corps of the Army, and Dr. Phair was chosen to replace him as Director.

In February 1943, Dr. Emanuel B. Schoenbach, who had been a member of the CES, received a commission in the Medical Corps and was assigned to The Johns Hopkins University. He was appointed to the Commission on Meningococcal Meningitis and took charge of the field investigations. He served as Acting Director during the two brief absences of Dr. Phair between 1 August and 1 November 1943 and between 15 August and 15 November 1945.

After not quite 3 years of existence, the Commission on Meningococcal Meningitis was terminated at the meeting of the Board in April 1946. Although the minutes of this meeting refer to the assignment of responsibility for streptococcal infections and pneumonia to CARD, no such assignment was recorded for meningococcal infections. Such infections were to be a continuing problem in the postwar years because an increasing proportion of meningococcal strains became resistant to sulfadiazine, rifampin was yet to be introduced for chemoprophylaxis, and an effective vaccine was still under development.

The personnel of the wartime CARD continued to make major contributions to infectious diseases and to other commissions. Dr. Long became Professor of Preventive Medicine and Chairman of the



PERRIN H. LONG, M.D.

Dr. Perrin H. Long served as Professor of Preventive Medicine, School of Medicine, The Johns Hopkins University. He was the first Director of the Commission on Meningococcal Meningitis, serving from March 1941 to August 1942 before joining the Army Medical Corps as a Colonel for service as a medical consultant to the Chief Surgeon of the Mediterranean Theater. He made major contributions to the early study of sulfonamides, the first effective antibacterial agents.



JOHN J. PHAIR, M.D., M.P.H.

Dr. John J. Phair served as Associate in Epidemiology, School of Hygiene and Public Health, The Johns Hopkins University. He was a charter member of the Commission on Meningitis, succeeded Dr. Perrin Long as its Director in August 1942, and served in this capacity until April 1946. He contributed to developing new knowledge of meningococcal, streptococcal, and respiratory tract diseases.

Department at SUNY-Downstate, before retiring in 1961. He died in 1965. Dr. Phair left Johns Hopkins in 1946 to join the faculty of the School Medicine of the University of Louisville before becoming chairman of the advisory committee to the Commissioner of Health of the City of Cincinnati and then Commissioner. He died in 1970. Dr. Schoenbach became Professor of Medicine at College of Medicine, SUNY-New York City and Director of Medical Services at Maimonides Hospital. He died of coronary thrombosis in 1952. Dr. Smith became a member of CARD while also serving as a member of the AFEB. The date of his death and that of Dr. Miller are recorded in earlier sections. After a distinguished career as chairman of the Department of Medicine at Washington University in St. Louis, Dr. Wood returned to Johns Hopkins as Vice President for Medical Affairs, a position he held for 3 years before returning to research as Professor of Microbiology; he died of myocardial infarction in 1971. Dr. Rantz continued his studies of hemolytic streptococci, but he too died of a heart attack at age 53 in 1965.

When CARD assumed responsibility for meningococcal meningitis, Dr. Feldman, Professor of Preventive Medicine, SUNY, Upstate Medical Center-Syracuse, was asked to head its Committee on Meningococcal Infections. He was well-qualified to do so. He (with Drs. Dowling and Sweet) was among the first to confirm, in 1942, the effectiveness of sulfadiazine in the treatment of meningococcal meningitis, reported the previous year by Drs. Dingle and Thomas (with Morton). When he entered military service in October 1942, Dr. Feldman was assigned to the Fourth Service Command Laboratory located at Fort McPherson, Georgia, a reference center that served more than 100 Army hospital laboratories. Meningococcal infections were prevalent from Florida to North Carolina, from the Atlantic to the Mississippi. Feldman developed methods for the identification of strains, for testing their sensitivity to sulfadiazine and participated in carrier surveys and field trials to evaluate sulfadiazine as a prophylactic agent. After the war, his laboratory at SUNY-Syracuse became a national and international reference center for meningococci, tracking the increasing resistance of strains to sulfadiazine and the eventual ineffectiveness of that drug for treatment or prophylaxis. Other members of the committee included, at various times, Drs. Denny, Dingle, Eickhoff, Finland, and Jordan of CARD, Malcolm S. Artenstein, WRAIR, Captain James Kingston, USN, John Y. Bennett, CDC, and Richard Roberts, Commission on Streptococcal Infections.

Although penicillin became available for treatment, the inability to eliminate the carrier state heightened the consternation and frustration that accompanied any outbreak of meningitis. At such times, largely for reassurance and public relations, members of the Committee on Meningococcal Infections were asked to visit bases experiencing epidemics. One such visit was made to Fort Ord, California, in September 1964 by Drs. Feldman, Austrian, Eickhoff, Finland, and Jordan with Dr. Gold representing Dingle, along with Drs. Ross L. Gauld, WRAIR, and Arthur W. Frisch, University of Oregon.

The incidence of meningococcal meningitis in California had shown a gradual increase since 1959, the case rate rising from 1.4 per 100,000 in 1959 to 3.0 in 1964. The build-up of cases at Fort Ord was as follows: 2 in 1960, 6 in 1961, 38 in 1962, 64 in 1963, and 108 in 1964. The first fatalities occurred in 1963, and it was in this year that Dr. Feldman was called to visit San Diego Naval Training Station to consult about the occurrence of meningitis. The call came while he was attending a meeting of the American Epidemiological Society in Washington. With the encouragement of Dr. Jordan, CARD Director, and the assistance of the AFEB Office, Dr. Feldman promptly headed west with little more than his toothbrush. He had a little more time to prepare for the visit to Fort Ord the next year.

As expected, most cases of meningitis at Fort Ord occurred in basic trainees in the first 8 weeks of training. No meningitis was noted in cadremen who were instructors and had daily contact with trainees or in physicians and nurses. A survey of Monterey County in which Fort Ord is located revealed only one case of meningococcal meningitis in the civilian population in January through September, 1964. This was the only case in that county in 1964, whereas 89 cases occurred in military personnel and 10 among civilian dependents. The carrier rate in new inductees was the same (20%) as in University of California students and was believed to reflect the current carrier rate in the male civilian population of California in ages 17 to 24. All of the strains of Neisseria meningitides were either serotype group B or C, with 90% being group B.

The occurrence of cases on the base had attracted growing media attention, with frequent bulletins on television and scare headlines in the press. After the Committee had assessed the situation and confirmed that meningococci were widely disseminated throughout the civilian population, Dr. Feldman appeared on television to point out that the safest place for a civilian in California to reside was in the vicinity of Fort Ord and that it was doubtful that military personnel posed any greater hazard to the civilian population than the hazard encountered by civilians in their daily exposure to civilian carriers. The public, press, and politicians were not convinced, and an episode the following month forced the closure of the base.

A basic trainee spent a day on leave with his fiancee. After his return to the base, she developed fulminant meningococcal meningitis caused by a group B organism and died. He remained well; a culture of his throat yielded a group B meningococcus. Not until after the assumed connection between the soldier and his girl had increased public anxiety further was it shown that the meningococci were probably different strains. The military was forced to suspend the intake of new basic combat trainees and Army Reserve personnel in support of a governor pressured and harassed by a frightened electorate.

In December 1964, the Board adopted the following recommendation:

> That, in view of the epidemiological behavior of meningococcal infections with cyclic recurrences of epidemics at approximately 10-year intervals, thought and planning be given now for studies to be carried out, especially at military posts, approximately 8 to 10 years from now.

Fortunately, group C meningococcal vaccine became available before this time (1972), just before CARD and its Committee on Meningococcal Infections were terminated.

Pneumonia

The Commission on Pneumonia was listed third among the first seven commissions formed by the Board at its first meeting on 6 February 1941. Its first meeting took place in May 1941, a month before the memorandum that stated the investigations required by The Surgeon General of the then eight commissions listed it fifth, with the shortest of charges:

> The Commission on Pneumonia will study the causes, prevalence, treatment and control of pneumonia. It will study epidemics in certain localities and will carry on work concerning the types of pneumonia caused by all the various kinds of germs and also the nonbacterial pneumonias.

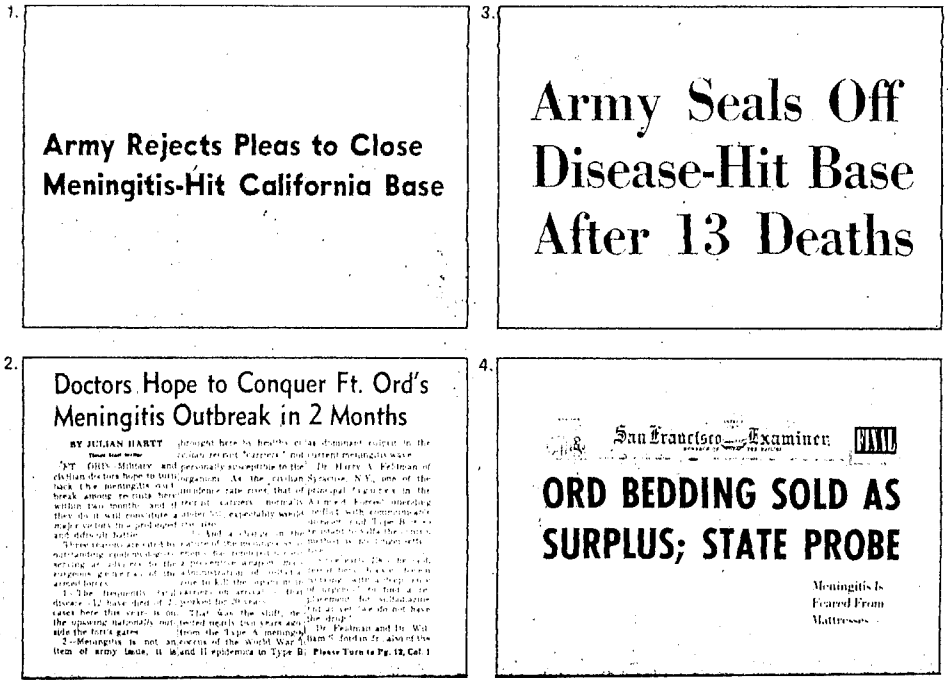
The fact that the Commission on Cross Infections now had been added as the eighth commission was a result of the program of interim and field investigations drafted by the Commission on Pneumonia in May and submitted to the Board in June. The program, as outlined then, was divided into the following sections: prophylaxis by nonspecific measures, therapy of pneumonia and its complications, and recommendations for field investigations. It was realized at the outset that the personnel and facilities available to the Commission could not possibly include all these activities. A recommendation was made that the question of air sterilization by ultraviolet irradiation and germicidal aerosols should become the province of a special commission to be composed of one member from each of the commissions already set up, because the sterilization of air was a problem common to all. As previously noted, the AFEB agreed.

The members in attendance at the organizational meeting were the Director, Dr. MacLeod (Professor of Bacteriology, New York University College of Medicine; Dr. Abernethy, Associate Professor of Medicine, George Washington University School of Medicine; Michael Heidelberger, Ph.D., Associate Professor of Biochemistry, College of Physician and Surgeons, Columbia University; Dr. Edward S.



HARRY A. FELDMAN, M.D.

Dr. Harry A. Feldman served as Professor of Preventive Medicine, State University of New York at Syracuse. He served the CARD in many ways, especially as Chairman of the Committee on Meningococcal Infections, and by providing a university base for the Laboratory on Housing and Illness when Sampson Air Force Base was closed. Highly respected for his extensive knowledge of infectious diseases, he was much admired for his willingness to assist in the investigations of outbreaks at military bases. One of the first to demonstrate that some meningococcal strains had become resistant to sulfadiazine, he used his laboratory to test isolates sent to him from throughout the world.



Press Accounts of 1964 Meningitis Outbreak.

Newspaper headlines reflect the public concern and subsequent political pressure occasioned by an outbreak of meningococcal meningitis at Fort Ord, California, in 1964. Panel 2 reproduces an account of a interview with Dr. Harry A. Feldman, Chairman of the CARD Committee on Meningococcal Infections, who visited the base with other members of the committee. Feldman also appeared on local television. His reassurances were to no avail; the Governor forced suspension of recruit training.

Rogers, Assistant Commissioner for Medical Administration, New York State Health Department; Dr. William S. Tillett, Professor of Medicine, New York University College of Medicine and a member of the Commission on Hemolytic Streptococcal Infections; and Dr. Wood, Associate, Department of Medicine, The Johns Hopkins Medical School and, later, Professor of Medicine, Washington University School of Medicine, already a member of the Commission on Meningococcal Meningitis. The records note that Drs. Dochez and Oswald T. Avery represented the AFEB at this first meeting. Original members not in attendance were Dr. Joseph F. Sadusk, Instructor in Medicine at Yale, and Dr. James Ruegsegger, Department of Medicine, University of Cincinnati, who also served briefly as a member of CARD before leaving both commissions to join the Navy Medical Corps. Dr. Sadusk also resigned to join the Army Medical Corps.

In subsequent years, four other members were added: Drs. Jacob Furth, Associate Professor of Pathology, Cornell University Medical College, Ithaca, New York; Clayton G. Loosli, Assistant Professor of Medicine, University of Chicago, who was commissioned a Captain in the Army Medical Corps; Wheelan D. Sutliff, Acting Director, Bureau of Laboratories, New York City Department of Health; and, in 1941, Paul B. Beeson, Assistant Professor of Medicine, Emory University Medical School, Atlanta, Georgia.

The CARD participated in its first field study in October 1941. Beginning in the summer of that year, a large number of cases of primary atypical pneumonia had been occurring at Camp Claiborne. Colonel Lucius Wright, Commanding Officer of the Station Hospital, was aware early of the nature of the disease, because he had previous clinical experience in Hawaii with a similar disease. A survey of the epidemic at Camp Claiborne was made in October by Drs. Dochez of the Army Epidemiological Board, Yale Kneeland, Jr. of the Influenza Commission, and MacLeod of the CARD. After this survey, a recommendation was made that a special commission be sent to Camp Claiborne to investigate the clinical and laboratory aspects of this disease. As detailed in the section on CARD, the commission for the study of atypical pneumonia at Camp Claiborne was under the directorship of Dr. Dingle of the Influenza Commission, assisted by Drs. Abernethy, Ruegsegger, and Wood of the Pneumonia Commission and others. Studies of a comprehensive nature were carried out through the winter and spring of 1942, when the group of investigators became the nucleus of CARD. Drs. Abernethy and Ruegsegger remained with the field staff of that CARD.

Dr. MacLeod's final report for the Commission on Pneumonia noted

> that prior to the original survey at Camp Claiborne, only a very small number of cases of atypical pneumonia were reported from Army installations in the United States. Based on the cases previously observed in civilian hospitals and the original survey at Camp Claiborne in October 1941, an official statement was prepared on the subject of primary atypical pneumonia by the Pneumonia Commission and issued by the Surgeon General's Office early in 1942. Following this description and despite the cumbersome name of primary atypical pneumonia, etiology unknown, the number of reported cases of the disease took a remarkable upswing, and throughout the whole period of the war, the incidence of atypical pneumonia far exceeded pneumonia caused by all other agents combined. It was apparent that the vast majority of cases had gone unrecognized until this clinical description was circulated and opportunity afforded to use the term as a specific diagnosis.

The proposed budget of the Pneumonia Commission for 1943-1944 was $27,380. The actual budget recorded for 1945 was $27,100. This funded a $19,800 contract with New York University for Dr. MacLeod, and two subcontracts, one with Cornell University Medical College ($3,900) and one with Columbia University College of Physicians and Surgeons ($3,400). The latter was for the "Work of Dr. Michael Heidelberger on the polysaccharides of pneumococci, particularly in connection with preparation and use of these polysaccharides in immunization against pneumonia." This modest investment yielded a great dividend.

The major contribution of the Commission on Pneumonia during its 4.5 year life was the development of an effective vaccine for the prevention of pneumococcal pneumonia in young adults. At the outset, as Dr. MacLeod reported, "the Commission felt that it could fill an important need by a thor-



COLIN M. MACLEOD, M.D.

Dr. Colin N. MacLeod served as Professor of Bacteriology, New York University College of Medicine. He was the first and only Director of the Commission on Pneumonia, May 1941 to December 1945, and subsequently served as President of the AFEB from 1947 to 1955. He used his administrative skills and scientific knowledge to champion the AFEB and its commissions, and to strengthen the effectiveness of this consultant system. At the Rockefeller Institute for Medical Research, he teamed with Drs. Oswald T. Avery and Maclyn McCarty to demonstrate the genetic transformation of inheritable traits in pneumococci, the first demonstration that DNA was linked to genes. As Commission Director, he encouraged Dr. Michael Heidelberger's research on pneumococcal polysaccharides, and had the satisfaction of conducting the first study to show that a multivalent polysaccharide vaccine would prevent pneumococcal pneumonia.

ough analysis of immunization with specific capsular polysaccharides of pneumococcus." A survey of previously recorded epidemics of pneumonia, both in the United States and abroad, showed that in all instances, types 1, 2, or 5 had been responsible. For this reason, it was proposed that attention be devoted specifically to these types and that the immunologic response of immunized subjects be assayed by quantitative methods. It was considered important to have on hand large amounts of the purified polysaccharides of these three types. Accordingly, in the event that immunization on a wide scale might be deemed necessary in case of an epidemic, 100 g of each were obtained commercially, the preparation being controlled by Dr. Heidelberger.

The opportunity to test a multivalent pneumococcal vaccine containing polysaccharides for these three serotypes, and in addition, type 7, was found at the Army Air Base in Sioux Falls, South Dakota. Lieutenant Richard G. Hodges, MC, had been assigned to Sioux Falls as epidemiologist in the summer of 1943, and he remained there for the next 2 years. The detailed epidemiological analyses of respiratory infections that he made in collaboration with the Pneumonia Commission contributed greatly to knowledge of pneumococcal pneumonia and its relation to other respiratory diseases. These analyses and the results of the pioneering vaccine trial are summarized in the section on scientific contributions. The Commission on Pneumonia was terminated in December 1945.

After the war, Dr. MacLeod served the AFEB as a member and President from his academic base at New York University and later from other positions as follows: Professor of Research Medicine, University of Pennsylvania; Professor of Medicine, New York University; Deputy Director of the Office of Science and Technology of the White House; Vice President for Medical Affairs of the Commonwealth Fund; and President of the Oklahoma Medical Research Foundation. A strong supporter of international health research, he died suddenly in London in 1972 while on his way to visit the Southeast Asian Treaty Organization Cholera Research Laboratory in Dhaka, Bangladesh. The subsequent histories of Drs. Abernethy, Hodges, Loosli, and Wood have been recorded in earlier sections.

Dr. Beeson became Professor of Medicine and Chairman of the department at Emory University Medical School, moving to the comparable position at Yale in 1952. From 1965 to 1974, he served as Nuffield Professor of Clinical Medicine at Oxford University before returning to the United States as Professor of Medicine at the University of Washington. Dr. Tillett continued as Professor of Medicine at New York University and Director of the Third Medical Division at Bellevue Hospital until becoming Professor Emeritus in 1958. He died in 1974.

Dr. Furth rose to Professor of Pathology at Cornell in 1945, leaving in 1949 to become Chief of the Pathology and Physiology Section of the Biology Division of the Atomic Energy Commission, Oak Ridge National Laboratory, Tennessee. He then held sequential appointments as Associate Director of Research, Children's Cancer Research Foundation, Harvard Medical School; Director of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York; and Professor of Pathology, Columbia University, becoming Professor Emeritus there in 1967.

Dr. Heidelberger advanced to Professor of Biochemistry at Columbia University's College of Physicians and Surgeons in 1945 and to Professor of Immunochemistry there in 1948. Although he became Emeritus in 1956, he remained active in the field of polysaccharide immunochemistry, becoming the recipient of numerous awards and medals for his contributions before celebrating his 100th birthday in 1988. Often referred to as the "father of modern immunology," he died of a stroke on 25 June 1991.

Dr. Rogers became Professor of Public Health and Medical Administration, School of Public Health, University of California at Berkeley in 1946, also serving as Dean of the school until 1951. He became Professor Emeritus in 1971 and died shortly thereafter.

Dr. Sadusk served as Assistant, then Associate Clinical Professor of Medicine at Stanford University School of Medicine for 13 years; Professor of Preventive Medicine and Community Health, George Washington University School of Medicine 1962 to 1966, during which time he was Medical Director of the Food and Drug Administration; and Professor and Associate Dean for Community Medicine at The Johns Hopkins University, 1966 to 1967. He then served as Group Vice President for Medical and Scientific Affairs for Parke-Davis & Co. from 1967 to 1972 and Senior Vice President and Director of Medical and Scientific Affairs for Warner-Lambert Co. He died in 1978.

Dr. Sutliff left the New York City Health Department to become chief of the Infectious Diseases Section of the Veterans Administration Hospital in Memphis and Professor of Medicine at the College of Medicine of the University of Tennessee. He became Professor Emeritus in 1971. He died in 1983.

SCIENTIFIC ACCOMPLISHMENTS

Respiratory Diseases

In 1942, the bacteriology laboratory was able to assist the clinician in the diagnosis of infections caused by meningococci, pneumococci, and streptococci. The virology laboratory could assist in the diagnosis of influenza, but that was all. Except for influenza, attempts to infect the chick embryo and other animals, including the mongoose, with secretions from persons with common colds or more severe nonbacterial respiratory diseases were unsuccessful. However, these nonbacterial, presumed viral, diseases were causing most of the hospital admissions and sick cell visits. Of necessity, clinical descriptions and epidemiological patterns were developed to separate cases into clinical syndromes that might indicate specific etiologies.

This was not easy. The first CARD annual report for 1942 and 1943 reflected the frustration experienced at Fort Bragg:

> Data which have been collected indicate that, in the differential description of respiratory disease of supposedly different etiology, a summation of symptoms and signs present at any time during the illness is inadequate. By the time of recovery, most patients with a respiratory disease have presented such a variety of signs and symptoms that their mere enumeration does little to aid in classification.

Nevertheless, an attempt was made to separate cases into clinical syndromes that might indicate specific etiologies. Although no sharp clinical distinctions on the basis of symptoms, physical findings, laboratory results, or the clinical course of the diseases had been observed, it was possible to separate patients into three groups, namely, primary atypical pneumonia, exudative pharyngitis, and acute respiratory disease. However, the epidemiological studies in the first year failed to show any relationship between cases or to elucidate any factors of importance in the spread of these diseases.

For subsequent special studies, the investigators developed the following classifications.

1. Acute undifferentiated diseases (ARD): This category [also termed acute respiratory disease (ARD) of recruits] included acute illnesses, usually febrile, with respiratory symptoms or generalized constitutional symptoms, or both, ordinarily lasting fewer than 2 weeks. Patients having exudative tonsillitis or pharyngitis, specific contagious diseases, antibody responses to influenza viruses A or B or to streptolysin O, or pulmonary infiltration demonstrable radiographically were excluded from this classification.
2. Nonstreptococcal exudative tonsillitis or pharyngitis: This diagnostic category included patients with respiratory illnesses characterized by exudative lesions on the tonsils, palate, or oropharynx without either b-hemolytic streptococci or an increase in titer of antistreptolysin antibodies during convalescence.
3. Primary atypical pneumonia: This diagnosis indicated a respiratory illness accompanied by roentgenographic evidence of pulmonary infiltration but not by clinical and laboratory evidence of bacterial pneumonia, bronchiectasis, or other causes of pulmonary consolidation.
4. Hemolytic streptococcal infection: This diagnosis was made only when the illness was clinically compatible with such infections and, in addition, when b-hemolytic streptococci were isolated from the throat and a significant rise in antistreptolysin titer was demonstrable during convalescence.

5. Other illnesses: A small number of patients admitted with tentative diagnoses of respiratory disease proved to be suffering from other types of illness, such as immunization reactions, contagious exanthemas, meningococcal infection, or acute or chronic allergic disease. Such cases were excluded from further consideration.

The above is from a retrospective review of the CARD studies at Fort Bragg prepared 25 years later by Drs. Dingle and Langmuir. This was published first in the *American Review of Respiratory Disease* and then as a monograph with a foreword by Dr. MacLeod in which he stated "because of the meticulous epidemiologic studies, enough was learned about the behavior and natural history of these diseases so that when putative etiologic agents were isolated during the next dozen years one could move quickly and confidently to test their causative role."

There is no better background for consideration of these etiologic agents and what has since been learned about the diseases they cause than the "synoptic view" of the Commission's work prepared by Drs. Dingle and Langmuir:

> Leads as to possible etiologic entities were sought from the clinical, epidemiologic, and laboratory observations, separately and collectively. Thus, the segregation of ARD as a possible entity was made primarily on the basis of the epidemiologic data supported, of course, by clinical and laboratory observations, whereas delineation of primary atypical pneumonia and non-streptococcal exudative tonsillitis and pharyngitis came principally from the clinical and laboratory data. Much effort was devoted to attempts to isolate agents from materials obtained from representative cases in these diagnostic categories, to induce illness or identifiable lesions in a variety of laboratory animals, and to obtain serologic indications of possible infectious agents. These attempts were unsuccessful because either nothing unusual was found or the results could be duplicated with what were thought to be appropriate control materials.
>
> The decision was therefore made to attempt to transmit some of these types of respiratory disease to humans, and volunteers were enlisted for this purpose. The results may be summarized as follows: (1) Primary atypical pneumonia, together with minor illness without radiographic evidence of pulmonary infiltration could be transmitted to volunteers using filtered bacteria-free secretions of the respiratory tract of patients having the naturally occurring disease and could be transmitted in second passage. (2) ARD could be similarly transmitted, and the volunteers were immune to a second challenge with the same inoculum. (3) Illnesses characteristic of the common cold could likewise be transmitted. (4) Volunteers who had experimentally induced ARD or common colds, or both, were not immune to primary atypical pneumonia. The clinical characteristics and incubation periods of the induced illnesses were in general consistent with what was known about the corresponding naturally occurring illnesses. No presumptive or definitive causative agents were isolated in the laboratory from any of the specimens obtained from either the donors or recipients of the inocula in these studies.

Drs. Dingle and Langmuir noted that it was then possible to make some inferences and interpretations and to draw certain conclusions, as follows:

1. An acute respiratory disease (ARD) was the predominant respiratory infection at military training posts, and affected recruits almost exclusively. Clinically, it was an acute, febrile or "grippe-like" infection resembling influenza, from which it was indistinguishable, at least in the individual patient. It was not a "coryzal" disease.

   Epidemiologically, it had a distinct pattern of behavior. Like most other respiratory diseases, its prevalence was higher in the winter than in the summer. The level of incidence, however, depended on the time and rate of influx of recruits into the training center. Those units of men inducted in summer months usually did not experience outbreaks of the disease until fall, and the outbreaks were rather prolonged and less abrupt, although the total number of men affected was approximately the same as in acute outbreaks. Those units inducted in fall or winter usually experienced an outbreak within the first 4 to 5 weeks of training, following which both the individual men and the unit seemed to be immune. During such outbreaks, from one quarter to one third of the men required hospitalization. A high turnover rate of recruits resulted in high prevalence of the disease. Thus, ARD seemed to behave as an epidemiology entity.

No then known and identifiable bacteria, viruses, fungi, or rickettsiae could be associated etiologically with the disease, nor could any new agent be isolated and shown to play a causative role. The infection could, however, be transmitted to volunteers by inoculation of filtered, bacteria-free secretions of the respiratory tract from a typical patient with the naturally occurring disease. The incubation period ranged from three to nine days with a median of five to six days. The resultant illnesses were similar to the "spontaneously occurring" infection. After recovery the volunteers were immune to challenge with the same inoculum. No cross immunity could be demonstrated between ARD and the common cold or primary atypical pneumonia as transmitted by inocula from the donors selected as having illnesses characteristic of these infections.

The conclusion was thus reached that the cause of ARD was most probably a virus or one or more of a closely related group of viruses.

2. Epidemic influenza A had an epidemiologic pattern that was distinctly different from ARD in that it affected both seasoned men and recruits simultaneously and to an almost equal extent.
3. Although the incidence of primary atypical pneumonia, which by definition required radiographic evidence of pulmonary infiltration for diagnosis, roughly paralleled that of ARD in a ratio of approximately 1 to 10, the relationship was not seasonally constant. Cold hemagglutinins developed in only about one-third of the patients during convalescence. In volunteer studies, ARD did not appear to confer immunity to primary atypical pneumonia. These findings suggested that some, but by no means all, of the cases diagnosed as primary atypical pneumonia could have been caused by the agent or agents responsible for ARD.
4. The occurrence of exudative tonsillitis and pharyngitis, not attributable to infection with group A b-hemolytic streptococci, was infrequent and in general correlated more closely with the incidence of ARD than with any other recognizable factors.
5. The occurrence of minor respiratory illness and symptoms among men on duty, as determined by weekly platoon surveys, at times correlated with hospital admissions for acute respiratory disease, but at other times, particularly in the fall, showed a definite divergence and suggested different etiologies.
6. The epidemiologic behavior of other infections and entities, such as group A b-hemolytic streptococcal infections, bacterial pneumonia, and rubella, was typical of those diseases and did not appear to be dependent on the occurrence of the acute respiratory diseases such as ARD.

Similar diagnostic limitations persisted when CARD investigators transferred their studies from the military population at Fort Bragg to a civilian population in the "Heights" suburbs of Cleveland, within a few miles of their laboratories at Western Reserve University. The study began in July 1947, with the recruitment of five families, all with children, to test the feasibility of data and specimen collection procedures. In addition to assessing the commitment of the parents, particularly the record-keeping mothers, to a long-term study, this meant enlisting the cooperation of the children in welcoming visits to their every illness by physicians and weekly visits by a field nurse. To this end, Dr. Rammelkamp sometimes arrived with a guinea pig in his pocket or with a number of white mice, and, at least once, with a goat (in his pocket!). The staff eventually recruited 86 middle-class families, with 443 individuals, to participate in the Cleveland Family Study.

As at Fort Bragg, this longitudinal study of the occurrence of illness in families with young children was largely descriptive. Apart from influenza, few respiratory viruses could be isolated or used for serologic studies until adenoviruses were isolated in the mid-1950s to be followed by respiratory syncytial and parainfluenza viruses. However, by this time, the 10-year study was nearly over. As a consequence, the investigators used a term — "common respiratory diseases" — previously used at Fort Bragg to classify respiratory admission based on weekly reports prepared by the hospital registrar. In the Cleveland Family Study, this designation included all nonbacterial illness except influenza, nonstreptococcal exudative tonsillitis and pharyngitis, and primary atypical pneumonia, these three accounting for only approximately 2.5% of total illnesses.

Common respiratory diseases included the common cold, rhinitis, bronchitis, and other acute respiratory illnesses of undifferentiated type. This group, now known to be caused by multiple viral agents, was responsible for 95% of all illnesses, of which the common cold accounted for approximately 60%, or

about 40% of all illnesses. An average of slightly over six common respiratory illnesses occurred per person-year. Incidence rates for children increased until the age of 3 years and then decreased progressively. In the absence of serologic studies, the decline appeared to be related more to the aging process than to the development of active immunity. Among children, males had higher incidence rates than females, but the reverse was true for adults. The highest attack rates for respiratory disease were found in young school children. Preschool children with siblings who attended school had consistently higher attack rates than did comparable children without school siblings, presumably because of increased exposure. In general, the larger the family, the greater the individual and family attack rates for common respiratory illnesses. No syndrome comparable to ARD in military recruits was observed, although cases of nonbacterial pharyngitis, some with exudate, that were seen during an epidemic in July and August 1954, were related to the then recently described type 3 adenovirus.

ARD — Adenoviruses

Acute respiratory disease of recruits (ARD), a major cause of morbidity in all military training camps, during and after World War II, and as defined clinically and epidemiologically at Fort Bragg, is a specific etiologic entity caused by several adenovirus types. The first adenovirus associated with ARD was isolated by WRAIR investigators Drs. Maurice R. Hilleman and J. H. Werner from cases that occurred during an influenza-like epidemic at Fort Leonard Wood, Missouri, during the winter of 1952 and 1953. One of the five strains, RI-67, isolated from the pharynx of a patient with the clinical diagnosis of primary atypical pneumonia, was used to demonstrate rises in neutralizing antibodies in the majority of patients studied, most of whom did not have pulmonary infiltration. This finding confirmed the prior observation at Fort Bragg that the percentage (10% to 25%) of patients with infiltrates, and therefore labeled atypical pneumonia, paralleled the incidence of ARD.

In the same year, investigators at the Laboratory of Infectious Diseases of the National Microbiological Institute, NIH, reported the isolation of three immunologically distinct agents from human adenoid tissue undergoing degeneration in tissue culture. They were termed adenoid-degenerating (AD) agents, becoming types 1, 2, and 3, with RI-67 becoming type 4. By the following December, six types had been observed, and the name was changed to adenoidal-pharyngeal-conjunctival (APC) agents to reflect the clinical manifestations of cases caused by type 3 that were seen in northern Virginia in association with swimming pools. The adenovirus name for the group was adopted in 1956.

Because sera collected from the donors of respiratory secretions and the volunteers who received them in the human transmission experiments in 1945 had been stored in Cleveland, it was possible to titer them for neutralizing antibody to the RI-67 virus (type 4). Two donors, one diagnosed ARD and one diagnosed bronchitis resembling atypical pneumonia, developed antibody rises. A donor classified as primary atypical pneumonia and two classified as common colds did not. Of recipients of ARD secretion, 20 of 24 developed antibody rises; 40 recipients who received either atypical pneumonia or common cold secretions did not. Tests with these and other sera that used the AD agents (types 1, 2, and 3) showed that they were not associated with ARD. Many subsequent studies have established type 4 adenovirus as a major cause of ARD. Curiously, type 4 infections are rare in civilian populations, and a search for such infections among young men in college or at the U.S. Military and Naval Academies found none.

Over 30 adenovirus serotypes are now known, most of the higher types being inhabitants of the gastrointestinal tract. The most prevalent types among military groups have been types 4, 7, 14, and 21 and, to a lesser extent, type 3. Types 4 and 7 are the predominant types in the United States; types 14 and 21 are prevalent in Europe. In civilian populations, most children become infected with types 1, 2, and 5 early in life. Type 3, as noted, may produce epidemics of pharyngitis or conjunctivitis or both. Perhaps 50% of childhood adenovirus infections result in disease, with 2% to 7% of lower respiratory tract disease in young children seeking medical care being attributed to adenoviruses, particularly type 7. The frequency of these illnesses is not great enough to justify immunization of children. Immunization of recruits, however, is a major success story.



CHARLES RAMMELKAMP, M.D., AND WILLIAM S. JORDAN, JR., M.D.

To encourage continued participation in the Cleveland Family Study (eg, frequent examinations and throat swabbing) Drs. Charles Rammelkamp (left) and William Jordan entertain the four sons of Mrs. John Marshall while their most cooperative mother looks on.

As a continuation of their studies of type 3 adenovirus, Dr. Huebner and his associates at NIH prepared a killed type 3 vaccine in 1955 that induced neutralizing antibody and prevented illness in volunteers challenged with homologous virus by the conjunctival route. That serum antibody may be protective was suggested in 1956 by studies at Sampson Air Force Base that showed that doses at 5 to 15 mL of gammaglobulin prevented illness caused by adenovirus types 4 and 7. With the demonstration that these serotypes were mainly responsible for respiratory disease in military recruits, Dr. Hilleman and his associates at WRAIR developed a killed bivalent types 4 and 7 vaccine with the use of viruses adapted to growth in monkey kidney cell cultures. When evaluated at Fort Dix in 1956, a single dose effected a 98% reduction in hospitalized cases of ARD caused by these agents. Subsequent trials were less successful, apparently attributable to the variable potency of different production lots. Then the oncogenic simian virus 40 (SV40) was found to be present in the killed adenovirus vaccine as well as in viral seed stocks, including adenoviruses and Sabin live polio viruses. A second deterrent to vaccine development was the demonstration of the primary oncogenicity of certain adenovirus types for newborn hamsters, particularly types 12 and 18, and a series of scientific articles reporting the recovery of adenoviruses from a variety of human tumors. Furthermore, the discovery was made that a portion of the SV40 virus genome could become incorporated into the type 7 adenovirus virion, resulting in the formation of a hybrid virus that possessed the oncogenic potential of SV40 virus. In consequence, the Division of Biologics, NIH, acted in 1961 to prevent the distribution of vaccines containing viable SV40 virus and in 1964 to ban additional studies of live adenoviruses in humans until the problem of oncogenicity had been resolved.

The NIAID successor to the National Microbiological Institute contracted with Dr. Maurice Green of the Institute of Molecular Virology, St. Louis University School of Medicine, to search for evidence of oncogenic adenoviruses in a wide variety of human tumors. Green found none. NIAID scientists could not implicate adenoviruses in serologic surveys of human cancer patients for antibody to adenovirus T antigens. Next, adenovirus seeds were obtained free of SV40 and propagated in human cells. When Dr. Chanock and associates at NIAID capitalized on the observation that human adenoviruses exhibit a predilection for infection of the lower intestinal tract, the stage was set for the development of live oral vaccine.

The NIH investigators, using virus grown in human embryonic kidney cell culture, showed that type 4 or type 7 adenovirus could selectively infect the lower intestinal tract when virus was administered in enteric-coated capsules. Virus did not spread from the lower intestinal tract. Selective intestinal adenovirus infection stimulated moderately high levels of neutralizing antibody and was not associated with any signs or symptoms of illness. Because human embryonic cell culture is not suitable for large-scale vaccine production, type 4 virus was propagated in human diploid fibroblast cultures to provide large pools of inocula. These were shown to be free of adventitious microbial agents and to be nononcogenic in thymectomized newborn hamsters. When administered to 40 volunteers in enteric-coated capsules, the virus infected the lower intestinal tract, induced moderately high levels of neutralizing antibody, and did not spread from enterically infected volunteers to susceptible contacts.

In collaboration with U.S. Navy scientists, Dr. Chanock and his associates at NIAID had observed that adenovirus infections were infrequent among recruits during their basic training at the Marine Recruit Depot at Parris Island, South Carolina but caused epidemics among them when they were transferred to Camp Lejeune, North Carolina for additional training. This sequence made it possible to assess the safety and antigenicity of encapsulated live type 4 virus at Parris Island and to evaluate the protective effect of the vaccine-induced enteric infection when the recruits were later challenged during a type 4 epidemic at Camp Lejeune. When such a placebo-controlled study was done in 1964, no differences in illness patterns were observed at Parris Island between vaccine and placebo groups. The vaccine induced neutralizing antibody within 10 days that reached a median level only twofold lower than that of recruits undergoing natural infection. Of 125 men in the vaccine group, none were hospitalized at Camp Lejeune, and only one experienced a febrile illness (without respiratory symptoms). Of 128 men in the placebo group, 32 were hospitalized and 38 experienced a febrile illness. This



MAURICE R. HILLEMAN, Ph.D.

Dr. Maurice R. Hilleman was Director, Merck Institute for Therapeutic Research and Adjunct Professor of Virology in Pediatrics, University of Pennsylvania School of Medicine, Philadelphia. During his early years, Dr. Hilleman was a staff member of WRAIR in Washington where, while working with Dr. Joseph E. Smadel, he contributed importantly to new knowledge of rickettsial, arbovirus, and respiratory infections. He was the first to culture adenovirus type 4, the major cause of acute respiratory disease of military recruits.

demonstration of the effectiveness of selective intestinal infection was followed by similar studies at other recruit bases, including the Great Lakes Naval Training Center, Illinois and Fort Dix.

Dr. Jackson and associates at the University of Illinois studied the communicability of live enteric type 4 vaccine in families of military dependents living in government housing at Great Lakes. When the vaccine was given to the mothers of 22 families, 1 of 8 nonimmune fathers and only 1 of 64 children developed evidence of infection. When the vaccine was given to a child in 26 other families, serologic evidence of infection occurred in 3 of 23 nonimmune parents and in 5 of 49 siblings. More extensive spread was recorded when 1 partner in each of 39 married couples drawn from the student population of the University's Medical Center was given vaccine and the other partner a placebo, but no illnesses occurred attributable to the vaccines. The investigators concluded that while the asymptomatic intestinal infection induced by the vaccine can be spread beyond the bowel to the oropharynx or to other persons by intimate physical contact, the vaccination was benign and highly immunogenic.

The studies at Fort Dix that were conducted by members of the Department of Virus Diseases at WRAIR were the first to show that suppression of type 4 virus by type 4 vaccine fostered the emergence of type 7 virus in the immunized population. A trial of type 4 vaccine in 1965 had reduced hospitalization for ARD by 67.1% and adenovirus type 4 infections by 95.5%; but in a second trial early in 1966, the vaccine apparently failed after 6 weeks of effective suppression. The explanation was the emergence of type 7 adenovirus. Once introduced, it replaced type 4 virus as the epidemic strain. Accordingly, once studies failed to implicate type 7 adenovirus as an oncogene for humans, WRAIR investigations assessed the safety, infectivity, and antigenicity of a live enteric type 7 vaccine in humans. Like type 4, type 7 vaccine virus reproducibly infected the gastrointestinal tract, stimulated neutralizing antibody in nearly all susceptible volunteers, and was not associated with illness. Simultaneous administration of type 4 and type 7 vaccines to volunteers confirmed that both types could be administered together without interference. When bivalent vaccine was administered to trainees at Fort Dix in 1969 during an outbreak of ARD caused by type 7 adenovirus, the rate of ARD associated with type 7 adenovirus was reduced by 96%, and no decrease in the immunogenicity of type 4 vaccine was evident.

By the following year, Wyeth Laboratories had replaced the capsules with enteric-coated tablets, and another controlled trial at Fort Dix confirmed the efficacy of tablets of type 4 virus containing between $10^{3.6}$ and $10^{4.7}$ $TCID_{50}$ and of tablets of type 7 virus containing between $10^{4.6}$ and $10^{4.7}$ $TCID_{50}$. The WRAIR investigators made the important observation that no other respiratory pathogens emerged to replace adenovirus types 4 and 7 as the major causes of ARD in military recruits. The routine use of types 4 and 7 vaccines for the immunization of recruits entering basic training was introduced at Forts Dix, Lewis, and Wood in fiscal year 1970, and at all Army posts in fiscal year 1971. WRAIR personnel estimated that these vaccines prevented nearly 27,000 hospitalizations during these two periods, saving $7.53 million at a cost of $4.83 million, including the cost of a comprehensive surveillance program. In May 1971, the AFEB recommended that type 4 vaccine be administered to recruits and advanced training personnel of all three services and that type 7 vaccine be studied further for clinical effectiveness. By September 1973, 9 months after the termination of the CARD, the AFEB could recommend that vaccine containing both types 4 and 7 adenovirus be administered routinely to these personnel in all services. Adenovirus types 4 and 7 vaccine continues to be administered to recruits in all military services. During the life of CARD and subsequently, Dr. Ginsberg and others characterized further the biochemical and structural properties of adenoviruses and defined the genetic control of their synthetic pathways. Adenovirus vectors containing gene coding for the key antigens of other pathogens are now being used to construct vaccines for other diseases.

Atypical/Mycoplasma Pneumonia

This is the disease that served as the stimulus for the creation of the CARD early in World War II. Historical records suggest that similar syndromes occurred during the Civil War and World War I. During World War I, a pneumonia of an atypical nature unrelated to influenza was recognized clinically. Although similar syndromes were described in Europe in the 1920s and in the United States in



ROBERT CHANOCK, M.D.

Dr. Robert Chanock, Chief of the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, provided outstanding scientific leadership during his years of service to CARD. His demonstration that the adenoviruses that cause ARD of recruits will induce an asymptomatic, immunizing infection when administered live by the enteric route provided the basis for the successful adenovirus vaccine now given to all military recruits. He and his associates confirmed that the causative agent of atypical pneumonia *Mycoplasma pneumoniae* is a pleuropneumonia-like organism and were the first to cultivate it on an artificial medium.

the early 1930s, Dr. Hobart A. Reimann, a Philadelphia internist, described a series of cases in 1938 and popularized the term "atypical pneumonia." Ironically, Dr. Reimann preferred the term "viral" because he believed the causative agent to be a virus. With mobilization, sporadic outbreaks of presumed "virus pneumonia" occurred in civilian and military populations, with the one at Camp Claiborne in the fall of 1941 attracting particular attention. Because the Army Medical Department considered it desirable to adopt a suitable term to differentiate the syndrome from other types of pneumonias, it published an Official Statement in March 1942, that included a clinical description prepared by Dr. MacLeod, Director of the Commission on Pneumonia, and mandated use of the term "primary atypical pneumonia, etiology unknown" because "the description virus pneumonia should be discouraged since a virus has not been demonstrated as the causal agent." The disease became officially reportable by direction of Circular Letter No. 19, Office of The Surgeon General, U.S. Army, 2 March 1942.

As investigators at Fort Bragg tabulated cases with this diagnosis, there were times when atypical pneumonia incidence paralleled that of total respiratory disease, but at other times it did not. It was not related to epidemic influenza, but could it be a manifestation of the agents of ARD and/or minor respiratory illnesses? Definitive epidemiological studies required a diagnostic test more specific than the rise in cold hemagglutinins observed in more severe cases of atypical pneumonia, but repeated attempts failed to yield an etiologic agent with which to develop a test. Accordingly, as noted above, a series of studies were undertaken to transmit the disease to humans to identify secretions that contained the then unknown infectious agent. It had not been possible to transmit the disease to animals.

A preliminary experiment that used unfiltered inocula prepared from pooled throat washings and sputa collected from seven patients on days 3, 4, 12, and 13 of typical illnesses and administered intranasally and by aerosol inhalation three times daily for 3 consecutive days induced respiratory illness in 10 of 12 volunteers, of whom 3 had roentgenographic evidence of pneumonia and 3, including one in the radiograph-positive group, developed cold agglutinins.

The second experiment was essentially a repeat of the first except that the inoculum was in three forms. Untreated, filtered, or autoclaved inoculum was administered to each man three times during the course of a single day. Of 12 volunteers given filtered inoculum, atypical pneumonia developed in 4 and minor respiratory illness in 5. Of 12 men given untreated inoculum, atypical pneumonia developed in 3 and minor respiratory illness in 9. However, of 12 volunteers given autoclaved material, atypical pneumonia, although mild, also developed in 3 and minor illness in 9.

The third experiment used a similarly prepared inoculum that consisted of pooled throat washings and sputa collected from six subjects in the second experiment, all of whom developed a rise in titer of cold hemagglutinins. The inoculations, administered by an atomizer and nebulizer, were given outdoors to minimize the opportunities for cross-infection. Professional personnel changed gowns and masks between the inoculation of each individual, perhaps because, although not mentioned in prior reports, a physician who administered the inocula for an earlier experiment developed atypical pneumonia. An outbreak of diarrhea among volunteers at the Holly Inn in Pinehurst also was not mentioned. This resulted in scrubbing, painting, and maximum efforts at infection control before it was discovered that someone had quietly put phenolphthalein in the alcohol to determine if the subjects were drinking the alcohol in their thermometer glasses.

The results of the third experiment were as follows: The filtered and untreated inocula each induced atypical pneumonia in 3 of 12 volunteers and minor illness in 5 of 12. The incubation period of the experimental disease was approximately 1 week in subjects who received untreated inoculum and approximately 2 weeks in those given filtrate. Autoclaved inoculum induced no pneumonia in 18 subjects and minor illness in only 1. Thus, infection with the agent of atypical pneumonia was carried through two successive groups of well persons. It was postulated that the minor respiratory illnesses induced might be caused by the same agent responsible for the pneumonia. Equally likely was the possible presence of multiple agents.

As recorded previously, the last volunteer experiment conducted at Fort Bragg demonstrated that two filterable agents, presumably viruses, could induce two types of minor respiratory illness: One was a coryza-like infection with an incubation of 24 to 48 hours (common cold); the other was charac-

terized by sore throat, minimal nasal discharge, and an incubation of 5 to 6 days (ARD). Surprisingly, those with ARD (shown later to have been caused by adenovirus type 4) experienced no greater febrile responses than those with colds. None developed atypical pneumonia. Volunteers recovered from ARD were resistant to challenge with homologous filtrate. Volunteers who had experienced common colds showed little or no resistance when challenged with homologous filtrate. This filtrate had been prepared with the use of pooled nasal and pharyngeal washings from four donors and may have contained more than one agent, perhaps rhinoviruses. Three volunteers who had one or more previous inoculations with ARD or common cold filtrates developed atypical pneumonia when inoculated with filtrate from a single donor who had atypical pneumonia, suggesting that the filterable agent that causes atypical pneumonia is distinct from the two agents that cause ARD and the common cold. All were presumed to be viruses, a presumption that clouded attitudes regarding the nature of the atypical pneumonia agent for over 15 years.

In December 1942, 2 months after the CARD laboratory was activated at Fort Bragg, Dr. Monroe Eaton and his associates at the Research Laboratory of the California State Department of Public Health reported that an infectious agent from cases of atypical pneumonia could be transmitted to cotton rats and to chick embryos. Passage in cotton rats yielded confusing results, raising the possibility of contamination with an indigenous agent. However, the agent propagated in chick embryos was specifically neutralized by convalescent sera from patients with atypical pneumonia. These studies continued with support of the Commission on Influenza (and the International Division of the Rockefeller Foundation) and were reported in greater detail in 1944. The agent, also thought by Eaton to be a virus, was now referred to as the Eaton agent. Several investigators attempted unsuccessfully to confirm or repeat Eaton's studies, and many viewed his results with skepticism. Those at Fort Bragg employed the following animals: ferrets, mice, mongooses, kittens, cats, dogs, cotton rats, guinea pigs, hamsters, hogs, monkeys, chimpanzees, chick embryos, chickens, doves, and Java rice birds. No record exists that the investigators obtained and successfully passaged the Eaton agent. After the Fort Bragg team moved to Western Reserve University in 1946, their attempts to isolate the "virus" of atypical pneumonia were minimal while time was devoted to creating a new department and initiating the study of illness in families.

A major advance was reported in 1955 by Dr. Chien Liu, who teamed up with Dr. Eaton, now in the Department of Bacteriology and Immunology of Harvard Medical School. He applied the fluorescein-labeled antibody technique developed by Dr. Albert H. Coons of that department to studies of Eaton agent in chick embryos. Antigen of the agent, still considered to be a virus, was consistently found in the cytoplasm of the epithelial cells lining the lower trachea, bronchi, and air sacs. Interestingly, no antigen was demonstrable in the bronchial epithelium of cotton rats. Between 1954 and 1956, seven strains of "virus" were isolated from patients with atypical pneumonia; one strain was isolated from the frozen lung of a patient who died at the Boston City Hospital in 1943. All isolates were antigenically closely related to or identical with Eaton's original Mac strain. When the indirect method of fluorescent staining was applied to paired sera from patients with atypical pneumonia, 67% to 92% of patients in several outbreaks showed a rise in antibody titer, including 34 of 38 boys at a private school in Exeter, New Hampshire.

When stored sera from 70 volunteers who participated in the transmission experiments were tested for fluorescent-stainable antibodies at Western Reserve with the use of Liu's method, 64% to 75% of volunteers showed fourfold or greater rises whether they had developed mild or severe illnesses or no illness at all. Although the greatest meanfold titer rise developed in 7 of 11 volunteers with atypical pneumonia, the data were puzzling and could not be interpreted as proof of the etiologic role of Eaton agent in the infections transmitted at Fort Bragg. Undoubtedly, it was.

When Dr. Chanock and associates at NIH joined with Navy investigators to apply the fluorescent antibody technique to a study of Eaton agent infections in Marine recruits at Parris Island, 161 of 738 patients with pneumonia were serologically positive. Approximately 44% of recruits were infected at some time during the 3-month training period, with only 1 in 30 such infections being manifest as clinical pneumonia.

The rate of advance accelerated greatly in the 1960s. British investigators B.P. Marmion and G.M. Goodburn were the first to suggest that Eaton agent was not a virus but a pleuropneumonia-like organism (PPLO), having observed minute coccobacillary bodies in infected chick embryo lungs and having noted that the organism was sensitive to an organic gold compound. Dr. Wallace Clyde, a new arrival at Dr. Dingle's department at Western Reserve, reached a similar conclusion about the same time. Next, Dr. Chanock and associates at NIH and then Dr. Clyde reported the growth of Eaton agent in monkey kidney cell cultures, the latter noting that the agent resembled other members of the genus *Mycoplasma* in being resistant to penicillin and sensitive to the tetracyclines. Finally, Dr. Chanock and colleagues succeeded in growing Eaton agent on fortified PPLO agar and in recovering fresh isolates from 12 of 13 serologically positive patients with pneumonia directly on agar.

As the organism was characterized further and distinguished from other mycoplasma, it was designated *Mycoplasma pneumoniae*. Dr. Clyde described a method for the identification of *Mycoplasma* species based on inhibition of growth on solid medium around antiserum-impregnated filter paper disks. Seventy-three percent of strains were inhibited by antisera against a strain (Patt prototype) previously unrecognized as a component of the microbiological flora of the normal human throat. This method confirmed that tissue cultures are frequently contaminated by *M. hominis* type 1. The Patt strain was first called *M. pharyngis* and is now classified as *M. orale* type 1.

A number of investigators were quick to use the newly available culture and serologic (complement fixation) methods to study the epidemiological and clerical characteristics of *M. pneumoniae* infections in selected populations. Chief among these were Drs. Grayston, Foy, Alexander, George Kenny, and their coworkers at the University of Washington. In studies of *M. pneumoniae* infection in 114 families in which a case of atypical pneumonia was noted, *M. pneumoniae* was isolated from the throat of an index patient in 36 families. Transmission to other family members occurred in 23 of these 36 families, with 84% of the children and 41% of the adults becoming infected. Of 59 patients with family-contact infections, 42 had lower respiratory tract symptoms, 6 had pharyngitis alone, 9 (all children) were asymptomatic, and 2 were judged to have unrelated symptoms. The results obtained indicated that *M. pneumoniae* spreads slowly but extensively, especially in families with small children, and the clinical response includes a spectrum from inapparent infection to pneumonia. Treatment with tetracycline did not abolish the carrier state.

After 5 years of surveillance of the population of a large medical cooperative, the Seattle investigators reported that *M. pneumoniae* was associated with 20% of all pneumonia. During an epidemic that lasted approximately 18 months, the highest attack rate occurred in children 5 to 9 years old, while the proportion of pneumonia caused by *M. pneumoniae* was highest among the teenagers. Treatment with tetracycline or erythromycin reduced the length of illness but not the antibody response.

Understandably, the incidence of atypical pneumonia stimulated attempts to develop a vaccine. The protective effect of an inactivated *M. pneumoniae* vaccine prepared by Pfizer Laboratories was evaluated by Chanock's group at NIH by first injecting volunteers with vaccine and then challenging them with the organism. Growth-inhibiting antibody developed in 10 of 19 seronegative volunteers; only 1 of these 10 became ill when challenged. Respiratory disease developed in 7 of 9 men who failed to respond to the vaccine and in 10 of 13 seronegative volunteers in the unimmunized control group. The most severe illnesses developed in men who failed to respond to the vaccine. The investigators suggested that the vaccine had a protective effect in those who developed antibody, while those vaccinees who failed to develop antibody may have been sensitized.

Dr. William Mogabgab of Tulane University, a contractor of the Commission on Influenza, evaluated an inactivated vaccine prepared by the Merck Institute for Therapeutic Research in trainees at Keesler Air Force Base, Mississippi, including over 10,000 men in each vaccine and placebo group. Because 40% of vaccinees showed no antibody response by complement fixation and 27% by neutralization, a second dose of vaccine was administered. Little increase in antibody response resulted. Serologic studies of 167 cases of pneumonia in the 2 groups suggested that the vaccine did reduce the number of men with pneumonia caused by *M. pneumoniae*, but the rate of all clinically diagnosed pneumonia was lowered by only 45%.

In the waning days of the CARD, investigators in Dr. Denny's department at the University of North Carolina administered an inactivated *M. pneumoniae* vaccine prepared by the Huntington Research Center under contract to NIAID/NIH to 12 antibody-negative children and 6 antibody-positive children. Few or no rises in complement-fixing (CF) or growth-inhibiting antibody were detected in the 12 subjects who were initially antibody negative, and minimal increases were observed in children with preexisting antibody. Peripheral lymphocytes obtained before immunization from antibody-negative children were not stimulated by *M. pneumoniae* antigen in vitro, but five of the six immune subjects had reactive lymphocytes. Antigen-reactive lymphocytes appeared in 58% of the antibody negatives after the first inoculation and in 91% after the booster dose. These data suggested that inactivated *M. pneumoniae* vaccine may be inadequate for primary immunization and that rises in antibody, when elicited, may be caused by anamnestic stimulation of naturally acquired immunity. This finding provided a possible explanation for the prior observation that some immunized volunteers who did not develop detectable antibodies experienced more severe disease after challenge.

In 1974, 2 years after CARD was terminated, former colleagues of Dr. Jordan at the University of Virginia evaluated an inactivated vaccine prepared under contract with NIH by investigators at Ohio State University. Dr. Richard Wenzel and associates followed 7,861 Marine Corps recruits at Parris Island in a double-blind study. Twenty-one vaccinees (5.5 per 1,000) and 43 placebo recipients (10.9 per 1,000) were hospitalized with pneumonia; the overall protective efficacy was 51%. Based on serologic data, the protective efficacy was 67%; based on culture for *M. pneumonia* it was 42%. No hypersensitization was observed.

Concurrently, attempts were made to develop an attenuated vaccine on the premise that infection of the respiratory tract with a living but avirulent organism would stimulate greater local immunity. These attempts were abandoned because the mutants developed were either overattenuated or there was fear of reversion to virulence. Work on vaccines ceased in the mid-1970s for a variety of reasons, including the unpredictable, sporadic occurrence of infection; the availability of effective antibiotic therapy; and the fear that immunization that does not result in a protective level of antibodies may lead to more severe disease in the face of natural challenge. The latter concern was based in large part on a series of observations made in Denny's laboratories at the University of North Carolina.

When Denny moved from Cleveland to Chapel Hill, Dr. Clyde went with him, and they were soon joined by others, particularly Dr. Gerald Fernald, to study *M. pneumoniae* infections in hamsters. Electron micrograph studies showed that a differentiated portion of *M. pneumoniae*, consisting of an extension of the unit membrane containing an electron dense core surrounded by a lucent space, serves as the means of attachment to host cell membrane. No mycoplasma were seen within cells. The initial infection was judged to be a superficial one that disturbs ciliary function and injures tracheal epithelium. When the protective effect of prior infection was compared with protection after immunization with killed vaccine, previous infection precluded infection in all animals, but parenteral vaccine was not protective despite high serum antibody titers. This suggested that local immunity, either humoral or cellular, plays an important role in resistance. Accordingly, hamsters were immunized with an attenuated strain. Resistance developed only after intranasal infection. Again, serum antibody levels did not correlate with protection. Avirulent vaccine prevented pneumonia in animals challenged with homologous virulent organisms but not in those receiving an unrelated strain. Virulent vaccine provided protection against both homologous and heterologous challenge. Clearly, local immune factors were of primary importance and it would be necessary to find a way to preserve the immunogenicity of live attenuated strains.

Histological and immunological studies of hamsters showed that a perivascular–peribronchial reaction occurred on the 3rd day on reinfection of previously infected animals. Very few cells were positive for immunoglobulin. These recall lesions suggested that delayed hypersensitivity is a major component of acquired immunity. On the contrary, could such an inflammatory response play a major role in the pathogenesis of the disease in humans? Could it be that primary, usually asymptomatic, infections in children sensitize them for more severe infections as teenagers and adults? Second infections have been reported by investigators at the University of Washington and others, but the data are

insufficient to answer these questions. They and the problems cited above have been sufficient, however, to eliminate *M. pneumoniae* from a priority listing of vaccines that merit development.

Common Cold/Rhinoviruses

The third acute respiratory disease identified clinically and epidemiologically by the CARD investigators at Fort Bragg and transmitted to volunteers was a coryzal illness with a short incubation characteristic of the common cold. Unlike the situation with atypical pneumonia and ARD, a number of prior studies in volunteers had provided evidence that the common cold was an infectious illness caused by a filterable agent. The first of these volunteer studies was reported in 1914 by Dr. W. Kruse, who suggested that the agent be called *A phanozoum coryzae*. During and after World War I, in Germany, between 1917 and 1928, approximately eight groups of investigators administered filtered (Berkefeld candle) secretions to volunteers, but four groups failed to demonstrate transmission. The results of the others were confounded by the detection of anaerobic, filter-passing, gram-negative microorganisms in the inocula.

Over 2 years in the late 1920s, Dr. Dochez and associates at the College of Physician and Surgeons, Columbia University, satisfied themselves that the microorganisms were contaminants and that another agent was responsible for causing colds in 44% of both chimpanzees and male volunteers. Dr. Long and his associates at The Johns Hopkins School of Hygiene and Public Health knew of this work and set out to confirm it in June and July 1930. They did so using female volunteers. Coryzal infections with incubations of 20 to 70 hours were transmitted singly and in series through 2 and 4 passages in 9 of 15 persons. Both groups concluded that the filterable infectious agent was a virus, and subsequent investigators tended to refer to the search for *the* virus of the common cold.

Dr. Dochez was to become one of the first members of the Board; Dr. Long became the first Director of the Commission on Meningococcal Meningitis. Through visits to the CARD laboratory at Fort Bragg and participation in meetings of the AFEB, they undoubtedly played a role in encouraging CARD to conduct its series of volunteer experiments. As a result of many other volunteer studies in the following years, conducted principally by Drs. Jackson and Dowling at the University of Illinois and by Sir Christopher H. Andrewes and his successor Dr. David Tyrrell at the Medical Research Council Common Cold Research Unit in Salisbury, England, it became evident that infectious secretions from different individuals with colds contained different viruses, observations validated with the identification of rhinoviruses.

Dr. Andrewes, the Head of the Department of Bacteriology and Virus Research at the National Institute of Medical Research in London, took on the challenge of the common cold after World War II when the prefabricated facilities first occupied during the war by the Harvard Hospital were given to the Ministry of Health. Dr. Andrewes had begun his studies by taking volunteers to the northern islands to expose them in drafty halls and to cold foot baths to mimic the changes that seemed to bring on colds. With the support of the Medical Research Council, Dr. Andrewes and his colleagues moved to "a wind-swept hilltop just outside Salisbury," in southern England, to found the Common Cold Research Unit. By the time he came to Boston in 1949 to deliver the Dunham Lectures, he was already able to report on observations in 1,500 volunteers inoculated with filtered or unfiltered nasal washings. Dr. Andrewes' host for the lectureship was Dr. Finland of the Thorndike Memorial Laboratory of the Harvard Unit at the Boston City Hospital.

One of Dr. Finland's Fellows, Dr. Jackson, was assigned to chauffeur Dr. Andrewes to his various appointments and social occasions. Dr. Jackson has recalled that Dr. Andrewes' "knowledge and enthusiasm about opportunities and puzzles in the emerging information about viruses as causes of disease bubbled over with a catching enchantment." When Dr. Jackson joined Dowling at the University of Illinois College of Medicine in Chicago, Jackson and his colleagues took full advantage of an elabo-

rate laboratory built by the university for the study of the biological effects of climatological environment to investigate the effect of chilling on the pathogenicity of infectious nasal washings. Using thermocouples for continuous recording of cutaneous, turbinate, and central temperatures of volunteers placed in chambers with precisely controlled temperature and humidity, they created their own Common Cold Research Unit under the sponsorship of CARD. A friendly rivalry continued between the two units and Drs. Jackson and Tyrrell, their leaders for many years, as they studied a variety of respiratory viruses. Dr. Jackson was to serve for several years as a Professor at the London Hospital Medical College and head of its Department of Virology before returning to his home state of Utah; Dr. Tyrrell retired in the late 1980s and the Common Cold Research Unit at Salisbury was deactivated.

That minor respiratory illnesses are caused by multiple agents could also have been inferred from data provided by the Cleveland Family Study. Families with young children living in the suburbs of Cleveland in the late 1940s and early 1950s experienced nearly 10 illnesses per person per year. Common respiratory diseases, a description that included the common cold, constituted 60% of all illnesses and 95% of all respiratory illnesses. An average of 6.2 common respiratory illnesses occurred per person per year. Babies acquired infections with considerable frequency after the first 30 days of life. Incidence rates for children continued to increase until the age of 3 years and then decreased progressively. The highest attack rates were found in young school children. Preschool children with siblings who attended school had consistently higher attack rates than did comparable children without school siblings. Once introduced into the home, the highest secondary attack rates were in preschool children (49%) and schoolchildren less than 6 years of age (37.5%). Among the parents, mothers (27.4%) had higher secondary attack rates than fathers (17.0%).

However, the investigators tended to analyze common respiratory disease as a clinical entity and to interpret the data as indicating a gradual development of immunity caused by an aging process rather than as the result of repeated experience with "the agent." This concept was reinforced by the observations that secondary attack rates for preschool children were similar regardless of whether there were schoolchildren in the family and whether the schoolchildren had higher total attack rates and a greater risk of infection outside of the home but had no greater secondary attack rate than did preschool children of the same age. The hypothesis was advanced "that there is little prolonged modification in immune status as the result of repeated experiences with infection, but that there is a gradual process which reduces susceptibility as age increases." The data were sufficient to predict the frequency of infections currently experienced by young children in day-care centers but, perhaps because there was still a tendency to think of "the agent," were not interpreted as predicting the eventual discovery of over 100 common cold viruses.

For the next decade, investigators depended on volunteers for studies of the common cold, efforts that did identify multiple cold viruses and that continue to the present to explore the mechanisms of their transmission, the pathogenesis of the resulting infections, and approaches to their treatment and prevention. For no other infectious disease have so many human subjects willingly agreed to suffer an experimentally induced illness.

In a series of thoughtfully designed studies, requiring first the use of an objective symptom score for assessing the presence of an illness and its severity, Drs. Dowling and Jackson and colleagues observed nearly 4,000 volunteers who participated in controlled challenge studies. Because their subjects were not isolated, extra controls were necessary. Among the first 1,034 subjects who received an infectious secretion as an initial challenge, 449 (42%) developed colds compared with 70 (10%) of 696 subjects who served as a control population and simultaneously received a buffer solution.

Among 73 subjects who developed no cold on initial challenge, 7 (10%) developed colds on rechallenge with the same infectious secretion. Among 71 subjects who developed a cold on initial challenge, 6 (8%) developed a cold on rechallenge. The interval between challenges varied from 3 to 45 weeks. No evidence was noted that the secretions had lost their infectivity between challenges.

In contrast, among 74 subjects who developed no cold on initial challenge with an infectious secretion, 31 (40%) developed a cold when challenged later with another secretion. Among 41 subjects who developed a cold on initial challenge with an infectious secretion, 19 (46%) developed a cold when challenged later with another secretion. The interval between challenges varied from 10 to 74 weeks.

Common Cold/Rhinoviruses

With the use of nasal secretions as inocula, the investigators induced colds in 35% to 40% of young adults. Secretions differed in infectivity; none infected all subjects. The "take rate" was slightly higher in allergic subjects but was not influenced by smoking or a history of tonsillectomy. The rate was higher in females in the middle third (77%) of the menstrual cycle than in the first and third of the cycle (28% to 30%). Neither sex nor season altered susceptibility. It was not possible to induce increased susceptibility of the subjects by chilling them with controlled alterations of temperature and humidity. In addition to specific immunity to reinfection to the same nasal secretion, pooled human gammaglobulin was shown to neutralize the infectivity of nasal secretions. Sera collected 6 and 12 months after infection provided nearly complete protection against infectious secretion. These observations suggested that the common cold is caused by a number of different viruses that are antigenically different and that following infection, human subjects develop a specific immunity against each virus.

The first rhinoviruses were isolated by Dr. Winston Price at The Johns Hopkins School of Hygiene and Public Health (JH strain) and Dr. W. Pelon and associates at Naval Medical Research Unit (NAMRU) No. 4, Great Lakes (2060 strain), using procedures that had been successful in isolating adenoviruses but substituting primary monkey kidney cells for HeLa cells. In view of the number of serotypes subsequently identified, it was a surprising coincidence that JH and 2060 viruses were shown to be antigenically identical. Drs. Jackson and Dowling, along with one of Dr. Pelon's coinvestigators, Dr. Mogabgab, soon demonstrated that JH and 2060 viruses produced colds in volunteers and that infection with one virus protected against not only the homologous virus but against the other, corroborating the close immunological relationship between them. They became prototypes for rhinovirus IA.

Dr. Mogabgab, who was to continue his studies at Tulane University School of Medicine, had observed that 2060 virus was also cytopathic for human embryonic kidney cells but not for HeLa cells. Then Dr. Tyrrell and associates reported the isolation of strains that would grow only in human cells, and Drs. Hamparian, Ketler, and Hilleman (now at the Merck Institute for Therapeutic Research) soon isolated at least six distinct serotypes by using human fetal kidney and human fetal lung cells. Drs. Hamparian, Ketler, and Hilleman proposed the name "coryzavirus," but this designation and Dr. Kruse's *A phanozoum coryzae* lost out to rhinovirus, the name suggested by Dr. Andrewes and the staff of the Common Cold Unit.

The use of readily available human diploid cells and of microneutralization tests, such as that developed by Dr. Jack N. Gwaltney in Dr. Jordan's laboratory at the University of Virginia, facilitated numerous epidemiological studies and resulted in the identification of multiple rhinovirus serotypes. Use of the 73 different antisera available in 1967 typed 75% of the rhinovirus isolates collected over a 3-year period. Forty-eight different types were identified; 61 strains were untyped. The most frequent isolate, type 14, was associated with only 8.4% of rhinovrus illnesses. In 1987, 100 types were classified officially, and at least 25 untyped isolates awaited full comparison with these 100.

The Charlottesville investigators found that rhinoviruses accounted for 23% of respiratory illness experienced by an industrial population during a 3-year period. Recurrent annual fall peaks occurred during which rates of rhinovirus isolation exceeded 45%. In a study of military recruits during 4 weeks of training, investigators at NAMRU No. 4, Great Lakes, found that 90% became infected with one or more of at least 12 different serotypes. Forty percent of recruits sustained two or more infections confirmed by virus isolations, with many infections occurring in the first week of training. During a 4-year period of observation of families in Seattle, Dr. John Fox and associates at the University of Washington recorded spring and fall peaks of rhinovirus infections. Such infections accounted for 16% of all respiratory illnesses (20% of upper respiratory), with rhinovirus illness in children being more severe and twice as frequent as in adults. Infants experienced a 78% secondary attack rate. Homeotypic immunity was associated with relative protection (52% to 59% effective).

As with other picornaviruses, rhinovirus immunity is serotype specific. Although studies that used volunteers have shown that experimental vaccines can reduce the rate of symptomatic illness and viral shedding (but not the overall rate of infection), the large number of specific antigenic types has caused

investigators to turn their attention to search for forms of prevention other than conventional viral vaccines (eg, receptor blockade, interferon prophylaxis).

Finally, during the Cleveland Family Study, antihistamines were shown to have no beneficial effect on the occurrence and subsequent course of common colds in families or in experimentally infected volunteers. This observation was confirmed by many others and reconfirmed by an extensive review in 1987. Neither the report in 1950 or the recent review has had any impact on the incorporation of antihistamines in cold remedies.

Of course, many other viruses exist that cause acute coryza. Among these are influenza; coronaviruses such as 229 E, OC43, and BB14; certain adenoviruses and enteroviruses; viruses important in childhood that reinfect both children and adults, particularly respiratory syncytial and parainfluenza viruses; and viruses yet to be discovered. Vaccines are being developed for some of these, but clearly there will be no universal all-purpose vaccine or antiviral for common respiratory disease.

Pneumococcal Pneumonia

The story of the prevention and treatment of pneumococcal pneumonia before, during, and after World War II has many stars, including a number of scientists associated with the AFEB and its commissions. This account focuses on vaccine development and particularly on the contributions of three outstanding investigators and their associates: Drs. Heidelberger and MacLeod of the Commission on Pneumonia and Dr. Austrian of the CARD. Effective treatment (eg, sulfonamides or penicillin) that became available late in World War II, is mentioned only to note that its arrival served to suspend and delay vaccine research for a number of years.

Dr. Heidelberger began his studies of the constituents of the pneumococcus in the 1920s with Dr. Avery of the Rockefeller Institute and soon became one of the leading students of bacterial polysaccharides, particularly those of pneumococcal serotypes. Dr. MacLeod, who also had studied the pneumococcus while a postdoctoral fellow with Dr. Avery before moving to New York University, later engaged in studies with Avery, in collaboration with Dr. Maclyn McCarty, which were to identify deoxyribonucleic acid (DNA) as the substance that could transform one type to another, ie, the carrier of genetic information. Dr. MacLeod was named Director of the Commission on Pneumonia before the report of this seminal observation was published and was to lead it through a successful trial of pneumococcal quadrivalent polysaccharide vaccine in military personnel in 1944 and 1945. Dr. Austrian, who collaborated with Dr. MacLeod on studies on the pneumococcus at New York University after the war, was to revive interest in the use of the vaccine 20 years later when he and Dr. Jerome Gold, at SUNY-Downstate Medical Center, documented the continuing importance of bacteremic pneumococcal pneumonia as a cause of mortality in Kings County Hospital, Brooklyn, despite the use of antibodies.

In the spring of 1963, Dr. Austrian reported at the annual meeting of the Association of American Physicians that the mortality of bacteremic pneumococcal pneumonia treated with antibiotics was still nearly 20%. Of all deaths, 60% occurred in the first 5 days after onset of illness, apparently from irreversible physiological injury that was unaffected by antibiotic therapy. When the details of this study were published 1 year later, Drs. Austrian and Gold emphasized that "evidence extant suggests strongly that the morbidity and mortality from pneumococcal infection can be reduced significantly by prophylactic vaccination of persons at high risk with a preparation of six pneumococcal polysaccharides."

Dr. Austrian has credited Drs. O. Schiemann and W. Casper with being the first to report in 1927 that specific soluble substances of pneumococci were immunogenic in the mouse. Similar observations were described in humans 3 years later by Drs. Francis (first Director of the Commission on Influenza and later President of the AFEB) and Tillett (one of first members of the Commission on Pneumonia). Then, studies by Dr. Finland (later an associate member of CARD) with Drs. Sutliff (later a member of the Commission on Pneumonia) and Ruegsegger (later a member of CARD) led to the first large trials of vaccines of pneumococcal capsular polysaccharides in the Civilian Conservation Corps in the late 1930s. Dr. Felton and associates administered a bivalent vaccine containing 1 mg each of the polysaccharides of types 1 and 2 to over 40,000 adult males; the results, although promising, were inconclu-

sive. Meanwhile, Dr. Heidelberger had been continuing his studies and was soon able to provide purified type-specific polysaccharides when the need arose at Sioux Falls Army Air Base.

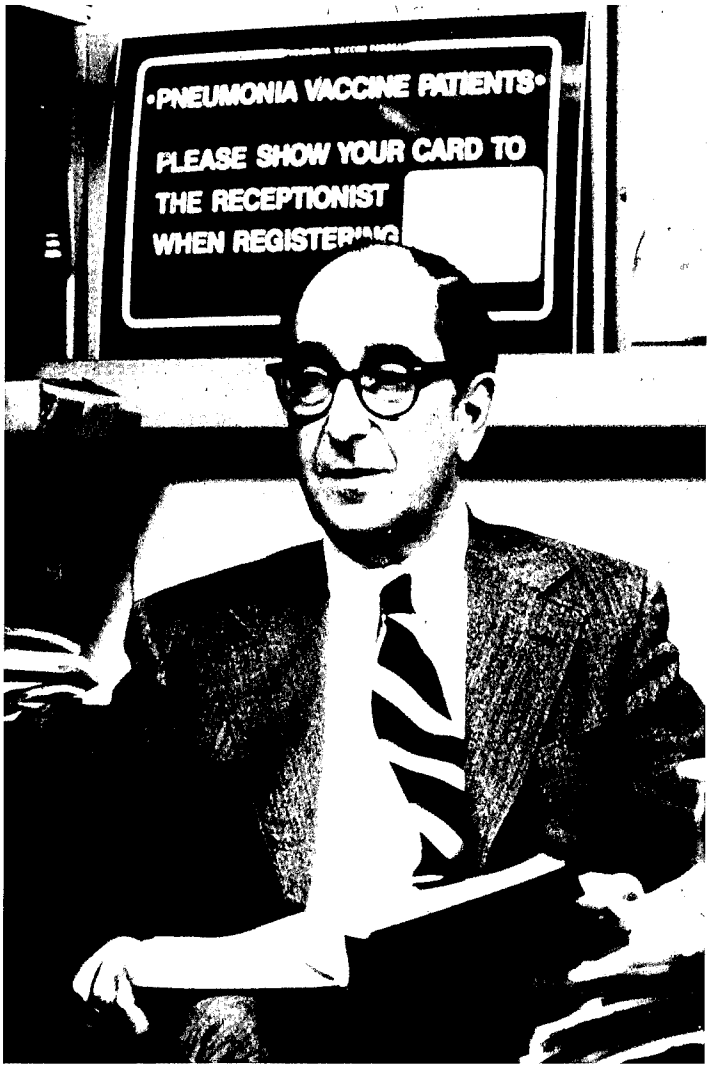
As previously noted, one of the first official acts undertaken by Dr. MacLeod was preparation of a clinical description of atypical pneumonia that became part of an official statement published in March 1942. In November of that year, he was sent to Sioux Falls Army Air Base to investigate an epidemic of atypical pneumonia. This base had been opened in the summer of 1942 as a Technical School for the training of radio operators and continued as such until the late spring of 1945. The epidemic of atypical pneumonia began shortly after the base opened, but beginning in December 1942, the picture changed; pneumococcal pneumonia appeared as the most important pulmonary infection and remained at epidemic levels throughout the whole period of operation of the school.

In the summer of 1943, Lieutenant Hodges was assigned to Sioux Falls as epidemiologist and remained there for 2 years. Facilities for typing pneumococci had been set up after Dr. MacLeod's visit and one technician had been trained in these techniques. Consequently, a picture of the type distribution of pneumococci became available.

In January 1944, the experience of the preceding years was reviewed, and from this analysis it became evident that six pneumococcal types were responsible for 75% to 85% of all cases of pneumonia. Type 2 was the most important epidemic type, causing approximately 35% of all cases, followed by types 1, 5, 7, 12, and 4, in that order. Because of the consistent behavior of these types of pneumonia throughout the preliminary study and because it could be anticipated that pneumonia would remain epidemic at this post, a controlled study of antipneumococcal immunization was suggested. This study was approved by the AFEB and, with the collaboration of Colonel William P. Holbrook and Major A. C. van Ravenswaay of the Army Air Force Rheumatic Fever Control Program, was put in operation in August 1944. The Office of the Air Surgeon constructed a special pneumonia laboratory and assigned trained personnel. The presence of Dr. Hodges and the provision of excellent facilities and laboratory personnel made possible extensive epidemiological studies, particularly with reference to distribution of pneumococci in the throats of normal and sick men and in their environment.

Between September 1944 and April 1945, a carrier survey for pneumococci was conducted. The subjects consisted of one squadron in the Technical School, whose members were cultured at intervals, and control subjects consisted of all admissions to the hospital for upper respiratory infections and a group of 100 surgical patients. The carrier rate was similar in each of these groups and pneumococci showed the same type distribution. Accordingly, it was concluded that the method of sampling provided a good cross-section of the population. From an analysis of cultures carried out on men at various periods after arrival at the post, it was shown that the infective or epidemic types were acquired after arrival. Moreover, the predominant types of pneumococci in the throats of the men could also be isolated regularly from the dust of the schoolrooms where the men spent their entire training time as well as from the dust of the barracks. The population thus became uniformly seeded with the infective types. Pneumococcus type 12 was of particular interest, because during 3 months between January and March 1945, more than 12% of the population of 10,000 men were carriers. At the same time, type 12 was the chief cause of pneumococcal pneumonia, far outstripping types 1, 2, 5, and 7, which in the preceding 2 years had been predominant, but as noted below were controlled during the winter of 1944 and 1945 by means of immunizing with specific capsular polysaccharides of these four types.

In addition to the widespread distribution of infective types of pneumococci, it was shown that nonbacterial respiratory disease was a second important factor contributing to the maintenance of epidemic pneumonia. Throughout the whole period of the operation of the school, one patient with pneumococcal pneumonia was admitted for every 10 patients with nonbacterial respiratory disease, and the incidence curves paralleled each other. As at other bases, this relationship held true even during the periods when influenza A and B were epidemic in 1943 and 1945, respectively. During both of these influenza epidemics, which involved a considerable portion of the population, the incidence of pneumonia also increased considerably, but the 10 to 1 ratio was maintained. Dr. MacLeod, from whose final report of the director this information has been reproduced, suggested that these findings appeared to indicate influenza A and B do not cause a greater predisposition to pneumococcal pneumonia than undifferentiated nonbacterial respiratory disease. Rather, the increased morbidity from pneumonia



ROBERT AUSTRIAN, M.D.

Dr. Robert Austrian, Professor of Medicine, University of New York Downstate Medical Center, and later Professor of Research Medicine at the University of Pennsylvania, documented the continuing importance of bacteremic pneumococcal pneumonia as a cause of mortality in 1963 despite the availability of penicillin and revived the interest in the use of polysaccharide vaccine that had been dormant since its effectiveness was first demonstrated by the Commission on Pneumonia in 1944. He is pictured here during his study of a polyvalent vaccine in South African gold miners that ultimately led to the currently available 23-valent vaccine.

during influenza epidemics is caused by the absolute increase in the number of cases of nonbacterial respiratory disease and not to a predisposing capacity of the influenza virus infections.

Although the pneumococcal carrier rate for infective types and the incidence of nonbacterial respiratory disease were the two most important components in the perpetuation of epidemic conditions, it was apparent that the constant inflow of young, susceptible individuals into the post was also of great significance. The greatest incidence of pneumonia occurred within the first 6 weeks of arrival of new men, during which they acquired the infective types of pneumococci. The nature of training favored the dissemination of not only pneumococci but also agents of nonbacterial respiratory disease, which maintained high levels throughout the whole of the operation of the school. All of the working hours were spent indoors in indifferently ventilated schoolrooms with dusty cement floors. Respiratory disease pathogens thus spread easily. It was not determined how the infective types of pneumococci were able to maintain themselves during the summer months when environmental conditions were clearly improved, although it was noted that pneumonia caused by the these types occurred even during the summer months.

Before undertaking the proposed vaccine trial, it was considered important to study more closely the optimal dosage of polysaccharides for immunization, quantitate the immune response, and measure its duration. These studies were carried out chiefly by Dr. Heidelberger with the assistance of Dr. Sutliff, who was responsible for the titration of sera in mice. Groups of medical students were injected subcutaneously with different amounts of the polysaccharides and with a whole bacterial vaccine. Bleedings were taken before immunization and at intervals for 2 years thereafter. It was found that 0.06 mg of each of the polysaccharides of types 1, 2, 5, and 7, injected subcutaneously in a single dose, gave a satisfactory immune response. Sera of subjects immunized showed type-specific antibody (types 1 and 2) by mouse protection tests as well as on determinations of specifically precipitable nitrogen. In general, the response to type 2 polysaccharide was better than to type 1, but individuals who responded well to one polysaccharide did not necessarily respond better than average to the other polysaccharide. The height of the antibody response, as measured by the quantitative precipitin technique, was found to occur about 3 weeks after immunization; the level remained more or less constant for 6 months thereafter, declining gradually, so that at the end of 18 months the titer had fallen to about 33% or 50% of the highest level. Injection of an additional dose of polysaccharide within the first year and a half after original immunization did not give a booster effect, in sharp contradistinction to the experience with protein immunizing agents such as diphtheria or tetanus toxins, an observation since shown to be true of other polysaccharide vaccines.

Beginning in September 1944, 50% of the students in the Technical School were immunized by subcutaneous injection of a single dose of 0.06 mg of each of the capsular polysaccharides of pneumococcus types 1, 2, 5, and 7 in a volume of 1 mL. Thereafter, alternate men arriving on the post were likewise immunized so that in the succeeding 7 months the population was divided equally into immunized and nonimmunized groups, selected by strict alternation. The nonimmunized controls received an injection of 1 mL of phenolized saline subcutaneously. Reaction to the injections was minimal. Immunization against types 4 and 12 was not carried out so that these important disease-producing types remained as controls. To determine the effect of immunization on pneumococcal carrier rates, a continuous carrier survey among normal men and men with upper respiratory disease was carried out throughout the study.

In the fall and winter of 1944 and 1945, 8,586 men were injected with quadrivalent vaccine; 8,449 were not. Only four cases of pneumonia caused by types 1, 2, 5, and 7 adenovirus occurred in the immunized population. The actual intervals between immunization and admission to the hospital with pneumonia for these four cases were 2, 6, 7, and 11 days, respectively. In the nonimmunized group, 26 patients developed pneumonia caused by the types in the vaccine. The incidence of pneumonia caused by all other types was identical in the two groups. These studies demonstrated clearly that immunization of humans with specific capsular polysaccharides of selected pneumococcus types was effective in preventing the development of pneumonia caused by those types.

Of equal interest was the observation that immunizing 50% of the population greatly reduced the incidence of pneumonia caused by the vaccine types in the nonimmunized subjects. This conclusion was based on the observed behavior of pneumonia caused by types 4 and 12 during the seasons of 1942 and 1943, 1943 and 1944, and 1944 and 1945. During these three seasons, the rates for pneumonia caused by types 4 and 12 were closely similar; during the 1942 and 1943 and 1943 and 1944 seasons the

ratios of the incidence of types 4 and 12 pneumonia to the incidence of pneumonia caused by 1, 2, 5, and 7, respectively, were similar. From the actual incidence of types 4 and 12 pneumonia in the 1944 and 1945 season, it was thus possible to calculate the expected incidence of types 1, 2, 5, and 7 pneumonia for the winter of 1944 and 1945, when immunization was in practice. The incidence of pneumonia in the nonimmunized fraction of the population caused by the four types in the vaccine was but 17.6% of the expected.

Explanation for the reduction in pneumonia caused by vaccine in nonimmunized men was provided by the carrier studies. The carrier rates for these types in the immunized population were significantly lower compared with the nonimmunized population. Thus, immunization prevented the development of the carrier state for these specific types or else shortened its duration, and because thorough mixing of the immune and nonimmune groups occurred, the immune subjects acted as a barrier in the transmission of these types of pneumococci from one man to another.

The study at Sioux Falls has been described at some length because it was the first definitive demonstration of the efficacy of a tetravalent vaccine. In his final report as Director of the Commission on Pneumonia, Dr. MacLeod prophetically stated, "There is no reason to believe that the number of polysaccharides to be used in a single injection could not be considerably increased, to include most of the predominant disease-producing types of pneumococcus." Indeed, he soon reported that six capsular antigens could be combined in a single vaccine and that most subjects responded to all antigens.

E. R. Squibb and Sons then developed and marketed two six-valent pneumococcal capsular polysaccharide vaccines. One vaccine, formulated for use in adults, contained polysaccharide types 1, 2, 3, 5, 7, and 8; the other vaccine, intended for use in children, contained types 1, 4, 6, 14, 18, and 19. Neither of Squibb's vaccines ever gained widespread acceptance. Physicians in the early 1950s chose to rely on new antimicrobial agents to treat bacterial pneumonia, rather than on prevention through immunization. In 1954, therefore, Squibb terminated its production of pneumococcal vaccine. The Laboratory of Biologics Control of the National Microbiologics Institute, NIH, withdrew without prejudice Squibb's license to produce these vaccines, and the Squibb subsequently abandoned all of its pneumococcal vaccine research and development programs.

After this, with increasing reliance on antibiotic treatment therapy, perception of the need for the development of a pneumococcal polysaccharide vaccine generally diminished until Drs. Austrian and Gold produced data between 1952 and 1962 showing that, despite antibiotic treatment, the mortality rate for bacteremic pneumococcal pneumonia was still high. In their study at Kings County Hospital, these researchers found that 10 types of pneumococci accounted for at least 70% of pneumococcal pneumonia cases. Of patients treated for bacteremic pneumococcal pneumonia with penicillin or other antibiotics, 17% died. Among patients over 50 years of age, the mortality rate was 28%, and among individuals with complicating illnesses such as heart disease, stroke, and pulmonary emphysema, the mortality rate was 30%. Patients died despite early treatment. In addition, other investigators found that the emergence of antibiotic-resistant strains of pneumococci was becoming a significant problem in the treatment of pneumococcal diseases. These findings sparked renewed interest in the development of a pneumococcal vaccine, with Dr. Austrian being its leading proponent.

In 1967, the newly created Vaccine Development Committee of NIAID recommended to Dr. Davis, the Institute's Director, that funds be provided for research and development of pneumococcal vaccine. NIAID contracted with Eli Lilly and Company to develop an experimental polyvalent polysaccharide vaccine with Dr. Austrian and other investigators to test it. In 1976, 13 years after his first report to the Association of American Physicians, Austrian informed that group of the convincing results obtained in a population of novice gold miners (strikingly like military recruits) in South Africa. In a trial of a tridecavelent vaccine, there were 17 cases were noted of radiologically confirmed putative pneumococcal pneumonia and/or bacteremia or both in 1,493 vaccinees versus 160 such illness in 3,007 control subjects, a 78.5% reduction in illness. There were 10 bacteremic infections noted that occurred later than 14 days after immunization with the vaccines versus 113 such infections in control subjects, an 82.3% reduction. Much less convincing efficacy was later demonstrated in trials in two elderly U.S. populations.

Just as Lilly's vaccine was being shown to be effective in South Africa, the company made a corporate decision in 1975 to stop producing it, terminating most of its other vaccine research, development, and production in the following year. Fortunately, Merck Sharp and Dohme intensified its efforts to develop a pneumococcal vaccine. Merck, with Dr. Hilleman leading its vaccine program, had committed itself earlier to the task of developing and producing a meningococcal polysaccharide vaccine for the Army. Merck conducted independent clinical trials among gold miners in South Africa and obtained levels of safety and efficacy comparable to those found by Austrian with the product produced by Lilly.

Merck applied to the Food and Drug Administration (FDA) in 1976 for a license to manufacture and market a 14-valent vaccine. The company was issued a product license on 21 November 1977, and began marketing PNEUMOVAX in February 1978. Lederle Laboratories, another vaccine producer, obtained a product license for its 14-valent vaccine in August 1979 and began marketing PNU-IMMUNE shortly thereafter. These vaccines were replaced by 23-valent vaccines in 1983 that contain polysaccharide antigens for the 23 capsular types, which cause 88% of bacteremia pneumococcal disease in the United States. The clinical effectiveness of these vaccines has varied greatly in different population groups in studies that are difficult to evaluate. No other testing opportunities have existed comparable to those presented by the illness in the recruits at Sioux Falls and the novice gold miners in South Africa. The consensus is that the 23-valent vaccine is 65% to 70% effective, and its use is recommended.

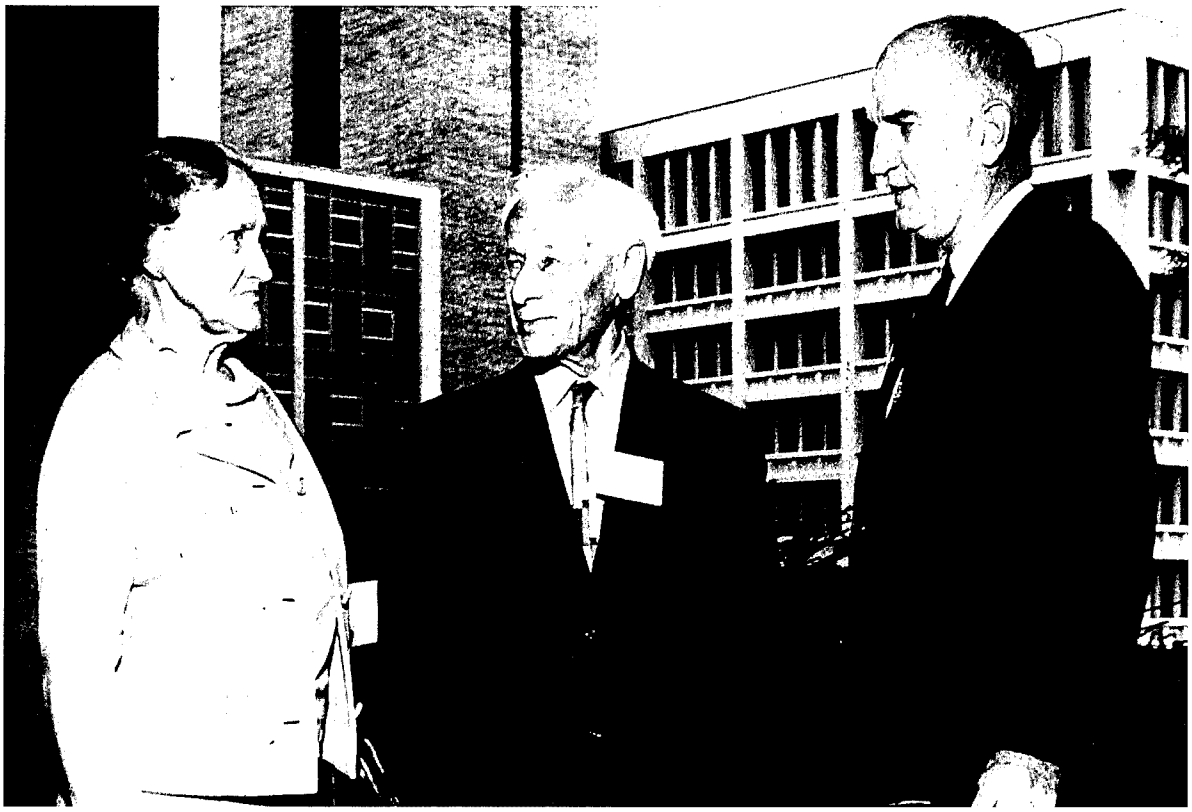
Streptococcal Infections

The respiratory tract is victimized by a multiplicity of microbes, so it is inevitable that those studying a particular respiratory pathogen will of necessity recover other agents and contribute information about them. Such is the case with hemolytic streptococcal infections and influenza, for which the AFEB formed separate commissions. Detailed accounts are to be provided of the work of these two commissions, so only observations made under the auspices of CARD at Fort Bragg and Cleveland are included here. In both locations, cultures were used to identify streptococcal infections and to describe their epidemiological behavior. At Fort Bragg, the absence of positive cultures in patients with exudative pharyngitis served to identify a new syndrome — nonstreptococcal-exudative pharyngitis. At other bases, the CABI used streptococci as markers to track the dissemination of bacteria in barracks. This section follows the one on *Streptococcus pneumoniae* with an account of CARD and CABI studies on *S. pyogenes*. The next section summarizes CARD studies of influenza.

A year after the CARD laboratory was activated at Fort Bragg, the occurrence of an extensive epidemic of streptococcal pharyngitis and tonsillitis as a result of group A, type 5 adenovirus in November 1943 presented an opportunity for a detailed study of the clinical, epidemiological, bacteriological, and immunologic aspects of streptococcal infection and an opportunity to conduct a controlled study of sulfadiazine therapy. The epidemic was confined to members of two companies of an airborne infantry regiment. Epidemiological evidence incriminated creamed eggs served at breakfast as the probable vehicle of infection.

The outbreak was explosive, with a median incubation period of 38 hours and a primary attack rate of 42%. The secondary attack rate was 30%, of which one half were cases and one half carriers. Of patients with type 5 infection, 100 were hospitalized from a group consisting of 32 officers and 228 enlisted men. None of the patients had scarlet fever.

The illnesses were mild to moderately severe and did not differ appreciably from sporadic contact or airborne cases caused by other types of streptococci. As in previous studies of sporadic streptococcal infection, the history and appearance of the throat were typical in the majority of cases, but in some the diagnosis could not have been made by clinical criteria alone. Pharyngeal or tonsillar exudate was present in 90% of the cases; in only 25% was it confluent and in another 25% it was no more than a pinhead. Although symptoms, physical signs, and fever were rapid in onset, maximal in intensity within 48 hours, and declined rapidly, complete return to normal was frequently protracted. Untreated patients who



MARGARET PITTMAN, M.D., MICHAEL HEIDLEBERGER, M.D., AND WILLIAM JORDAN, JR, M.D.

Drs. Margaret Pittman, FDA (left); Michael Heidleberger, Columbia University (middle); and William S. Jordan, Jr. (right) discuss the rebirth of interest in polysaccharide vaccines at an ad hoc meeting on that subject at the National Institutes of Health on 30 September and 1 October 1970.

previously had a tonsillectomy exhibited somewhat more fever than those with tonsils, but other significant or consistent differences in clinical severity between the two groups were not found.

Alternate patients were treated with sulfadiazine. A slight reduction was demonstrated in fever and in the daily frequency of certain symptoms, particularly sore throat, but no objective evidence of benefit was found with regard to the local inflammatory reaction. It was concluded that no benefit was derived from sulfadiazine chemotherapy.

Suppurative complications were few, but a number of nonsuppurative complications were detected. These included three cases of acute rheumatic fever and two others in which that diagnosis was suggested but not established. One probable exacerbation of chronic glomerulonephritis was encountered, but no examples of acute glomerulonephritis were found. Transient microscopic hematuria was detected frequently early in the course of illness.

A significant rise in titer of antistreptolysin or antifibrinolysin was found during convalescence in 85% of hospitalized cases. Another 12% of cases had a rise in titer of antistreptolysin of less than two tubes. No correlation was found between the severity of illness and either the initial titer of antistreptolysin antibody or the maximum titer during convalescence. However, the termination or persistence of the convalescent carrier state did appear to be related to the height of the antistreptolysin response. Similar antibody responses appeared in nearly half of the "healthy" carriers, indicating that a proportion of these carriers were subclinical cases. Transient carriers did not exhibit an antibody response, whereas those who carried the organisms for more than 10 days did.

Subsequently, an analysis of approximately 3,000 consecutive admissions to the hospital for respiratory disease was made to establish the importance of hemolytic streptococci as a cause of respiratory illness. The patients were new recruits studied from March 1943 through April 1945. On admission to the hospital, a throat culture was obtained, and in those patients showing exudative lesions of the pharynx or whose first culture showed hemolytic streptococci, a second and usually a third culture of the throat was taken. A blood specimen was taken at the time of admission to the hospital and approximately 3 weeks later. Antistreptolysin O and antifibrinolysin titers were determined on all acute and convalescent sera obtained from patients harboring streptococci. All subjects whose convalescent sera showed an increase in either the antistreptolysin or antifibrinolysin titer were considered to have a streptococcal infection.

Of the 3,000 hospital admissions, 466 or 15.6% were found to harbor streptococci. The carrier rate of new recruits in the field was approximately 10%. Group A streptococci, or group A in combination with other groups, accounted for approximately 90% of the infections. Group C infections were found in 5.5% and group G in 3%. Acute- and convalescent-phase sera from 92% of the 466 patients harboring streptococci were available for study. Of the convalescent sera of the patients, 38% exhibited a significant increase in streptococcal antibodies. When all soldiers hospitalized for respiratory disease were considered, cultural and serologic results indicated that only 6% had immunologic evidence of streptococcal infection, although more than twice this number harbored streptococci in their throats. Nonstreptococcal exudative pharyngitis was twice as common as true streptococcal exudative pharyngitis.

In sum, streptococcal infections accounted for very few respiratory illnesses among new recruits at Fort Bragg. In his Director's report for 1945, Dr. Dingle stated, "The etiology of non-streptococcal pharyngitis is unknown but its clinical pattern suggests a close resemblance to ARD." As noted previously, he was correct; adenoviruses , along with other viruses, were the most important cause of disease.

At other bases, CABI investigators had used streptococci to test sampling procedures for assessing the bacterial content of air in barracks. In the process, they identified the nasal carrier as the "dangerous carrier" of hemolytic streptococci. Individuals with strongly positive nasal cultures were shown to disperse, on average, nearly 100-fold as many streptococci as throat carriers.

In the Cleveland Family Study, streptococcal pharyngitis and tonsillitis accounted for 2.8% of approximately 15,000 respiratory illnesses. No case of streptococcal respiratory disease was diagnosed during the first year of life. After that, attack rates increased to a peak during ages 5 to 7 years, then decreased with advancing age. By age 5.8 years, children had experienced, on average, one case per child, by 8.5 years, two cases, and by age 13, three cases per child. A detailed study from 1

January 1948 through 1 July 1952, undertaken to describe the frequency of the acquisition of group A streptococci and the factors influencing the spread within families, disclosed certain similarities between the epidemiology of streptococcal acquisition and the occurrence of common respiratory diseases.

Acquisition most commonly occurred during January through June, with rates of acquisition being highest in young schoolchildren. Once a group A streptococcus was acquired, there was a 40% rate of streptococcal illness, but types 4 and 12 resulted in higher illness rates and were the most common types isolated in the study. Schoolchildren most commonly introduced a group A streptococcus into the family unit — six times as frequently as their parents. The secondary carrier rate was 25% when the index carrier had a group A streptococcal illness but only 9% when he or she did not have such an illness. Children 3 and 4 years old had the highest risk of becoming secondary carriers (50%).

The spread of streptococci in the family unit often occurred quite slowly, and the carrier state frequently persisted for a long time. No cases of rheumatic fever were recognized, but the occurrence of a case of acute glomerulonephritis after a type 12 infection in November 1950, accompanied by asymptomatic hematuria in other members of the family, provided the clue that led Dr. Rammelkamp to postulate that only certain types of group A streptococci are nephritiogenic. This hypothesis was reinforced by the occurrence of a second case of nephritis after a type 12 infection in March 1953.

Influenza

During the first 3 years of the CARD studies at Fort Bragg from December 1942 to April 1945, paired sera were collected from 2,433 patients with respiratory disease and tested for increases in titer of hemagglutination-inhibiting antibodies to influenza A and B viruses. During an epidemic of influenza A in December 1943 and early January 1944, 120 serologically confirmed cases were documented. In nonepidemic periods, eight fourfold or greater increases in titer of antibodies to influenza A and 10 to influenza B were detected in cases that were not recognized clinically. Such endemic occurrence of sporadic cases was proposed to constitute the reservoir of virus between epidemics, but of course, no viruses were isolated to support this suggestion.

During the epidemic, influenza, in contrast to ARD, attacked seasoned men and recruits without preference. Subclinical infections, as determined serologically, were apparently three times as common as overt clinical illness. Although no unusual incidence was noted of pneumonia during the epidemic, a shift occurred away from the predominant occurrence of atypical pneumonia toward an increased incidence of pneumococcal pneumonia.

A comparison of the clinical features of cases of epidemic influenza with the clinical features of cases of ARD observed during the epidemic of influenza and the succeeding epidemic of ARD showed that the clinical picture in these two types of respiratory illness were similar. This conclusion also was reached during the epidemic because difficulty was encountered in making a differential diagnosis between the two syndromes, a problem encountered at other bases. The first adenovirus isolated from a patient with ARD came from a specimen collected during overlapping influenza and ARD epidemics.

A correlation was noted between the preepidemic titer of antibody and the incidence of febrile illness during the epidemic. A titer of 16 or less indicated a relative susceptibility to febrile illness, and a titer of 64 or more indicated a relatively high degree of immunity. Similar results were subsequently obtained by others, and roughly equivalent antibody levels ($\leq$10 and $\geq$40) are still cited by those interested in influenza immunization as indicative for relative susceptibility or immunity.

Studies on the distribution of influenza virus were carried out to determine the duration of infectivity of cases of influenza and to search for carriers of the virus. A total of 247 throat washings were collected from hospitalized and well soldiers. Tests on 110 washings obtained from 46 hospitalized patients whose convalescent sera showed a twofold or greater increase in titer of antibody to influenza A virus showed that patients with influenza commonly carried the virus for as long as 5 days and occasionally as late as the 11th day. Influenza virus was most readily isolated from washings obtained during the first 3 days of illness.

Serial throat washings were obtained from 38 well soldiers during the epidemic. A total of 108 washings was obtained. Influenza virus A was isolated from the washings of two individuals. Each of these two men admitted having had a mild illness, but neither had reported to sick call. Convalescent serum from each showed a definite increase in antibody titer to influenza virus A. Virus was not isolated from any individual whose serum failed to show an antibody response. Thus, cases of influenza were shown to have been infectious for the first 3 to 5 days after onset of illness and occasionally for as long as 11 days. No true carriers of influenza virus were found.

Epidemic influenza B was encountered in Puerto Rico when members of the CARD were on the island carrying out studies in the mongoose on the etiology of atypical pneumonia. An epidemic of respiratory disease in soldiers occurred during late July and August 1943 in Puerto Rico and St. Thomas, Virgin Islands. Tests on acute and convalescent sera from 16 patients were negative for influenza A (PRB strain). Sera from six patients showed fourfold or greater increases in titer and sera from three patients showed at least a twofold increase in titer when tested with influenza virus B (Lee and Bon strains). The increases in titer were of greater magnitude with the Bon strain in seven instances and with the Lee strain in one instance. Thus, the epidemic strain was more closely related to the Bon strain than to the Lee strain. (The Bon strain was isolated by Sir McFarland Burnet in Australia; the Lee strain was isolated by Dr. Francis in the United States) This was one of the early demonstrations that influenza B viruses, like influenza A, exhibit antigenic variation.

An imaginative attempt to find a cyclical pattern to recurrent epidemics of influenza and to define their periodicity was made by the CARD staff, almost certainly at the initiative of Dr. Langmuir. A theory was devised by examining the 16 widespread epidemics that occurred between 1920 and 1944. The theory classified the 16 epidemics in an orderly fashion on the assumption of a 2- or 3-year cycle for influenza A and a 4- to 6-year cycle for influenza B. This concept of the periodicity of influenza varied from earlier theories in two essential respects: "1) was based on the knowledge that two serologically distinct viruses may cause epidemics, an essential point unknown until recent years; and 2) no attempt was made to establish rigid or fixed cycles but rather a definite but limited degree of variation in the cycles is postulated." The investigators proposed that four implications regarding the epidemiology of influenza seem warranted if their theory was correct:

- There is no need to postulate a third variety of influenza virus (exclusive of pandemics);
- The probability rather than the actual prediction of an epidemic in any specific year becomes possible;
- Influenza survives between epidemics as an endemic or sporadic disease; and
- The epidemics of influenza depend, in addition to the factors, upon an upset of the balance between susceptible and immune in the population.

Dr. Langmuir was sufficiently confident in his ability to predict the year and viral type of the next epidemic that he wagered a bottle of Scotch that he could do so with any colleague. The theory had a short life, and Dr. Langmuir probably lost more bets than he won. Things changed, particularly the influenza A virus. In 1947, a new A variant, prototype FM/1/47 (FM for Fort Monmouth) replaced the H_1N_1 virus of the late 1930s and early 1940s, the PR8 strain. The viruses were sufficiently different as to cause PR8 to be classified initially as H_0N_1. In 1950, progressive antigenic drift brought another set of H_1N_1 viruses, which persisted until a major antigenic shift brought the H_2N_2 (Asian) pandemic. H_2N_2, in turn, exhibited progressive antigen drift until replaced by the H_3N_2 (Hong Kong) pandemic. Then an H_1N_1 virus antigenically similar to those of 1950 reappeared in China in 1977 and spread through Russia and the rest of the World. H_2N_2 virus has not yet reappeared.

Thus, the passage of time and new data have invalidated the first assumption on which the theory of periodicity was based. More than two serologically distinct viruses exist because there is more than one A virus. In recent years, two A strains (H_1N_1 and H_3N_2) and a B strain have caused illnesses every year, although some outbreaks have been predominantly A or B.

Both viruses undergo progressive antigenic "drift"; A viruses undergo more major antigenic changes referred to as "shifts," once suggested to occur roughly every 10 years. However, this periodicity has

not held up either, unless the reappearance of H_1N_1 be counted as such. Despite elegant studies that have described the three-dimensional structures of the two surface glycoproteins—the hemagglutinin (HA) and neuraminidase (NA)—and have located the amino acid substitutions that distinguish one A variant from another, it has not been clearly established how influenza survives between epidemics, other than in humans. Because animals and birds have their own influenza A viruses, and ducks, in particular, have viruses with many HA antigens, including H_1, H_2, and H_3, it has been suggested that genetic recombination between a human virus and an animal or avian, particularly duck, virus produced the new pandemic human viruses in the past. As yet, no one has proposed a theory to predict when this gene transfer will occur in the future.

The Cleveland Family Study was carried out from 1947 to 1957 when influenza H_1N_1 viruses were prevalent and was well-prepared to assess the impact of Asian (H_2N_2) influenza during its initial epidemic appearance in the United States. The laboratory was well-established by 1948. H_1N_1 viruses were isolated in 1949, 1950, 1951, and 1953, and influenza B viruses were isolated in 1950 and 1952. Thus, measurement of the occurrence and recurrence of influenza in the same individuals and families was possible over a period of years. Furthermore, it was possible to examine simultaneously the importance of two variables — immunity and antigenic variation — in relation to recurrent infections with members of the H_1N_1 set of viruses. In addition to the study of epidemics in 1950, 1951, and 1953, an opportunity existed to examine sera collected at 6-month intervals since 1948. These serologic studies spanned a 6-year period and provided information regarding the pattern of antibody response during and between epidemics.

Moreover, the population was suited for the collection of data regarding the impact of Asian influenza during its initial epidemic appearance in the United States in the fall of 1957. Therefore, the study, which had been terminated in May 1957, was reestablished for this purpose. Clinical and serologic attack rates were determined and measurements made of the influence of this new influenza virus on the bacterial flora of the upper respiratory tract. Furthermore, the clinical characteristics of the illnesses produced by the H_2N_2 strain and those produced by the previous H_1N_1 strains were compared.

In the three H_1N_1 epidemics, virus was isolated from 71 individuals: 30 adults and 41 children. Viruses were isolated from one person in two different years, 1950 and 1953. Virus was isolated only once from specimens collected from asymptomatic individuals. Thus, 70 individuals, representing 40 families, were infected as demonstrated by virus isolation studies, but recurrent infection in the same individual apparently was rare. A rather constant percentage (25% to 28%) of families yielded virus in each of the 3 years. Of the 14 families with virus in 1950, 11 remained in the study in 1951, and virus was isolated from 1. Ten of the 1950 virus-positive families were under observation in 1953, and viruses were isolated from three. Of the 15 families with virus in 1951, 14 were in the study in 1953, and viruses were isolated from 4. Of the 18 families with viruses in 1953, 17 had been observed in both 1950 and 1951, and viruses were obtained from 7 in one of these years. In each instance, the numbers observed are the numbers expected if the virus isolation rates for the given years are applied to the various families in the groups, except in the case of the 1950 positive families when three isolations would have been expected in 1951. Thus, on the basis of presence of virus in the families, a slight suggestion was noted that those families infected in 1950 were spared in 1951 but not in 1953. On the basis of presence of virus in families, those families infected in 1951 showed no evidence of family immunity in 1953.

Of the individuals exposed to virus in the families in three different years, about the same percentage developed respiratory symptoms. Thus, the occurrence of H_1N_1 infections in the community in the two preceding years (1949 and 1950) did not reduce the clinical manifestations of the disease in 1951. Indeed, a greater percentage of individuals had influenzalike illnesses in 1951 than in 1953 after an interval of 1 year, during which influenza infections were not recognized clinically or by isolation.

Although analysis of virus isolation data alone showed little or no evidence of immunity and the clinical expression of influenzalike infection did not diminish in the total population in successive epidemics, the clinical data suggested that natural infection did confer some degree of immunity. When the occurrence of influenzalike illnesses during the three epidemic periods was tabulated in relation to



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Dr. Alexander D. Langmuir served as Deputy Commissioner of Health of Westchester County, New York, a position from which he was recruited to CARD and one which followed an M.D. from Cornell, an internship on the Harvard Medical Service at the Boston City Hospital, and an M.P.H. from Johns Hopkins School of Hygiene and Public Health. Alex Langmuir was a major contributor to the design and analysis of epidemiological studies at Fort Bragg in the 1940s, and joined Dr. Dingle in 1968 to publish a retrospective review of the significance of those studies.

After the war, Langmuir returned to Johns Hopkins, but became "disenchanted with academic life," a realization that was to be of great benefit to epidemiology, for it prompted him to move to the fledging Centers for Disease Control. There he created the Epidemic Intelligence Service (EIS) to train young epidemiologists to undertake population-based surveillance of disease and to investigate outbreaks or unusual clusters of cases in the U.S. or abroad. Over 2,200 EIS graduates now serve medical schools, schools of public health, health departments, and other agencies with distinction.

the previous virus experiences of the family of the individual, the occurrence of such illnesses in the members of a given family during one epidemic apparently was influenced by whether or not virus had been isolated from that family during the preceding epidemic. Of those individuals in virus-positive families in 1950, 6% had influenzalike illnesses in 1951. In contrast, of those not in demonstrated contact with the virus in 1950, 24% had such illnesses in 1951. Of those individuals living in families from which virus was isolated in 1951, 6%had influenzalike illnesses in 1953; in contrast, 20% of persons not in contact with the virus in 1951 suffered influenzalike illnesses in 1953. Thus, prior familial contact with the virus effected an approximate 70% reduction in rates of influenzalike disease after an interval of either 1 or 2 years.

Individuals who developed fourfold or greater increases in titer as a result of the 1951 epidemic experienced a 50% reduction in development of such increases during the 1953 epidemic. However, individuals who had influenza in 1950 did not have a reduced attack rate in 1953. Thus, when influenzalike illnesses in the families were used as the criterion for immunity, individuals in families infected in 1950 had significantly less influenza in 1951, and individuals in families infected in 1951 had less influenza in 1953. Some degree of immunity, then, persisted for 1 or 2 years but not for 3.

Hemagglutination-inhibition tests on sera collected at approximately 6-month intervals indicated that infections with influenza viruses were constantly occurring. During epidemic periods, 15% to 25% of individuals showed significant increases in titer to the prevalent viruses, both A and B in 1950, A in 1951 and 1953, and B in 1952. During each endemic period, rises in titer were found. The majority of increases in the endemic periods were measured with antigens closely related to the current strain; when FM1 was examined for a single antigen, FM1 virus, 17% to 60% of significant increases were eightfold or greater. These facts support the conclusion previously drawn at Fort Bragg that the titer increases were indeed induced by endemic infections; again, infection was not documented by virus isolation.

Tabulation of the increases and decreases in antibody titers showed that before the influenza A epidemics of 1951 and 1953 and the influenza B epidemics of 1950 and 1952, the population exhibited more falls than rises and thus, in a sense, had developed a negative antibody balance. Similarly, the B epidemic of 1952 and the A epidemic 1953 were preceded and followed by periods during which the average antibody titer of the population decreased.

In summary, studies during the 6 years from 1948 to 1953 provided information particularly regarding the occurrence of infection with H_1N_1 viruses. During the H_1N_1 epidemics of 1951 and 1953, approximately 25% of the population demonstrated serologic evidence of infection. As measured by virus isolation, approximately 25% of the families were infected in each of the three H_1N_1 years, and 50% to 75% of the individuals in these families suffered respiratory illness at that time.

In anticipation of the 1957 Asian (H_2N_2) epidemic, two teams were sent to South America (see below), and the Family Study was reactivated when the 60 remaining families agreed to participate again in the collection of detailed clinical and epidemiological data. H_2N_2 virus was first isolated in Cleveland in June 1957, and two other sporadic infections were documented in July and August. The first known case in the study population occurred on 2 September just after the study resumed; Cleveland schools opened 9 September; the next two cases occurred on 19 and 20 September at the beginning of the epidemic.

As in previous years, respiratory disease rates had risen after the opening of schools and were already high by the week of 22 September. For the next 2 weeks, nearly all of the respiratory illnesses resembled the common cold and its variants. Then more severe, influenzalike illnesses increased in frequency, reaching a peak during the week of 13 October. In 8 weeks, the epidemic was over. Approximately 73% of all respiratory illnesses were sampled; H_2N_2 virus was recovered from 42.5%. Virus was isolated from 92% of those thought clinically to be influenza, and 27% of milder illnesses were classified clinically as common respiratory diseases. Viruses were isolated from 52 (86.7%) of the 60 families and from 126 (40.9%) of the 308 members of these families. The combined results of the complement-fixation and hemagglutination-inhibition tests showed that 93% of persons from whom virus was isolated developed fourfold or greater increases in antibody titer. All told, 60% of the population developed increases in antibody titer during the epidemic. Attack rates for children were much higher than for adults and were

maximum in the age 5 to 15+ year groups. The pattern of attack rates in the family resembled that of the common respiratory diseases, being lowest in the fathers and highest in the schoolchildren. The importance of the school was emphasized by additional examination of the data. Considering the first virus-positive case as the index case, influenza was introduced into the 52 households as follows: 43 times by a schoolchild (83% of all introductions), once simultaneously by a schoolchild and mother, 3 times by a mother and preschool child, and only twice by a father.

With members of the H_1N_1 set of viruses, the occurrence of influenza was related to at least three factors: (1) chance, (2) persistence of immunity for 2 years, and (3) the emergence of minor antigenic variants. A major variant was responsible for the Asian pandemic. When H_2N_2 virus appeared, few, if any, members of the population had specific antibody. In contrast to serological attack rates of 15% to 25% observed with the H_1N_1 strains, the serological attack rate in unvaccinated persons was 55% for the H_2N_2 virus. In comparison with the earlier H_1N_1 epidemics, Asian virus infected more than three times as many families and two to three times as many persons. Despite this high attack rate, the clinical disease produced resembled that caused by the H_1N_1 strains; no significant alterations in the bacterial pharyngeal flora in the population accompanied or followed the virus infections, and no complications occurred. There were no individuals over age 60 years in the particular population under study, and this may be the reason no complications were observed, for in the greater Cleveland area, as throughout the United States and the world, the Asian influenza epidemic was associated with an excess number of deaths from influenza and pneumonia. Dr. Masaro Kaji, a visiting scientist, isolated virus from the extrapulmonary tissues of some of these fatal cases. Because schoolchildren, to an even greater extent than military recruits, are immunological virgins, the importance of the school was of interest. The attack rate was highest in the age 5 to 15+ year group, and schoolchildren were responsible for more than 80% of the introductions of virus into the homes. Furthermore, the length of the intervals between the onset of the index and subsequent virus-positive cases in the families suggested that many of the secondary infections were acquired at school rather than in the home. The median interval of 7.4 days between the first and all subsequent cases was similar to the interval observed in outbreaks in other cities. These data suggested that during the initial wave of Asian influenza, community spread of the virus was greater than intrafamily spread. Although no ready explanation existed for this apparently paradoxical behavior of a highly infectious agent, one explanation that was offered was that it was the result of a combination of the greater susceptibility of children plus the opportunity for greater multiplicity of contact within the school. Virus had been present in the community for more than 3 months before the epidemic, and in Cleveland, as elsewhere, the opening of schools seems to have been one of the provocations that triggered the epidemic.

Because influenza often occurs in the southern hemisphere during its winter season before occurring later in the northern hemisphere in its winter season, the appearance of the H_2N_2 influenza A variant in Asia prompted the decision to explore the possibility of studying the anticipated epidemic of Asian influenza in South America before its arrival in the United States. In July 1957, a team composed of Dr. Keith Jensen, University of Michigan, for the Influenza Commission; Dr. Jordan, Western Reserve University, for CARD; Captain John R. Seal, for the U.S. Navy; and Dr. Arturo Saenz, Pan American Health Organization, visited health officials and laboratories in Brazil, Uruguay, Argentina, and Chile to select a site for such studies. Santiago, Chile, was recommended. Health authorities in Santiago planned to organize a Committee on Influenza under the chairmanship of Dr. Abraham Horwitz, Professor of Preventive Medicine and Sub-Director of the National Health Service. This team and the subsequent Influenza Study Group were greatly assisted by Dr. Manuel Borgono of the subdepartment of infectious diseases, National Health Service.

An Influenza Study Group composed of members of three commissions was formed to collaborate with the Chilean Committee. On 8 August 1957, four members of the group, Dr. Houser, SUNY at Syracuse, Field Director (CARD), Dr. Davenport and Mr. Peterson, University of Michigan (Influenza); and Dr. Willard C. Schmidt, Western Reserve University (Streptococcus), arrived in Santiago to learn that Asian influenza had occurred aboard a naval ship in Valparaiso the day the first team departed.

The rapid spread of the disease in Santiago and Concepcion precluded vaccine trials, but joint observations were made of the epidemiological, clinical, virological, bacteriologic, serologic and pathological features of the epidemic.

As the survey team later learned, influenza was first noted in the north of Chile in the second week of July 1957. A week later it was in Santiago and subsequently in the central and southern provinces of the country. The epidemic was accompanied by a high rate of pulmonary complications. The sharp increase of pneumonia in Santiago on 2 August came 10 days after the sharp increase of influenza cases. The twofold increase in deaths during the epidemic was coincidental with the increase in pneumonia, and most of the increase in deaths was attributable to influenza and pneumonia. The very young and the elderly contributed predominantly to the fatalities, but an increase was noted in deaths in all age groups. Postinfluenzal pneumonia was more severe than the typical pneumonia of past years but responded relatively well to antibiotics with only a slight increase in hospital fatality rates. Although a variety of organisms was associated with the fatal cases of pneumonia, *S. pyogenes* was most frequently isolated. Some fatal cases were attributed to primary influenzal pneumonia. The majority of the patients with pneumonia developed antibodies against the Asian virus.

These observations alerted those in the United States as to what to expect, although with not as much lead time as hoped. The successful collaboration between United States and Chilean scientists also led to continuing studies of streptococcal infections and rheumatic fever under the auspices of the Commission on Streptococcal Diseases.

An account of vaccine studies is found in the history of the Commission on Influenza. As for another form of prevention, Dr. Jackson of CARD and his associates were among the first to confirm reports of Soviet scientists that amantadine prophylaxis will prevent influenza A virus infections in volunteers. The drug has been shown to be about as effective as vaccine in field trials when given early in an influenza A epidemic. Unfortunately, resistant viral mutants have appeared that may diminish its usefulness in the future.

Meningococcal Meningitis

Epidemics of meningococcal infection and its most dramatic manifestation, meningitis, have occurred in all wars since the illness was first described in the early 1800s in Europe. Within a month of mobilization in World War I, the incidence began to increase in the U.S. Army; within 7 months, an explosive outbreak of meningitis had begun. The AFEB anticipated that a similar sequence would occur in World War II.

In 1941, when the Commission on Meningococcal Meningitis was first formed, the incidence of meningococcal meningitis was low and sporadic in nature. Beginning with the fall of 1942, cases of meningococcal meningitis began to increase among both the Army and civilian personnel. From 1942 through 1944, the United States experienced the most severe epidemic ever recorded by the Public Health Service. Army personnel shared in this experience, and the CARD, from July 1941 through June 1943, received over 5,000 case records from Army personnel stationed in the continental United States.

Among Army personnel the disease was one of new recruits. Of the cases, 67% occurred among men in the Army fewer than 3 months, 15% in those who were in the Army for 4 to 6 months, 7% for 7 to 9 months, and 4% for 10 to 12 months. Although this was a period of rapid expansion in the Army, the concentration of cases in the first 3 months of service was consistent throughout the entire period.

When compared with previous experience, the mortality from meningococcal meningitis and meningococcemia was exceedingly low because of the availability and effectiveness of sulfadiazine therapy. In 1937, Drs. Schwentker, Gelman, and Long had reported from the Sydenham and Johns Hopkins Hospitals of Baltimore that the then new compound sulfanilamide cured 10 of 11 patients with invasive meningococcal disease. In 1940 and 1941, during the previously mentioned outbreak in Halifax, Nova Scotia, Drs. Dingle, Thomas, and A. R. Morton showed that a successor sulfonamide, sulfadiazine, was effective in another small group of patients. Extensive use of sulfadiazine during the

major group A epidemic in late 1942 and early 1943 confirmed the value of the drug as a therapeutic agent and related studies showed that small doses eliminated the carrier state and could be used for prophylaxis.

In the last paragraph of his final report as Director of the Commission on Meningococcal Meningitis, Dr. Phair summarized its contributions as follows:

> A disease like meningococcal meningitis whose symptomatology is so striking and whose mode of spread is so mysterious often occasions far more concern than the associated morbidity or mortality warrants. Through study of the disease and its mode of spread the Commission has been able to represent the probable mode of dissemination. The bulk of the epidemic wave was found to result in subclinical or inapparent infection. Clinical cases were erratic and unreliable indicators of the extent of infection. These subclinical infections apparently stimulated and increased capacity to resist future clinical infection. The organism could be eradicated quickly and easily with the sulfonamide drugs. In this way fear was allayed, and the shifting and deployment of troops, so urgent at this period, were not affected.

During the life of the Commission on Meningcococcal Meningitis, its members assisted in a number of field studies. In these instances, an investigative team and equipment from the central laboratory at The Johns Hopkins School of Hygiene and Public Health were dispatched to the post in question. These were Jefferson Barracks, Missouri, Fort Eustis, Virginia, and Fort George G. Meade, Maryland. All involved carrier surveys; at Fort Meade it was shown that 2 g of sulfadiazine a day for 3 days caused an abrupt drop in the carrier rate from 51% in the control group to 0% in the group 3 days after the last day of therapy.

At Jefferson Barracks, a sample of 200 men selected from permanent party personnel were cultured once a week for 10 weeks. The weekly carrier rate varied between 24% and 42%, and during the period, 75% of the men were found to be carriers of meningococci at one time or another. Group A meningococci were isolated from 25.6%, group B from 46.7%, group C from 23.6%, and group D from 10.5% of the men cultured during the interval. Negative cultures were found in 50 men or 25% of the sample. Later, Drs. Phair and Schoenbach were to report an average composite prevalence rate of 40% during carrier studies of an Army Medical Service Unit. Infections with at least one type were found in 92.9% of men during the 10-week study. Most significantly, a single dose of 2 g of sulfadiazine reduced the carrier rate to 0% without toxic reactions.

Because of the early success of Drs. Heidelberger and MacLeod in demonstrating the immunizing capabilities of pneumococcal polysaccharides, Dr. Kabat, an associate of Dr. Heidelberger's at Columbia University, undertook the purification of group A (then group I) meningococcal polysaccharide. His product gave a specific precipitin reaction with group A sera of horse, rabbit, and chicken, and reacted with convalescent sera of cases. However, the polysaccharide was not antigenic in animals and when injected into 60 humans induced low-level antibody responses in only 20%. After April 1946, other investigators were to take on the twin challenges of vaccine development and emerging sulfadiazine resistance.

At the April 26, 1945, meeting of the AFEB, Dr. Phair reported that a strain of group A meningococci had been made resistant to sulfadiazine by serial passage through fertilized eggs containing increasing concentrations of drug. Thus, the potential for the development of resistance after widespread use of sulfadiazine was anticipated. Dr. Feldman was later to test a number of group B strains from the collection of Dr. Sarah Branham made available to him by Dr. Margaret Pittman of the Bureau of Biologics of the FDA. One strain isolated in Baltimore in 1937 showed low-level resistance, whereas another obtained in 1938 in Washington was markedly resistant. By 1954, 14 (28%) of 50 strains in one collection were resistant. In the spring of 1963, sulfadiazine prophylaxis proved to be ineffective at the San Diego Naval Training Center; and the prevalent group B strains were highly resistant. As previously noted, a group B epidemic at Fort Ord the following year attracted statewide attention. Among civilian strains examined by Dr. Feldman during 1965 and 1966, approximately 50% were found to be resistant. In



Interagency Team Arriving in Santiago, Chile.

An interagency team in Santiago, Chile, in July 1957, after visiting major research laboratories in South America to select a site for studying the anticipated epidemic of Asian influenza. Left to right: Captain John R. Seal, U.S. Navy; Keith E. Jensen, Ph.D., Influenza Commission; William S. Jordan, Jr., M.D., CARD; Arturo Saenz, M.D., Pan American Health Organization; Manuel Borgono, Chilean National Health Service.

1968, investigators at NAMRU No. 7, Naples, reported the occurrence in Morocco of the first epidemic caused by sulfadiazine-resistant group A meningococci. Of the strains, 90% were resistant to 1 mg of sulfadiazine per 100 mL of serum.

A partial solution to chemoprophylaxis was found when investigators at NAMRU No. 4, Great Lakes Naval Training Station, demonstrated that 600 mg of rifampin administered orally for 4 days reduced the meningococcal carrier state by 89%, compared with a group given placebo. A similar dose was 94.7% effective in eradication of nasopharyngeal carriage in a trial among Air Force students at Lowry Air Force Base. However, as reported by Dr. Eickhoff, four rifampin-resistant strains were identified during the follow-up period. Four resistant strains also emerged after a 4-day course of therapy of recruits at Fort Lewis. Because the high rate of emergence of meningococcal strains resistant to rifampin promised to limit the usefulness of this drug for prophylaxis, as with sulfadiazine, it is fortunate that a team of scientists at WRAIR pursued the vaccine studies initiated by Kabat and Heidelberger.

In June 1969, three members of the Department of Bacteriology at WRAIR (Drs. Malcom Artenstein, Irving Goldschneider, and Emil Gotschlich) together with Dr. Teh Yung Liu of the Department of Biology at Brookhaven National Laboratories published five classic papers reporting studies previously presented to the AFEB and the Committee on Meningococcal Infection. These studies brought together evidence for the protective role of circulating bactericidal antibodies, described the preparation of purified groups A, B, and C meningococcal polysaccharides, confirmed that groups A and C polysaccharides were immunogenic in humans, and reported that intradermal injection of 50 mg of group C polysaccharide significantly reduced the acquisition of group C meningococci by recruits at Fort Dix.

Next, a 1969 trial of two lots of group C vaccine followed: one prepared by the Division of Biologics Research at WRAIR, the other by E. R. Squibb under contract. One dose of 50 mg of polysaccharide administered either by jet injector or subcutaneously by needle and syringe effected an 87% reduction in group C disease among nearly 14,000 recruits at five basic training centers. When the lot prepared by Squibb was tested in a smaller number of Marine recruits at San Diego by a team from NAMRU No. 4, no cases of group C disease occurred in 3,018 vaccinees compared with three cases in a similar number of control subjects.

At the meeting of the Board on 14 and 15 May 1970, the Committee on Meningococcal Infections submitted several recommendations that were endorsed, in modified form, by the Board on 28 May 1971, as follows:

1. The Committee desires to continue to facilitate the development and assessment of prophylactic measures and aid in the planning and execution of vaccine trials. The current use of group C polysaccharide vaccine is endorsed. Problems are anticipated in trying a group A vaccine which is now available, and a product manufactured in France is under test by the World Health Organization (WHO).
2. The Committee is concerned that there is no useful group B antigen, nor does its availability appear likely in the immediate future. The problem requires attention be given to suitable chemo- or antibiotic prophylaxis as alternatives to immunoprophylaxis for group B infections. Continued effort toward isolation of the basic antigen in the group B meningococcal is recommended.
3. It is of increasing concern that when the group C antigen is used as vaccine, meningococci belonging to groups B and Y may become important causes of disease in the military.

On 26 September 1972, the Secretary of the Army recommended that group C meningococcal vaccine be administered to all individuals entering basic combat training. The following May the AFEB recommended that group C vaccine be used on a routine, year-round basis in all Navy and Marine Corps personnel entering training. Only minor problems were encountered in manufacturing the group A vaccine. That produced in France by Institut Merieux for the WHO proved to be effective in Africa. That produced by Merck Sharp and Dohme was shown to be safe and effective in Finnish military recruits. There is still no effective group B vaccine despite persistent efforts by investigators at WRAIR and elsewhere. As detailed below, the concern about other groups was addressed by adding antigens for groups Y and W-135 to A and C antigens to make a tetravalent vaccine.

With the demise of CARD and its Committee on Meningococcal Infections, responsibility for vaccines was assumed by the rechartered AFEB's Subcommittee on Disease Control. Recommendations regarding the use of group A vaccine were developed after a meeting on 15 September 1977 at which data were reviewed relative to three topics of concern to The Surgeon General: meningococcal vaccines for military recruits, alternative therapy for penicillin-resistant gonorrhea, and the administration of live virus vaccines to female recruits. The AFEB made the following recommendations regarding protection of recruits against meningococcal disease:

> That the licensed bivalent, group A and group C, meningococcal vaccine be administered to miliary personnel entering recruit training during those periods of the year for which epidemiological experience indicates that protection against meningococcal disease is necessary in that locality.
>
> That the use of this vaccine should be accompanied by a program designed to identify meningococci causing disease so that a continuing evaluation of the program is possible.

By the time the first recruits received the bivalent A and C vaccine in January 1979, the question of the inclusion of antigens for groups Y and W-135 had already arisen. In 1978, 50% of military cases of meningococcal meningitis were caused by either Y or W-135, stimulating scientists at WRAIR to accelerate efforts to purify specific polysaccharides for these types. Encouraging progress was reported at the AFEB meeting in June 1982. Because the Y and W-135 antigens induced levels of bactericidal antibody comparable to those produced by A and C antigens (and antibodies to the latter had been shown to be protective), the Y and W-135 antigens were accepted as efficacious without extensive field trials. Administration of tetravalent A, C, Y, and W-135 vaccine was instituted in 1982. Unfortunately, group B continues to be an important cause of meningitis and no effective vaccine is available.

Control of Airborne Infections

Recruit training camps are the military counterpart of civilian day-care centers. New input of young adults from diverse geographic areas creates a population of immunologically naive subjects susceptible to each others' pathogens and to organisms (eg, adenovirus type 4) with a peculiar predilection for such settings. The more the characteristics of housing and the conditions of training facilitate the exchange of bacteria and viruses, the greater the incidence of respiratory disease. Accordingly, with the encouragement of the Committee on Sanitary Engineering of the National Research Council and the Sanitation and Hygiene Division of the Office of The Surgeon General, CABI and CARD undertook studies to determine whether it was possible to control illness by reducing the spread of airborne microbes with the use of any one or a combination of measures: altering living and sleeping quarters; reducing dissemination of organisms into the air; and sterilizing the air with germicidal vapors.

Oiling of floors had been used in World War I, more to reduce dust than to control disease. Germicidal mists had been used since the days of Lister. Dr. Robertson had studied the effectiveness of propylene glycol as an aerosol against a number of organisms. The publication of the results of this work in 1941 coincided with his appointment as the Director of CABI.

The initial CABI studies examined oiling. At Camp Carson, oiling of floors reduced the bacterial content of air in barracks by 70%, compared with similar barracks with unoiled floors. Oiling of both floors and blankets reduced the bacterial count, particularly of streptococci, by as much as 90%. At the ninth meeting of the AFEB in April 1944, it was reported that studies in 16,000 subjects showed that there were 28% fewer hospital admissions for common upper respiratory infections among soldiers housed in oiled barracks than in untreated barracks and 16% fewer admissions for streptococcal infections.

Turning to Dr. Robertson's interest, CABI investigators showed that propylene glycol and ethylene glycol applied in small concentrations as an aerosol also resulted in reductions in the bacterial content of air in buildings. They developed a device for metering the aerosol into the air and determined that

ethylene glycol was preferable to propylene glycol because it was effective at lower concentrations. In five separate studies, triethylene glycol vapor introduced into the air in scarlet fever wards reduced the number of β hemolytic streptococci by 38% to 100%. Glycolization together with oiling of floors and bed clothes gave maximum reduction in bacterial content of the air, up to 95% in some circumstances.

The CABI studies were conducted under endemic conditions; the CARD studies at Fort Bragg encompassed both endemic and epidemic periods of respiratory disease. The study of the effect of oiled floors and bedding on the incidence of disease was conducted at Fort Bragg during the winter of 1944 and 1945. Four battalions of approximately 1,000 men each were chosen for the study, and the men in alternate batteries (approximately 250) were housed in barracks having oiled floors and bedding. The remaining men were housed in untreated, control barracks. Oil was applied to the floors, and bedding by techniques evolved by CABI and the effectiveness of the procedure were checked by inspection and bacterial analyses of air, blanket, and floor dust. The incidence of respiratory disease was measured by hospital admissions, dispensary visits, and interviews with platoons of soldiers on active duty. Standardized criteria were established for allocation of patients to quarters or to the hospital and for clinical diagnosis of illnesses.

During the entire study, 20 batteries were observed, 10 oiled and 10 controls. The air of the oiled barracks constantly yielded from 75% to 90% fewer organisms than were obtained from the air of untreated barracks. Cultures from blankets having an oil loading of 2% or more oil as dry weight grew out from 90% to 95% fewer organisms than did those from unoiled blankets. Of 307 cultures from oiled beds, 8.5% were positive for hemolytic streptococci. Of 441 samples from unoiled beds, 36.3% yielded similar streptococci. The period of observation was divided into two parts. During the first, beginning 22 October and ending 30 December, the incidence of ARD was regarded as being within the usual or endemic limits. During the second period, from 31 December to 17 March, ARD were regarded as being epidemic. During the endemic period, in agreement with CABI results, there appeared to be a reduction of between 30% and 40% in the cases of ARD from the oiled group compared with the control group. During the epidemic period, however, the reduction was approximately 6% to 12%. The investigators concluded from a practical point of view that the results indicated that oiling of floors and bedding had a moderate effect in reducing ARD during a period of low endemic incidence but was ineffectual in controlling an epidemic of ARDin new recruits. Contaminated dust in barracks may be a contributing factor in the spread of the endemic illnesses, but this mode of spread appeared to be relatively unimportant during the epidemic. Hemolytic streptococcal infections and other respiratory diseases of known etiology did not occur with sufficient frequency for the effects of the oiling procedures to be evaluated. Some years later, Dr. Rammelkamp at the Streptococcal Diseases Laboratory at Warren Air Force Base showed that dust contaminated with streptococci did not induce illness when placed in the throat of a volunteer, an observation that emphasizes the importance of close personal contact.

Prior to the oiling studies at Fort Bragg, CARD investigators examined the effect of double bunking in barracks on the incidence of respiratory disease. The study was begun in October 1943, in a battalion of 1,000 men. Alternate barracks were equipped with double-decked bunks, without changing the total number of men in each barracks. The weekly incidence rates of duty and quarters cases and of hospitalized cases of influenza A and ARD from double-bunked and control groups were carefully monitored. The procedure had little, if any, effect on the incidence of duty and quarters cases or on hospitalized cases of influenza A or endemic ARD. During an epidemic of ARD in January 1944, however, the incidence of hospital cases from the double-bunked barracks was markedly lower than in the control barracks. These results indicated that double bunking may be a desirable procedure for housing troops in barracks provided that it is not used as a means of crowding larger numbers of men into the same space.

Apart from studies on the heating and ventilation of barracks conducted until 1946 under non-AFEB auspices by the NRC Committee on Sanitary Engineering, no additional studies on housing were undertaken until the Laboratory on Housing and Illness opened at Sampson Air Force Base in 1954. When this base served as a Naval Training Center in 1943, it was used by the Navy and the

Committee on Sanitary Engineering to investigate the use of ultraviolet irradiation to sterilize air. A unit of 22 barracks with 4,400 men was divided into four groups—one treated with high-intensity ultraviolet irradiation, one with low-intensity ultraviolet irradiation, and the other two serving as control groups. The training period of 5 weeks allowed only short observation of any group of men; in all, some 30,000 men passed through the unit between 15 December 1943 and 1 June 1944. The low-intensity ultraviolet irradiation showed little effect, but hospital admissions for respiratory infections in the high ultraviolet irradiation groups were 25% lower than in the control groups. Bacterial counts showed a reduction of about 50% in airborne organisms in the irradiated barracks compared with control barracks. It was concluded that an average reduction of cross-infection of about 18% occurred.

In summary judgment of all these studies, the minutes of the April 1944 AFEB meeting record the conclusion of the CABI that sterilization of air by ultraviolet light or glycol vapors does not appear to be practicable either in barracks or hospital wards, and the marginal benefit of oiling was judged to be insufficient to counter its objectionable features. Accordingly, the reactivated studies at Sampson Air Force Base focused on features of barracks construction that impact on contact between occupants. Two types of barracks, open bay and closed bay, were studied. The methods used and the results obtained were well described in the final report of Dr. Houser, the project Field Director.

The recruit population was divided geographically and administratively into two troops. Little close association occurred among recruits in these two troops. However, common classrooms, recreational facilities, dispensaries, and other meeting places created opportunity for close and frequent contact among the recruits within a troop. One of the troops was divided into two geographical areas: G and H. G area contained two squadrons and H area, three squadrons. The number of men per squadron varied according to the total troop strength, but at any given time the number of men in each squadron was similar as the result of rotational assignment of new recruits. Each squadron was composed of flights of 60 or 72 men (occasionally 80 men would be assigned to a flight). Each flight went through training as a unit, but transfers of men in and out of the flight because of missed training for a variety of reasons — among them absence because of illness — did occur. The training period was 12 weeks. Each flight was housed by itself on a single floor of two-floored barracks. Double decked bunks were in use.

All barracks in G area were of the dormitory or open-bay type. The barracks in H area were identical in size and construction to those in G area except that individual rooms opening onto a central corridor had been constructed. Each room in these closed-bay barracks contained three double bunks. Because supporting pillars and clothes racks divided the open-bay barracks into units of three bunks each, the relative relationship of each man to any other in his flight was similar in the two types of barracks. The difference between the two barracks was that men in the closed bay occupied the three bunks in a closed space, whereas in the open-bay barracks men occupied three similarly located bunks in a space open to the entire barracks.

Comparison of the hospital admission rates of recruits from the two types of barracks showed no difference either in total rates for the entire training period of individual flights or in the time of training that hospital admission occurred. This was true not only during times of high rates of admission but also during interepidemic periods. When adenovirus infections, influenza B, and streptococcal infections were considered separately, no differences were observed between the two types of barracks. Maximum admission rates occurred during the 3rd and 4th weeks of training for ARD and during the 5th week for streptococcal infections. Influenza B admissions were influenced by the time of the epidemic rather than the time in training. Thus, under the conditions of training and barrack occupancy during the study, no advantage of one type of barrack over the other was apparent when hospital admissions for respiratory disease were considered.

When looking at floor space per man and cubic feet of air space per man, more crowding occurred among men occupying closed-bay barracks. In an open-bay barrack, 72 men resulted in floor space of 60 ft^2 and an air volume of 687 ft^3 per man; the same number of men in the closed-bay barracks had 36 ft^2 of floor space and 414 ft^3 of air volume per man. These differences in floor space and air volume did

not appear important in the spread of respiratory disease under the conditions of this study. To test the effect of reducing intraroom crowding by 50% while other factors in intraflight contacts remained the same, flights of men housed on two floors of barracks were compared with flights with the usual arrangement of a single floor. Such experiments in the open-bay barracks showed no differences for streptococcal and nonstreptococcal disease. However, in the closed-bay barracks streptococcal disease rates were less for the flights occupying two floors; no difference was noted in the admission rates for nonstreptococcal disease.

It was concluded that the two types of housing studied, closed bay and open bay, with differences in floor space and air volume per man, showed no difference in hospital admission rates for nonstreptococcal respiratory diseases, which were predominantly adenoviral and influenzal infections. Streptococcal disease appeared less likely to occur when the number of men per room was reduced; however, at the level of crowding normally present, the rooms did not result in a reduction of infection.

Additional comparisons of the two types of housing were made in six pairs of flights. One of two flights that arrived on the base within a few days of each other was assigned to an open-bay barrack and the other was placed in a closed-bay barrack. Serum specimens were obtained every 1 or 2 weeks from each man; throat cultures were obtained two or three times per week; and direct questioning of each man in relation to respiratory symptoms was done two or three times per week. Analyses of data obtained in this manner were summarized as follows:

1. A fairly typical pattern of respiratory symptoms was present in the men of all flights. Within one or two days after arrival, coryzal symptoms were frequent and this pattern persisted for a few days. On about the tenth day, more severe symptoms began to appear. These were sore throat, cough, malaise, and feverishness. The men as a group were free of these symptoms after about the fourth week, and minor respiratory symptoms again were prominent for the remainder of training.
2. Units of five and six men occupying a single room in a closed-bay barrack were less likely to have illness introduced into the unit than were similar units in open-bay barracks, and there was a longer interval before introduction when it did occur in the closed-bay units.
3. Once illness was present in a closed-bay unit, there was no increased secondary attack rate among the men in the unit when compared to the open-bay units.
4. Although there was less risk of early acquisition of illness in the closed-bay units, the total risk during training was similar in the two types of barracks.

On the basis of these results, the investigators drafted a plan for the study of environmental conditions that influence the spread of respiratory pathogens in military populations, particularly recruit camps. Unfortunately, Sampson Air Force Base was closed, necessitating termination of the field studies. Dr. Houser's report concluded with a summary of the research plan and brief protocols for three specific studies. The important factors to be considered were as follows:

1. Bed spacing or crowding;
2. Size of the population occupying a common living or dormitory area;
3. Communal gathering places within the barracks such as latrine and dayroom;
4. Presence or absence of barriers to limit person-to-person contact or to reduce droplet and droplet nuclei spread;
5. Sources of infection outside the barracks; and
6. Inanimate objects as intermediate sources of infection within barracks.

In addition to the above, certain basic factors in the epidemiology of respiratory disease were to be evaluated. These were the following:

1. The effect of environment — heat, humidity, ventilation — on the susceptible individual, on the infectious agent, and on the human source of infection;

2. Characteristics of the human source of infection;
3. Characteristics of the susceptible individual; and
4. Characteristics of the infectious agent.

The three protocols were for investigations of the following factors:

1. The effect of crowding on the spread of respiratory disease.
2. The influence on the spread of respiratory disease of reduced barrack contact between men by the use of rooms and cubicles.
3. The effect of distance between beds and duration of exposure on the spread of respiratory disease.

Details are available in Dr. Houser's report. The issue of housing is still lively, as emphasized by the recent study by WRAIR investigators, who reported that the rates of febrile ARD were significantly higher among trainees in modern (energy-efficient design and construction) barracks than in old barracks. These results led to "the hypothesis that tight buildings with closed ventilation systems significantly increase risks of respiratory-transmitted infection among congregated, immunologically susceptible occupants."

Coccidioidomycosis

In 1944, CARD investigators assisted in studies of an outbreak of pulmonary disease that occurred in men who had spent time in an abandoned storm cellar on the military reservation at Camp Gruber, Oklahoma. Although etiologic studies failed to identify a causative agent at the time, the disease was later shown to have been histoplasmosis. Shortly thereafter, the CARD was to inherit from the Commission on Epidemiological Survey (CES) another mycotic infection (coccidioidomycosis) and Dr. Smith of California, who had contributed much to knowledge of the epidemiology of that infection, known locally as "California disease" or "San Joaquin Valley Fever."

Dr. Smith had trained in the laboratory of Dr. E. C. Dickson, a pioneer student of the fungus *Coccidioides immitis* at Stanford University School of Medicine, then located in San Francisco. The studies of Dr. Smith in the late 1930s had contributed to the recognition that the disease was frequently benign and that a high rate of infection occurred among newcomers to endemic areas. In 1940 and 1941, many newcomers arrived in the San Joaquin Valley when the Army Air Forces began construction of airfields for a year-round aviation training program. When the hazard posed to military personnel was called to the attention of the commanding officer of the West Coast Training Center, and in turn to the AFEB and the CES, a plan was developed for a study of coccidioidomycosis, including research into its epidemiology. This plan, approved by the AFEB in June 1941, called for the study to be centered in Dr. Smith's laboratory in the Stanford University Department of Public Health and Preventive Medicine. He was assisted by Dr. Rodney R. Beard, then a member of that department (Dr. Beard subsequently became Director of the Commission on Environmental Hygiene and Chairman of the Department of Preventive Medicine at the new medical facilities at Stanford University in Palo Alto).

In collaboration with the Western Flying Training Command and Army Ground Forces, Drs. Smith and Beard and their associates arranged to skin test all new arrivals at Gardner, Lemoore, Merced, and Minter airfields and other bases in Southern California with coccidioidin. At Gardner Field, "dust was ankle deep and swirled in clouds over the fields." At Minter Field, 20% of all susceptible individuals were infected during the summer and fall of 1941. At the fourth meeting of the AFEB in November 1941, Dr. Smith reported that more than 2,000 men in the Ninth Service Command had been tested with coccidioidin. Men from the east and midwest were all negative; a few from western Texas, New Mexico, Arizona, and, of course, the San Joaquin Valley reacted. All soldiers with lesions of erythema nodosum at Camp Roberts were coccidioidin positive. Every 6 months, personnel previously coccidioidin negative were retested.

The same procedures were extended in 1943 to the California–Arizona maneuver area (the desert area of southeastern California and western Arizona) when a problem was recognized there. It was later concluded that southern and central Arizona were the most highly infected areas in the United States. In time, skin testing was extended to additional bases in California and Arizona, including a camp for prisoners of war in Florence, Arizona, where all tubercular prisoners of war were hospitalized at the Station Hospital. Ten tubercular prisoners were found to have been infected while hospitalized. Although the superimposed coccidioidal infections did not appear to affect the tuberculous infections adversely, the decision was made by authorities in Washington to transfer the prisoners to other hospitals to avoid any criticism of violation of policies governing hospitalization of prisoners of war.

Dr. Smith insisted that coccidioidin skin testing be coupled with accurate records. He required that all personnel previously coccidioidin negative who converted to positive at retest be recorded on standard "clinicoepidemiologic" forms and that blood be drawn from them for serologic tests. The results provided useful data regarding pathogenesis and prognosis. Of those infected, 60% were asymptomatic; only 25% manifested sufficient clinical symptoms to be diagnosed. Erythema nodosum occurred in 24% of infected white females, in 4.3% of infected white males, but rarely in blacks. Dissemination occurred in approximately 1% of clinically manifest infections in white males and in 0.25% of all their infections. Disseminated infections occurred over 10 times as frequently in blacks, the most dangerous form being meningitis. Residual pulmonary cavitation, usually benign, occurred in 2% to 6% of subjects.

Coccidioidin, an antigen prepared from the mycelial phase of the fungus, was produced in Dr. Smith's laboratory and distributed as a service of the CES. The first test site near Bakersfield was a "large tent equipped with an electric hot plate and an empty vegetable can for a sterilizer" and served as the dispensary; coccidioidin was then distributed to bases throughout the west, to Europe, North Africa, India, Australia, China, the Philippines, and South America. This eventually led to the detection of two new arid endemic areas: Lara, Venezuela, and Paraguayan Chaco. Dr. Smith has been credited with proposing that histoplasmosis might account for pulmonary calcifications in coccidioidin- and tuberculin-negative subjects and with suggesting to Dr. Carroll Palmer of the Public Health Service that the histoplasmin skin test be used to define endemic areas of histoplasmosis. He continued to provide coccidioidin to the armed forces after the war on behalf of CARD and each year made a point of reporting that the commercial value of the antigen distributed exceeded the cost of his contract by at least tenfold.

Coccidioidin is a weak immunogen, so repeated skin testing did not induce humoral antibodies. Disease did, and these antibodies were measured in simultaneous precipitin and quantitative complement fixation (CF) tests in Dr. Smith's laboratory as another service function of the CES. Dr. Smith noted that the precipitin test was more useful early in the course of infection while the complement fixation test was more useful later, an observation subsequently explained by the demonstration that the former measures serum immunoglobulin M (IgM) and the latter measures serum immunoglobulin G (IgG) antibodies. Dr. Smith's analysis of his meticulous records showed that the titer of complement fixation increased with the severity of infection. Less than one in 40 of patients with nondissemination disease had CF titers in excess of 1:16, whereas more than 50% of patients with disseminated disease and 95% of those with fatal lesions exceeded that level. The Stanford laboratory continued to function as a reference laboratory for all three services, performing over 100 tests per week until the 1960s. By this time, Dr. Smith had monitored the response of patients treated with intravenous amphotericin B and could report that 69% of 68 patients with nonmeningeal dissemination had favorable results. Improvement occurred more often (88%) in those who underwent a fourfold reduction in CF titer than in those who did not. The initial results in patients with meningitis were less encouraging; only 5 of 47 patients had a complete remission.

As for control measures, it was clear that the infection was acquired from soil containing the anthroconidia (spores) of the mycelial phase. Smith could attest to this from personal experience. His wife was infected by contact with his clothing after he transported highly infectious dirt from San



CHARLES E. SMITH, M.D.

Dr. Charles E. Smith was Professor of Preventive Medicine, Stanford University School of Medicine at San Francisco and subsequently Dean, School of Public Health, University of California at Berkley. He used the coccidioidin skin test to identify endemic areas of coccidioidomycosis that should be avoided during training exercises or where dust control was essential to prevention. He served as a member of both the CARD and the AFEB.

Benito. On the other hand, patients harboring spherules and endopores were not contagious. Appreciating the need to control dust at installations in endemic areas, at its annual meeting in 1944, the AFEB requested the CES to determine what more could be done. Before this, local dust control measures consisted of establishing grass areas and the construction of surfaced roads. A decision was made to try oiling areas without turf, such as playing fields and training grounds, where asphalt was not satisfactory. Highly refined oils were effective when applied to heavy, adobe-type soil but ineffective when the soil was fine, loose silt. The most effective way to prevent infection was to avoid new construction and the holding of maneuvers in endemic areas.

Dr. Smith's personal experience also gave him a great respect for the hazard of the laboratory. In the period between 1929 and 1945, the Dickerson/Smith laboratory was judged to be the source of about 20 infections with *Coccidioides*. When two visitors, including Dr. Smith's son, were infected, culturing was restricted to a separate locked room. In 1946, infection of four monkeys one floor above the laboratory and in four individuals on all three floors of the building revealed contamination of the exhaust ventilating system. The ventilation louver of the transfer room was closed. Two infections in 1947 and an epidemic of five individuals in 1948 occurring on all three floors led to the discovery that the ventilating inlet louver was incompletely closed. The louver was sealed and a closed transfer chamber constructed. However, in 1949, as later reported to the AFEB, Dr. Smith discovered that his laboratory was still hazardous. Just after he had transferred stock cultures of *C. immitis* using all precautions, including the transfer chamber and chemical decontamination, "the natural air currents and ventilating system distributed the spores like the wind and dust storms of the endemic areas" throughout the medical school building.

Thirteen medical students, instructors, laboratory, and clerical personnel became ill, 12 two floors above on the third floor and 1 on the first floor. As a result, Dr. Smith ceased handling any cultures on solid media. In 1950, he arranged to have the preparation of coccidioidin switched to facilities at Cutter Laboratories.

Drs. Smith and Pappagianis, now located at the School of Public Health in Berkeley, in collaboration with investigators of the Naval Biological Laboratory, also in Berkeley, and Dr. H. S. Lawrence of New York University (CSSD) continued studies of the immunological properties of coccidioidin. They found that repeated intradermal testing of negative reactors with coccidioidin alone did not ordinarily induce delayed sensitivity to the antigen. However, repeated intradermal testing of reactors with weak or latent sensitivity may effect an anamnestic delayed reactivity. Healthy subjects living in an area endemic for coccidioidomycosis may exhibit a delayed allergy to coccidioidin in the absence of detectable serum complement-fixing antibody, and occasionally, serum antibody may be present in such subjects without delayed allergy to coccidioidin. They concluded that these findings suggest that the delayed type of allergic inflammatory response to coccidioidin need not necessarily be correlated with the presence or absence of serum antibody, an expression of another parallelism between fungal hypersensitivity and bacterial allergy of the tuberculin type.

In pursuit of the parallel with tuberculin allergy, the investigators found that generalized delayed sensitivity to coccidioidin can be transferred in human subjects with deoxyribonuclease (DNase)-treated leukocyte extracts obtained from sensitive donors. Attempts to transfer coccidioidin sensitivity with leukocyte extracts obtained from a negative donor were unsuccessful in eight of nine consecutive trials. Sensitivity to coccidioidin after transfer persisted up to 15 months, in the absence of exposure to *Cimmitis* or repeated skin testing. Thus, the results of transfer of coccidioidin sensitivity by this means paralleled those obtained in humans after the transfer of bacterial hypersensitivity with the use of extracts of specifically sensitive donor leukocyte extracts said by Dr. Lawrence to contain the elusive substance called "transfer factor."

Dr. Smith also collaborated with investigators at the National Biological Laboratory to test the efficacy of killed spherule vaccines in monkeys and mice. Multiple subcutaneous doses protected monkeys against progression of disease, but not infection, after respiratory challenge with arthrospores. Mice immunized intramuscularly showed an intranasal LD_{50} of >3,000 arthrospores compared with approximately 50 in control animals. Vaccines prepared from mature spherules were superior to those prepared from immature spherules, consistent with the postulate that the mature cell wall is the primary locus of the immunogen. In continuation of these studies after his move to the University of

California School of Medicine at Davis, Dr. Pappagianis has attempted to identify subcellular components that confer protection. Purified antigens are desirable, for the spherule vaccine is moderately toxic. Furthermore, three doses of a killed spherule vaccine were shown to be ineffective in a trial conducted between 1980 and 1985 in 2,867 skin-test-negative volunteers in California and Arizona.

Tuberculosis

The armed forces of the United States benefited greatly from the steady decline in the incidence of tuberculosis that occurred in the first half of the 20th century in populations of industrial countries. Fewer and fewer recruits were exposed to tuberculosis in the United States before induction. However, rates did not decline as fast in the developing world, and recruits from these areas, particularly the Philippines, were at greater risk of prior infection and the subsequent development of active disease. Screening of recruits eliminated those with pulmonary lesions detectable by radiograph, but endogenous disease often did not become manifest until after months of service. Furthermore, personnel free of infection on entry — as indicated by a negative tuberculin — ran the risk of being infected in areas of the world where rates were high in the local population. The management of those who did become infected was markedly improved by the timely arrival of effective drugs; first, streptomycin for therapy; then, isoniazid for both therapy and chemoprophylaxis.

CARD did not sponsor any research projects related to tuberculosis but was called on from time to time for advice on the various aspects of the problems outlined above. Most of the questions directed to the AFEB came in the mid-1960s, stimulated particularly by the occurrence of epidemics traced by the Navy to dissemination of organisms aboard ship. One such outbreak had occurred on the destroyer *U.S.S. Longbeach* in 1959. In August 1962, the Navy requested that the AFEB provide guidance regarding the use of baccillus Calmette-Guérin (BCG), a request stimulated in part by two strong proponents of BCG at Duke University, Dr. D. T. Smith, Professor of Microbiology and Chairman of the Department of Preventive Medicine, and Dr. Wilbert C. Davison, Professor of Pediatrics and founding dean. These colleagues had recommended to The Surgeon General and to members of Congress that BCG be given to all tuberculin-negative members of the armed forces. To address this recommendation and other concerns, CARD created a Committee on Tuberculosis in 1964, chaired by Dr. Gardner Middlebrook. Dr. Middlebrook had worked with Dr. Rene Dubose at the Rockefeller Institute to develop an improved medium for the growth of tubercle bacilli. He then moved to the National Jewish Hospital in Denver and later to the School of Medicine of the University of Maryland. Other members of the committee included Dr. Palmer, Public Health Service, Dr. James Hirsch, Rockefeller Institute, Dr. Arthur B. Robins, New York City Department of Health, and Dr. Elmer Becker, WRAIR.

The Committee on Tuberculosis recommended that BCG not be used by the military, emphasizing the value of the tuberculin skin test for detecting converters who can then be treated with isoniazid. Among other recommendations endorsed by the AFEB were that tuberculin-positive Filipino recruits be studied to determine the usefulness of isoniazid in preventing active disease and that more studies be made by the services to determine the conversion rates of personnel serving in potentially high-risk environments overseas.

The AFEB's position on choosing to not use BCG was reaffirmed in 1969, when a recommendation for its use was again made, after additional outbreaks on three ships, to Dr. Louis M. Rousselot, Deputy Assistant Secretary (Health and Medical) by the Research Foundation of Chicago, the producer of Dr. Sol Ray Rosenthal's BCG vaccine.

Q Fever

The last of the respiratory diseases to be considered by this review — Q fever — was an important airborne, especially dust-borne, cause of illness in the Mediterranean theater, and cultivation of the

causative rickettsial agent, *Coxiella burnetii* proved to be far more hazardous than cultivation of *C. immitis*. Unknown to allied physicians at the time, Q fever existed outside of Australia. It was endemic in Bulgaria and Greece where German troops affected in 1943 referred to it as "Balkan grippe." Using blood from patients involved in an epidemic of "unusual" influenza in Athens in the winter of 1944, Dr. A. J. Caminopetros of the Pasteur Institute of Greece had established a febrile illness in guinea pigs readily transmitted by inoculation of infected blood.

In January 1945, an epidemic of 40 cases of pneumonitis occurred in one company of a battalion of British paratroopers who had come to Rome, Italy, from Athens. The men recalled exposure to dust in an abandoned silk mill used as a bivouac. The initial description of this outbreak as one of "atypical pneumonia" was responsible for the first involvement of CARD. Dr. Dingle, Director, joined Lieutenant Colonel Gauld and Major Robbins of the 15th Medical General Laboratory in Naples to investigate the epidemic at the request of Brigadier E. R. Boland, Royal Army Medical Corps. Dr. Robbins (who subsequently shared a Nobel prize with Drs. John Enders and Thomas Weller for the growth of poliovirus in cell culture) was soon called on to assist in the study of a series of an outbreaks in Italy. Patients from two of these were seen at the 15th Field Hospital, a medical evacuation unit located behind the U.S. II Corps in the Apennines North of Florence. Dr. Charles A. Ragan, Jr. (later, Professor of Medicine at Columbia University College of Physician and Surgeons) was Chief of the Medical Service.

Within 3 months after it was set up in December 1944, the 15th Field Hospital admitted 33 members of the Headquarters company, 339th Infantry, with febrile illnesses, and 20 additional patients from the same unit were seen in other 5th U.S. Army hospitals with similar symptoms. From the blood of one of the patients with pneumonitis a strain of *Rickettsia* characterized as *Rickettsia burnetii* later renamed *Coxiella burnetii* was isolated by inoculation into guinea pigs and subsequent transfer to chick embryo yolk sac (Henzerling strain). All convalescent sera from 53 patients contained complement-fixing antibodies to this strain.

A second outbreak occurred in April 1945, involving 269 members of the 3rd Battalion of the 362nd Infantry, 80 of whom were admitted to the 15th Field Hospital. The 900 men of the 3rd Battalion had been billeted in tents in the mountains north of Florence for rest and recuperation and attended training and recreational films in a dusty barn used as a makeshift cinema. No attempt was made to recover rickettsia from the dust. No specific rickettsial arthropod vectors were identified. High complement-fixing antibody titers to the Henzerling strain were found in civilians from the epidemic area. No person-to-person spread was recorded. Thus, a good case existed for dust-borne infection, to which the occurrence of 20 cases in personnel of the 15th medical laboratory lent strong support.

The disease contracted in the laboratory appeared to be somewhat more severe than that seen in the field; otherwise, the clinical picture in all outbreaks was similar. The men complained of headache, feverishness, and often pleuritic pain. Upper respiratory symptoms and signs were rare. Roentgenograms of the chest showed patchy consolidation in almost all of the cases. The temperature ranged between 103° and 105°F and dropped by lysis, becoming normal in a week. Complications were not frequent, and convalescence was rapid. When sera from some of the patients were also tested with antigen prepared at the NIH from the rickettsiae of Q fever, they were found to contain complement-fixing antibodies, confirming the results obtained in Italy. The next involvement of CARD came on 1 June 1945, when it began an investigation of an outbreak of atypical pneumonia in the 717th Bomb Squadron, which had just returned to the United States from Italy. The transport *West Point* had debarked approximately 7,000 troops on 24 May, including the 379 men of the 717th Bomb Squadron. Seventeen cases of respiratory disease were admitted to the Station Hospital at Camp Patrick Henry, Virginia, from the Squadron on its arrival, and 38 on the following day. From 5 to 14 per day were admitted during the succeeding 5 days. Routine temperature and roentgenographic surveys helped to find more cases, 90% of whom had pulmonary infiltration. A total of 143 cases were hospitalized, constituting an attack rate of 38%. The men presented a rather uniform clinical picture, corresponding for the most part with that noted in Italy. A different feature was that many of the men complained of malaise and especially of nuchal aching. The white count was normal; the sedimentation rate was elevated. The fever was associated with only a slight increase in pulse rate. The most typical physical findings were

fine rales, usually heard at the end of inspiration and sometimes not elicited except on deep breathing or after coughing. No associated rash or splenomegaly was noted. Cough and chest soreness were infrequent. The roentgenographic lesions were widespread, irregularly distributed, and frequently peripheral. The patients recovered rapidly and usually experienced no postfebrile asthenia. The uniform occurrence of the syndrome suggested that the disease was not primary atypical pneumonia but a separate entity.

Epidemiological studies were directed toward an elucidation of the place and time of infection and the manner and mode of transmission. The 717th Bomb Squadron was stationed for 17 months at Grotagile, near Taranto, Italy, along with the 716th, 718th, and 719th Bomb Squadrons, which together formed the 449th Bomb Group. Small service units also were present at the base. Operations at the base ceased approximately 1 May 1945, and on 13 May, the 717th moved as a unit to the Bagnoli staging area near Naples. On 15 May, this unit embarked and 9 days later arrived at Hampton Roads. The 716th, 718th, and 719th Squadrons departed at about the same time but staged at Taranto and were brought by a different ship to Boston.

The first case of illness in the 717th occurred two days after embarkation. The onset in 35 cases developed prior to the arrival of the *West Point* in the United States. The peak of the epidemic was at the time of arrival, and new cases continued through 6 June, 12 days after arrival. The absence of cases among other units aboard the transport strongly suggested that infection occurred before13 May, when the Squadron staged at Bagnoli, because from then on constant intermingling with other organizations occurred. The explosiveness of the outbreak suggested a common source of infection or an exposure during a period of a few days to some common vector.

For this reason the hospital records at the Station Hospital, Camp Miles Standish, Massachusetts, were reviewed to determine the incidence and character of respiratory disease in the 716th, 718th, and 719th Bomb Squadrons, and Headquarters of the 449th Group. A total of 31 men from these organizations had been hospitalized, one of whom was diagnosed as having bronchopneumonia, one as lobar pneumonia of undetermined cause, one as acute gastroenteritis, and the rest as nasopharyngitis. Onsets of illness ranged from 20 to 22 May. Rales were reported in three cases, in two of which radiographic films of the chest were obtained; both showed pulmonary infiltration having the same characteristics observed in the patients from the 717th Bomb Squadron. Additional evidence of the occurrence of illness in the 716th, 718th, and 719th Squadrons was gathered at the time of the rendezvous of the 449th Group for redeployment. A questionnaire revealed that each of the squadrons had experienced an epidemic of acute illness, the cases being clearly concentrated between 17 May and 3 June. Little question existed that the infections were acquired at Grotaglie; therefore, the incubation period was in the range of 10 to 20 days or longer. The source of the epidemic and its mode of spread were never clearly established.

Attempts to isolate rickettsiae from case subjects in the 717th Bomb Squadron were unsuccessful. Blood taken during fever was inoculated into chick embryos intravenously and into the yolk sac, into guinea pigs intraperitoneally and intramuscularly, and into mice intraperitoneally and intracerebrally. Blind passage yielded no agent. Therefore, two human volunteers and three baby chimpanzees were inoculated intramuscularly and intradermally; none developed fever or pulmonary infiltration, and no reactions were noted at the sites of inoculation. However, serologic identification of the outbreak was accomplished when it was shown that sera taken from patients during convalescence fixed complement in the presence of antigen prepared from Q fever rickettsiae and also contained agglutinins for an antigen prepared from the rickettsiae of Balkan grippe.

The Balkan grippe antigen was prepared at Fort Bragg from infected guinea pig blood transmitted from Dr. Caminopetros in Athens via Major C. J. D. Zarafonetis of the USA Typhus Commission. Just when Dr. Zarafonetis picked up the tube of blood is not known. Dr. Woodward, also a member of the Typhus Commission, has reported that the tube was taken to Cairo and kept there for several days without refrigeration before being sent to General Bayne-Jones in The Surgeon General's Office in Washington. After several days on the General's desk, again without refrigeration, it was sent to the CARD laboratory in May 1945. The rickettsia in the tube were viable!

After Dr. Caminopetros' procedure, the agent was first established in guinea pigs. After 12 serial passages, the agent killed intraperitoneally inoculated guinea pigs at a dilution of 10^{-5}. Some animals inoculated with lower dilutions died within 2 days. No characteristic gross pathological changes were found in infected guinea pigs. Recovered guinea pigs were not susceptible to reinfection. The agent in plasma was able to be filtered through sintered glass filters that held back bacteria and grew in the yolk sac of embryonated hen's eggs, killing the embryos in 4 to 6 days after inoculation. Impression smears of yolk sac stained with Macchiavello, Castaneda, or Giemsa stains showed minute pleomorphic organisms, sometimes in very large numbers. They varied in shape from rodlike or even filamentous forms, to coccoid forms that were often difficult to see. Intracytoplasmic masses of organisms occurred in the enlarged spleens and livers of mice inoculated intracerebrally or intraperitoneally.

The antigen used in agglutination tests was prepared from infected yolk sacs. An ether-extracted, formalinized suspension of the ground yolk sacs was put through several cycles of low- and high-speed centrifugation and was made up in saline. Large numbers of rickettsiae were present in smears made from the antigen. Serum dilutions were made with 5% sodium chloride solution. The agglutination tests were incubated at 48°C for 3 hours, followed by 18 hours at 4°C, before reading. The antigen was agglutinated in the presence of sera from recovered guinea pigs but not by sera from normal guinea pigs. Sera from many of the cases of atypical pneumonia in the British parachute troops studied by Drs. Gauld, Dingle, and Robbins also agglutinated the antigen, and as has been mentioned, sera from the 717th Bomb Squadron contained agglutinins. Sera from well persons and from 20 cases of undifferentiated respiratory disease at Fort Bragg had no agglutinins for the Balkan grippe antigen.

One of those who carried out the above procedures was Dr. Irving Gordon, then a young virologist, who has recalled the "thrill" he got "when Balkan grippe specimens, acquired after our troops took Greece, grew out rickettsiae detectable in Macchiavello stains of yolk sacs." Not so thrilling was the fact that Gordon became case no. 7 in a protracted laboratory outbreak of Q fever that involved 15 (31%) of 49 CARD employees and 1 visitor with onsets of illness between 30 July and 22 December 1945.

The first case occurred in a male technician about 3 months after work began with the agent at Fort Bragg. He used no precautions while autopsying infected animals and working with eggs. The number of eggs processed had increased in mid-July, with eggs being harvested every 3 to 7 days. The preparation of antigen from pooled yolk sacs included grinding and certification. Two other cases followed, with onsets on 10 and 15 August, after which all infected animals were killed and strict precautions introduced. The precautions were not strict enough, for cases continued to occur in individuals who were recorded as not having worn masks. One case occurred in a colonel who insisted on inspecting the laboratory. One of the last cases, no. 15, occurred in a secretary (Betsy Smith) who worked in the separate office building but had stood in the doorway of the animal room on several occasions. She experienced a severe illness followed by a relapse associated with infectious mononucleosis. As Mrs. William Ogletree living in Baltimore, she recalled white-coated attending physicians huddled in conversation in her hospital room and hearing one of them express concern that she might die. Fortunately, no one did. Not only did Dr. Gordon survive Q fever, he experienced an episode of influenza with pneumonitis and an attack of atypical pneumonia during his tour, all without reactivation of the tuberculosis that had interrupted his training just a few years before.

One other individual who worked in the office building and occasionally entered the serology laboratory became ill. This was Dr. Badger, the group's biostatistician, who became case no. 11, much to his dismay. Thus, of 15 office workers, 2 (13%) became infected. Of the 34 laboratory workers, 13 (38%) became infected. The evidence pointed to the airborne route as the means of transmission. An agent that induced fever in guinea pigs was isolated from the blood of five of six patients studied during the acute phase of illness and from pleural fluid of the patient whose blood was negative. All of these guinea pigs developed agglutinins for the Balkan grippe strain, as did all 16 of the patients. None of the 31 members of the laboratory staff who remained well developed agglutinins.

After additional studies, including those by Dr. Norman H. Topping and his associates at the National Microbiological Laboratory, NIH, it was agreed that the Balkan grippe rickettsia was identical with the rickettsia of Australian Q fever, then known as *R. burnetii.* Within the year after the laboratory

outbreak at Fort Bragg, the NIH investigators in Bethesda, Maryland, experienced an explosive epidemic of 18 cases in February 1946, with the total number of cases reaching 47 by 31 May. Many of these cases occurred in employees in the same building who did not work directly with the agent. In contrast to the Fort Bragg cases, pneumonitis occurred in only 13 of the 45 patients studied; many of the other illnesses were mild. Penicillin, sulfadiazine, and transfusions of immune blood had no definite effect on the course of the disease. When antigens prepared from American and Italian strains of *Rickettsia* were compared, the highest serum titers were obtained with the "Italian Q antigen." Subsequently, the organism of Q fever was named *Coxiella burnetii* in recognition of Dr. Harold R. Cox of the NIH Rocky Mountain Laboratory, who reported the isolation of the agent (called *R. diaporica* at the time) from ticks in 1938 while studying Rocky Mountain Spotted Fever.

A few years after the two laboratory outbreaks, the occurrence of Q fever in California established the importance of airborne spread in nature. In California, which did not require the pasteurization of milk, *C. burnetii* was shed in the milk of infected cattle, sheep, and goats, but the use of raw milk failed to account for many human cases. Dr. Lennette, who was to serve as a President of the AFEB, and his associates recovered *C. burnetii* from the dust-laden air of a dairy, sheep ranch, and goatery in California and proposed that many infections arose from the contaminated environment. Although not established then, it is probable that this was true of the epidemics in the Balkans and Italy during World War II.

Concurrent with the studies in California and for 15 years thereafter, experience at the Army Biological Laboratories, Fort Detrick, Frederick, Maryland, (now U.S. Army Medical Research Institute of Infectious Diseases [USAMRIID]) emphasized the hazard of the laboratory. Fifty cases of Q fever occurred there between 1950 and 1965, only five of which resulted from known laboratory accidents. Sixteen others occurred in others working with rickettsiae who had no recognized accidents; 28 occurred in other employees, including many without known exposure. Immunization with the then-available vaccine (Formalin-killed rickettsial suspensions) did not prevent the disease nor obscure serologic diagnosis.

Since then, progress has been made in both treatment and prevention. Administration of tetracycline or chloramphenicol shortens the duration but is not as dramatically effective as with the other rickettsioses. A more effective phase-1 vaccine is available for use in laboratory workers but must be administered only to those who skin-test negative to avoid adverse reactions. Investigators at both NIH and USAMRIID are seeking to develop an improved vaccine. None is yet available commercially; the inactivated whole-cell phase-1 vaccine can be obtained from USAMRIID.

OTHER DISEASES

Pretibial (Fort Bragg)Fever

In the months just before CARD was activated and its laboratory established at Fort Bragg, that base found its name attached to an acute febrile illness characterized by a bilaterally symmetrical rash located primarily on the anterior areas of the legs. Colonel Worth B. Daniels and H. A. Grennan called the disease "pretibial fever" when their first clinical description was published the following year, but Colonel Daniels chose "Fort Bragg Fever" as the title for his splendid chapter on the subject published by the Historical Unit, U.S. Army Medical Service 20 years later. Recent texts are about equally divided or use the combination title above. Now that the etiology is known, at least one text recommends that all old names be dropped. It has seemed appropriate to use both in this historical account.

Between 29 July and 11 September 1942, 40 soldiers from a group quartered in the same area of the reservation were hospitalized at Fort Bragg. Colonel Daniels described the illness as follows:

> The history was one of relatively sudden onset characterized by malaise, mild general aching, lumbar pain, severe frontal headaches, and postorbital pain. On the first or second day of symptoms, mild respiratory manifestations consisting of coryza, sore throat, pain and soreness in the chest, and cough occurred in 30 percent of the patients. The respiratory symptoms were not persistent and were never suggestive of primary respiratory involvement.... In about one-fourth of the cases, nausea and vomiting occurred, rarely accompanied by abdominal pain. Shaking chills or chilliness and fever developed. The fever was consistently spiking and frequently showed two or more peaks each day. Recurrent chills often accompanied the elevations. During the periods of temperature elevation, severe accentuation of the frontal and postorbital aching was experienced, but during the periods of lower temperature, the patients felt relatively well. The fever persisted for 2 to 8 days — averaging 5.4 days — with maximum elevations ranging from 99.8 to 105.6°F. In five patients, a transient elevation of temperatures, sometimes as high as 101.4°F, occurred from 2 to 7 days after the original febrile period. Stiffness of the neck accompanied headache in three patients, but examination of the cerebrospinal fluid revealed it to be normal: there was no noticeable relief of headache following lumbar puncture. Adenopathy was not remarkable. A firm spleen was palpable early in the disease in 95 percent of the patients. Splenomegaly persisted in some patients for as little as 5 days; in others, there was still noticeable enlargement after 2 weeks.
>
> The most distinctive feature of the disease, however, was the appearance of an unusual rash on or about the fourth day of illness. In 60 percent (24) of the patients, this was bilaterally symmetrical and limited in distribution to the pretibial areas; in an additional 20 percent (8 patients), the pretibial areas were the primary site of the rash, and a few lesions were scattered elsewhere. Two patients had splotchy, generalized cutaneous manifestations including the anterior surface of both legs. One had a single lesion on the hand. In five cases, typical in all other respects, no rash was observed. Individual lesions consisted of an erythematous localized blush of irregular outline with ill-defined borders fading into the surrounding skin. These were often from 2 to 5 cm in their largest diameter, gradually coalescing with adjacent lesions. The lesions were raised, warmer than the surrounding skin, and sometimes slightly tender to touch. In some patients, the lesions vaguely resembled erythema nodosum. In two patients, the rash became diffusely distributed over the entire body, and in a few it appeared urticarial. Following the generalized type of rash, there was a residual pigmentation which persisted for about 2 weeks. None of the lesions were purpuric. In most instances, the cutaneous manifestations lasted 2 days, but they persisted longer in a few patients....
>
> Leukopenia was noted sufficiently often to constitute a typical feature; it was present, in all except five patients, at some time during the acute illness. It developed most often between the third and the fifth day of illness. At the termination of the febrile period, the leukocytes again rose to normal, and in 14 patients a slight leukocytosis occurred.

The men were housed near a small stream and its tributaries. Some, but not all of the patients, had been swimming in several ponds, particularly McFadgen's Pond, but no other local environmental factors were apparent. Ticks or other insect vectors were not incriminated. Because a search of the literature did not reveal a description of a similar clinical entity, here was a new disease presumably caused by an unknown infectious, but not contagious, agent acquired by unknown means.

This resulted in the formation of a three-man "Commission for the Study of an Unidentified Disease at Fort Bragg, NC" composed of Dr. Topping (National Microbiological Institute, NIH), Dr. John R. Paul (Director, Commission on Neutropic Virus Diseases, and Professor of Preventive Medicine at Yale University School of Medicine), and Major Cornelius B. Philip, SnC. They arrived on 2 September, reviewed the records, examined patients still in the hospital, and agreed that the illness was unknown to them. A survey of illness records in one of the involved regiments indicated that a number of febrile illnesses had not been classified as this new entity because no rash was apparent. Data on the movement of personnel suggested that the incubation period was 10 to 15 days or longer. Entomological observations provided no useful clues. A long list of possible diagnoses was considered; from available accounts, the correct diagnosis was not on the list. Blood was collected from acutely ill patients and frozen for transportation to the institutions of the ad hoc Commission members. All attempts to transmit the disease to a variety of animals, including humans, failed.

In the summer of 1943, another outbreak of a clinically identical disease occurred at Fort Bragg. Lieutenant Tatlock, who had reported for duty with CARD on 1 July, collected blood from the last case of that year's outbreak and injected approximately 5 mL into each of five guinea pigs. After incubation periods of 3 to 5 days, three of these guinea pigs became febrile. After a few passages, the agent became lethal for guinea pigs, appearing predominantly intracytoplasmic in impression smears of the spleen. The organisms appeared as small pleomorphic bacillary forms, staining red by the Machiavello method and gram negative. They were larger than the known rickettsiae, as well as *Francisella tularensis* and *Brucella*, and were immunologically distinct from them. They grew fairly well in the yolk sac of the fertile hen's egg but could not be cultivated on artificial media.

Recovered guinea pigs were found to be immune, with elevated levels of complement-fixing antibody to yolk sac antigen, but it was not possible to demonstrate complement-fixing or agglutinating antibodies in human sera. Dr. Tatlock reported the isolation of the agent, termed it "rickettsia-like" for descriptive purposes, and carefully pointed out that its origin was in doubt. In the light of Dr. Tatlock's studies with another agent the following year, it was assumed that the "rickettsia-like" organisms had been latent in guinea pigs, and the matter rested for 35 years until the discovery of the true nature of the bacterium was to again cause confusion.

During July, August, and early September of 1944, there appeared for the third consecutive year at Fort Bragg a small epidemic (30 to 40 cases) of the disease. These cases occurred in the same limited areas of the post as during the preceding 2 years. From the freshly drawn blood of one of these patients, Dr. Tatlock, now a Captain, isolated a filterable pathogenic agent in guinea pigs that was different from the organism isolated the preceding year. The agent failed to grow on ordinary bacteriologic media either aerobically or anaerobically. It was filterable through a Corning fritted glass filter but failed to pass a single Seitz pad. It was inactivated by freezing, and no method of preserving in an infectious state was found other than serial passage of blood in guinea pigs. After intraperitoneal or intracerebral inoculation, an asymptomatic, febrile disease was produced in the guinea pig, resulting in solid immunity to reinoculation. The incubation period varied from 4 to 9 days, depending on the strength of the inoculum. Pathological changes were confined to the liver, where focal necrosis was found. No inclusion bodies were demonstrated. Transmission of the infection to other animal species was successful only in rabbits and Syrian hamsters, producing a lethal disease in the latter. The agent could be propagated in embryonated hen's eggs and was maintained by passage in this host. Dr. Tatlock and his associates were now confident that this agent was a virus.

On 1 April 1945, Dr. Tatlock was ordered to Walter Reed General Hospital, Army Medical Center, for clinical duties as Chief of the Communicable Disease Section. He took the "virus" with him, maintaining it by passage and by — as was discovered — frozen storage in a skimmed milk medium. By this time, it was assumed that freezing had foiled the previous transmission attempts of the ad hoc Commission. One year later, with the encouragement of Lieutenant Colonel Smadel of WRAIR, Dr. Tatlock was ordered on detached duty to Cincinnati, Ohio, to undertake human transmission studies with the cooperation of Dr. Albert B. Sabin (Commission on Neurotropic Virus Diseases) and the staff of Longview State Hospital. The subjects were patients undergoing fever therapy at that hospital.

By this time, the agent had been through 80 passages in guinea pigs and 23 passages in embryonated eggs. The first group of three volunteers was injected with a 10% suspension of infected embryonated chick liver in saline, 3.0 mL intramuscularly and 0.4 mL intracutaneously. All three developed a short febrile illness beginning on the 9th day. Blood drawn for these patients was defibrinated, pooled, and injected into a second group of three subjects, 5.0 mL intramuscularly and 0.4 mL intracutaneously. All developed similar febrile illnesses after 11 to 14 days. A third group consisted of eight subjects: two normal, two recovered from sand fly fever, and four recovered from dengue. Seven of the eight developed febrile illnesses within 8 to 14 days; five developed rashes of varying extent, for the most part limited to the anterior and lateral surfaces of the legs. A few developed skin lesions on the pronator areas of the forearms. Of the total of 13 induced cases, five showed a slight leucocytosis late in the incubation period followed by a slight leukopenia with a relative lymphocytosis beginning about the

third day of the febrile phase. Inoculation of hamsters showed that the "virus" appeared in the blood of the patients shortly before the onset of fever and disappeared rapidly thereafter.

Dr. Tatlock had reproduced pretibial (Fort Bragg) fever in humans by inoculating an agent that clearly was different from the previously described rickettsialike organism. Although CARD had adopted a policy of group authorship, Dr. Tatlock was the sole author of the article that described the recovery of the "rickettsia-like" organisms at Fort Bragg. He was also the sole author of the article that described the transmission studies on a "virus" from a patient with Fort Bragg fever (see list of publications). Thus, his name became linked to Fort Bragg and to two different agents. Afterward, when reference was made to "the Tatlock agent" and Fort Bragg fever, it wasn't always clear which agent was meant. This identity problem was to cause confusion even after the true nature of both agents was determined. Characterization of the true etiologic agent was accomplished first.

One year after the volunteer studies in Cincinnati, Drs. Joseph L. Melnick and Paul (Commission on Virus and Rickettsial Diseases) of Yale University School of Medicine succeeded in transmitting the "virus" to chimpanzees with the use of a suspension of brains from hamsters infected with material provided by Dr. Tatlock. Virus was recovered from one of the first three animals to develop fever by transfer to another chimpanzee and from another by transfer to hamsters. A rash appeared on the skin and forearm of an inoculated animal. A hamster neutralization test demonstrated the development of antibodies during convalescence in four chimpanzees given "active virus." The agent was still considered to be a virus.

Then came the Korean War. A young Army physician, Captain John Hightower, who had been a Chief Medical Resident in Dr. Woodward's Department of Medicine at the University of Maryland, was sent to Puerto Rico, where he saw a number of cases of leptospirosis. Later, when looking at the charts of patients with Fort Bragg fever with Dr. Joseph Smadel, he suggested leptospirosis as a possible diagnosis. However, when sera from patients with Fort Bragg fever were tested with antigens from *Leptospira icterohaemorrhagiae* and *L. canicola,* the results were negative. Dr. Smadel did not give up.

On 22 August 1951, he wrote the following note to Major William S. Gochenour, Chief of the Department of Veterinary Microbiology at the Army Medical Service Graduate School, Walter Reed Army Medical Center (WRAMC), who had just augmented his collection of leptospiral strains:

> Exp. Pre Tibial Fever
> Question is could this disease be caused by one of the odd leptospira which would not cross with L. can. or icte. Would appreciate your testing these two pairs of very valuable sera against the various leptospires. If any of the samples remain, please return.

The sera showed high titers of agglutinating antibodies against *L. autumnalis.* So did paired sera collected by Dr. Tatlock from six soldiers at Fort Bragg in 1944 and from three volunteers in Cincinnati in 1946, as did paired sera from the four chimpanzees shown by Drs. Melnick and Paul to have developed neutralizing antibodies to Dr. Tatlock's "virus." A leptospiral organism was cultured from the 259th hamster passage, 365th total passage, of Dr. Tatlock's second agent since its original isolation at Fort Bragg. Cross-agglutination tests showed it to be similar to *L. autumnalis* akiyami A, the cause of autumnal fever in Japan. No member of this group had been detected previously in the United States. In 1973, it was classified as *L. interogans* sera group a*utumnalis*, serovar *fort-bragg*. It pays to store serum and other key specimens and to be persistent!

What of Dr. Tatlock's first agent? It has turned out to be the earliest isolate of the *Legionella* species, a strain different from *L. pneumophila,* the cause of the epidemic of Legionnaires' disease in Philadelphia in 1976. Other isolates soon followed, including one from renal-transplant recipients in Pittsburgh who developed pneumonia. The Pittsburgh pneumonia agent was then shown by Dr. G.A. Hebert and associates to be identical to Dr. Tatlock's rickettsialike organism, now named *L. micdadei* in recognition of Dr. Joseph McDade of the CDC who was the first to culture *L. pneumophila*. Because of Dr. Tatlock's

linkage with Fort Bragg fever, the Pittsburgh pneumonia agent became mistakenly associated with that disease, and the literature about legionellosis began to include Fort Bragg fever as an example. This confusion stimulated Dr. Tatlock to publish an editorial in early 1982 in which he summarized the history outlined above and pointed out that the etiologic agent of Fort Bragg (pretibial fever) was not *Legionella miedadei* but *Leptospira autumnalis*.

With the understanding that civilian investigators supported by the commissions were working for the Army, which indeed they were, it seems appropriate to end this section with a quotation from the opening paragraph of Dr. Daniel's chapter:

> The recognition of Fort Bragg fever as a specific new disease entity and the ultimate proof of its etiology is a contribution of the U.S. Army Medical Department to the science of medicine. The disease was described by Army clinicians, studied by Army medical personnel with the assistance of Army-consigned consultants, transmitted to animals by an Army research worker, and finally proved as to etiology by an Army veterinarian and others .... The story of Fort Bragg fever indicates, too, the superior opportunities which were available to military medical personnel for clinical research. Larger groups of patients with the same disease are more often available for study in military installations than in civilian institutions. It is doubtful whether this disease would have been recognized as an entity had the outbreak occurred in an urban civilian community; there, each patient might have been cared for by a different physician and treated in a different hospital, whereas, on an Army post all were concentrated in one hospital under the care of a closely knit medical service.

Viral Gastroenteritis

Infectious gastroenteritis was the second most common cause of illness in the population of the Cleveland Family Study. It was considered "nonbacterial" in that no enteric bacterial pathogens were identified at the time. Although some of the illnesses possibly were attributable to enterotoxigenic *Escherichia coli* and other *E. coli* strains now known to be pathogenic, it is believed that most of the illnesses recorded were caused by enteric viruses. After elimination of gastrointestinal symptoms considered to be secondary to another illness or caused by some cause other than illness, a total of 4,057 cases were classified as infectious gastroenteritis. They accounted for 16% of all illness and occurred at an incidence rate of 1.52 cases per person per year.

The incidence of gastroenteritis fluctuated from year to year; unlike the incidence of respiratory disease, it did not decrease with time. The incidence was lower in both male and female infants under age 1 year than in older children. From age 1 through age 9 or 10 years, the incidence was relatively constant for both sexes. Schoolchildren had a higher incidence at ages 3 and 5 years, and rates were higher among preschool children who had siblings in school than among children of the same age who did not. As expected, the number of cases per year increased with increasing family size. Secondary attack rates varied from infancy through age 7 years, but no trend was discernable. Among these young children, approximately one in every five or six intrafamilial exposures to gastroenteritis resulted in recognizable illness. Children aged 8 years and older and adults had secondary attack rates that were almost 50% as great as those of younger children. The seasonal pattern was constant from year to year, with a sharp rise in October or November followed by a gradual decline during the winter and spring and a low incidence during the summer. Sequential cases of vomiting in a family during cold weather were reminiscent of the illness previously described as "Winter Vomiting Disease."

A detailed analysis of 1,104 cases that occurred during 1948 to 1950 developed a clinical description based on the frequency of the occurrence, severity, and duration of three major gastrointestinal symptoms — nausea, vomiting, and abdominal pain. Afebrile illnesses with only one major gastrointestinal symptom made up almost 50% of the total; among these, diarrhea was the most frequent symptom. Illnesses involving various combinations of two gastrointestinal symptoms occurred with ap-

proximately the same frequency as those in which all three were present. The proportion of illnesses that were febrile varied from 8% of the cases with diarrhea only to 28% of the cases in which all three gastrointestinal symptoms were present. The relative frequency of vomiting was fairly constant throughout childhood but was lower for adults. Diarrhea was recorded in approximately 66% of the cases in infants and young children. This symptom, however, was recorded in only 33% of such illnesses among children age 4 years or older, whereas it was present in about 74% of cases in adults. The most likely explanation for the difference in the frequency of occurrence of diarrhea in the various age groups was considered to be the failure of toilet-trained children to report the event. The relative frequency of abdominal pain increased progressively with age through early childhood, probably reflecting the increasing ability of the child to describe this symptom. Fever occurred less often among adults than among children. The illnesses of mothers and fathers were quite similar except for greater frequency of vomiting among mothers. The explanation for this difference was not apparent.

The onset of infectious gastroenteritis was usually abrupt. If vomiting or abdominal pain occurred during an illness, it usually began on the 1st day of gastrointestinal symptoms, whereas diarrhea began on the 2nd day or later in approximately 15% of all illnesses during which it was present. Fever of 100°F or more was first recorded on the day after the onset of gastrointestinal symptoms or later in about 25% of the cases in which it occurred.

About 12% of cases consisted of a single episode of vomiting or one diarrheal stool. In only 6% of cases was the temperature 102°F or higher. This degree of fever was less common in older children than in those under age 5 years and was quite unusual in adults, being present in less than 2% of adult illnesses. In only 12% of cases did the individuals vomit four or more times in a single day; no consistent relation to age was noted. Four or more stools occurred in a single day in about 21% of all cases. This degree of diarrhea was more common in children under age 2 years and in adults than in older children.

The duration of infectious gastroenteritis was short in most instances. Fifty-nine percent of illnesses lasted 1 calendar day or less, and in only 12% did symptoms last more than 3 days. In summary, the clinical picture was that of a mild illness of abrupt onset and short duration. Almost 50% of the cases were afebrile illnesses consisting of only one major gastrointestinal symptom. It was unusual for an individual to vomit repeatedly, to have a large number of diarrheal stools in a single day, or to have high fever. Although early observations suggested that at least two types of gastroenteritis — afebrile and febrile — were occurring in the population and subsequent volunteer studies indicated the existence of more than one viral etiologic agent, it was not possible to identify or separate the two types epidemiologically. Epidemiologic analysis did, however, identify a "respiratory–gastrointestinal" syndrome where the associated respiratory and gastrointestinal symptoms were related more often than would be expected by chance. Whether this syndrome represented a distinct entity or the fact that gastrointestinal symptoms are more likely to be noticed and recorded when symptoms of respiratory disease are present could not be determined.

The primitive cell culture systems then in use identified polioviruses and coxsackie viruses, but no viruses etiologically related to gastroenteritis could be cultivated. Accordingly, in January and February 1951, stool specimens were collected and processed with the view to reproducing the naturally occurring disease in volunteers. Bacteria-free supernate of a stool from a mother who experienced anorexia, nausea, abdominal pain, and diarrhea without feverishness induced mild symptoms in one of seven young adult males 56 hours after ingestion. Supernate of stool from another mother who had headache, nausea, vomiting, abdominal cramps, and a temperature of 101°F but no diarrhea induced similar illnesses in four of eight young adult males 26 to 30 hours after ingestion. The afebrile, diarrheal disease resembled that successfully transmitted to volunteers by Drs. Gordon, H. S. Ingraham, and Robert F. Korns, who referred to the unidentified agent in stool filtrates as the Marcy strain. Japanese investigators had earlier induced gastroenteritis in volunteers after oral administration of bacteria-free fecal filtrates derived from diarrhea cases in the Niigata Prefecture. In later cross-challenge studies, the Niigata and Marcy strains were found to be related. No additional studies were done with the inocu-

lum from the afebrile family study case, but collaborative studies were undertaken by Dr. Jordan with Dr. Gordon, then Chief of the Virology Laboratory at the Division of Laboratories and Research, New York State Department of Health, in Albany, to compare the family study agent (FS1), which induced febrile illnesses, with the Marcy agent. The Director of the Division was Dr. Gilbert Dalldorf who had recently isolated the first strains of a new group of enteroviruses from the feces of patients with poliomyelitis in the nearby town of Coxsackie, New York.

FS inoculum consisted of unfiltered supernate of a 20% suspension of three loose stools from a case induced on first human passage in Cleveland. Marcy inoculum consisted of unfiltered diarrheal feces collected from a volunteer during the sixth human passage in New York. Inocula were freed of bacteria by centrifugation and addition of antibiotics; poliovirus was excluded by intracerebral inoculation of monkeys. The isolation unit established by Dr. Gordon at the New York State Vocational Institution, West Coxsackie, New York (a prison reformatory) was used for a series of experiments designed to compare FS and Marcy strains. In a cross-immunity experiment, two groups of volunteers in individual isolation were fed FS and Marcy inocula, respectively. Each group was reinoculated twice at approximately 2-week intervals, first with homologous, then with heterologous, inocula.

Six of the seven men given 7 mL of Marcy inoculum had typical attacks of diarrheal disease. Only one of eight men given 2 mL of FS inoculum — the amount used for the first successful passage — had a definite illness; he developed a temperature of 101.8°F, nausea, anorexia, and headache after an interval of 24 hours. Sixteen days later the men ingested the same inocula; however, 10 mL instead of 2 mL of FS were administered. The Marcy group remained well, but one of the FS group became ill. Cross-immunity was tested 13 days after the second inoculation. Marcy inoculum induced diarrhea in seven of eight men, including two previously sick after FS inoculum. FS inoculum induced febrile disease in three of seven men, all convalescent from experimental Marcy gastroenteritis.

Illnesses induced with the FS inoculum differed from the afebrile Marcy disease. The average incubation period of experimental Marcy illness was 60 hours, whereas that of the FS type was 27 hours. Fever was characteristic of the FS illness, constitutional symptoms were more marked, and the watery diarrhea of Marcy disease was lacking. It was believed that FS illness, like Marcy disease, represented an infection, because the feeding of 10 mL of autoclaved supernate prepared from stools from 5 individuals to each of 18 volunteers and the ingestion of 10 mL of autogenous stool supernate by 8 subjects failed to produce such symptoms. Thus, evidence was obtained that at least two agents were responsible for nonbacterial gastroenteritis. At the time, neither disease could be associated serologically with enteric human orphan (ECHO) viruses, types 7, 8, 9, 11 and 12, or reovirus, type 1.

In recent years, a number of viruses have been shown to be causally related to gastroenteritis, most notably rotaviruses (at least four human serotypes), and the Norwalk group of viruses (at least six serotypes). Both agents were first described in 1972. Rotaviruses can be grown in cell culture; Norwalk viruses are identified only by electron microscopy. Clinically, Norwalk illnesses resemble the febrile FS1 illness and winter vomiting disease, but a clear-cut seasonality has not been apparent with known Norwalk-virus associated outbreaks. Both groups of viruses are transmitted by the fecal–oral route. In view of the postulated "respiratory-gastroenteritis" syndrome, it is of interest that throat garglings obtained from volunteers with experimentally induced rotavirus diarrhea failed to yield rotavirus. Similarly, nasopharyngeal washings from a volunteer with experimentally induced Norwalk illness failed to induce illness in three volunteers. However, an outbreak of Norwalk illness in a Toronto Hospital gave rise to the postulate that Norwalk-like virus could be transmitted by respiratory droplets since the implementation of strict enteric precautions infection failed to halt the spread of infection. A number of rotavirus vaccines have been developed and are undergoing efficacy trials.

Other viruses associated with diarrhea in children include several higher type adenoviruses and caliciviruses. Unfortunately, the nature of the FS1 and Marcy agents will never be known, because neither Drs. Gordon or Jordan could retrieve appropriate inocula or sera 20 years later after moving to other institutions.

RABBIT EARS AND ENZYMES

This last section on scientific accomplishments does not deal with a specific disease but is included to illustrate that basic studies supported by the AFEB, while directed toward a particular disease, often resulted in observations that illuminated broad aspects of biology. Such was true of the research conducted by Dr. Thomas during those years when streptococcal infections were the responsibility of the CARD.

Dr. Thomas and his associates at the University of Minnesota studied the effects of cortisone on infection, the mechanism of the generalized Schwartzman reaction (GSR) and the pathogenesis of rheumatic fever. Blockade of the reticuloendothelial system by cortisone, thorium dioxide, trypan blue, or systemic streptococcal infections, before administration of endotoxin resulted in bilateral cortical necrosis of the kidneys. Fibrinoid necrosis of coronary arteries and valvular fibrinoid vegetations were produced in rabbits by intravenous injection of gram-negative bacterial endotoxin after infection with group A streptococci. It was also demonstrated that cortisone would reactivate latent group A streptococcal infections in rabbits as long as 3.5 months after the intravenous inoculation of the streptococcus. A preliminary study was made of an outbreak of acute glomerulonephritis associated with streptococcal skin infections in an Indian reservation in northern Minnesota. Details of this study will be found in the historical account of the CSSD.

After moving to New York University, Dr. Thomas reported that lesions indistinguishable from the GSR were induced in rabbits when a single intravenous injection of endotoxin was accompanied or followed by an injection of synthetic, heparinlike polymers. These reactions were produced by doses of polymer or of endotoxin that were without effect when given singly. Heparin, in doses known to protect rabbits against GSR, prevented reaction to the combined injection. Circulating fibrinogen disappeared after polymer-endotoxin injection, suggesting that lesions of GSR may be caused by the intravascular precipitation of fibrinogen by acidic polymers.

Dr. Thomas made a fascinating observation that an intravenous injection of crude papain caused the ears of rabbits to begin to collapse within 4 hours and collapse completely at 24 hours. Within 3 or 4 days after papain, the ears gradually resumed their normal form. Ear collapse was associated with depletion of the ear cartilage matrix and the disappearance of basophilia from the matrix. At the time, when the ears were restored to normal shape, the basophilic matrix reappeared in cartilage. Similar changes occurred in all other cartilage tissues, including bones, joints, larynx, trachea, and bronchi. When the arterial circulation to one ear was occluded for 15 minutes at the time of injection of papain, this ear was protected against collapse. Repeated injections of papain, over a period of 2 or 3 weeks, brought about immunity to the phenomenon of ear collapse. Cortisone prevented the return of papain-collapsed ears to their normal shape and rigidity. It was postulated that this reflected a capacity of cortisone to impede the synthesis or disposition of sulfated mucopolysaccharide in tissues.

Initially, the effect of crude papain could not be reproduced by crystalline papain protease or crystalline papain lysozyme. To be effective, crystalline papain had first to be inactivated by thiol antagonists such as oxidation or sulfhydryl agents before administration. Crysteine-activated crystalline papain, when injected intravenously, produced little or no change in cartilage. The changes that occurred in cartilage after an injection of inactivated crystalline papain were indistinguishable from those produced by crude papain. Activation of crude papain by cysteine before injection resulted in loss of its capacity to produce in vivo changes in cartilage.

The progressive changes that took place in cartilage in vivo also occurred in vitro in isolated rabbit ears removed shortly after an injection of crude papain or inactivated crystalline papain. In vitro ear collapse occurred rapidly at 37°C but did not occur at 4°C. Collapse was enhanced by exposing the cartilage to crysteine and prevented by exposure to iodoacetamide or p-chloromercuribenzoate. The direct action of crystalline papain on plates of normal cartilage in vitro resulted in the same gross and histological changes that were observed in vivo. The direct action was accelerated by crysteine and inhibited by iodoacetamide or p-chloromercuribenzoate. Dr. Thomas suggested that the reason for the

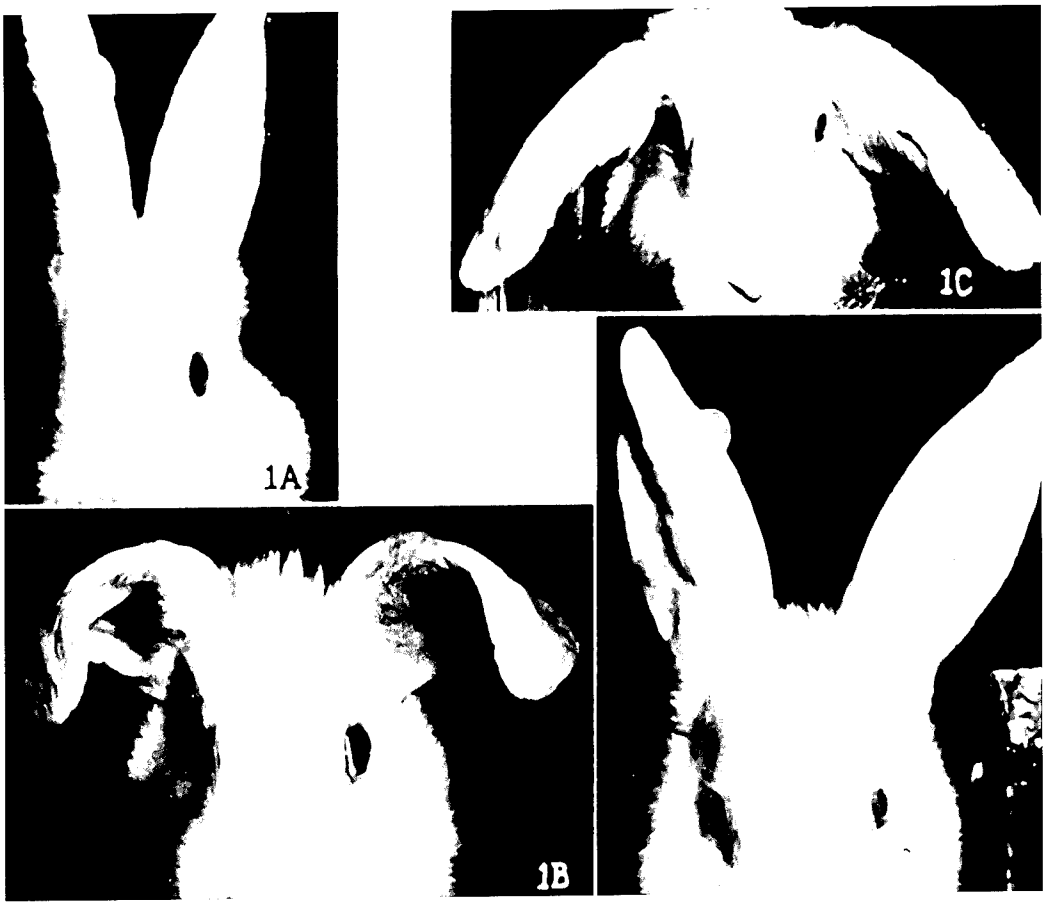
failure of activated papain to enter cartilage, after being injected intravenously, was that it probably reacted with a substrate in the blood, the assumption being that oxidized or otherwise inactivated papain was readily taken up by cartilage and converted there to its active form.

These interesting studies have not yet led to any practical therapeutic advances or public health applications, but the fact that Dr. Thomas was encouraged to pursue them reflects the encouragement extended by the AFEB to basic research and the flexibility of the Army Research and Development Command in supporting the AFEB's recommendations. In the post-World War II years, a continuing increase in funding for biomedical research was provided by the NIH, the AFEB, and its commissions that sustained the laboratories of investigators who used such new technologies such as cell culture to develop new viral vaccines and those who were to trained the next generation of microbiologists and immunologists. When the AFEB was rechartered without commissions, certain groups considered the focus provided by a commission to have been so valuable as to the merit continuation in some form. The members of the CSSD established the Lancefield Society; those of the Commission on Rickettsial Diseases created the American Society for Rickettsicology and Rickettsial Diseases. Members of CARD contributed to a number of national and international groups that sought ways to reduce the morbidity and mortality of respiratory diseases. Thus, the influential work of CARD continued long after its last meeting in November 1972.

SUMMARY

During the World War II period, 1941 to 1946, approximately 75 civilian consultants, some temporarily in uniform, served four of the commissions of the AEB concerned with diseases transmitted by the respiratory route. Some individuals were members of more than one of these commissions, a practice that, along with periodic AFEB meetings, facilitated the exchange of information regarding the epidemiology and control of respiratory illnesses. As in previous wars, the burden of such illnesses was borne primarily by immunologically naive recruits. Studies during World War II defined three distinct acute respiratory illnesses: primary atypical pneumonia, ARD of military recruits, and the common cold; established the efficacy of a quadravalent pneumococcal polysaccharide vaccine; demonstrated that mass prophylaxis with sulfadiazine controlled epidemics of meningococcal meningitis; showed that attempts to reduce the number of organisms in the air of barracks were of little value in reducing the incidence of illness spread by close personal contact; used the coccidioidin skin test to locate geographic areas of endemic coccidioidomycosis that should be avoided by training exercises or where dust control measures should be instituted or both; confirmed that a form of pneumonia first described in Australia (Q, or Query, fever) was the cause of epidemics in U.S. troops in the Mediterranean Theater; and recognized a new disease entity — pretibial (Fort Bragg) fever.

From 1946 to 1972, approximately 50 civilian scientists served as members or associate members of CARD under the AFEB. They assumed responsibility for the concerns of three short-lived commissions (Air-Borne Infections, Meningococcal Meningitis, and Pneumonia) and, for 3 years, the program of the Commission on Streptococcal Infections. Under four directors, studies during this quarter century described the epidemiology of common respiratory disease in a population of civilian families; detailed the behavior of sequential epidemics of H_1N_1 influenza and of the pandemic of H_2N_2 influenza (Asian) in the same population; used challenge studies in over 1,000 volunteers to demonstrate that nasal secretions from different donors with common colds contained different infectious agents; identified adenoviruses as the cause of ARD and developed an effective vaccine for the prevention of this important recruit disease; identified *Mycoplasma pneumoniae* as the cause of atypical pneumonia; cultivated a number of new viruses that can cause the symptoms of the common cold, the most important being over 100 rhinovirus serotypes; encouraged the commercial production of a 23-valent pneumococcal polysaccharide vaccine; recognized that certain group A β-hemolytic streptococci are nephritogenic;



Surprising Collapse of Rabbit Ears.

The surprising collapse of rabbit ears observed by Dr. Lewis Thomas following the intravenous injection of papain. A: before infection. B: 4 hours after. C: 24 hours after. D: 5 days after X 2/3. Reprinted with permission from the *Journal of Experimental Medicine.* 1956, Vol. 104, Plate 19. © Rockefeller University Press.

demonstrated that more than one nonbacterial agent causes acute gastroenteritis; assisted military physicians in the management of epidemics of meningitis after meningococci became resistant to sulfadiazine and before Army scientists developed effective meningococcal vaccines; found no difference in hospital admission rates for respiratory infections (adenovirus, influenza B, streptococcal) between recruits housed in open-bay versus closed-bay barracks; applauded the demonstration by Army scientists in 1951 that the agent transmitted to guinea pigs in 1944 from a patient with Fort Bragg fever was a leptospira and, most importantly, provided a group of experts familiar with the military medical services and their preventive medicine officers, experts prepared to respond promptly to requests for advice and guidance and willing to undertake specific studies as needed.

It is not possible to determine the cost of these advisory and research activities to the federal government. The early, wartime budgets of the four commissions have been given, but data regarding the subsequent contracts sponsored by CARD are incomplete. A search of available archives has failed to provide a credible list of all investigators and their budgets, so the budgets have not been tabulated and totaled. The investigators and their institutions can be ascertained from the list of publications. Even if available, a sum of CARD contract budgets would be imprecise, because travel and meeting costs were charged to a central fund. Even during World War II, research budgets were supplemented by grants from foundations. Later, funds from other agencies, particularly the NIH, helped to sustain laboratories holding commission contracts under the auspices of the AFEB. Whatever the investment by the Department of Defense, it is estimated that the prevention of illness and concurrent interruption of training schedules through the use of adenovirus vaccine alone have saved that much money, if not more.



MAXWELL FINLAND, M.D., RICHARD M. KRAUSE, M.D., AND WILLIAM S. JORDAN, JR., M.D.

Commission discussions are carried on in the civilian sector as Drs. Maxwell Finland, CARD and Distinguished Professor at Harvard; Richard M. Krause, Commission on Streptococcal and Staphylococcal Infections and Director of the National Institute of Allergy and Infectious Diseases; and William S. Jordan, Jr., CARD and Director of that institute's Microbiology and Infectious Diseases Program attend a "Symposium on the Impact of Infections on Medical Care in the United States" at the National Institutes of Health in May 1978.



The last meeting of the Commission on Acute Respiratory Diseases, November 1972.

Seated, left to right: Drs. Harry A. Feldman, Maxwell Finland, Floyd W. Denny, Jr., George Gee Jackson, and William S. Jordan, Jr.

Standing, left to right: Drs. Jay P. Stanford, Demosthenes Pappagianis, Theodore C. Eickhoff, Malcolm S. Artenstein, J. Thomas Grayston, Robert M. Chanock, Robert C. Austrian, and Wallace A. Clyde, Jr.

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*Joint Report with Commission on Meningitis (Reprint Number 411)

†Joint sponsorship with Commission on Streptococcal and Staphacoccal Diseases

‡Joint sponsorship with Commission on Immunization.

§No reprints available and joint sponsorship with the Commission on Immunization.

¥No reprints available

**Joint sponsorship with the Commission on Viral Infection.

††Joint sponsorship with the Commission on Influenza.

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SECTION 1—APPENDIX 1

ADMINISTRATIVE CHRONOLOGY

27 December 1940	Lieutenant.Colonel James S. Simmons transmitted letter prepared for the signature of Major General James C. Magee, The Surgeon General, recommending establishment of a "Board for the Investigation of Influenza and Other Epidemic Diseases in the Army."
11 January 1941	Secretary of War authorized the establishment of "The Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army."
6 February 1941	First meeting of Board; Dr. Francis Blake, President; Commissions on Influenza, Meningitis, and Pneumonia among the first seven commissions proposed. Influenza Commission to include "related acute respiratory diseases."
27–28 February 1941	Second meeting of Board. Drs. John H. Dingle and Alto E. Feller listed among 17 consultants for Commission on Influenza.
19 March 1941	Organizational meeting of Commission on Meningococcal Meningitis; Dr. Perrin Long, Director.
May 1941	Commission on Pneumonia activated; Dr. Colin M. MacLeod, Director.
19–20 June 1941	Third meeting of Board. A new commission on Cross Infections in Hospitals proposed; Dr. Oswald H. Robertson, Director.
26 June 1941	Now eight commissions. Memorandum to The Adjutant General summarized the investigations that The Surgeon General had determined "are required by the respective commissions." Board approved plan for study of coccoidioidomycosis at Army air fields in San Joaquin Valley by Commission on Epidemiological Survey to be centered in laboratory of Dr. Charles E. Smith at Stanford.
1 July 1941	Central laboratory for Commission on Meningococcal Meningitis established at The Johns Hopkins School of Hygiene and Public Health under direction of Dr. John J. Phair.
21 October 1941	Commission on Cross Infections in Hospitals met to prepare a program of investigation and budget.
29–31 October 1941	Representatives of Board (Dr. A. R. Dochez) and of the Commissions on Influenza (Dr. Yale Kneeland, Jr.) and Pneumonia (Dr. MacLeod), plus Dr. Kenneth Goodner surveyed epidemic of atypical pneumonia at Camp Claiborne, Louisiana.
28–29 November 1941	Fourth Meeting of Board. Board approves Dr. MacLeod's recommendation "that a team of investigators be sent to Camp Claiborne to investigate atypical pneumonia, etiology unknown."
9 December 1941	Dr. Dingle (Commission on Influenza) and Dr. W. Barry Wood, Jr. (Commission on Pneumonia) dispatched to Camp Claiborne.
January 1942	Group of investigators at Claiborne expanded by addition of Drs. G. John Buddingh and Feller (Commission on Influenza), Theodore J. Abernethy and James M. Ruegsegger (Commission on Pneumonia), Dr. Alexander D. Langmuir (epidemiologist), and George F. Badger (biostatistician) to form Commission for the Investigation of Atypical Pneumonia and Other Respiratory Diseases at Camp Claiborne.

12–13 May 1942	Fifth meeting of Board. Following report on atypical pneumonia by Dr. Dingle, Board recommended that provision be made for a year-round study of respiratory disease by a permanent commission. Commission on Tropical Diseases established; Dr. William A. Sawyer, Director.
19 July 1942	Dr. Blake, President of Board, Dr. A. R. Dochez, Board member, Brigadier General J. S. Simmons, administrator of Board, and Dr. Dingle consulted with Brigadier General. H. C. Coburn, Jr., Post Surgeon and Colonel Sanford W. French, Surgeon, Fourth Service Command at Fort Bragg, North Carolina.
24 July 1942	Board recommended to The Surgeon General that a Commission on Acute Respiratory Diseases (CARD) be established at Fort Bragg under the direction of Dr. Dingle.
1 August 1942	Commission on Acute Respiratory Diseases (CARD) activated. Initial members: Dr. Dingle, Director; Dr. Abernethy, Associate Director; Dr. Langmuir, Assistant Director; Drs. Badger, Feller, and Ruegsegger. Personnel were based temporarily at The Johns Hopkins School of Hygiene and Public Health.
15 August 1942	Decision made to establish a laboratory for CARD at the Station Hospital (later Regional Hospital) at Fort Bragg; ward building to be remodeled for this purpose.
19 October 1942	Activities of CARD centered at Fort Bragg.
31 August 1942	Dr. Phair succeeded Dr. Long as Director of Commission on Meningococcal Meningitis.
Late 1942	Allotment of 25 officers' ranks obtained by Preventive Medicine Division for assignment to the Board.
6–7 May 1943	Commission on Cross Infections in Hospitals renamed Commission on Air-Borne Infections (CABI); Dr. Robertson continued as Director.
November 1942–1943	Additional members added to CARD: Major Norman L. Cressy, Captain Hugh Tatlock, 1st Lieutenant. Elias Strauss and Drs. Charles H. Rammelkamp, Joseph W. Beard, and Irving Gordon. Dr. Beard remained at Duke University. Dr. Ruegsegger resigned for a commission in the Navy.
29 November 1943	CARD laboratory designated a Class IV installation under the Office of The Surgeon General.
November 1943	Military increment of officers for Board activities placed administratively under CARD at Fort Bragg.
29 November 1943	Laboratory established at Camp Carson, Colorado, by CABI, in collaboration with Commission on Hemolytic Streptococcal Infections.
July 1944	Work of Board military officers designated a miscellaneous War Department activity; allotment no longer charged to The Surgeon General.
November 1944	Laboratory at Camp Carson closed. Personnel and equipment moved to Madigan General Hospital, Fort Lewis, Washington.
August 1945	Army Medical Research and Development Board constituted to supervise and coordinate all research activities, including those of Army Epidemiological Board.
December 1945	Commission on Pneumonia terminated.

15 April 1946	Commission on Meningococcal Meningitis terminated.
15–16 April 1946	Eleventh meeting of Board. Commission on Environmental Hygiene directed to continue studies of Commission on Air-Borne Infections; CARD asked to incorporate activities of Commissions on Pneumonia and Streptococcal Infections.
30 June 1946	CARD Laboratory at Fort Bragg closed. Biological specimens transferred to School of Medicine, Western University, Cleveland, Ohio.
24 January 1949	Streptococcal Disease Laboratory established at Warren Air Force Base, Cheyenne, Wyoming, under direction of Dr. Rammelkamp.
21 February 1949	Secretary of Defense directed Secretary of the Army to assume responsibility for expanding the Board to reflect the needs of all three services.
26–27 February 1949	First formal meeting of revived Commission on Streptococcal and Staphlococcal (CSSD) Infections; Dr. William S. Tillett, Director.
2 March 1949	Secretary of the Army delegated responsibility for triservice coordination to The Surgeon General, Department of the Army.
19 April 1949	Name of Board changed to Armed Forces Epidemiological Board (AFEB).
29–30 September 1949	First annual meeting of AFEB.
8 October 1953	Secretary of Defense issued directive placing AFEB more firmly at Department of Defense level. This document became the "charter" for the AFEB.
January 1954	CARD established Laboratory on Housing and Illness at Sampson Air Force Base, New York; Dr. Harold B. Houser, Field Director.
1955	Dr. Feller succeeded Dr. Dingle as Director, CARD.
June 1956	Sampson Air Force Base closed. Records and biological specimens of Laboratory on Housing and Illness transferred to Upstate Medical Center, State University of New York at Syracuse.
1959	Members of CARD assisted in development of Virology Division at Naval Medical Field Research Laboratory, Camp Lejeune, North Carolina.
1959	Dr. William S. Jordan, Jr., succeeded Dr. Feller as Director, CARD.
1960	Members of CARD and Commission on Influenza began service on Adenovirus Committee, later designated Panel for Respiratory and Related Viruses, at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), to develop specifications for standardized reagents.
1961	Members of CARD prepare a *Manual of New Viruses Causing Respiratory Illnesses in Man*. World Health Organization requests permission to reproduce.
1963	Committee on Meningococcal Infections formed, Dr. Harry A. Feldman, Chairman. Dr. Feldman consulted on outbreak at Naval Training Station, San Diego, California.
1963	Members of CARD and Commission on Influenza appointed to NIAID's Board for Vaccine Development.

1964	Members of Committee on Meningococcal Infections consulted on outbreak at Fort Ord, California.
1967	Dr. Floyd W. Denny, Jr., succeeded Dr. Jordan as Director, CARD.
18 May 1971	Report of management survey of AFEB presented to AFEB and Commission Directors.
September 1971	Dr. George G. Jackson served as Acting Director for one year during Dr. Denny's sabbatical.
12 July 1972	AFEB and Commission Directors discussed management survey report.
1972	CARD explored the feasibility of developing a federally supported facility for vaccine research and development for certain vaccines that are not likely to be developed or marketed commercially.
18 December 1972	Report of Task Force to develop plan for a new advisory system for Army Medical Research and Development command submitted. New charter for AFEB adopted.
31 December 1972	All commissions terminated.
19 April 1973	First meeting of AFEB under new charter.

SECTION 1—APPENDIX 2

RESEARCH CHRONOLOGY

1941	A sharp increase in the number of cases of coccidioidomycosis was observed at military bases in southern California.
1942	Clinical, epidemiological, and etiologic studies of primary atypical pneumonia in military recruits at Camp Claiborne, Louisiana, confirmed it to be a common communicable illness, most likely caused by a new agent, probably a virus.
1942	An outbreak of a dengue-like illness with rash on legs (pretibial fever) was observed at Fort Bragg, North Carolina.
1942	Polysaccharides of types 1 and 2 pneumococci were shown to be immunogenic in humans.
1942	Investigators for Commission on Influenza repeated that an agent from cases of atypical pneumonia was transmissible to cotton rats and chick embryos.
1942	Pneumococci were identified as an important cause of pneumonia at the Army Air Base, later Army Air Force Technical School, Sioux Falls, South Dakota.
1943	A marked difference in the incidence of acute respiratory disease (ARD) between new recruits and seasoned soldiers was recorded during 3 consecutive years at Fort Bragg. Atypical pneumonia was continuously present with a 10 to 1 ratio of respiratory admissions to cases of pneumonia.
1943	A clinical illness that manifested as nonstreptococcal endemic exudative pharyngitis and tonsillitis was recognized that, except for the presence of exudate, did not differ from cases of ARD.
1943	Influenza A and B viruses were purified and characterized as particles consisting of lipoprotein with associated nucleic acid of the desoxypentose type, with sizes by electron microscopy of 77.6 μm (A/PR8), 78.3 μm (A/swine), and 97.3 μm (B/Lee).
1943	Studies at Camp Carson, Colorado, showed that there were 28% fewer hospital admissions for upper respiratory infections among soldiers housed in oil-treated barracks than among soldiers housed in untreated barracks and 16% fewer admissions for streptococcal infections.
1943	A rickettsialike organism was isolated from three of five guinea pigs injected with blood from a patient with "Fort Bragg or Pretibial Fever." It was not affected by human convalescent sera. Over 30 years later, it was found to be the first isolate of *Legionella* species; named *L. micdadei*.
1943	Atypical pneumonia was transmitted to volunteers using as inocula unfiltered throat washings and sputa obtained from patients early in the course of characteristic disease.
1943	Illnesses produced by a foodborne epidemic of type 5 streptococcus infection did not differ appreciably from sporadic or airborne cases of tonsillitis and pharyngitis caused by other types of streptococci at Fort Bragg.
1944	Titers of cold hemagglutinins in patients with atypical pneumonia were shown to be proportional to the severity of illness.

1944 Meningococcal carrier studies in an Army Medical Service Unit showed an average composite prevalence rate of 40%. Infections with at least one of several types were found in 92.9% of men during a 10-week study period. A single dose of 2 g of sulfadiazine reduced the carrier rate to zero without toxic reactions.

1944 Pretibial fever was recognized at Fort Bragg for the third consecutive year. A filterable agent was isolated in guinea pigs from the blood of one patient that differed from the rickettsia-like agent previously isolated. This presumed "virus" was serially transmitted in guinea pigs; able to infect hamsters, rabbits, and chick embryos; and neutralized by convalescent sera.

1944 Atypical pneumonia was transmitted to volunteers using bacteria-free filtrates as inocula.

1944 Epidemic evidence pointed to a single common exposure in a storm cellar as the source of a severe outbreak of an unusual form of pulmonary disease at Camp Gruber, Oklahoma; subsequently (1947) shown to be histoplasmosis.

1944 Studies of epidemic influenza A at Fort Bragg and Camp Mackall, North Carolina, were complicated by the appearance of epidemic ARD. The two diseases could be differentiated serologically. The incidence of pneumococcal pneumonia increased sharply at Camp Mackall but not at Fort Bragg; the incidence of atypical pneumonia remained constant.

1944 Members of the Commission on Influenza expanded their report on the isolation of a filterable agent ("Eaton agent") from cases of atypical pneumonia that could be propagated in chick embryos.

1944 Triethylene glycol vapor introduced into the air in scarlet fever wards reduced the number of β streptococci by 38% to 100%. The combination of vapor in air and dust control to floors and bedding resulted in a reduction of airborne streptococci of 93% when the wards were quiet and of 97% during bed-making periods.

1944 Oiling of floors and bedding at Fort Bragg effectively controlled the degree of bacterial contamination of air in treated barracks but had little or no effect on the incidence of hospitalized illness during the epidemic occurrence of ARD.

1945 Significantly lower incidence rates of respiratory disease were observed among men living in barracks equipped with double bunks than in control barracks. The procedures used in this study made possible the definition of distinct epidemiological patterns for influenza A, streptococcal pharyngitis, atypical pneumonia, and ARD.

1945 Vaccine containing pneumococcal polysaccharides types 1, 2, 5, and 7 greatly reduced the incidence of pneumococcal pneumonia at the Army Air Force Technical School, Sioux Falls, South Dakota.

1945 An epidemic illness among troops returning from Italy to Camp Patrick, Virginia, was identified as Q fever. The agent of "Balkan Grippe," later shown to be *Rickettsia (Coxiella) burnetii*, caused a laboratory outbreak of Q fever.

1945 A strain of meningococcus type 1 was made resistant to sulfadiazine by serial passage through fertilized eggs containing increasing concentrations of drug.

1945 CARD proposed a theory to explain the periodicity of influenza epidemics.

1946 Presumed agent of pretibial fever induced a similar clinical picture in patients undergoing fever therapy and did so on three successive passages.

1946 Only 6% of cases among recruits hospitalized at Fort Bragg were due to streptococcal infections; 90% were group A, 4% group C, and 3% group G.

1946 Two types of minor respiratory illness were demonstrated by transmission of filter-passing agents to volunteers. One with a long (5 to 6 days) incubation period (ARD) induced immunity to rechallenge; the other with a short (24 to 48 h) incubation period (common cold) induced no immunity to rechallenge. Cross-immunity was not demonstrable with either filtrate.

1946 An outbreak of coccidioidomycosis occurred when spores from a laboratory were disseminated throughout a medical school.

1946 Four of 350 strains of meningococci were found to be resistant to 0.5 mg.% of sulfadiazine. Epidemics of meningitis could still be aborted or prevented by prophylactic use of sulfadiazine.

1947 Investigators for the Commission on Virus and Rickettsial Diseases showed that presumed "virus" of pretibial fever induced illness in chimpanzees; "viremia" was demonstrated by transmission to another chimpanzee and to young hamsters.

1947 Studies of respiratory disease at Fort Dix, New Jersey, initiated jointly with Commission on Influenza, confirmed occurrence of cycles of ARD in recruits.

1947 Study of illnesses in a group of Cleveland, Ohio, families initiated.

1947 An investigator for the Commission on Immunization showed that fluorescein-labeled antibody can detect Eaton agent in bronchial epithelium of infected chick embryos. Sixty-seven percent to 92% of patients in several outbreaks of atypical pneumonia showed a rise of fluorescent-staining antibody during convalescence.

1948 The antibody response in humans after the injection of six type-specific pneumococcal polysaccharides was the same for each type as after the injection of fewer antigens.

1948 The mouse virulence of pneumococcal types 2, 3, and 7 was shown to correlate directly with the amount of specific polysaccharide synthesized.

1949 Study of streptococcal infections was initiated at Fort Francis E. Warren, Wyoming, under joint auspices of CARD and the CSSD.

1949 The "dangerous carrier" of β hemolytic streptococci was identified as a nasal carrier. Nasal carriers dispersed, on average, nearly 100 times as many streptococci as throat carriers.

1949 Human subjects injected 3, 5 to 6, or 8 years previously with type-specific pneumococcal polysaccharide usually showed measurable and sometimes relatively high levels of antibody after the periods indicated. In instances in which an antibody had disappeared or remained low, reinjection of homologous polysaccharide usually caused antibody to reappear or to increase, although rarely to the original maximum.

1949 Early penicillin therapy (relatively small doses) of pneumococcal pneumonia did not suppress the production of agglutinins or mouse protective antibodies.

1949 Three types of staphylococcal coagulase and anticoagulase were identified as being immunologically distinct.

1950 Nonbacterial gastroenteritis was found to be the second most frequent cause of illness in civilian families.

1950 Antihistamine drugs had no beneficial prophylactic or therapeutic effect on naturally occurring respiratory infections or on common colds transmitted to volunteers.

1950 It was demonstrated that rheumatic fever can be prevented by the treatment of exudative streptococcal pharyngitis or tonsillitis with penicillin.

1950 A case of poststreptococcal glomerulonephritis and hematuria in other members of a family of five provided the first clue that group A, type 12 streptococci are nephritogenic.

1951 The agent of pretibial fever was shown by Walter Reed Army Institute of Research (WRAIR) investigators to be similar to *Leptospira autumnalis*; it was subsequently designated *Leptospira interrogans*, serogroup *Autumnalis*, serovar *fort bragg*.

1951 Pneumococcal polysaccharides were shown to lack the capacity to induce a primary antibody response in rabbits.

1952 Rabbits immunized with pneumococcal whole-cell antigens were shown to respond to types 1 and 3 polysaccharides.

1952 Although there were fewer admissions for respiratory disease from oil-treated barracks than from control barracks, the differences in one study were not significant, and considerable numbers of hemolytic streptococcal infections continued to occur in oil-treated barracks.

1952 It was demonstrated that cortisone will reactivate group A streptococcal infections in rabbits as long as 3.5 months after intravenous inoculation of the bacteria.

1952 Stool supernates fed to volunteers induced two clinically different forms of gastroenteritis; no cross-immunity was demonstrated.

1953 Members of a group of Cleveland, Ohio, families experienced approximately 10 illnesses per person per year, approximately 65% being common upper respiratory infections. Gastroenteritis was responsible for 15% of the total.

1953 Cytopathogenic agents isolated by NIH investigators from human adenoids and by WRAIR investigators from patients with acute respiratory disease at Fort Leonard Wood, Missouri, were shown to be multiple types of similar viruses; subsequently named adenoviruses.

1954 Twenty-eight percent of strains of meningococci were now resistant to sulfadiazine.

1954 The adenovirus isolated at Fort Leonard Wood (RI-67; type 4) was related etiologically to ARD illnesses induced in volunteers at Fort Bragg by tests with stored sera.

1954 A small epidemic of nonbacterial pharyngitis caused by adenovirus type 3 was documented in Cleveland, Ohio, families.

1955 Adenoviruses types 3, 4, and 7, particularly type 4, were shown to be the most important cause of ARD in military recruits.

1955 No adenovirus type 4 infections were identified at Army or Navy military academies.

1955 An investigator sponsored by the Commission on Immunization reported that the "virus" (Eaton agent) of atypical pneumonia could be demonstrated in the lungs of chick embyros by the use of fluorescein-labeled antibody.

1955 Lesions indistinguishable from the generalized Shwartzman reaction (GSR) occurred in rabbits when a single intravenous (IV) injection of endotoxin was accompanied or followed by an injection of synthetic, heparin-like, polymers.

1955 No differences were observed between men housed in open-bay or closed-bay barracks in hospital admission rates for adenovirus infections, influenza, and streptococcal infections.

1956 As measured by antibody acquisition, infection with adenovirus types 1 and 2 are common in the first 5 years of life, less so types 5 and 6. Children aged 1 to 18 years had no type 4 antibody.

1956 A Formalin-killed bivalent adenovirus vaccine developed by WRAIR, containing types 4 and 7, was effective in reducing the incidence of cases requiring hospitalization at Fort Dix.

1956 A Formalin-killed trivalent adenovirus vaccine (types 3, 4, and 7) reduced febrile respiratory illnesses at Great Lakes Naval Training Center, Illinois, by an estimated 50% to 75%.

1956 The level of complement-fixing antibodies in patients with coccidioidomycosis whose disease became disseminated remained elevated and indicated a poor prognosis.

1956 Gamma globulin in doses of 3, 6, 9, or 15 mL reduced hospital admissions for acute nonstreptococcal disease. Illness, but not infection, caused by adenovirus types 4 and 7, was prevented. Later, doses of 5 to 15 mL again protected against adenovirus infections, but not against influenza A.

1956 Chilling of volunteers given infectious nasal secretions had no effect on the frequency of colds nor did the presence or absence of tonsils. Volunteers with an allergic history were slightly more susceptible (45% vs 31%), as were smokers (55% vs 34%).

1956 An IV injection of papain caused rabbit ears to collapse within 3 to 4 hours.

1956 A review of the longitudinal study of influenza in families showed that during influenza A (H_1N_1) epidemics in 1950, 1951, and 1953, viruses were isolated from 9% to 12% of individuals and from 25% of families. In 1950, the serologic attack rate was 15%; in 1951 and 1953, it was 25%.

1956 Inactivated bivalent types 4 and 7 adenovirus vaccine developed at WRAIR reduced hospitalized cases caused by these agents by 98% at Fort Dix.

1956 Growth of the first rhinoviruses in cell culture was reported by investigators at Hopkins (JH virus) and at Great Lakes Naval Training Station (2060 virus). The isolates were similar and became prototypes for type 1.

1957 Rechallenge of 55 volunteers with either JH or 2060 viruses resulted in 5% colds compared to 38% colds on first challenge.

1957 Experimental colds developed in approximately 35% to 40% of young adults following a single challenge with infectious secretion. Neither sex nor season altered susceptibility. The incubation periods were 24 to 72 hours. Illnesses were rarely associated with

fever. Pooled human immune globulin was 65% affective in neutralizing two infectious secretions.

1957 A team composed of representatives of the Commission on Influenza, CARD, Navy, and the Pan American Health Organization visited laboratories in South America to assess their capacity to study the anticipated epidemic of Asian influenza before its arrival in the United States.

1957 An Influenza Study Group was organized by CARD and the Commissions on Influenza and Streptococcal Diseases to obtain early information on pandemic Asian (H_2N_2) influenza. It reported that influenza in Santiago and Concepcion, Chile, during July and August was accompanied by a high rate of pulmonary complications and a two-fold increase in deaths.

1957 The observation of Cleveland, Ohio, families that had been discontinued was reinstituted in September in anticipation of an epidemic due to the new influenza A variant (H_2N_2). Infection occurred in 90% of families and in 47% of individuals. There were no fatal cases in the families.

1957 Asian influenza caused fulminant, fatal cases in the Cleveland, Ohio, community. Virus was isolated from the lung or trachea of 25 of 33 patients and from extrapulmonary organs in 3 of the 25.

1958 Review of volunteer experiments involving 1,034 subjects showed that installation of one of five infectious secretions obtained from patients with a common cold gave specific protection against the development of a cold when the same secretion was instilled up to 45 weeks later, whereas there was no protection against a cold produced by any other secretion.

1959 Intravenous amphotericin B produced a favorable response in three-quarters of patients with progressive primary coccidioidomycosis and led to complete remission in 5 of 47 patients with meningitis.

1959 Tissue culture technology permitted the isolation of many new viruses from respiratory (parainfluenza types 1, 2, and 3; respiratory syncytial; coxsackie) and gastrointestinal (enteroviruses or enteric human orphan [ECHO] and reoviruses) tracts, creating a "viral smog."

1960 Fluorescent-stainable antibody responses to Eaton agent, measured in infected chick embryos, were detected in convalescent sera collected in 1944 from volunteers who developed atypical pneumonia during transmission experiments. Because volunteers who had no illness or minor illness also developed such antibody responses, proof of the etiologic role of Eaton agent could not be established.

1960 Studies of respiratory illnesses in recruits at the Marine Recruit Depot, Parris Island, South Carolina, using fluorescent-stainable antibody in Eaton agent-infected chick embryos showed that 68% of patients with atypical pneumonia developed evidence of infection versus 6% with no illness.

1960 Eaton agent was shown to be inhibited by gold salts and to grow as minute coccobacilli in chick embryos and tissue, leading to the conclusion that the agent is not a virus but a member of the genus *Mycoplasma* (pleuropneumonia-like organisms).

1961 Three soluable antigens were separated from cells infected with type 5 adenovirus: "early eluting" (type specific), "late eluting" (group specific), and "toxic," also group specific. The antigens were produced before infectious particles and were precursors of such particles.

1961 Of 68 coccidioidomycosis patients with nonmeningeal dissemination treated with amphotericin B, 68% had favorable results. Improvement occurred more often (88%) in those who underwent a fourfold reduction in CF titer than in those who did not (33%).

1961 It was shown that saline-soluble deoxyribonucleic acid (DNA) is produced as a requirement of adenovirus synthesis and is a precursor, if not a subunit, of the virus. The accumulation of "surplus" DNA and protein results in the formation of the nuclear inclusion bodies that are the hallmark of adenovirus-infected cells.

1962 Eaton pleuropneumonialike organism (PPLO) was recovered directly on agar from 12 of 13 serologically positive patients with atypical pneumonia. The isolates produced distinctive colonies on an agar-yeast extract-horse serum medium.

1963 Eaton PPLO was designated *Mycoplasma pneumoniae.*

1963 Types 4 and 7 adenoviruses grown in human embryonic kidney cell culture were shown to selectively infect the lower intestinal tract when virus was administered in enteric-coated capsules.

1963 Sulfadiazine failed to reduce carrier rates of meningococci among recruits at the San Diego Naval Training Center. Cases of meningitis continued to occur despite mass prophylaxis.

1964 An epidemic of meningococcal meningitis at Fort Ord, California, was linked to cases that occurred first in the civilian community of California away from the base, rather than vice versa.

1964 Now 53 rhinovirus serotypes.

1964 Effectiveness of different lots of inactivated adenovirus vaccine, both aqueous and adjuvant, shown to vary in trials at Great Lakes Naval Training Station.

1964 Biosynthesis of ribonucleic acid after adenovirus infection was shown to be essential for production of virus-specific DNA, virus antigens, and infectious particles.

1964 Interferon was demonstrated in the dermal cells of vaccinia lesions of humans and in acute sera from 7 of 51 patients with clinical viral infections.

1964 Type 4 adenovirus grown in human diploid fibroblast cell culture was shown to selectively infect the lower intestinal tract, stimulate moderately high levels of neutralizing antibody, and not spread to susceptible contacts.

1964 Live type 4 adenovirus vaccine given to Marine recruits at Parris Island prevented type 4 infection when the recruits were transferred to Camp Lejeune, North Carolina, where type 4 infection was epidemic.

1965 Amantadine given 20 hours before challenge protected a volunteer with a low level of antibody against intranasal challenge with live influenza A virus.

1965 Fifty percent of civilian strains of meningococci were now resistant to 1 mg·% or more of sulfadiazine. Penicillin treatment of meningitis was recommended.

1965 An inactivated *M. pneumoniae* vaccine prepared by NIH investigators induced resistance to multiplication of mycoplasma in the lung of vaccinated hamsters and was well-tolerated by 36 human subjects.

1966 Inactivated *M. pneumoniae* vaccine induced growth-inhibiting antibody in 10 of 19 volunteers who initially lacked this antibody; challenge with live *M. pneumoniae*-induced illness in 1 of 10 men who responded to vaccine, in 7 of 9 men who did not respond, and in 10 of 13 controls who lacked antibody.

1966 *M. pneumoniae* infections were detected in 36 of 114 families in Seattle, Washington. Transmission occurred in 23 of 36 families, with 84% of children and 44% of adults becoming infected. Tetracycline treatment did not abolish the carrier state.

1966 In a field trial of adenovirus type 4 vaccine conducted at Fort Dix by WRAIR investigators, suppression of type 4 virus fostered the emergence of type 7 virus in the immunized population.

1966 Adult employees in an industrial population experienced an average of 2.3 respiratory illnesses per year during a 3-year period. Rhinoviruses accounted for 25% of the illnesses. Recurrent annual fall peaks of illness occurred during which rates of rhinovirus isolation exceeded 45%.

1966 A microneutralization test was developed for identification of rhinovirus serotypes.

1967 Neutralizing antibody responses were measured in 77% of paired serum specimens from patients with rhinovirus illness; only 5% had hemologous titers of eight or more in the acute phase of illness.

1967 Use of 73 different antisera then available successfully typed three-quarters of the rhinovirus isolates collected in Charlottesville, Virginia, over a 3-year period. Forty-eight different types were identified; 61 strains were untyped. The most frequent isolate, type 14, was associated with only 8.4% of rhinovirus illnesses. Multiplicity of serotypes dimmed prospects for an effective vaccine.

1967 Only 3 of 59 male volunteers given a Formalin-killed spherule vaccine of *Coccidioides immitis* developed a serologic response.

1968 Continued observation of recurrent fall peaks of rhinovirus illnesses in families showed no demonstrable effect of school openings on peak illness rates in working adults with school children compared to those without school children.

1968 Studies of childless young married couples showed that enteric live adenovirus type 4 vaccine spread between partners without producing illness.

1968 Enteric live adenovirus type 4 vaccine given to mothers of 22 military families with children spread to only 1 of 8 nonimmune fathers and 1 of 64 children. In 26 similar families, vaccine virus given to a child spread to 3 of 23 nonimmune parents and to 5 of 49 siblings but induced no illness.

1969 In a prospective study of military recruits at Fort Dix, investigators at WRAIR found that 51 of 54 cases of meningococcal meningitis were deficient in antibodies to homologous and heterologous strains of pathogenic meningococci. The group-specific polysaccharides of group A and group C meningococci were purified and shown to be excellent immunogens in six human volunteers.

1969 Navy investigators showed that group C meningococcal polysaccharide vaccine prevented the acquisition of group C meningococci by Marine recruits at San Diego, California. Three cases of meningococcal disease occurred among more than 3,000 controls but none among a similar number of vaccinees.

1969 WRAIR investigators demonstrated that group C vaccine effected an 87% reduction in group C disease in 13,763 Army recruits at five basic training centers.

1969 In a hamster model of *M. pneumoniae* infection, previous infection precluded pneumonia in all animals, but parenteral vaccines were not protective despite high serum antibody titers.

1970 Hamsters immunized with a chemically induced, temperature-sensitive attenuated mutant of *M. pneumoniae* developed resistance to pneumonia only after intranasal infection. The level of serum antibody did not correlate with protection.

1970 A combined groups A and C meningococcal vaccine was shown to be immunogenic in greater than 90% of children 4 to 12 years of age.

1970 *M. pneumoniae* was isolated from 38% of recruits at Great Lakes in late summer.

1970 Simultaneous immunization of recruits at Fort Dix with both live adenovirus type 4 and type 7 vaccines during an outbreak of ARD caused by type 7 led to 96% suppression of type 7-associated ARD hospitalizations.

1971 At Great Lakes, meningococcal carrier rates, predominantly group Y, were as high as 70% during the winter of 1970 and 1971. Subsequently, group C became predominant at Great Lakes and Orlando Naval Training Stations.

1971 On 19 May the AFEB recommended that type 4 adenovirus vaccine be administered to recruits and advanced training personnel of all services and that type 7 be evaluated further for clinical effectiveness.

1971 Electron micrograph studies of hamsters showed that a differentiated portion of *M. pneumoniae*, consisting of an extension of the unit membrane containing an electron-dense core surrounded by a lucent space, serves as the means of attachment to host cell membrane.

1971 In a field trial among students at Lowry Air Force Base,Colorado, rifampin given orally in a daily dose of 600 mg for 4 days to 47 carriers of meningococci proved to be 94.7% effective in eradication of nasopharyngeal carriage. Four rifampin-resistant strains were identified during the follow-up period. Emergence and spread of resistant strains were also documented at Great Lakes and Camp Lejeune.

1971 During the peak month of influenza (A_3/Hong Kong/68) activity at Lowry Air Force Base, serologic evidence of meningococcal infection was over five times as frequent among those who concurrently had serologic evidence of influenza infection than in those who did not. There was no such correlation with adenovirus infection.

1971 During an 8-year study of working adults in Charlottesville, Virginia, 4% of all colds and 8% of winter and spring colds were serologically related to infection with coronaviruses 229E and OC43.

1972 Routine administration of group C meningococcal polysaccharide vaccine was instituted for all incoming military recruits. Bivalent A and C vaccine was licensed for selective use in 1975 and administered to all recruits in 1979. Use of tetravalent (A, C, W-135, and 4) vaccine was instituted in 1982.

1972 Two doses of inactivated *M. pneumoniae* vaccine were administered 77 days apart to 12 antibody-negative and 6 antibody-positive children. Few or no rises in antibody titer were detected in those who were antibody negative and only minimal increases developed in those with preexisting antibody.

1973 On 13 September, the AFEB recommended that vaccine containing both adenovirus types 4 and 7 be administered by all three services to recruits and advanced training personnel.

SECTION 2

Commission on Influenza

Dedicated with respect and grateful appreciation to Thomas Francis, Jr., founder and first commission director. He contributed so much to our understanding and control of influenza. Dr. Francis' pioneering work and wise counsel were instrumental in making possible a vaccine that played a major role in controlling influenza and preventing it from becoming a significant health hazard in the military services during World War II and thereafter.

Foreword

The specter of epidemic diseases, such as influenza and pneumonia, during World War II was the major stimulus that led to formation of the Armed Forces Epidemiological Board (AFEB) in 1940, called originally "The Board for the Investigation and Control of Influenza and Other Epidemic Diseases" in the Army. Its success was practically ensured simply because there was great need for solution of these always threatening epidemiological scourges for the military services and the general public. Moreover, there were key and well-informed medical scientists in America who were poised and anxious to serve their country. *Need* and *desire* are impelling ingredients for success of any venture.

A decision of great and lasting importance was the choice of Thomas Francis, Jr., a product of Yale, New Haven, Connecticut; the Rockefeller Institute, Princeton, New Jersey; and the University of Michigan, Ann Arbor, to organize and direct a team effort directed toward control of influenza. Simultaneously with directing this effort, he participated as a "sleeves rolled up" investigator. There is an old adage that says, "if you want to solve a difficult problem, ask a busy person to do it." This epitomized Francis. Impressive, in so many ways, was his insight into the solution of pressing problems sparked always by his epidemiological sense and his clinical astuteness. These attributes enabled him to help determine the proper roads to take and which routes to abandon.

The team of Commission on Influenza members that he led was the best possible group ever to be assembled, and it is to their great credit and his strong and wise guidance that the work of the Commission helped relegate influenza to the realm of effectively controlled infections. Dr. Francis' dedicated associate and friend, Fred Davenport, succeeded him as Director and Dr. Davenport, in turn, was followed by Gordon Meiklejohn, who directed activities of the Commission until its termination in 1973. Dr. Meiklejohn continues to perform surveillance evaluations that afford valuable data regarding antigenic changes through studies performed at the Lackland Air Force Base, San Antonio, Texas. This information has been most helpful in selecting the proper types of influenza virus to be incorporated in new vaccines from year to year.

This success story on influenza is an example of coordinated effort and cooperation between academically oriented and military scientists who collectively spearheaded a major effort aimed at the solution of a common health problem. Influenza, although not fully eradicated, is now effectively controlled when the public accepts and follows the available guideline recommendations. The military has a simple built-in mechanism for controlling influenza—military personnel all take the influenza vaccine.

A very important spin-off of the accomplishments of the Commission on Influenza has been the training and development of a hard core of medical investigators and educators who have filled and now grace many important professorships in our leading educational institutions. They continue to serve the Department of Defense and Public Health Service through their wise advice in determining the character of influenza vaccines and other means of control, all of which are persistent problems requiring ceaseless evaluation.

Grateful appreciation is expressed to Dr. Meiklejohn for preparing this history, which is now a document of historic and lasting importance. Ms. Patricia Graves, his devoted Research Associate, has our sincere thanks for helping re-

trieve much valuable information from numerous files, correspondence, reports, and reprints. Colonel Robert Wells and Ms. Jean Ward aided materially in this search. Without such contributions, this history would not have been completed.

— *Theodore E. Woodward, M.D.*

History of the Commission on Influenza

Gordon N. Meiklejohn, M.D.

PREFACE

When Dr. Theodore Woodward first contacted me about writing a history of the Commission on Influenza, I was somewhat overwhelmed by the prospect. As I thought about it more, it seemed to me very important to have a record of the accomplishments of this remarkable group. I had been involved in the 1943 field trials in which the influenza A vaccine was first shown to be effective in a massive field trial and have continued to work on the control of influenza in the Armed Forces up to the present time. The only other two survivors of the early days of the Commission, Drs. Jonas Salk and Edwin Lennette, have since left the influenza field.

It seemed to me that the best source of information would be the massive annual reports of the Commission. I contacted Colonel Robert A. Wells, Executive Secretary of the AFEB. He made a major effort to find them and came up with a number of the reports, but many were missing and could not be found anywhere. He was most helpful, and the reports that were found were invaluable. He provided me with a history of the first 5 years of the Commission, which Dr. Francis had written in 1945, that covered the early years very well. There still were many gaps in the story, particularly during the 1950s and 1960s. Consequently, I turned to Dr. Hassan Maassab in Ann Arbor, Michigan, for assistance. He did not have the full Commission reports but was able to provide me with the Director's summaries of all years from 1950 to 1970. From this source material I was able to find most of the main points of activity. The reader, however, must be aware of the fact that the Director's Commission reports may have been somewhat biased presentations. I may have added a bias of my own in trying to pick out what was important for the mission of control of influenza in the Armed Services. To any individuals who feel their contributions were not rightly recognized, I apologize.

At the time when the Commission began its studies there was a great deal of uncertainty and fear about what influenza might do as mobilization increased. Memory of the disaster of 1918 and 1919 was bright in the minds of many of the senior Preventive Medicine Officers and in the minds of Drs. Francis, Francis Blake, and Stanhope Bayne-Jones, who had a large part in the early organization of the Commissions. This concern is reflected in the name that they gave to the original Board, namely the "Board of the Control of Influenza and other Epidemic Diseases in the Army."

When the Commission activities began in 1941, relatively little was known about influenza. Influenza B had been discovered only a couple years earlier by Dr. Francis. The agglutination of chicken red blood cells had just been described by Dr. George Hirst in New York and Drs. Ronald Hare and L. McClelland in Toronto. Before that time, the laboratory diagnosis of influenza was based on the isolation of virus in ferrets or by complement fixation tests. The latter were not widely used. Elsewhere, during the epidemic, efforts were made to use clinical criteria to make a diagnosis, and it was obvious that these efforts were not satisfactory. Neutralization tests were carried out only in mice. These were expensive and required an enormous number of animals at a very considerable cost in dollars, time, and effort. The notions of epidemiology of influenza were rigid, and it was believed that influenza would reoccur every 2 years. This was a source of considerable concern because 1942 was supposed to be a year when an epidemic of influenza would occur.

The expected epidemic did not materialize, and to save time, Drs. Francis and Salk with their colleagues at the University of Michigan conducted a series of rather remarkable and daring experiments. They sprayed large amounts of wild influenza virus into the nasal passages of large numbers of

"volunteers" from mental institutions in Michigan. The recipients developed influenza within a very short period of time with typical symptoms and many developed ≥4 fold increases in antibody titers. Performed today, experiments of this type would be considered highly unethical. Fortunately, no one was seriously harmed by the virus challenge. In another experiment, conscientious objectors were challenged with large amounts of wild virus to determine whether an aerosol of immune serum could protect against the virus as the Russians had claimed. None of the study participants became seriously ill. Much was learned about the immunity to influenza, and it was clear that immunity was far from solid. This led the Commission to minimize its efforts to develop an attenuated live vaccine because it appeared that even infection by wild virus would not provide solid protection for much longer than 4 months. The Surgeon General of the Army at that time was especially concerned that an attenuated live virus vaccine might revert to a virulent virus of the type that caused such havoc in 1918 and 1919.

In military personnel it was accepted practice to divide troops on a random basis into vaccinated and control groups and to administer placebo injections to the controls. Field trials have never been better controlled. Once the vaccine had been declared to be effective, it was considered unethical to withhold vaccine from any member of the Armed Services. This policy was accepted by the Army in 1970.

Apart from the scientific contributions made by the members, associate members, and persons holding contracts supported by the Commission, something must be said about the personal qualifications and personal relationships of the members of the Commission. Dr. Francis served as Director of the Commission from its inception until 1957. He was admired and liked by all members of the Commission and his military colleagues. Dr. Davenport served as Director from 1957 to 1970. He also had extreme dedication and moved the Commission activities along very well. The morale of the group was exceptionally high, and the early members took on any assignments thought necessary by the Commission as a whole. They were a remarkable group of professionals who worked together in their common effort to solve a major health problem. It is hard at the present time to realize that the Commission members received no financial compensation apart from the small honorarium for each day of the meetings that they attended each year. This fact alone attests to their interest in and dedication to the public welfare.

Preparation of this history has been a time-consuming effort, but well worth it. As references were found, I could not resist reading many of them from beginning to end. All persons interested in immunity to influenza should be familiar with these early studies.

Finally, a word of appreciation must be expressed to a number of persons who were most helpful in this enterprise. Assistance provided by Colonel Wells, Executive Secretary of the AFEB, and Dr. Maassab, Professor of Epidemiology at the University of Michigan School of Public Health, Ann Arbor, has already been mentioned, and their help is again acknowledged. I am certain that all members of the Commission recognize the assistance provided by a series of Executive Secretaries of the AFEB, and particularly by Ms. Betty L. Gilbert, the Board's long-term secretary. Dr. Woodward has been most helpful and supportive in encouraging me to prepare this manuscript and in reviewing an earlier draft. Ms. Pat Graves has been exceptionally helpful, particularly in finding many of the earlier references and in the assistance in the whole project.

You will note that in some instances we were unable to find references in published articles and were forced to refer to the Director's Summary of the Annual Commission reports. Anyone who wishes to pursue further details can contact me. Every attempt will be made to provide additional data.

INTRODUCTION

The Board for the Investigation of Influenza and Other Epidemic Diseases was created on 11 January 1941. During 1940 the United States had experienced a large increase in the number of recruits

introduced into the armed services in response to the war in Europe. A number of thoughtful medical authorities in the armed services, who recalled the disastrous epidemics, particularly influenza, during and after World War I, felt a need for additional assistance in developing new methods for coping with the potential risks and problems. The solution recommended was organization of Commissions made up of civilian scientists who were active in research and were well-informed of the needs in specific areas. It was conceived that Commission members would work side by side with their military counterparts in attacking these problems. Twelve Commissions were initially envisioned. Invitations were extended to highly qualified health professionals to direct these commissions and to arrange control programs required to meet projected needs.

On 10 February 1941 Dr. Blake, President of the Board, invited Dr. Francis, professor of epidemiology at the University of Michigan, Ann Arbor, to organize and serve as director of the Commission on Influenza. The invitation was immediately and enthusiastically accepted.

The original Board was called the Board for Investigation and Control of Influenza and Other Epidemic Diseases in the Army. In 1949 the name was changed to the Armed Forces Epidemiological Board.

Approximately 30 highly qualified scientists with backgrounds as epidemiologists, virologists, and educators whose interests covered wide ranges of disease categories were recruited from various areas in the United States. Each was appointed as a Consultant to the Secretary of the Army. The common goal was to detect outbreaks of influenza and institute control measures. The original Commission members and their host institutions were

Hattie E. Alexander, M.D.
College of Physicians and Surgeons, Columbia University, New York

Gaylord Anderson, M.D.
University of Minnesota Medical School

M. Dorothy Beck
California State Department of Health, Berkeley, California

John W. Brown, M.D.
University of California Hospital

G. John Buddingh, M.D.
Vanderbilt University Medical Center, Nashville, Tennessee

Frank A. Calderone, M.D.
New York City Department of Health, New York

Paul R. Cannon, M.D.
University of Chicago Medical School

John H. Dingle, M.D.
Thorndike Memorial Laboratory

Monroe D. Eaton, M.D.
California Department of Health

Alto E. Feller, M.D.
University of Iowa Medical School

Francis B. Gordon, M.D.
University of Chicago Medical School, Chicago, Illinois

Irving Graef, M.D.
New York University College of Medicine, New York

William H. Hale, M.D.
The George W. Hooper Foundation, San Francisco, California

George K. Hirst, M.D.
Rockefeller Institute

Frank L. Horsfall, M.D.
Rockefeller Institute

Louis A. Julianelle, Ph.D.
Washington University Medical School, St. Louis, Missouri

Dr. Yale Kneeland
College of Physicians and Surgeons
Columbia University

Clayton G. Loosli, M.D.
University of Chicago Medical School
Chicago, Illinois

Thomas P. Magill, M.D.
Cornell University Medical School, New York, New York

Robert A. Moore, M.D.
Washington University Medical School
Saint Louis, Missouri



FRANCIS BLAKE, M.D.

When he rebuilt the Yale University School of Medicine, Dean Milton Winternitz was fortunate to attract Dr. Francis Blake, a Harvard Medical School graduate, to New Haven. Schooled in internal medicine, Dr. Blake ultimately chaired the Department of Medicine at Yale for 3 decades and he simultaneously served the School of Medicine as its Dean. Francis Blake was the compleat physician, an academician in the fullest sense; he was a teacher who taught by precept, a clinician accomplished in diagnosis, and a leader in curative and preventive medicine. Additionally, he was an accomplished clinical investigator and researcher in infectious diseases, particularly influenza, pneumonia, viral diseases, and the scrub typhus fevers.

It is no surprise that the original AFEB succeeded; it was blessed with the membership of accomplished clinicians and medical scientists such as J. Steven Simmons, Stanhope Bayne-Jones, and Colin MacLeod, and the presidential leadership of Francis Blake.



THOMAS FRANCIS, JR., M.D.

Thomas Francis graduated from Yale University School of Medicine where he was a protégé of Dr. Francis Blake, who introduced him to the field of infectious diseases, particularly influenza and pneumonia. This relationship led to Dr. Francis's being "passed on" to serve under Rufus I. Cole, chief of the hospital of the Rockefeller Institute in New York. At the Rockefeller Institute, Francis worked with Thomas M. Rivers, William T. Tillett, Oswald T. Avery, Homer T. Smith, Colin MacLeod, Joe Smadel, and Frank Horsfall. His interests were directed to the field of virology and, specifically, to influenza. He is credited with having been the first scientist to isolate the influenza virus in this country, in 1935. His contributions to the field of influenza research included his clarification of the antigenic shifts that characterize this complicated virus. He directed the Department of Epidemiology in the School of Public Health at the University of Michigan, where he gained national prominence when he designed the trials for, and analyzed the results of, the Salk poliomyelitis vaccine. Jonas Salk was one of his protégés.

In 1941, Thomas Francis was chosen to be the first Director of the Commission on Influenza of the AFEB. The contributions of this Commission to the prevention and control of influenza with biological vaccines is a remarkable achievement in American medicine. He was proud that his associate, Dr. Fred Davenport, succeeded him as Director of the Commission on Influenza. From 1958 to 1960, Dr. Francis was President of the AFEB.



ORIGINAL AFEB, 1942

The original members of the Board for the Investigation and Control of Influenza and Other Epidemic Diseases
12–13 May 1942

Front row, left to right: Dr. Oswald F. Avery; Colonel J. Steven Simmons; Dr. Francis G. Blake, President of the Board; Lieutenant Colonel Stanhope Bayne-Jones, Administrator; and Dr. Ernest W. Goodpasture.

Second row, left to right: Dr. Kenneth F. Maxcy; Dr. A. R. Dochez; Dr. Andrew J. Warren; and Dr. O. H. Perry Pepper.

Norman Plummer, M.D.
Cornell University Medical College
New York, New York

Elsmere R. Rickard, M.D.
Minnesota Department of Health
Minneapolis, Minnesota

James F. Rinehart, M.D.
University of California Medical School
Saint Louis, Missouri

Oswald H. Robertson, M.D.
University of Chicago Medical School
Chicago, Illinois

Jonas E. Salk, M.D.
University of Michigan
Ann Arbor, Michigan

Wilson G. Smillie, M.D.
Cornell University Medical School
New York, New York

Douglas H. Sprunt, M.D.
Duke University Medical School
Durham, North Carolina

Dr. W. M. Stanley, Ph.D.
Rockefeller Institute
Princeton, New Jersey

Ernest L. Stebbins, M.D.
College of Physicians and Surgeons
Columbia University
New York, New York

Members of this group met on a number of occasions and developed a program to be presented to the Board. The composition of this group was reduced to a more efficient size in 1943 when the Commission on Influenza consisted of the following members:

Monroe D. Eaton, M.D.
California Department of Public Health
Berkley, California

George K. Hirst, M.D.
Cornell University of New York Medical and Dental Colleges
New York, New York

Norman Plummer, M.D.
Cornell University and New York Medical and Dental Colleges
New York, New York

William M. Hale, M.D.
University of Iowa
Iowa City, Iowa

Thomas Francis Jr., M.D.
University of Michigan
Ann Arbor, Michigan

Jonas E. Salk, M.D.
University of Michigan
Ann Arbor, Michigan

Elsmere R. Rickard, M.D.
University of Minnesota
Duluth, Minnesota

The Commission was heavily weighted with former associates of Dr. Francis at the Rockefeller Institute where much of the early work on the influenza virus had been conducted. Throughout this period, the Rockefeller Foundation continued to provide personnel support to a number of Commissions.

An outline of the plan presented to the Board on 27 and 28 February 1941 was as follows.

Outline for Plan of Commission on Influenza —
Presented to the AFEB on 27 and 28 February 1941

I. Study of Control Measures
   1. Hygienic and Environmental Controls
      a. Influence of housing, size of cantonments, troop movements.
      b. Isolation of individual or post; the use of masks.
      c. Disinfection sterilization of dishes, sterilization of air with aerosols or ultraviolet light.
   2. Specific Control
      a. The efficacy of vaccination against influenza virus infection in man.
      b. Prophylactic use of immune serum.

II. Study of Epidemics
   1. Clinical
      a. Attempts to establish clinical criteria for differentiation of disease caused by different types of influenza virus or by other agents.
      b. Possible study of chemoprophylaxis or bacterial complications.
   2. Epidemiological
      a. To ascertain incidence of immune, subclinical, and clinical cases in correlation with laboratory studies.
      b. The method of introduction, the factors influencing spread, and the patterns of epidemics.
   3. Bacteriological
      a. To determine whether any particular bacterium constantly accompanies influenza virus infection.
      b. Concentrated study of *H. influenza*.
      c. Significance of bacteria as superimposed infections during the course of the disease.
   4. Virus
      a. To identify virus in epidemics, especially in recurrent waves, and the relation of illness to the immunological state.
      b. To evaluate the importance of factors other than circulating antibody in resistance.
      c. To institute prophylactic measures.
      d. To ascertain complications caused by virus alone.
   5. Pathological
      a. To correlate the picture in fatal cases with etiologic studies.
      b. To search for diagnostic criteria when illness was not caused by known virus.
   6. Cooperative studies with other Commissions, especially in the fields of complications and chemotherapeutics.

The proposed program for the Commission on Influenza was developed and discussed with the Board along with a proposed budget estimate in the middle of April 1941. The organizational plan provided for geographic coverage of all parts of the country. The Commission planned to function during a specific outbreak by utilizing the laboratories of the State of New York and the Rockefeller Institute to cover epidemics in the first, second, third, and fourth Army areas. The Midwestern group, centered at the University of Chicago, would serve the fifth, sixth, seventh, and eighth Army areas. The ninth corps in the western states would be covered by the laboratory in the California Department of Health at Berkeley, California.

Among the goals recommended were (*a*) t o study the protective efficacy of vaccines; (*b*) to investigate air sterilization by aerosols; (*c*) to study the effectiveness of masks to control infection; and (*d*) to collect data on the clinical, pathological, and bacteriological aspects of the investigation. In addition, during field studies, epidemiological data would be collected on the character and dissemination of the illnesses, the type of influenza virus involved, pathological studies on fatal cases, and evaluation of various forms of treatment.

A series of recommendations was made to provide for one mobile laboratory in each of the geographic divisions and to integrate studies with those of other Commissions, such as the Commissions on Pneumonia, Streptococcal Diseases, and Epidemiological Survey. It was also proposed that a trial mobilization be organized as soon as possible to test the mechanisms by which the Commission might function in the event of an epidemic. It was considered essential that the investigative units work at the site of the outbreak in collaboration with the appropriate medical armed forces personnel.

The original proposal called for a total budget of $53,200 for each of the three units, for a total of $159,600 to be utilized as follows:

Proposed Budget for One Division for 1 Year

(a)	Commission travel	$ 6,000
	Commission per diem	6,000
		$ 12,000
(b)	Technicians and secretaries	
	16 part time (average 4 months, at $1,800/year)	$ 9,850
	2 full time	3,200
		$ 13,050
(c)	Expendable supplies	
	Media, glassware, instruments, etc.	$ 10,475
	Animals	7,500
		$ 17,975
(d)	Durable equipment	
	Icebox, incubator, microscopes, etc.	$ 4,175
	Mobile laboratory (trailer)	6,000
		$ 10,175
	TOTAL	$ 53,200
The sum for the three divisions would be		$ 159,600

It is significant to mention that salaries of most of the investigators were derived from their own institution or were through funds provided by the Rockefeller Foundation; it was assumed that individual investigators would receive supplemental compensation only during their assigned duties in the field.

The original proposal was consequently revised and reduced. The Rockefeller Foundation provided, without cost, the facilities of their laboratories in New York and California and offered the Medical Department of the Army the use of their laboratory services and the opportunity to obtain and store materials for the Commission's purposes. Arrangements were made for the close scrutiny of weekly surveillance reports for possible outbreaks of influenza by the members of the Commission of Acute Respiratory Diseases. Authorization was given for (*a*) experimental trial of an influenza vaccine should the vaccine of promise be available and a suitable opportunity arise; (*b*) studies of the efficacy of respiratory masks; (*c*) laboratory studies of materials and samples collected in the field bearing on the etiology, epidemiology, and immunology of influenza and its complications.

The contract between the University of Michigan School of Public Health and the Commission on Influenza was completed on 15 December 1941. From this time on, the Ann Arbor unit became the focal center for the Commission and remained the core unit throughout the Commission's existence. The Commission had by this time in December 1941, reached a point of coordinated intent, alert to the

techniques of early detection of influenza disease at any site. It was prepared primarily to study the medical features of influenza. There was little else available except application of general public health measures to control virus infection.

DEVELOPMENT OF INFLUENZA VACCINE

The possibility for development of an inactivated vaccine, effective for prophylaxis against influenza, had been the main focus of attention since 1935 when Drs. Francis and Thomas McGill had first shown that active virus cultivated in tissue culture produced antibody in humans without producing an illness.[1] It was also well established that vaccination could be effective against influenza virus in mice. There was wide experience in using live virus given intranasally in humans without producing overt illness.

To obtain further information on the usefulness of immunity produced by live wild influenza strains administered intranasally, Dr. Francis and his colleagues at the University of Michigan conducted a remarkable series of studies in "volunteers" at Ypsilanti State Hospital. The results were surprising when 27 of 30 men developed sharp attacks of influenza within 24 hours or less. The discovery of infection among nonlitigated individuals in the same quarters was obtained by serologic tests.

Four months later the 27 persons described above were challenged with a different preparation of the same influenza B virus. The virus induced fever and clinical illness in many of the same group, accompanied in eight persons by additional antibody rises. There was evidence that the earlier infection had exerted some effect, because a milder illness occurred in most of those previously infected. A spray of irradiated influenza virus material produced no significant reaction, which indicated that the favorable effects observed were related to active virus.[2]

The fact that these persons lacked very strong resistance to the same virus, after a period of 4 months, raised serious doubts about the probable efficacy of vaccination with live attenuated strains. Furthermore, the consideration that inoculation of humans with live attenuated virus carried the possibility of a revival of virulence that might initiate another epidemic. The Surgeon General, Major General Norman Kirk, concluded that this was an inadvisable risk; hence, further work with live vaccine was not carried out at this time.

It was concluded that (*a*) vaccine must be given before the appearance of influenza because of the rapid spread of the virus, (*b*) large numbers of individuals were needed to obtain definite results, (*c*) these studies would have to be performed in vaccinated and unvaccinated (control) population groups under similar observation, and (*d*) the vaccine evaluations must be regarded as experimental. Always there was concern that an epidemic of influenza A might appear before the study got underway. Considerable attention was given to evaluation of methods of demonstrating vaccine effectiveness and detection of antigenic drift.

It was ultimately decided that the best source of virus for the vaccine would be infected egg allantoic fluid inactivated with Formalin and kept at 4° C in the fluid state. Lyophilization reduced the amount of available antigen. Antigenicity of the vaccine was planned to be tested in mice inoculated intraperitoneally. All vaccine testing was conducted on an experimental basis.

1941 and 1942

The Commission was authorized by the Board to undertake a study of influenza vaccine of type A and B viruses conducted by Dr. Monroe Eaton in California should an appropriate opportunity arise. Two thousand doses of vaccine were provided by Dr. Hirst of the International Health Division of the Rockefeller Foundation. The process of finding a satisfactory study group was abandoned with the entry of the United States into World War II. It was considered impractical to undertake a study in

troops, particularly when influenza was not prevalent at the time.

After consultation with five commercial firms (including Parke Davis and Co., Lilly, Lederle, Sharp & Dohme, and Squibb) plans were made to prepare 100,000 doses of inactivated vaccine from allantoic fluid. It was concluded that this could be accomplished in 4 to 8 weeks at a cost of 7 to 60 cents for a 1.0-mL dose. Each company then was asked to furnish sample lots of 250 mL. Samples were tested in mice for vaccine potency in Dr. Francis' laboratory in Michigan. There was extremely wide variation in antigenic potency, and sterility was also a problem.

1942 and 1943

Because influenza A epidemics were said to occur every 2 years, there was concern that an epidemic caused by the virus would occur in the years 1942 and 1943. Efforts to organize an evaluation within the armed services were unsuccessful. Two civilian-sponsored trials were conducted, the first under the direction of Drs. Wilson Smillie, Magill, and Norman Plummer at Cornell University through the University Health Service. A total of 2,885 student volunteers were enrolled in the study, of whom 1,673 received vaccine and 1,213 served as controls. Serum specimens were collected from one-sixth of those enrolled in the study before, 3 weeks after, and 4 or 5 months after vaccination. The vaccines, manufacturers, and method of preparation are shown below:

A number of epidemiologists had tried previously to predict when influenza epidemics were likely to occur. The prevailing dogma was that influenza A occurred every 2 or 3 years and influenza B every

Vaccines Used in Cornell University Study

Vaccine	Origin	Method of Preparation	No. of Persons
A & B	Hirst	Freezing, thawing, formalinized	782
A & B	Sharpe & Dohme	Freezing, thawing, formalinized	582
A	Sharpe & Dohme	Freezing, thawing, formalinized	308
	Total Vaccinated	Freezing, thawing, formalinized	1,672
Controls	Sharpe & Dohme	Formalinized saline placebo	1,213
TOTAL			2,885

5 or 6 years. Dr. Alex Langmuir, Senior Epidemiologist at the Centers for Disease Control, tended to support this belief. This worked to the advantage of Dr. Davenport and me. Each year at the Atlantic City meetings of the American Society of Clinical Investigation and The Association of American Physicians, we would wager with Alex about what type of influenza A or B would occur during the next winter. Dr. Langmuir, with his profound knowledge of epidemiology, never had any doubts of what was coming. My friend, Fred Davenport, and I had observed enough outbreaks of influenza to realize that no prediction was justifiable and that whatever influenza had occurred in the past was no longer applicable. More rapid means of transportation provided by air travel had changed all the earlier rules. It seemed folly to predict what might happen.

Sera were also collected from all persons who reported to the Health Service with acute respiratory disease. No epidemic of influenza occurred, and it became obvious that influenza vaccine had no influence on other types of respiratory diseases. The serologic results suggested that influenza B had occurred but there was no evidence that it had affected the number of visits to the clinic. The reactions to the inoculations were of interest. Eleven percent of those who received vaccine experienced systemic reactions compared with 2.1% in the controls. Local reactions also were observed in 8.7% to 17.5% of individuals who received vaccine compared with 0.5% in the controls.

When no influenza appeared, Drs. Francis, Salk, and Harold Pearson at the University of Michigan conducted experimental trials in the inmate population at the Ypsilanti State Hospital in Ypsilanti, Michigan, and Eloise Hospital and Infirmary, Eloise, Michigan. Both institutions were occupied mainly by mental patients. The vaccine was prepared by absorbing the virus onto chick embryo red blood cells and then eluding the virus from the red cells. The virus was inactivated with Formalin and a mercurial bacteriostatic agent was added. Blood specimens were obtained from approximately 10% of the vaccinated and control groups before and 2 weeks after vaccination. The mean hemagglutination inhibiting (Hemagglutination Inhibition) titers of the vaccinated group against types A and B were increased approximately nine- and eightfold, respectively. The geometric mean titers decreased by approximately 35% after 4 months, and at the end of a year the titers decreased by approximately 50%. Influenza A infection did not appear in this population. Influenza B apparently infected approximately 20% of this group even though clinical influenza was not detected in those persons who reported with respiratory illness. Thus, it appeared that influenza B occurred essentially as a subclinical infection.[3,4]

Despite the lack of an epidemic and in an effort to gain information regarding the effectiveness of the vaccine, groups of vaccinated and untreated subjects were tested for resistance by actual intranasal spray with active virus. Two milliliters of the virus were delivered into each nostril of each volunteer with an atomizer. One hundred two (102) men were exposed to artificial infection with a strain of influenza A virus (A/Baum/40), which differed from the PR/8 strain used in the vaccine. The control group of the subjects had not been previously vaccinated. Fifty percent of the controls developed temperature elevations of 100°F or more associated with clinical manifestations. Of those vaccinated 4.5 months earlier, 32% had similar reactions, whereas of those who were vaccinated 2 weeks previously, approximately 14% had fever as high as 100°F, but none as high as 101°F (see Appendix 1).

Ninety-six (96) men were exposed to influenza virus, type B, in the same manner. Of the 27 unvaccinated controls, 41% developed fever of 100°F or more with clinical symptoms. Of the 69 who had been vaccinated up to 4.5 months earlier, 7% to 13% had fever of 100°F; in no instance did it reach 101°F (see Appendix 1).

These results showed clearly that the vaccine exerted a protective effect against artificial infection of a severe degree. There was a tendency for resistance to be related to higher levels of antibody. However, even at the lowest antibody level, only about half the individuals became ill. The results well confirmed the concept that vaccination could induce resistance.

1943 and 1944

In June 1943 authorization was obtained from The Surgeon General of the Army to conduct a vaccine study against influenza in the Army Student Training Program (ASTP) unit at Cornell University and other Army personnel at a few selected posts. A meeting was held on 2 September 1943 in the Office of The Surgeon General to discuss this program. The following individuals were present:

Dr. Francis Blake

Dr. Monroe D. Eaton

Dr. George K. Hirst

Major Norman Plummer

Lieutenant Colonel Elliott S. Robinson

Captain Phillip E. Sartwell

Colonel Stanhope Bayne-Jones

Dr. Thomas Francis, Jr.

Lieutenant Colonel Esmond Long

Dr. Colin MacLeod

Dr. Thomas P. Magill

Dr. Elsmere R. Rickard

Dr. Jonas E. Salk

It was agreed that vaccination in the various ASTP units be put on a compulsory basis with half of each unit to receive vaccine and half the control inoculum. The test vaccine would be of the eluate type with vaccination contemplated to begin in October.[5] If no influenza appeared before 15 January 1944, the vaccination was to be repeated. A follow-up plan provided that approximately 5% of the vaccinated subjects and 10% to 25% of the controls would provide blood specimens for antibody studies at the time of vaccination and 2 weeks later. The purpose of taking blood specimens from a larger number of controls was to obtain information on the frequency of subclinical infections. Throat washings and paired sera were to be obtained from as many of the volunteers with cases of respiratory infection as possible. Two virus strains, namely PR/8 and the Weiss strain, an influenza A virus isolated in an Army camp in May 1943, would represent the A component. The B component would be equal to the A component and would be made up entirely from the B Lee strain of virus. The contemplated arrangements concerning the university groups and their supervision by the members of the Commission on Influenza were

Dr. Monroe Eaton
California Department of Public Health

Dr. Thomas P. Magill
Cornell University and New York Medical and Dental Colleges

Major Norman Plummer
Cornell University and New York Medical and Dental Colleges

Dr. Wilson G. Smillie
Cornell University and New York Medical and Dental Colleges

Dr. George Hirst
Princeton University

Dr. William M. Hale
University of Iowa

Dr. Thomas Francis, Jr.
University of Michigan

Dr. Jonas E. Salk
University of Michigan

Dr. Elsmere R. Rickard
University of Minnesota

Obligingly, an epidemic of influenza appeared in sufficient extent and severity and covered the United States with readily detectable illness. It was a mild, and, in most instances, an uncomplicated disease. The scope of the epidemic was observed to be higher than in any other epidemic since 1918 and 1919.

On the basis of clinical results, it was found that among 6,263 vaccinated individuals, there was an attack rate of 2.22%. Among the 6,211 control participants, the attack rate was 7.11%. Estimated vaccine efficacy (VE) was 69%.[6] This trend was the same in all study groups. In some areas the ratio of control to vaccinated was as high as 6:1. In California, however, the trend was less pronounced. There was a suggestion from the serologic data obtained that the virus in California had shown some antigenic change and differed more from the Weiss strain contained in the vaccine than at the other institutions.

It was also observed that in both vaccinated and control groups, the greatest percentage of cases of illness occurred in those individuals with low antibody titers. Persons with the higher antibody titers, whether produced through natural causes or by vaccination, were much less frequently affected.[7,8]

It was also noted at Iowa[9] and at City College of New York,[10] where the influenza appeared before the vaccination was completed, that in the first week after vaccination there was no difference between the incidence of disease between controls and the vaccinated subjects. Thereafter, incidence in the groups deviated with a sharp reduction in the frequency of illness in the vaccinated population. Cases of pneumonia, which were few in number, occurred almost entirely in unvaccinated persons. In institutions where *Streptococci* were isolated from the pharynx of up to 20% of persons, pneumonia cases were few in number. No deaths were recorded among the approximately 12,474 individuals under observation. Subclinical infections occurred in up to 40% of individuals. Toxic reactions to vaccine were considered unimportant. Two cases were presumed to be due to a sensitization reaction to the egg component of the vaccine: an asthmatic reaction in one patient and an urticarial rash in another. Systemic reactions occurred in 2% to 3% of those vaccinated and were similar to the mild reactions observed after typhoid vaccination. When the data were sufficiently compiled to provide a clear indication of the

effect of the vaccination, a conference was held at the Rockefeller Foundation on 2 February 1944. The participants were

Dr. Francis G. Blake

Dr. Thomas Francis, Jr., Chairman

Dr. George K. Hirst

Dr. Thomas P. Magill

Dr. Jonas E. Salk

Major Norman Plummer

Dr. Joseph W. Beard (by invitation)

Dr. Wendell M. Stanley (by invitation)

Colonel Stanhope Bayne-Jones

Colonel Karl R. Lundeberg

Lieutenant Colonel Arthur P. Long

It was agreed that the results obtained had shown that the vaccine used was highly, although not completely, effective in preventing influenza A.

Dr. Francis was asked to prepare a statement of the results obtained in the Commission's studies on the effectiveness of vaccine in experimentally induced influenza, the field trial of vaccination against influenza A, reactions to the vaccine, and specifications for the production of vaccine. This statement was anticipated to serve as a basis for evaluation and recommendations to The Surgeon General. After full discussion, Commission members voted to recommend the following to The Surgeon General: (*a*) All troops deployed overseas and other military personnel in this country should be vaccinated against influenza, as the amount of vaccine permitted. (*b*) Special controlled field trials should be continued with modifications of influenza vaccine. These should be undertaken on a selected basis under the supervision of the Commission on Influenza in certain units of the Army, at an appropriate time when vaccine became available. (*c*) The type of influenza vaccine currently used should be the same as that used by the Commission in the ASTP test (mixed A present and B formalinized vaccine), according to the specifications in the statement submitted by Dr. Francis.

Further conferences with representatives of biological firms were held. Finally, on 1 July 1944 the program was officially approved. This provided for the acquisition of 10,000,000 doses of vaccine for use throughout the entire U.S. Army, if necessary. The vaccine to be prepared was to be the eluate from chick embryo erythrocytes with the possibility of changing to other procedures as new information warranted.

TOXICITY, STABILITY, ANTIGENICITY

In January 1944 Dr. Joseph Beard[11] of Duke University and Dr. Wendell Stanley[12] of Princeton University, each of whom had worked under Office of Scientific Research and Development contracts, suggested that the influenza vaccine could be prepared by Sharples centrifugation with a high degree of purity. This procedure was conceived to increase the amount of virus in the vaccine and at the same time remove practically all the nonvirus protein. At the time there was no information available on the stability of the purified vaccine or on its toxicity. Stability and toxicity were thought to be caused by the amount of virus in the vaccine rather than the egg protein.

At a conference held on 2 February 1944, it was recommended that investigation of more purified concentrations of the vaccine prepared by Sharples centrifugation be sponsored and supervised by the Commission on Influenza through collaboration with Drs. Stanley and Beard. Controlled field trials were contemplated. The field trials were proposed to discover the following: (*a*) The protective value of the vaccine in animals; (*b*) the degree and duration of antibody response in humans; (*c*) the frequency and severity of reactions in humans with different concentrations of virus; (*d*) the practicality of com-

mercial mass production, because any increase in the number of fertile eggs required per dose proportionately increased the cost; and (*e*) prophylactic value in humans.

The eluate vaccine that had been proven effective in the 1943 field trials served as a point of reference. It was estimated that the amount of virus in that vaccine was about 0.2 mg/mL.

Dr. Salk, who worked at Eloise Hospital in Michigan with vaccine prepared by Dr. Beard, found that three of six individuals given vaccine containing 0.2 mg of B Lee influenza virus, developed fevers of more than 100°F with troublesome symptoms; in the controls who received the PR/8 strain, none showed fevers over 100°F. Three of the six who received 0.4 mg of the B virus vaccine developed febrile reactions between 101°F and 102°F with overt manifestations. Three of the six persons given this amount of type A vaccine had fevers of 100°F. These data suggested that this dosage level represented the upper limit of tolerance.

Dr. Hirst at West Coxsackie, New York[13] and Dr. Salk tested different dosages using vaccines by Dr. Stanley's methods and vaccine prepared by Sharp & Dohme (double cycle centrifugation).[12] Of those men who received 2.0 mg of vaccine, 80% had fever and symptoms of toxicity that clearly indicated that this dosage was unacceptable. A dose of 0.2 mg elicited fever of 100°F in 4% to 15% of subjects. The Commission vaccine referred to earlier had induced a slightly higher incidence of reactions. Dr. Hirst gave a few volunteers 10 mg of vaccine; all had sharp, severe reactions. It appeared that the desired amount of antigen should probably not be more than 0.2 mg.

Another batch of vaccine using Dr. Stanley's method prepared by the Squibb Company caused considerably less toxicity. Using 0.5 mg produced similar reactions in only 16% of the subjects, and a preparation of eluate vaccine made by the same firm produced the same results.

Dr. Beard and his associates in Durham, North Carolina, conducted another study on the toxicity of vaccine in swine. This was performed on his premises, which he had converted into a large pig farm. The swine received doses of virus varying from 0.125 mg to 2.0 mg. In animals that received 0.5 mg or more of vaccine, general reactions were noted followed by loss of weight. These studies helped define the upper limit of acceptability.[14,15]

Over the 16-fold range of dose employed, antibody response differed by only twofold. Revaccination with the same dose at 1-week intervals showed little effect. As the interval before the second dose was lengthened, the response increased and reached higher levels; antibody titers were more prolonged, regardless of the amount of virus injected. These results were of interest because of the insignificant difference in antibody response that resulted from relatively large increases in the amount of antigen used. Dr. Beard also tested alum-precipitated vaccine and concluded that there was little gained by this procedure.

Drs. Hirst and Salk followed the serologic response to different amounts of virus in the vaccine. Dr. Hirst found that the antibody response to 2.0 mg was definitely better than 0.2 mg after 2, 18, or 60 weeks. The results obtained with vaccine used by Commission members in 1943 fell between the three. The response to the Weiss strain of influenza A was less than the PR/8 strain of A or the Lee strain of influenza B. Although these data indicated the possible advantages of doses approaching 2.0 mg in humans, these were counteracted by the fact that five to six eggs were needed to obtain that amount of virus. In addition, the toxic reactions in humans were proportional to the virus concentration. This was taken to indicate that the amount of virus, as presently prepared, was probably appropriate. Stability studies at Michigan and in Dr. Stanley's laboratory showed that vaccine prepared by centrifugation was stable at 4°F for as long as 1 year.

On 30 March 1945 at The Surgeon General's Office, a meeting was held that included representatives of the National Institutes of Health (Dr. Joseph Bell), Army Procurement of The Surgeon General's Office, and Drs. Beard, Stanley, and Francis. Centrifugation was accepted as an alternate method for production of influenza virus vaccine for Army use. The technique to be employed was essentially that described in Dr. Stanley's publication.[12] It was specified that the material would contain 0.03 mg/mL of nitrogen of stated minimal agglutinating titer. Despite some contrary opinions, it was concluded that the potency test in mice was desirable and should be retained. The producers now had a choice of two approved methods.

On 21 June 1945 Commission members and representatives of The Surgeon General's Office met at the Rockefeller Institute in New York City to consider the subject of vaccination. Recognized epidemics of influenza B had occurred during May and June of that year. Those in attendance were

Dr. Francis G. Blake, President of the Board

Dr. Thomas Francis, Jr., Director of the Commission on Influenza

Dr. Joseph W. Beard

Dr. Alto E. Feller

Dr. William R. Hale

Dr. Thomas P. Magill

Dr. Jonas E. Salk

Dr. Wilson G. Smillie

Major John H. Dingle

Captain George K. Hirst

Dr. Ronald Hare of Toronto, Canada (by invitation)

Dr. Wendell M. Stanley (by invitation)

For The Surgeon General's Office:

Colonel Elliott S. Robinson

Major Norman Plummer

At that time there was a general discussion of the desirability of vaccination with the aim to avoid the effects of a gradual intensification of the disease such as had occurred in 1918. Colonel Robinson stated that as of 1 June 1945, 3,000,000 doses of vaccine had been delivered. According to planned schedules, enough vaccine for recruits would be on hand by 1 October 1945.

The following recommendations were made to the AFEB: (*a*) Provide influenza vaccine in sufficient amounts; (*b*) if there was no epidemic of sufficient severity to justify vaccination earlier, vaccination should be carried out by the Army during October 1945; (*c*) further field trials should be carried out if suitable locations could be found. Dr. Stanley stated that vaccine prepared by centrifugation would be available for these purposes.

A committee chaired by Captain Hirst was appointed to study and make recommendations concerning common laboratory procedures. Drs. Beard and Stanley were also requested to study the methods of estimating influenza virus quantitatively, which, at that time, gave quite different results in different laboratories.

The recommendation for the use of vaccine in the Army was presented by Dr. Blake to The Surgeon General in a communication dated 2 July 1945. It was approved by General Kirk on 10 August 1945. Final approval of the Secretary of War was recorded on 25 August 1945. The program of vaccination with eluate was carried out by the Army in October and November 1945.

An increasing incidence of influenza B developed in the United States during November and December 1945. It was reported that Army personnel who were vaccinated experienced a much lower incidence of illness than unvaccinated Naval and civilian groups.

The results to that point had demonstrated that vaccination effectively prevented epidemic influenza A. However, this was only one important step in the development of an effective vaccine prophylaxis for this important epidemic scourge. Yet, it was a major accomplishment and served as a stimulus to find more effective vaccines. The various progressive steps were made not only by members of the Commission, but by numerous associates and assistants. They called on, without reservation, the President of the Board, other Board members, General J. Steven Simmons, General Bayne-Jones, and Preventive Medicine officers continuously for their advice and assistance in making arrangements for the investigative work. Contributions of pharmaceutical firms to solution of production problems and safety matters were very significant. These firms continued to investigate with methods and procedures at their own expense, as requested, and contributed valuable suggestions to make procurement of vaccine for testing possible. The experience gained in the process of virus cultivation, harvesting,

and control of contamination was both troublesome and costly. The field trial in ASTP units represented a unique example of the conduct of difficult experimentation made possible through the cooperation of groups of many persons engaged in a wide variety of activities.

INTRANASAL SERUM PROPHYLAXIS

The possibility that influenza could be prevented by intranasal administration of appropriate immune serum had been shown by results reported by some investigators in studies with mice. In addition, the interest in this approach had been heightened by the report in 1939 of A. A. Smorodinsev and his associates in the USSR. He reported that administration of spray containing as little as 2.0 mL of immune horse serum in humans once in 2 weeks had reduced the incidence of influenza infection by 10- fold (82/1,000).[16] (In California a prominent magazine featured, under a banner heading reading "Flu is Through," a photograph of 12 men in naval uniforms each with a tube in his mouth connected to a chamber that was said to contain atomized immune horse serum.) It was considered important to gain information on the efficacy of this procedure as an emergency measure alternative to uniform vaccination.

The Army Epidemiological Board in May 1942 recommended that the Commission on Influenza undertake studies on the prophylactic and therapeutic effect of convalescent serum given intranasally should the proper opportunity arise.

Discussions were held with Dr. Paul Cannon, who was interested in local immunization of the respiratory tract, and with Dr. O. H. Robertson whose group was working with aerosol techniques and routes of infection. Dr. Clayton Loosli, who had been working with Dr. Robertson, undertook the developmental aspect of the investigations. A subcommittee of members of the Commission comprising Drs. Cannon, Irving Gordon, Loosli, Robertson, and Francis was formed as an epidemic study group in 1942.[17] However, no epidemic occurred during 1942.

Volunteers for experimental studies were recruited at a camp for religious conscientious objectors at Wellston, Michigan. Dr. Salk joined the Committee members to help in conducting studies there. After it was shown that the influenza B virus preparation that had been planned for use was unsatisfactory, allantoic fluid was used containing a new strain of influenza A isolated in 1940. The results of the two completed experiments that were performed are summarized in Appendix 2.

Two experiments were performed, each in healthy, husky volunteers. In Experiment 1, the allantoic fluid produced illness in almost all of the volunteers who received 1.0 mL of saline aerosol before an aerosol of the virus. With no exception, the control volunteers who received immune serum followed by inactivated virus escaped illness. The serum had no demonstrable effect.

Experiment 2 was carried out with a different preparation of virus. On the assumption that the virus challenge might have been too strong, the amount of high titer convalescent serum was far greater than that used in the first experiment. It was given in three doses before administration of the live virus and also 7 and 17 hours after the virus challenge; in all, a total of 37 mL were given. The second group received doses of saline at the same intervals and in similar amounts. The test was milder in that only 8 of 15 (53%) controls were ill, and the febrile reactions were less marked than in the first experiment. Of those who received immune serum, 11 of 16 (69%) had fever of 100°F or more; the distribution of severity was approximately the same as in the controls. There was no effect on the incubation period (see Appendix 2).

To gain a better idea of the amount of virus in the challenge preparation, the virus was titrated in volunteers at the Ypsilanti State Hospital. Results of the titrations are also shown in Appendix 2. It appeared that the amount of virus was by no means excessive.

The evidence was conclusive even though unexpected. Further studies were not carried out because the results of the vaccination study in 1943 were far more satisfactory. It was hoped to carry out further studies during the epidemic of 1943, but suitable conditions did not occur.

Investigation of the contraindications caused by sensitization to the various antisera that had been proposed were carried out in guinea pigs by Dr. Cannon's group. Normal horse serum, "despeciated" anti-influenza horse serum, Lilly's purified horse serum, goat serum, swine serum, and crystalline egg albumin were all tested in guinea pigs. All produced anaphylactic sensitization. This provided fair warning against continued use of such sera in humans.[17]

METHODS FOR DIAGNOSIS AND ISOLATION OF VIRUS

A number of investigators undertook studies to develop protocols for rapid diagnosis of influenza infection. The agglutination-inhibition test of Hirst proved to be of great value, and a number of modifications were made to expand the value of the test.[18] One test that had been extensively used was the one described by Dr. Salk.[19] The time required for identification of influenza virus in the throat washings had been reduced to between 36 and 72 hours. Drs. Rickard, Eaton, and Hirst each attempted an evaluation of different procedures with somewhat different results. Nonetheless, both amniotic and allantoic inoculations served to speed the diagnosis of influenza considerably.

ADJUVANT EFFECTS

The possibility of finding adjuvant materials that would heighten the antibody response and prolong immunizing effects was undertaken particularly by the Ann Arbor, Michigan, group, and their studies suggested that the adsorption of virus to calcium phosphate was not promising.[20]

CENTER FOR THE STUDY OF STRAINS OF VIRUS

One of the constant problems encountered was whether a virus strain was suitable for vaccine production. There was enough antigenic heterogeneity to raise serious questions about the capacity for one strain to induce immunity to others of the same type. In the 1943 epidemic the suggestion had been advanced that the vaccine had not stimulated a satisfactory antibody response to the current epidemic strains. The PR/8 strain of influenza A was consistently shown to be one of the most effective ones studied.

To gain further information about these characteristics, Dr. Magill accepted the invitation of the Commission on Influenza in 1944 to establish a center for the collection of strains of virus submitted for study of their antigenic patterns and immunizing potencies.[21] His work was also to include the preparation of specific antisera and a broad hyperimmune serum for purposes of strain identification. In this connection it was noted that Dr. Francis reported apparent variation in two lines of the same strain of virus grown in different media.

INFLUENCE OF PHYSICAL FACTORS ON INFLUENZA VIRUS

In the course of studying the aerial transmission of respiratory infection, Dr. Loosli evaluated the influence of temperature and humidity on survival of influenza virus. In the experimental spray chambers[22] he found that the virus remained infectious at low humidity (17% to 24%) for as long as 24 hours. As the humidity progressively increased, the period of survival was reduced so that at humidity of 80% to 90% it was infective for no longer than 1 hour. The same trend was followed with virus found on the floor in dust. What relation these facts had with the general epidemiology of influenza was a subject of speculation.

TOXICITY OF INFLUENZA VIRUS FOR MICE

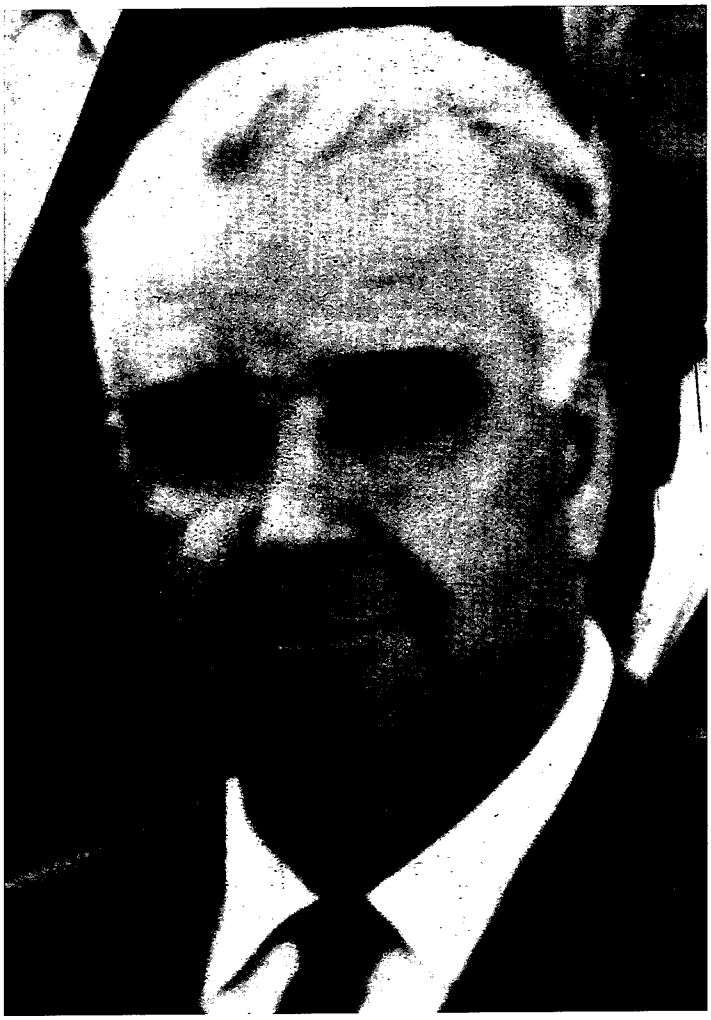
In studying a strain of influenza isolated in 1943, Dr. Hale noted that intracerebral inoculation of mice caused convulsions. These were not associated with multiplication of virus in the brain. This convulsion-producing factor was heat labile and was absorbed and eluted from erythrocytes with the virus activity; it was neutralized by specific antibody.[23] The significance of this intrinsic toxicity of the virus in relation to the symptomatology and pathogenesis of the disease was considered important for future studies.

DIAGNOSTIC TESTS FOR PSITTACOSIS-LGVA GROUP OF VIRUSES

Dr. Francis Gordon at the University of Chicago investigated the specific diagnosis of Psittacosis-lymphogranuloma venereum group (LGVA) closely related group of viruses. Sera prepared in chickens were shown by neutralization tests to have a high degree of specificity. In the course of these tests, information was obtained on nonspecific reactions to chicken sera that had probably been the chief obstacle to the use of serum from chickens in serologic tests.[24]

ATYPICAL PNEUMONIA

During the fall and winter of 1942 the increased prevalence of atypical pneumonia in the Army and the lack of information regarding its etiology justified an extensive investigation. Drs. John H. Dingle and G. John Buddingh, who had been members of the Commission on Influenza, joined the Commission on Acute Respiratory Disease (CARD). As work expanded, Dr. Alto Feller joined the CARD group. The Commission on Influenza provided a laboratory technician and a statistical assistant. In February 1942, Dr. Francis spent 2 weeks with the CARD at Camp Claiborne in Louisiana, aiding in the investigation and participating in other aspects of the study. Following this, the Commission on Influenza laboratory at Ann Arbor, Michigan, in an effort to isolate virus, tested throat washings in mice from nine patients and sputum from two characteristic cases at Camp Claiborne, Louisiana. Eggs, mice,



CLAYTON LOOSLI, M.D.

Dr. Clayton Loosli was an Idahoan who attended the University of Chicago. He worked closely with Dr. O. H. Robertson. He was particularly helpful to the Commission in developing effective means of delivering virus in suspension for experimental challenges in human beings. He was also instrumental in developing the "glycolizers" that were used to create suspension of propylene glycol in the air. These were widely used at Camp Detrick for the protection of the staff who were working with particularly lethal agents. Later, after he became Dean of the School of Medicine at the University of Southern California, he continued to be an active participant in the affairs of the Commission. He worked with mice, trying to produce a controlled antigenic change in the virus. He also obtained interesting, and somewhat surprising, data on the effect of Los Angeles smog on mice infected with influenza virus. At one point, it appeared that the smog actually helped the animals, rather than hurt them. He was a very friendly person with broad interests who was exceptionally well qualified to be dean of a medical school.

cotton rats, hamsters, ferrets, monkeys, rice birds, doves, and chickens were used. No influenza virus was recovered. In four instances, a virus similar to the meningo-pneumonitis virus of mice was recovered from the sputum or throat washings by passage through mice or rice birds. In each of these instances, the patients were blacks who had significant levels of complement-fixing antibodies to LGV in their sera. Serologic tests of the patients against influenza A and B were negative. The results of complement fixation tests using both meningo-pneumonitis and psittacosis virus performed with serum collected from more than 300 patients and controls were essentially parallel. Although a relatively large number of persons showed positive reactions, it was uncommon to find any increase in titer during the course of illness. Analysis of the results showed that positive results were concentrated largely in blacks, suggesting that this was probably a reflection of a common antigen with LGV virus.

From July to November 1942, Dr. Feller, working in the laboratory in Michigan, in an effort to isolate a virus, tested large numbers of specimens from a variety of military bases in the Midwest. In two instances, viruses resembling meningo-pneumonitis were recovered. One of these patients showed a significant antibody rise in complement fixation tests.

With the establishment of the permanent CARD at Fort Bragg, North Carolina, the materials stored at Michigan were transferred to its laboratories, and investigations of atypical pneumonia at Ann Arbor, Michigan, were discontinued. Repeated clinical and epidemiological studies at Fort Custer, Michigan, led Dr. Francis to the opinion that "atypical pneumonia" was occurring in the Army probably as a single entity. The relatively low transmissibility and its random distribution suggested that pneumonia might be a rather infrequent manifestation of a more common disease in the trachea and upper respiratory tract. The whole course of the disease differed from that of influenza in that the peaks of the outbreaks were long plateaus rather than sharp spikes and only the recruits were infected. With influenza, both recruits and permanent personnel were affected. There were also sharp differences in the clinical manifestations of the two diseases.

The solution to the cause of this disease became highly competitive. Dr. Frank Horsfall and his group at the Rockefeller Institute reported transmission of an agent to mongooses.[25] This group also isolated a *Streptococcus* (M.G.) and showed that the agglutination titers of convalescent sera of many patients with atypical pneumonia were higher than those in the acute phase sera.[26]

Dr. Eaton had demonstrated in 1942 that when sputa from patients with atypical pneumonia were inoculated into cotton rats or hamsters, small lung lesions developed in a large proportion of the animals.[27] Serial passage of these lung specimens produced even better lesions, but it was found that a number of wild viruses was being picked up. Material from patients at Cowell Memorial Hospital in Berkeley, California, when inoculated into eggs, was shown to produce a similar pneumonic lesion and could be passed using a suspension of amniotic fluid, and trachea and lung of the embryo.[28] It was shown in neutralization tests that fourfold increases in antibody titers were obtained in 68% of the paired sera from patients with atypical pneumonia. An additional 16% showed a twofold rise.[29–31] These were the same patients in whom rises in titer of cold agglutinins had previously been demonstrated.[32] Dr. Eaton and his collaborators were convinced that they had excluded wild animal viruses, but others refused to accept their interpretation until Dr. Robert M. Chanock at the NIH showed that the agent (*Mycoplasma pneumoniae*) could be grown on synthetic media.[33] Drs. Eaton of the California Department of Public Health and K. F. Meyer of the Hooper Foundation of the University of California differed so strongly on the importance of psittacosis-like virus that they stopped speaking to one another.

HAEMOPHILUS INFLUENZAE

Under the direction of Dr. Hattie Alexander, a laboratory was organized in 1941 for the typing of *Haemophilus influenzae* and for the preparation of diagnostic reagents. Antisera of various types were

produced in rabbits on the basis of agglutinin nitrogen. Beginning with the influenza epidemic of 1943 and continuing through the spring of 1945, a study of throat cultures was carried out on normal young adults to obtain background information on severe pneumonia. No encapsulated strains of *H. influenzae* were found. Only 2% of those cultures were potentially encapsulated. Tests on the susceptibility of these organisms to sulfonamides revealed considerable variation.[34] Classification of *H. parainfluenzae* was also attempted and suggestive evidence of three serologic groups was obtained.

The value of these studies had been a continuing evaluation to determine the significance of the presence of microorganisms in respiratory diseases, especially influenza, when characteristic association is expected. In the event of an upsurge of these bacteria, the availability of a diagnostic center seemed essential to maintain a state of preparedness. Support of the work was discontinued on 30 June 1945.

MASKS

At the first meeting of the Executive Committee of the Commission in April 1941, Drs. Robertson and Dingle agreed to review the available investigations concerning masks designed to prevent dissemination of respiratory discharges. They obtained advice and recommendations from Drs. Charles K. McKhann of Harvard University, Cambridge, Massachusetts, and M. W. Jennison of the Massachusetts Institute of Technology (MIT), Cambridge. The latter recommended a gauze-covered mask with a Canton flannel filler and a flexible nose band. In September 1942, it was suggested that a conference be held to include those investigators actively engaged in the study of masks.

A meeting held 26 September 1942 was attended by the following persons:

Dr. Thomas Francis, Jr.
Chairman: Commission on Influenza

Dr. Deryl Hart
Duke University, Durham, North Carolina

Dr. M. W. Jennison
M.I.T., Cambridge, Massachusetts

Dr. Charles K. McKhann
Commission on Measles and Mumps

Dr. Ronald Rooks
University of Iowa, Iowa City

Major A. P. Long
The Surgeon General's Office

Conference members agreed that the masks ordinarily worn were worthless and recommended use of the type shown by extensive physical and bacteriological studies to be most effective. Specifications were formulated by Dr. McKhann and approved by other members of the conference. The report of the conference was transmitted to the President of the Board on 10 October 1942.

CHEMOTHERAPEUTIC STUDIES OF EXPERIMENTAL, COMBINED BACTERIAL, AND INFLUENZA VIRUS PNEUMONIA

At Washington University, beginning in 1943, Dr. Barry Wood assisted by Dr. Carl Harford initiated studies on the influence of sulfonamides in pneumonia in which influenza virus was associated with type I *Pneumococcus* or hemolytic *Streptococcus* in animals.[35] The following observations were made: (*a*) In mice, even in the presence of subsequently fatal infection due to influenza virus, a concomitant bacterial invasion was eliminated by sulfonamide. (*b*) In rats, the bacterial component of a combined infection was also controlled. (*c*) In mice, the inhalation of finely dispersed type I pneumo-

cocci did not produce infection, but if the mice had been previously infected with a sublethal virus infection 5 days earlier, they died of a pneumococcal infection. The bacteria did not enhance the virus effect before treatment with sulfonamide brought about recovery.

They concluded that in the event of an epidemic of influenza, chemotherapeutic measures would probably aid in controlling pneumonia if a pneumococcal infection was superimposed on an influenza viral infection. This coincided with a comment made by Drs. Eaton and Meiklejohn that of six instances of pneumonia that occurred in their unvaccinated controls of 1943, all responded promptly to sulfadiazine.

PENICILLIN IN STREPTOCOCCAL TONSILLITIS

In 1944 at Fort Jay Regional Hospital, Governor's Island, New York, Dr. Plummer and his associates showed that in severe tonsillitis caused by *Streptococcus hemolyticus*, continued treatment with 15,000 units of penicillin given intramuscularly every 4 hours promptly produced negative throat cultures. However, discontinuation of treatment within 6 days resulted in relapse and return of infection. With longer treatment, pharyngeal cultures remained negative.[36] The study emphasized the dangers in casual treatment of acute streptococcal infections of the throat.

PSITTACOSIS

In 1945, Dr. Eaton reported a study of the effects of some 60 compounds, unrelated to sulfonamides, on viruses of the psittacosis group. All results were negative. It was shown in certain species of animals that a drug might show some activity against a given virus, but against the same virus it would have no effect in a different animal species. This was an interesting observation. Chemotherapy of influenza virus infections showed no progress, which emphasized the need for further exploration using different methods.[37]

HEPATITIS — EPIDEMIOLOGY

Investigation of Postvaccination Jaundice at Chanute Field, Jefferson Barracks, Scott Field, and Fort Sheridan — 12–20 April 1942

On 12 April 1942, Dr. McKhann of the Commission on Measles and Mumps and Dr. Francis of the Commission on Influenza undertook an investigation of jaundice, which was occurring at Army camps. At each installation, clinical and epidemiological studies were conducted and specimens were obtained for investigation in the laboratory of the Commission of Influenza in Michigan. As data on icteric patients were assembled at Chanute Field, Illinois, it became apparent there that the most prominent common factor was the prior vaccination with yellow fever vaccine, lot no. 335. The incubation period in 80% of the cases varied from 62 to 84 days. Lack of contagious spread was clearly demonstrated. At Scott Field, Illinois, information was obtained from additional personnel vaccinated with lot no. 335. Ten thousand men at that post who were vaccinated with other lots were not infected. The results

indicated that in this area, that yellow fever vaccine lot no. 335 was seriously implicated. The incidence of hepatitis in vaccinees was 10% to 15%. There were a few instances in which other lots were indicated, such as lot nos. 338, 351, 334, and possibly a few others. At this time it was learned that lot no. 368 had been used at Fort Sheridan, Illinois, at the end of February 1942 without any recognizable effect by April. Attention was called to the fact that the resulting illness was severely incapacitating and that sequelae were anticipated. The disease was clinically comparable to that ordinarily called catarrhal jaundice. In view of the extended incubation period, comments were made regarding pathogenesis of the disease and whether it might be due to yellow fever virus or to an extraneous agent accidentally incorporated in the vaccine. The report suggested that a commission be organized to study the biochemistry, treatment, and prognosis of the disease.[17]

Fort Custer — 4 and 5 June 1942

Dr. Francis also investigated the same illness at Fort Custer.[17] At that time there were 212 cases of jaundice, which increased to a total of 650 cases by the end of July 1942. Yellow fever vaccine lot no. 368 appeared to be responsible for all the cases. It was the same lot that had been used at Fort Sheridan, where no cases had been detected within 2 months after vaccination. The illness at Fort Custer seemed less severe than that observed earlier in the spring and the incubation period was most commonly 90 to 100 days. Urticaria was observed to occur in a certain number of persons 1 or 2 weeks before onset of signs of acute hepatitis. A group of officers of the 12th General Hospital, then located at the post, were interested in conducting an extensive study of the disease and recommended that the Commission on Influenza conduct these studies. As a result, a committee was appointed by the Commanding Officer with Lieutenant Colonel N. H. Barker as President. In their studies, the committee emphasized the frequency of non-icteric cases with apparently similar disturbances and the adverse effect of exercise upon patients who were at this stage of illness or who were in the early stage of convalescence. Further attempts were made at the University of Michigan laboratory to establish an etiologic agent. The excellent report to the Board included a large number of determinations of liver function tests, effect of exercise and therapy, and a description of relapses. This report was submitted to The Surgeon General's Office late in 1942 and represented a major contribution of new knowledge regarding hepatitis.

INFECTIOUS HEPATITIS

The differentiation between infectious hepatitis and what is now known as serum hepatitis was clarified by Dr. Francis, who spent approximately 6 weeks in Sicily and Italy at the invitation of the Surgeon of Natousa (North Africa theater of operations) and his colleagues in the Armed Services. After considering many possibilities, they noted a correlation among the occurrence of hepatitis, malaria, and dysentery. They also noted a relationship between traumatic injuries and blood transfusion to transmission of the agent but obtained no supporting data to support this concept. Insect transmission was also considered. Dr. Francis collected a number of specimens, particularly blood, which were transported to Ann Arbor for further study. A full report was made to The Surgeon General, Department of the Army.[17]

CLINICAL INVESTIGATION WITH MATERIALS FROM NATOUSA

In the summer of 1944, arrangements were made for volunteers from the state prison at Dearborn, Michigan, to participate in experimental studies involving the sera and tissue specimens obtained in North Africa. Captain A. W. Frisch, an experienced microbiologist, was reassigned from Camp Custer to work at the Commission's laboratory in Ann Arbor and to assist in these studies.

Experiment 1

Four volunteers received a filtered dilution of serum subcutaneously from a patient taken 7 days after the onset of symptoms. Four other persons were given a 20% suspension of filtered feces orally from the same patient. Four volunteers were given 1 mL of serum subcutaneously taken from a patient 3 days after the onset of jaundice. Four volunteers received the same amount of the similar serum that they gargled and swallowed. No jaundice occurred.

Experiment 2

On 13 April 1945, a study was carried out using mosquitoes that had fed on the same patient and were killed at various times after feeding on the patient. The mosquitoes had been allowed to feed for 1 day after the onset of symptoms. Five were sacrificed after 1 day of feeding and the others 8 days after feeding. A suspension was made of a pool of mosquitoes and injected into four volunteers subcutaneously. No jaundice resulted in any of the recipients.

Experiment 3[38]

In May 1944, serum was obtained from an apparently well soldier who had served as a donor to a man who was recovering from a gunshot wound. Two days later the donor reported to sick call with icterus. The disease developed rapidly and he died 5 days after serving as donor. The recipient had his first suggestive symptoms of hepatitis 11 days after the transfusion. After 19 days his liver edge was palpable and tender. More definite systemic symptoms, including fever, were noted on the 20th day, and jaundice was first detected on the 21st day after transfusion. Samples of serum were taken 8 days after transfusion (13 days before the onset of jaundice) and also 14 days after transfusion (7 days before the appearance of jaundice). On 13 April 1945, four men received subcutaneously 1 mL of the filtrate from the first sample of serum and another four men received 1 mL of the filtrate of the second sample. Thirty-eight days after inoculation of the first group, one of the patients became ill. Jaundice developed on the 41st day and the patient died on the 46th day. The second subject developed symptoms on the 39th day, jaundice on the 44th day, and a relatively mild, uneventful course of hepatitis thereafter. The third subject had onset of symptoms on the 44th day, jaundice on the 49th day, and a moderately severe illness afterward. The fourth subject had intermittent symptoms from 21st to the 41st day without evidence of jaundice or hepatitis detectable by biochemical tests.

In the second group, one volunteer had onset of symptoms on the 43rd day and jaundice on the 47th day followed by a moderate illness and uneventful recovery. The other three subjects had intermittent periods of digestive disturbance, but no jaundice was noted over a period of 135 days.

The experiments were useful but inconclusive in solving the problems of hepatitis. It became obvious that the limitations in the use of human subjects was such that only very vital questions dealing with the problem should be investigated in this manner. Other specific tests useful for detection of virus or the mechanisms of its action must be sought.

No further studies were performed in volunteers because World War II came to an end and Captain Frisch was demobilized.

ETIOLOGIC STUDIES

At the laboratory of the Commission on Influenza in Ann Arbor, Michigan, studies of hepatitis were carried out with the aim to induce the disease in experimental animals. This was performed with material taken from 14 acutely ill patients and 5 fatal cases. The materials included stool specimens,

defibrinated blood serum, duodenal drainage fluid, liver sections, and suspension of duodenal wall. Monkeys, lambs, pigs, cats, rabbits, guinea pigs, ferrets, mice, eggs, chicks, and chickens were utilized in the studies. Presumably infected tissue was introduced by feeding and by the intravenous, intracerebral, intraperitoneal, intrahepatic, and subcutaneous routes. In all instances animals were kept under observation for at least 4 months. There was no further opportunity for testing the presence of virus in human subjects.

COMMENT

Throughout this period Dr. Francis enjoyed excellent working relationships with Board members, with practically all civilian workers in the field, and with his military counterparts, who respected him greatly not only for his skills as an epidemiologist but his ability as a clinician. He maintained a continuous interest in clinical affairs and was a fine physician. His reports always generously acknowledged the help of many individual contributors during the war years. Under his leadership, the Commission answered numerous questions that came to it from multiple sources.

ALERT FOR INFLUENZA

While the vaccination program was under development, there were continuous efforts to become aware of early prevalence of influenza. The weekly incidence reports of respiratory diseases made it possible to note trends or sudden changes, but it was impossible to investigate all potential threats. Various members of the Commission, through their continued association with military posts in their respective areas, were able to obtain estimates of the character of current respiratory diseases. This was particularly true of Dr. Eaton in California, who was freely called upon by the Ninth Service Command. Similar responses by Michigan laboratory personnel involved repeated trips to Fort Custer, a large base in Michigan, where special examination of materials obtained from other areas was performed. Dr. Hirst also made repeated tests in civilians and at certain Army bases in the New York area. At the bases where vaccination studies were in progress, there were continuous efforts to identify the presence of influenza. Despite all these efforts during the last 6 months of 1941 and throughout 1942, there was no evidence of influenza A or B except for a few positive serum tests for influenza A found by Dr. Eaton at Camp Roberts, California, in February 1942.

In early 1943 influenza B was detected in Michigan in several civilian groups and at Fort Custer. At the Eloise Hospital, Eloise, Michigan, a study of vaccination was in progress and examination of sera suggested that an incidence of influenza B of nearly 20% of the complement had occurred among the 2,900 unvaccinated controls. In spite of this, clinical illness was infrequent, although two instances of influenza A were suggested by the serologic tests. There was widespread infection so mild that it was rarely detected clinically despite intensive efforts to record all cases of respiratory disease regardless of their character. Influenza B was again identified in May 1943.[17]

Influenza A was identified in Michigan and found to be of the same type as previously isolated from an outbreak among a group of interns in New York City in April. Influenza A was also identified at Fort Custer. These observations clearly demonstrated an important, previously unidentified fact regarding influenza, namely, the occurrence of widespread patchy distribution recognized only because of the constant support and vigilance of several diagnostic laboratories. Influenza A had previously been considered to be an epidemic disease of varying severity, but evidence of its sporadic, not epidemic, nature was established.

To intensify the active alert, members of the Commission initiated a program of detection with the following assignments: Dr. Hirst and the Commission on Acute Respiratory Diseases, Second and Third Service Commands; Dr. Buddingh, Fourth Service Command; Dr. Francis and Dr. Salk, Sixth Service Command; Dr. Rickard, Sixth and much of the Seventh Service Command; Dr. Hale, Seventh Service Command; and Dr. Eaton, Ninth Service Command. From May to November 1943, no cases of influenza A were detected. In November, influenza A was detected in Michigan, Minneapolis, and St. Louis, Missouri, where other studies on influenza were in progress. Within a matter of days this information was transmitted to all other groups. The early identification of this epidemic was very helpful in evaluation of the effect of vaccine because all cases could be identified. In 1944, the sampling was augmented by Dr. Magill in the First and Second Service Commands and by Drs. Wood and Harford in the Seventh Service Command. No outbreaks of influenza A were detected up to the end of April 1945.

The effectiveness of the committee organized for the detection of influenza was well demonstrated during 1945. During the rest of that year members of the Commission or their affiliated units identified 16 outbreaks of influenza B of varying magnitude. Most of these episodes were small but some sharp outbreaks affected civilians as well as military personnel. Large numbers of cases were observed in Hawaii, and an outbreak of influenza B occurred in students at Yale University at the end of the year. It was reported by Dr. Blake and the virus identified by Dr. Hirst. Dr. Francis learned of overseas outbreaks on Tarawa, Guam, and Saipan. On Tarawa, it was said 83% of natives were affected, but there was little infection among caucasians.

The Commission members derived great satisfaction from visiting Army laboratories and observing efforts to acquire information quickly. In many instances, because of previous experience with Commission members, each visit was welcomed. It served to stimulate interest in the entire field of communicable diseases. Without these cooperative activities in spatial and temporal relationships, a long and drawn out incidence of influenza B of such mild and irregular distribution might have been overlooked. The Commission, through these procedures, maintained a broad picture of the patterns of illness and brought into perspective numerous isolated occurrences that formed a composite epidemiological picture. This enabled the Commission to advise the Army effectively and accurately as to the most desirable technical control measures. The experience seemed to reinforce the impracticality of waiting until an epidemic began to institute prophylactic vaccination. In nearly every instance mentioned in the report, the peak had been reached before the investigation succeeded in identifying the cause of the disease. The data obtained in the 1943 episode showed clearly that vaccination should be carried out before the virus made its appearance. As a result, data of great value were obtained.

THE COMMISSION — 1946 TO 1950

Continuation of the Commissions

When World War II ended, the question arose as to whether the AFEB would continue to function as it had during the war. Use of the Commission structure had been highly successful in field investigations of infectious diseases, and such activities continued to provide protection to the Armed Services against a variety of diseases. The Commissions had already made substantial progress in many areas. Furthermore, it was obvious that the demobilization of the Armed Services would by no means be complete and that the draft would continue for an indefinite period. In view of the uncertainty of the world situation, it was anticipated that a substantial number of recruits would enter military service during the coming years.

Research on influenza had progressed considerably toward achievement of the goals that the Commission had established. A number of experiences made it patently clear that many problems needed

considerable more study before solutions were reached. Commission members had taken part in a number of studies at military installations. Generally, they had learned how to work well with their colleagues in the Armed S ervices. A concern that the Commission system might be abolished prompted a decision by Dr. Francis to prepare a history of the Commission on Influenza during the World War II period. It was with considerable relief that Commission members learned that their activities would continue, at least for a while. Some of the most important lessons learned up to that time were that behavior of the influenza virus was extremely difficult to predict, many older notions had to be discarded, and new problems would appear almost every year. All of these potential problems would require study and solutions.

1946 and 1947

Influenza B

Influenza B had not been detected since 1940 except in 1943 when a few scattered cases were encountered in Michigan. In 1945, however, the disease was identified as having caused outbreaks in practically all parts of the country as well as in Alaska and Australia. The alert system established earlier had functioned extremely well; laboratory data sufficient to identify the cause of the disease were obtained during most outbreaks. An extensive outbreak among civilians on Oahu, in the territory of Hawaii, led the Theater Surgeon to request aid from the Commission on Influenza. Captain Hirst and Dr. Francis left their posts on 27 June 1945 to investigate the outbreak. The number of civilians reported ill during that time was approximately 7,000. The number of admissions for respiratory disease in the Army totaled 2,600 between 1 June and 18 July. Vaccine had been administered to medical personnel, but the illness was so mild that there appeared to be no need for general vaccination. Drs. Francis and Hirst proceeded to Saipan and Guam where they found an increased incidence of respiratory infection identified by workers at NAMRU 2, on Guam, as influenza B. They subsequently obtained information that the Eighteenth Medical Laboratory on Okinawa had identified influenza B and also that it had information regarding another outbreak on Leyte, Philippine Islands. Dr. Salk visited Germany to establish diagnostic outposts in Army laboratories in the European theater.

In July 1945, Dr. Eaton identified influenza B in troops who became ill aboard a ship that had just arrived from the Pacific; a small local outbreak occurred in Stockton, California. Thereafter, in late August, outbreaks occurred at Fort Hood, Texas, Fort Dix , New Jersey, and at Fort Bragg, North Carolina. By November the illness was very widespread and was detected across the United States. Information from Australian workers indicated that this was the first time in their experience that influenza B was responsible for a large general epidemic.[39] Thus, it was demonstrated that influenza B, which had behaved like an endemic disease, had attained epidemic characteristics and caused sharp epidemics in specialized segments of the population.

Influenza A

Influenza A was not noted during most of the time that influenza B was prevalent. However, there were scattered cases of influenza A detected in the Fourth Medical Laboratory; this supported the belief that influenza A had occurred in 1945 and suggested the possibility that the current cases were forerunners of a more extensive epidemic in autumn of 1946.

Effectiveness of Vaccine Against Epidemic Influenza B

There was no system similar to that which had been used in 1943 available to demonstrate the effectiveness of vaccine against influenza A. However, several observations were made that indicated that the influenza B component of the vaccine was effective, possibly more so than the A component. None of these observations was as well controlled as the 1943 study. At the University of Michigan, the comparison of the attack rates in a small number of vaccinated Army personnel compared with unvaccinated Navy students showed a hospitalization rate of 1.15 in the vaccinated Army group and 9.91 in the Navy group, which was unvaccinated. At Yale University in Army and Navy student training units, Dr. Blake requested that Dr. Hirst visit the infirmary on November 19. The situation there was slightly better controlled. All persons with temperature levels of 100°F or more who could not attend classes had to visit the infirmary. Vaccine coverage was good for Army personnel. Navy personnel were not vaccinated. Obviously, many people failed to report to sick call.

Dr. Orville Rogers at the Yale University Department of Health, with the aid of Dr. Frederick C. Robbins, attempted to separate the cases into the following categories: (*a*) Influenza with typical picture; (*b*) influenza complications, indicating typical influenza followed by some other disorder such as otitis media; (*c*) influenza, questionable; (*d*) URTI, upper respiratory tract infection noninfluenzal. In each of these groups there was a heavy preponderance of cases in the Navy group compared with Army personnel. The difference in rates was 16.9% in unvaccinated and 1.9% (vaccine efficacy 89%) in vaccinated subjects. This showed obvious protection afforded by the vaccine.[40] The study also pointed to the effectiveness of vaccine given before an epidemic occurred and the value of an "alert system" that was organized to provide information on the prevalence of influenza B throughout the general population. Also, it was shown that influenza B, as well as influenza A, could be prevented by use of inactivated vaccine. This experience provided more valuable data obtained by the cooperative work of the Commission on Influenza control program.

Studies on Influenza Vaccines

Stability

Dr. Stanley studied the influence of various chemical agents on the stability of centrifuged vaccines.[40] Vaccine at a concentration of 1 mg/mL, when held at pH 7.6 and 4°C, showed a marked loss in agglutinating activity. The virus had been formalinized, in different concentrations, with buffers at pH 7.0 with no loss of titer at 4°C at 30 weeks. Virus treated with concentrations of Formalin of 1:640 and 1:570 also showed considerable loss of titer at 4°C. There was no loss at concentrations of 1:2000.

Dr. Salk showed that the stability of the virus in allantoic fluid exposed to temperatures between 56 and 65°C varied considerably from strain to strain. The Weiss strain (1943) was destroyed in 1.5 hours, the PR strain in 6 hours, whereas the B/Lee strain was stable for at least 10 hours but was destroyed in 24 to 36 hours.

Laboratory Studies

Tests by Dr. Hirst showed that there was no difference between the antibody levels of persons who had been vaccinated with either Commission-provided vaccine or vaccine prepared by Sharples cen-

trifugation at intervals of 2 weeks, 18 weeks, and 14 months after vaccination. Most vaccinees showed titers higher than their original level.[41]

Dr. Salk also compared the antibody levels at the end of the year of a group vaccinated with double-cycle centrifuged vaccine in amounts of 0.1 mg to 2.0 mg and compared with eluate vaccine prepared in 1943.[42] The best results were obtained with the 2.0 mg material. The differences were evident when measured against B/Lee, but less distinct against the type A viruses. There was no evidence that centrifuged vaccine, because of its purity, was superior antigenically to the eluate material except when the doses were increased beyond a practical level.

The results of the two studies established the fact that there was no standardized method for measuring HI antibodies. Dr. Salk continued to determine the possibility of increasing the potency of influenza vaccine by absorption to calcium phosphate. When influenza virus was absorbed to calcium phosphate, there was an increase in titer 2 weeks after vaccination. No data were obtained on persistence of antibody 1 year after vaccination.

Protective Effect of Vaccination in Swine

Dr. Beard and his associates continued to test the degree of immunity to induced infection after subcutaneous or intranasal vaccination of swine influenza virus in hogs.[43] Those animals that received vaccine subcutaneously appeared somewhat more resistant than those that were unvaccinated. This effect was most marked in those vaccinated three times before infection. All vaccinated animals showed sharp antibody rises after the intranasal administration of active virus. Animals that had recovered from intranasal infection showed a more complete and uniform resistance than any of the vaccinated groups. Some animals were revaccinated after 13 weeks and then rechallenged a month later. One fourth of the animals showed mild clinical infection randomly distributed between vaccinated and revaccinated animals. There was no evidence that revaccination enhanced the resistance of the recovered animals, although a further antibody increase took place. Dr. Beard and his colleagues next investigated the effect of combined intranasal and subcutaneous vaccination. Subsequent exposure to intranasal virus did not cause typical infection.

It appeared that antibody titers had an inverse relationship to clinical response to infection. In general, the results did correspond with those obtained in ferrets, demonstrating that subcutaneous vaccine did not produce a consistent solid immunity to infection.

Intranasal Vaccination in Humans and Ferrets

Dr. Francis and Dr. Joseph Quilligan investigated the effectiveness of an intranasal spray of inactivated vaccine on antibody response of children 8 to 12 years of age.[44] They found that a single spray produced a modest antibody response that was considerably increased when the spray was administered five times. After intranasal vaccination, the mean titer was less than one-half that following subcutaneous vaccination.

Intranasal spraying of vaccine in ferrets uniformly produced antibodies in all animals. However, all were susceptible to both influenza A and B viruses despite the antibody production.



JONAS E. SALK, M.D.

Dr. Jonas Salk, a New Yorker, received his medical degree from New York University in 1939. This was followed by internship at the Sinai Hospital from 1940 to 1942. He was attracted to the University of Michigan School of Public Health, Ann Arbor, by Dr. Thomas Francis, where he progressed through the ranks between 1942 and 1947 as fellow, research fellow of epidemiology, to associate professor of epidemiology. Here, during the war years, he worked closely with Dr. Francis and participated actively, with AFEB support and collaboration, pursuing and adding new important knowledge to the fields of influenza, pneumonia, related respiratory infections, and vaccine development. This outstanding work was conducted in the laboratory and in various U.S. military field sites throughout the country and abroad. Dr. Salk moved in 1947 to the University of Pittsburgh School of Medicine, where he directed the virus research laboratory and painstakingly developed the inactivated poliomyelitis vaccine. This was a contribution of immeasurable significance that has assured him lasting national and international recognition.

Strain Study Center

Drs. Magill and J. V. Sugg accepted the responsibility for rapid development of a center to identify influenza strains for the Army and for other laboratories where such facilities were lacking. Hyperimmune sera had been prepared. Sera were obtained from persons vaccinated during the 1943 and 1944 trials and then tested against various strains to determine the important antigenic differences. Similar data were obtained from ferrets.

The data showed that the differences among strains presented a fundamental problem that could not be ignored. The collection of strains had been continued. In addition to virus strains submitted by the various members of the Commission and associates in the United States, a large number of strains were received from Dr. Christopher Andrewes in England. There was no suitable method of systematic classification, and it was very difficult to predict the relationship of one strain to another. The question of whether a strain would be a good antigen had not been solved. The most feasible plan appeared to include standard strains such as WS and PR/8 and also several strains from recent epidemics. The latter should be derived from widely separated localities rather than from a single place.

Toxicity of Influenza Virus

Dr. Hale from the University of Iowa concerned himself with studies on mechanisms of toxicity and worked with a type B virus isolated on 19 November. Small amounts of this strain killed mice in 48 to 72 hours after intranasal inoculation and produced the same type of destruction of the respiratory epithelium as that produced by mouse-adapted virus.[45]

Vaccination

Dr. Francis and Dr. Salk began a study of the comparative effect of repeated doses of influenza virus given for five doses on alternate days, the effect of vaccine given every 2 weeks for five doses, and the effect of a single large dose. They also investigated an inhibitor found in allantoic fluid of newly isolated virus strains.

Vaccine obtained from Army stock supply was given to a large number of students and personnel at the University of Michigan. The vaccine appeared not to have lost potency and produced a satisfactory antibody response in a number of individuals. To determine the frequency of adverse reactions, 370 residents of girls' dormitories were carefully followed after vaccination. Four (1.1%) had fever of 100°F the following day, and nine (3.2%) others complained of malaise without evaluation of temperature. The mildness of these reactions was fairly surprising.

Early in March 1947, an increased number of respiratory illnesses occurred in Michigan. During the first part of the epidemic there was a high incidence of nausea, vomiting, and diarrhea in certain groups. Other cases appeared more characteristic of influenza. It seemed likely, on a clinical basis, that at least two different diseases were present. Attempts to isolate virus by egg inoculation were unsuccessful. Three strains were isolated in ferrets. They were type A but quite distinct from standard strains.

Other Field Investigations

Dr. Salk investigated an outbreak of respiratory disease at Chanute Field and Scott Field in Illinois during the last week of February 1947. The disease was characteristic of mild influenza. One of five



GEORGE K. HIRST, M.D.

George Hirst, a distinguished scientific product of the Rockefeller Institute, worked collaboratively with Frank Horsfall, Ed Kilbourne, and many others who contributed so importantly to our knowledge of influenza. His seminal discovery in 1941 was demonstration of the agglutination of erythrocytes by the influenza virus and that the elution reaction following hemagglutination was mediated by enzymes and that the neuraminidase enzyme was an important part of the virus molecule.

His work, with associates, on genetic manipulation of influenza viruses provided the basis for construction of better vaccines. Among his many accomplishments was editorship of the *Journal of Virology* (1955) and directorship of the Public Health Research Institute of the city of New York (1956). The Commission on Influenza of the AFEB was enriched by his contributions.

throat washings yielded a virus by egg inoculation. Type A virus was identified. The interesting observation was made that the disease had a much higher attack rate in students than in the permanent personnel. A like observation was subsequently made at Scott Field, where a similar illness occurred almost simultaneously with the administration of vaccine. The serologic (HI) tests did not distinguish cases of influenza from the response to vaccines.

During an outbreak of typical influenza, Dr. Hale at the University of Iowa inoculated throat washings from 15 patients into eggs. He used both amniotic and allantoic routes and multiple passages of each specimen. No virus had been isolated up to this point. Convalescent sera had not shown a rise in antibody against virus type A or B.

Dr. Hirst in New York isolated a number of strains of influenza A. The strains were difficult to identify by serologic tests. The outbreak was not sharp, but appeared to be low grade and long continued. One strain was isolated from the Army personnel at Fort Monmouth, New Jersey (FM-1). Dr. Magill in New York received no materials from Army hospitals. Throat washings from civilians were tested but none were positive. Dr. Eaton in California reported that influenza had been recognized in January, and identification of virus was made by the Army laboratory personnel at Monterey. Cases of influenza appeared among several civilian populations in northern California.

Dr. Harold Diehl at the University of Minnesota investigated the effect of influenza vaccine against the common cold. No favorable protective effect was demonstrated.[46]

1947 and 1948

Following an epidemic of mild influenza in the early months of 1947, numerous laboratory groups isolated strains of influenza A virus and studied the serologic responses of patients. It was clearly established that the virus was related to type A but was serologically distinct from the strains such as PR/8, which was contained in the vaccine. In addition, observers noticed that the vaccine provided poor protection against the new virus strains. These strains were more difficult to isolate in eggs, adapt to good growth in the allantoic sac, and adapt to mice. Serologic tests were difficult to evaluate because of the high inhibitory effect similar to that observed in 1945 with the new strains of influenza B. It was suggested that the group be called "A-prime" (H1N1). During the remainder of the year strains of influenza A-prime were isolated in a number of areas, but no epidemic occurred until November. A sharp rise in cases was recognized in California with an incidence comparable to that in early 1947. Influenza A virus circulated for a full year, with behavior similar to influenza B in 1945.

Influenza Vaccine

At the annual meeting of the AFEB in May 1947, it was recommended that (*a*) influenza vaccine be used throughout the Army in the autumn of 1947; (*b*) the FM-1 strain of the 1947 variety (A-prime) be incorporated into the vaccine; and (*c*) controlled studies be made on a continuing basis for the evaluation of influenza vaccine in the Army.

Because of the short time interval, most pharmaceutical companies were reluctant to provide vaccine. The contract was finally made with Lederle Laboratories for the preparation of vaccine by centrifugation. The delivery of this vaccine was delayed because of production difficulties.

Tests of these vaccines in humans suggested that the material was not as effective as might have been anticipated and was less effective than older material that was on hand. It was suggested that the FM-1 strain was not as stable as PR/8 and that the antibody response to the A-prime strain was not as high as against other type A strains. The stability and behavior of these A/prime viruses remained a problem.

Field Studies

A large study comparing the rates of illness in vaccinated and unvaccinated individuals was undertaken at the University of Michigan. In this study involving 17,000 vaccinees, the results clearly showed failure of the prophylactic effect of vaccination.

Because the recommendation had already been approved to vaccinate all Army personnel in the fall, a problem had been created because testing controlled by use of placebo could not be done. It seemed feasible, however, to compare the value of the "old" vaccine containing the PR/8 virus and the "new" vaccine containing equal amounts of FM-1 and PR/8 as one-half of the A component. Approval for such a study was obtained from The Surgeon General's Office and the study was begun 14 November 1947 by Dr. Salk at Fort Dix. Another study designed to evaluate vaccine and compare attack rates on vaccinated Army personnel was arranged at Fort Belvoir, Virginia, and the Marine Base at Quantico, Virginia, where vaccine was not to be given (control group).

The ad hoc committee appointed by the Board to plan for these studies consisted of Drs. Francis, Dingle, and Joseph Smadel together with Drs. Salk and MacLeod, Lieutenant Colonels Robert Bauer and Arthur Long, and Colonel Thomas Whayne. It met again on 15 March 1948. There had been no peak of influenza A during the previous season, and the great bulk of illnesses occurred on the west coast. Dr. Meiklejohn reviewed the prevalence in California and pointed out that the incidence was about the same as the previous year and that the strains were antigenically similar. Dr. Salk had encountered difficulties in his field studies because Army personnel specifically assigned to assist in the work were not available at the installations.

The Committee did not recommend uniform vaccination for the coming year; it suggested that reasonable stockpiles of vaccine containing type A, A-prime, and B be prepared. The Committee recommended that (*a*) a controlled evaluation in the Army be conducted in the coming year, especially in view of the experience with the A-prime strains that were encountered over the previous 2 years; (*b*) a controlled study be conducted at Fort Dix employing monovalent A, A-prime, and B vaccines in the same units; (*c*) the study at Ft. Belvoir and Quantico be continued if conditions were advantageous; and (*d*) the situation at Fort Ord be explored by Dr. Meiklejohn with a view to conducting a study similar to that at Fort Dix. The Committee formulated a number of specifications for the new vaccine and considered that its ad hoc functions had been fulfilled.

Strain Study Center

The Strain Study Center that had been maintained by Dr. Magill was reactivated and expanded. Efforts were being made to obtain standard sera and to follow standard procedures. The committee of Drs. Magill, Feller, Ross Gauld, and Salk were asked to confer about the adoption of a procedure as a standard of reference for HI tests. The facilities of the Center were offered for cooperation with the World Health Organization's (WHO) plan to establish listening posts like those that the Commission had maintained for 6 years. It seemed likely that this Center would be the major center for the Americas.

Other Studies

To determine the effect of repeated inoculation of one strain of virus on the breadth of the antibody response to strains of different degrees of relationship, groups of children (average age 3.2 years) were given vaccine in various doses and at various intervals. It was found, in general, that children over 4

years had probably been previously infected and produced their maximum response after their first dose of vaccine. Titers changed little with subsequent doses. Children under age 3 years behaved somewhat differently and reached their maximum titer after the third dose and did not increase thereafter. The study showed that children may not produce the broader heterologous response of the type observed in experimental animals such as the ferret. It also showed that when children were given small dosages, more than one dose should be given.[47]

Dr. Salk obtained evidence that intramuscular injection of virus might produce a better antibody response than the usual procedure of subcutaneous injection. In association with Dr. Dionyz Blaskovic, he also obtained data that indicated that the HI antibody and virus neutralizing antibody were separate entities as measured in the egg neutralization tests.[48] He continued his studies on potency tests of vaccines.

Dr. Meiklejohn reported from California that there had been a moderately widespread incidence of influenza A-prime starting in the southern part of the state. A-prime viruses had been isolated from 8 of 11 separate throat washings following amniotic inoculation of chick embryos. The first passage of the virus showed hemagglutination with only one of the seven strains, but all of the viruses agglutinated red blood cells readily in the second passage.[49] In comparing the results of HI and complement fixation tests on 40 serum pairs from early 1947 and 90 pairs from 1947 and 1948, it was found that only 64% developed a significant increase in HI titer to the PR/8 strain. The complement fixation tests appeared to have been the most useful single diagnostic procedure.

Following through on recommendations of the special committee on A-prime strains, contact was made with Colonel Alvin L. Gorby, Sixth Army Surgeon at Fort Ord, and with Colonel Francis E. Council, also of the Sixth Army Medical Laboratory. This was with the aim to arrange a study at Fort Ord analogous to the one conducted at Fort Dix. It appeared probable that satisfactory arrangements could be made. A comparison of the administration of vaccine by the intradermal route and the subcutaneous route was carried out in three groups, one in children and two in adults.

Dr. Loosli compared the response to inoculations of 1 mL given subcutaneously and 0.1 mL intracutaneously against five virus strains. The intracutaneous method appeared to produce a response as satisfactory as the subcutaneous route when tested with PR/8 and Lee strains of virus, but not with the A-prime, the FM-1, and J-16 strains. The response to FM-1 was unsatisfactory with either method of vaccine administration.

1948 and 1949

Six years had passed since the last characteristic epidemic of influenza A and 4 years since the last sharp epidemic of influenza B. It appeared that widely held opinions on the epidemiology of influenza held in the past were inaccurate. In the first parts of 1947 and 1948, A-prime viruses were distributed widely. Influenza B was also present in Germany; in Australia a sharp outbreak of A-prime occurred early in the year, and later in the year an outbreak of influenza B. In Europe, influenza B occurred rather widely and in the United States both A-prime and influenza B were present throughout the year. Interestingly, in Germany during the period from 1948 to 1949, all three viruses were isolated, the most numerous isolates being influenza A-prime.

World Health Organization Program

During 1949, the program initiated by the WHO had been more definitely formulated. The members of the Commission (see list of members, next page) continued to try to detect influenza as they had since 1942. They also agreed to transmit information to the Information Center established by the Public Health Service. There was a strong conviction that the Commission on Influenza should retain its integrity and functions in relation to the AFEB. The Strain Study Center established by the Commission

at Cornell under Dr. Magill was transferred along with him to the Long Island College of Medicine. It was recommended and agreed that this would serve as the Strain Center of the WHO for the hemisphere. The Commission members agreed that, when consulted about matters such as selection of strains for the next year's vaccine for civilian use, the Commission would speak as a group rather than as individuals.

Members of the Commission — 1948 to 1949

Members
Dr. George K. Hirst
Dr. Thomas P. Magill
Dr. Gordon Meiklejohn
Dr. Jonas E. Salk

Director
Dr. Thomas Francis, Jr.

Associates
Dr. G. John Buddingh
Dr. Monroe D. Eaton
Dr. William M. Hale
Dr. Edwin H. Lennette
Dr. Clayton G. Loosli
Dr. Frederick A. Rasmussen

Standardization of Procedures

A committee with Dr. Magill as Chairman and composed of Drs. Salk, Meiklejohn, Feller, and Gauld (of the Army Medical School) met to devise an HI test for the influenza virus to serve as a standard of reference for all the modifications used in different laboratories. The last meeting was held on 3 March 1949, in Ann Arbor, Michigan. It was recommended that both HI and complement fixation tests should be used for routine serologic diagnosis.

Laboratory Studies

Dr. Oti in Japan provided a strain of A-prime virus isolated from swine in Korea. The virus was not neutralized by standard Swine 15 serum or by PR/8 serum. It was found, however, that the anti-Oti serum in the Michigan laboratory did neutralize that virus to some extent. It was felt that the antibody responses were essentially parallel to that observed with the A-prime strain Rhodes. The results suggested that either the strain was of human origin fortuitously isolated from swine or that a swine strain had become prevalent in the human population.[50]

Strain variation was demonstrated by Dr. Cheng-i Wang, who studied two lines of the Rhodes A-prime virus. One had been isolated and maintained in eggs; the other was adapted to mice. When the strains were introduced into mice, it was shown that the mouse-adapted line multiplied rapidly so as to reach its peak in about 12 hours; hemagglutination titers developed later. The egg-adapted strain reached its peak in about 48 hours, and only a minimal titer of hemagglutinin developed. The results suggested that the strains in epidemics may be those that, by selection, can multiply most rapidly in the human host.

THE COMMISSION — 1950 TO 1957

By 1950, the composition of the Commission had changed. The number of members remained relatively small. Dr. Lennette was made a member of the Commission when Dr. Meiklejohn left California to join the faculty of Medicine at the University of Colorado. The number of associate members was



JOSEPH E. SMADEL, M.D.

For 32 years, Dr. Joseph Smadel was a physician and investigator whose contributions to medical science either saved or prolonged the lives of thousands of people. At the time of his death in 1963, Joe was recognized as one of the outstanding scientists of the mid-20th century. Expecting no reward, he performed research because he liked it, and his labors provided the essential bridge between the laboratory and the physician who cares for infected patients. One of his most satisfying experiences was the therapeutic triumph with chloramphenicol in the treatment of typhus and typhoid fevers, and the successful field trials that showed that this antibiotic effectively suppressed scrub typhus infection.

A major contributor to the Armed Forces Epidemiological Board, he organized and directed three of its Commissions: those on Immunization, Rickettsial Diseases, and Epidemic Hemorrhagic Fever; each of these Commissions bears the indelible Smadel mark. He was also a member of the Commissions on Epidemiological Survey, Virus Diseases, and Influenza, and his stabilizing influence during the developmental phases of the poliomyelitis vaccine trials contributed significantly to that success.

Joe had little patience for armchair philosophy, and he crusaded against shallow thinking. He demanded unswerving performance from his associates, who were expected to exercise good judgment and to adhere to his personal brand of integrity. He never allowed his personal burdens to interfere with his dedication to his work, and his enthusiasm sparked the enthusiasm of his associates. He worked intently and set an example for others.

increased considerably and included many investigators in the country involved in influenza research. In addition, representation from the Public Health Service (Dr. Bell) and the Navy (Commander John Seal) and from Canada (Dr. Henry van Rooyen) were invited to attend the meetings. It was generally accepted that influenza vaccine had been shown to prevent both influenzas A and B, but the results showed there was need for improvement in the vaccine at the level of protection and duration of immunity.

Work continued by members and associate members on the problems of improving the vaccine and developing a better understanding of the mysteries of influenza virus. Most of the laboratories associated with the Commission continued to identify viruses and to evaluate the antigenic composition of the strains. Requests for assistance from the Armed Services were infrequent, and the Commission no longer received direct information from any of the Services concerning influenza. The reports on respiratory disease rates in the Army usually contained information that was 3 to 4 weeks old. It appeared that the service laboratories had reached the stage of development that enabled them to function adequately on their own. In addition, the laboratories at WRAIR had developed rapidly under Dr. Smadel and Dr. Maurice Hilleman and regularly carried on their own activities at a top level. The Commission decided at its annual meeting to initiate a pattern of performance that was to continue throughout most of its existence.

The members and associate members met annually in Ann Arbor, Michigan, along with members of the preventive medicine branches of the three services. The meetings began with a report from each of the services on the status of influenza and of respiratory diseases in their respective services. These were followed by reports from members of the Commission or others directly concerned with vaccine studies and subsequent reports by all members of the Commission, associate members, and contractors who were engaged in other types of research. These were lively, delightful meetings that were moderated by Dr. Francis, who was a very effective leader for the meetings. He had a great regard for vigorous proof of any claims that were put forth and in a good natured way was able to distinguish between good and bad science. The meetings had a congenial character that was helped by the fact that the participants were all housed in the Michigan union, where they could get to know the other participants well. The last evening was usually spent at Dr. Francis' house where the group again enjoyed a very friendly atmosphere. The relationships developed there lasted for many years. Dr. Francis, in the following years, assembled a very able and productive group of investigators in his department at Ann Arbor, Michigan. Dr. Salk came in 1941 as a National Research Council Fellow and remained until 1947, when he moved to the University of Pittsburgh. There he continued his adjuvant vaccine activities for a while and then shifted to the development of poliomyelitis vaccine. He stated that after trying to make a good influenza vaccine, it was very easy to make a vaccine for polio following the discovery by John Enders, Thomas Weller, and Robbins that polio virus could be grown in non-neural tissue.

After Dr. Salk's departure, Dr. Davenport was recruited, also from the Rockefeller Foundation. Dr. Davenport was an extremely dedicated person who worked very hard to move the program ahead. He also tried his best to maintain close relations with the Army medical personnel with somewhat dubious success. He was a very direct person, always honest and friendly. Other members of the staff included two pediatricians, Dr. Albert V. Hennessy and Dr. Quilligan, who obtained much information on immunity to influenza viruses in children and defined most of the difficulties in immunizing young children.

Drs. P. K. Brown and W. W. Ackerman, both basic scientists, were also valuable members of the team. Finally, Elva Minuse, the personal assistant of Dr. Francis, must be acknowledged. She had had long experience with influenza viruses and was thoroughly familiar with all procedures involved in isolating viruses and propagating them in eggs and mice. She was available to help any of the other investigators who worked with different laboratory procedures. It is of some historical interest that she had a major role in the isolation and adaptation of influenza B virus in mice.

The University of Michigan became the national center of influenza research. Among the investigators who became prominent in influenza research were the following: From the United States, Drs.

Keith Jensen, Gary Noble, Walter Dowdle, and William Marine. The first three of these subsequently went to the Centers for Disease Control, Atlanta, Georgia. Dr. R. Q. Robinson and Allan Kendal from England, Dr. Hideo Fukumi and several others from Japan, and Drs. Rob Webster and Fajekas van Groth from Australia all gained valuable experience at Ann Arbor, Michigan. The investigators at the laboratory remained in close contact with their British colleagues, who were under the direction of Dr. Christopher Andrewes.

Adjuvant Vaccine

Dr. Salk ceased his work with other possible adjuvants for influenza vaccine in favor of an adjuvant of mineral oil (Bayol F) and with Arlacel A (Freund's adjuvant without mycobacteria). The animal work had progressed well and he investigated the advantages of the adjuvant vaccine in humans. The same amount of virus in adjuvant produced far higher titers than aqueous vaccine; titers continued to rise for 6 weeks. At the end of the year, titers were far higher than they were for aqueous vaccine. One year after receiving vaccine containing 300 chicken cell agglutinating (CCA) units of virus, 90% to 96% of those who received the adjuvant vaccine showed titers of 256, compared with 28% with aqueous vaccine. Titers against the B-Lee and A-prime/Cuppett strains were lower than with earlier A strains.[51]

The dose of vaccine was studied in considerable detail.[52] It was also shown that with a dose of 0.25 mL of adjuvant, as little as 10 CCA units of antigen would evoke an antibody response comparable to 300 CCA in aqueous vaccine. It was shown that when the volume of the material was increased from 0.25 to 1.0 mL of suspension, the antibody response was better with the larger volume. In terms of heterologous antibody, Dr. Salk demonstrated that the Cuppett strain in adjuvant produced a far broader heterologous antibody response than the same strain in the aqueous vaccine. It was also shown that the B-Lee strain of influenza (1940) produced a response parallel to the Warner virus (1948).

The prophylactic studies of adjuvant vaccine contained 500 CCA units per dose, considerably more than that used in any of the other vaccines. This amount of virus caused some local discomfort for 3 days in a number of persons. Furthermore, in 4,200 persons inoculated with the vaccine between 24 October and December 1951, 17 (0.4%) developed subcutaneous fluctuant cystic swellings at the site of inoculation after 3 to 4 months. These swellings subsided after aspiration and were invariably sterile. They developed from the subcutaneous administration of the vaccine and appeared to be related to the lot of emulsifying material in the vaccine. Dr. S. H. Sell had observed 7 (0.2%) such incidents after vaccination of 3,000 persons with a similar vaccine.[53]

Dr. Hennessey at Michigan expanded studies to obtain information on the combination of influenza C virus with red cells.[54] Dr. Frederick A. Rasmussen continued studies with the synthetic polypeptides and demonstrated that sequential blockade could actually be demonstrated in one system with influenza virus. His efforts to demonstrate recombination were unsuccessful.[54]

Dr. Loosli continued his studies of the effect of active and passive immunity in mice. His work with cortisone showed that mice tended to develop a spontaneous bacteremia from their own organisms. Cortisone was not found, however, to exhibit any influence on the antibody response to influenza virus, although after intraperitoneal inoculation of influenza virus, the agent persisted considerably longer and in larger amounts than in control animals.[54]

Field Studies

Parallel studies were conducted at Fort Ord and Fort Dix. Polyvalent aqueous vaccine containing PR/8, FM-1, and Cuppett strains of A and the Lee strain of B and a control vaccine of formalinized saline were given to equal numbers of volunteers. Influenza A-prime occurred in both areas in January, February, and March. A final summary of the results showed an approximately 4:1 (VE 75%) result in favor of the A vaccine in groups of essentially equal numbers.[54, 55]



EDWIN H. LENNETTE, M.D., Ph.D.

Dr. Edwin Lennette graduated from the University of Chicago, and was on the staff of the Rockefeller Institute at the same time as Dr. Monroe Eaton. He had worked on influenza while at the institute. He had been in charge of the viral encephalitis unit in Brazil. Almost all of his laboratory staff had been infected by airborn Venezuelan encephalitis virus, and he himself had been one of the victims. When Dr. Eaton moved to Harvard as associate professor, Dr. Lennette was brought to Berkeley as his replacement. Dr. Lennette's interests in virology were very wide, and he soon developed diagnostic facilities at Berkeley that were probably unmatched in the country at the time.

He was highly active in discussions at meetings of the Commission. He liked to point out how frustrating it was to put in all the work and time in setting up field studies, and find that the disease that one was trying to prevent did not appear. This was an experience shared by other investigators who had set up studies on influenza or adenovirus disease in various parts of the country. In many years, either more, or only one or two, of the units had enough disease to provide significant results. After some time, his colleagues on the Commission developed what they called "Lennette's Law." "Lennette's Law" stated in essence "that it was impossible to evaluate a vaccine in the absence of the disease which the vaccine was supposed to prevent."

Fort Dix — Fort Ord studies

	Vaccine		Placebo
Cases of Influenza	A	B	C
Fort Dix	26	99	96
Fort Ord	13	54	51
Total	39	153	147

A study performed at the University of Michigan in an uncontrolled student population had failed to show any vaccine effectiveness. It is worth pointing out that both at Forts Dix and Ord, the number of cases was relatively small and was based only on patients admitted to the hospital. Presumably this was due to the fact that influenza A-prime produced only mild illness and did not require too many hospitalizations.

In two other studies at the University of Michigan, Dr. Francis obtained evidence that the vaccine reduced the incidence of influenza B. Captain Robert O. Peckinpaugh at Great Lakes Naval Training Center, Great Lakes, Michigan, also reported that Navy personnel experienced some influenza B, none of which occurred in persons who had received the B vaccine.

Other Studies

A study at Michigan that compared the antibody response of humans to mouse and egg lines of the same virus suggested that the mouse line was a better antigen in humans.[54]

Antigenic Analysis

Dr. Magill reported that an analysis of 100 strains of influenza virus from different years and different locations suggested to him that they represented five different subgroups of type A and four subgroups of type B. The groups seemed to be related to different time periods, and it was suggested that a relatively orderly progression was taking place. The dominant antigens of the early strains were less likely to be encountered in recent strains.[54] This interpretation was not universally accepted. There was a suggestion that the pattern was either recurrent or periodic. The studies were important in helping establish the antigenic constitution of the various strains and in providing information on the usefulness of the different components of future vaccines. Dr. Hirst, following the same lines of interest, used antibody absorption tests.

Dr. Keith Jensen at Michigan studied antibody absorption using the Oudin procedure of antibody migration in a semisolid medium to demonstrate the number of antigen–antibody reactions that could be detected.[54]

Drs. Magill and Beard undertook a study to establish methods to measure the relations of viruses to their biological activity, such as infectivity, agglutination, etc. There was, at that time, no proper reference standard. They suggested that the activity of the virus particle was related to the spheroid particles and that the filamentous forms did not interfere with potency determinations. It appeared that further studies were needed to clarify a number of points.[54]

Dr. Davenport conducted studies on adaptation of virus.[56] When the viruses were used in diluted concentrations, adaptation appeared to be sharply retarded. These data suggested that the virus population becomes homogenous during passage. There was a definite correlation between the capacity to produce pulmonary lesions in mice and the concentration of virus as measured by hemagglutination. This was not true for infectivity in eggs. The mouse-adapted strain was less influenced by an inhibitor in normal mouse lung suspensions, indicating another capacity acquired by the virus during adaptation.



FREDERICK M. DAVENPORT, M.D.

No one connected with a commission of the board was more faithful and persistent in his effort to reach the right conclusion than Dr. Fred Davenport. His former chief, Dr. Thomas Francis, passed the baton on influenza to Fred. Control by vaccine was under intense development as was the need to evolve a better understanding of the pathogenesis and epidemiology of influenza. He collaborated with the Commission as a member and directed its activities from 1955 to 1971. He was deliberate and thorough in all of his investigative studies, and the comments that he made during various meetings of the Commission and board were incisive. Michigan should be very proud of Fred Davenport and Tom Francis, who served the board and the public so effectively.

Dr. Harry Rose continued his investigation of a substance in human sputum that had a pronounced favorable effect on eggs infected with influenza viruses. The substance appeared to be a protein, very labile in character, and not a specific antibody. In eggs injected with 1,000 egg infective dose 50, the inhibitor reduced virus multiplication and delayed the death of the embryo. It appeared to have a limiting effect on multiplication of virus and a protective effect in the mice. He was attempting, at the time, to establish the nature of the material.

Administrative Affairs

The Commission on Influenza met in Ann Arbor on 31 March and 1 April 1952. Attendees included Colonel Fratis L. Duff, Chief of Preventive Medicine of the U.S. Air Force, and Colonel Adam J. Rapalski, Executive Secretary of the AFEB, in addition to those listed in Appendix 3. The following recommendations were made: (*a*) Continued studies on the evaluation of influenza vaccine have consistently demonstrated that vaccine is effective in the prophylaxis of influenza caused by strains of virus prevalent in recent years. (*b*) It is essential that vaccination be carried out 2 weeks or more prior to an outbreak of an epidemic in an area. (*c*) There is no reason why vaccine should not be used uniformly if the avoidance of influenza is of sufficient importance. (*d*) The number of essential antigens is not known and a decision as to the most effective composition of vaccine is not possible at present. (*e*) Studies of influenza virus vaccine suspended in mineral oil (Bayol F) and in Arlacel A had shown great efficiency in stimulating extremely high and persistent levels of antibody. Furthermore, the amount of virus required was small. However, because of insufficient knowledge about those certain factors and occasional reactions of an undesirable nature, adjuvant vaccine should not be recommended for routine use. (*f*) The investigation of applicability should be continued under the direction of Dr. Salk.

There was further discussion of a number of points, such as the duration of resistance after vaccination and the stability of the vaccine. It was suggested that vaccine aged several years should be tested to determine its effectiveness in producing antibody. The possibility of conducting studies on Air Force bases such as Camp Sampson in New York state was also considered.

Dr. van Rooyen asked whether the Commission would make recommendations concerning the use of influenza vaccine for visitors within the Arctic Circle. The Commission thought this was an interesting problem, but the decision on such a matter was outside the jurisdiction of the Commission. At the conclusion of the meeting, Dr. Francis made the following notes about future plans:

> No sharp shift of emphasis in studies has been planned for the coming year. The scope of activities is, at the present time, extremely broad and the extension of them in various directions will constitute a wide and diversified approach to the problem of influenza. It must be emphasized that in all activities the increased cost has been a serious item and the obtaining of personnel a continuing obstacle.

The last year of the A/H1N1 decade, 1957, was an unusually interesting one. An epidemic of influenza A-prime occurred in the Orient in November 1956 and later spread to the United States and Europe. The virus was identified at Great Lakes Naval Training Center, Great Lakes, Michigan, in December, and a sharp outbreak occurred at Lowry Air Force Base, Denver, Colorado, in January. By late January and February, influenza A-prime was reported from Washington, Michigan, Tennessee, California, Virginia, Arkansas, and New Jersey. The disease appeared to be mild but widely disseminated in many areas. The virus showed considerable antigenic drift from earlier A-prime strains, similar to those studied in 1956 by Dr. J. Mulder in the Netherlands. Influenza B was also present.

Dr. Meiklejohn reported that despite the considerable antigenic drift, aqueous vaccine containing 750 CCA units of strain A/Ann Arbor/56 provided a protection of 6:1 (vaccine efficacy 84%) in recruits.[57] In seasoned (permanent party) troops, protection was considerably less apparent. The attack rate in the vaccinated persons was essentially the same as in the recruit population, but the attack rate in those not vaccinated was far lower, presumably due to the fact that the level of immunity was considerably higher. At Fort Dix the incidence was too low to permit an evaluation of protection.

THE COMMISSION — 1957 TO 1961

In 1957 the Asian influenza virus appeared, first on the continent of Asia and subsequently around the whole world. This was by far the most damaging pandemic of influenza since 1918 and 1919. The virus, although still clearly an influenza A virus, had changed both its hemagglutinin and neuraminidase. The population at large had no HI antibody to this virus and was almost entirely vulnerable.

The virus was identified in the fall in the United States by Dr. Hilleman at the Respiratory Disease Division at the Walter Reed Army Institute of Research (WRAIR) and was confirmed by Dr. Keith Jensen at the Centers for Disease Control and at the Ann Arbor Virus Laboratory. The director of the Commission traveled to Australia, the Philippines, Japan, Hawaii, and to Santiago, Chile.

It soon became clear that vaccine would be in short supply at the time when the virus reached the various bases. A number of studies were performed comparing the effect of intradermal injection of 0.1 mL with that of an intramuscular dose of 1.0 mL. A number of investigators showed that a satisfactory antibody response could not be obtained with a single subcutaneous dose of 200 CCA units of vaccine. The 400 CCA units dose was distinctly superior. However, two injections of 200 CCA units of vaccine given 2 months apart produced a response better than a single injection of 400 CCA units.[58] Subcutaneous injection of 20 or 40 CCA units in two doses, 2 weeks apart produced an antibody response similar to that produced by a single injection of 200 CCA units.[59] Reasonably satisfactory results could be obtained by two intracutaneous or subcutaneous injections of 20 CCA units given 1 week apart.[60] When 100 and 200 units were given subcutaneously, antibody response was clearly superior.

The Commission was able to obtain limited amounts of vaccine containing 200 or 400 CCA in September and provide enough for studies at Lowry Air Force Base, Fort Dix, Great Lakes, and Fort Ord. The last three based their data on hospital admissions; at Lowry Air Force Base diagnosis was confirmed by serodiagnosis; with vaccine containing 200 CCA units, the VE was 60%; with vaccine containing 400 CCA units, the VE was 72%. Much helpful information was obtained about vaccines containing A strains. The protection was better with larger doses of virus but was less than that found in previous outbreaks.[61]

It was clear that a single dose of vaccine did not produce a satisfactory antibody response in persons who had no prior experience with that virus. Persons who had previously been exposed by infection or vaccination had a higher response when given vaccine after 3 months.

Administrative Affairs

The Commission was confronted by a decision of the Army to discontinue annual influenza vaccination. The decision was administrative, based on the fact that during the last 5 years, influenza had been a mild illness of low incidence. The Commission pointed out that outbreaks had occurred in unvaccinated forces and intense outbreaks had been observed in civilian and military populations where vaccination was not carried out. It was pointed out that periods of major outbreaks had been preceded by a period of low incidence.

> The decision not to use influenza vaccines apparently has been made on administrative grounds; from the scientific standpoint it is considered by the Commission to be untimely and unjustified. It is the belief, therefore, that vaccination against influenza should be continued on an annual basis throughout the Armed Forces.[62]

The second topic was a reappraisal of the direction of the Commission's activities. Each contractor had been requested to submit his views in writing to the Director prior to the meeting. The consensus was that the Commission should continue the studies on acute respiratory diseases. It seemed wise to reduce the size of these studies but to expand their scope so that more clinical, virologic, and serologic information could be obtained.

The outlook for efficacy of Asian virus vaccines in future epidemics was perceived to be much more promising because of the demonstration that a high level of antibody followed vaccination in persons previously exposed by infection or vaccination, at intervals of 6 weeks or 3 months.[58] The two-dose program of vaccination adopted by the military for 1958 and 1959 was expected to be highly effective if Asian influenza reappeared.

Influenza—Associated Deaths

Asian virus strains were isolated from 24 fatal cases by 7 members or associate members of the Commission. The findings reemphasized the importance of *Staphylococci* in promoting a fatal outcome. However, in 12 of the fatal cases identified, no significant bacterial pathogen was found. Pregnancy or preexisting heart disease were conditions that predisposed to a fatal outcome.

Other Studies

Drs. Davenport and Hennessy compared Asian antibody levels in persons in different age groups in Ann Arbor. Their findings confirmed observations by Dr. Mulder that antibodies to Asian strains were present in sera of persons over 60 years of age; this suggested that a similar virus was present around the time of the pandemic of 1889 and 1890. These results suggested that a recycling of viruses was occurring.[63]

Adenovirus Vaccine

Adenovirus vaccine continued to give conflicting results, sometimes very favorable, sometimes disappointing. Dr. Loosli at San Diego, in laboratory-confirmed cases, reported protection against type 4 was about 72%.[64]

Dr. J. O. Culver at Fort Ord reported 93% effectiveness against type 4 adenovirus.[65] Type 4 was a relatively poor antigen with great variability in the quality of the vaccine.

In all instances, the reduction of specific adenovirus rates was considerably greater than the overall reduction in the respiratory disease rates. It was estimated that a large percent of patients experienced illnesses other than those caused by adenoviruses. For that reason, the possibility of an adjuvant vaccine containing not only types 4 and 7 adenovirus, but also the JH agent, hemadsorption viruses (parainfluenza), and other uncharacteristic agents should be present and evaluated. The Commission proposed to develop studies of this nature.

Influenza Prevalence in 1959 and 1960

In 1959 and 1960, Asian influenza again appeared on a large scale. The incidence was high, and the excess deaths attributed to influenza and pneumonia exceeded the number observed at the peak of the fall outbreak of 1957. Curiously, little attention was paid to this by the public and press. The virus, which had been present since 1957, appeared four times in 4 years with no evidence of antigenic drift, which was unique in the history of influenza A infection. Despite a number of outbreaks with high attack rates in civilians, military personnel vaccinated in accordance with recommendations made by the Commission on Influenza were not significantly involved in the sharp outbreaks that civilians experienced in the surrounding communities.

A number of controlled studies during this outbreak demonstrated the effects of combined vaccine for both influenza and adenovirus infections. At Lowry Air Force Base, Dr. Meiklejohn tested the efficacy of a multivirus vaccine in emulsified mineral oil. The vaccine contained 350 CCA units of influenza viruses composed of the following: A/Jap/305/57 (H2N2), 100 units; A-prime (H1N1), 50 units; PR/8, 50 units; Swine, 50 units ; B-Lee/40, 50 units; and B-Great Lakes/54, 50 units. In addition, one-half the standard amounts of types 4 and 7 adenovirus were included. The crude reduction of illness in

this outbreak was 4:1. Adenovirus, type 7, and influenza infections occurred at the same time and this outbreak was fairly extensive. The serologic data indicated that protective efficacy against influenza A was approximately 94%, and against adenovirus type 7, was approximately 90%.[66]

Dr. Rose, working at Fort Dix, used a multivirus aqueous vaccine that contained, in addition to the types 4 and 7 adenovirus, 1,000 CCA of aqueous influenza vaccine divided as follows: 400 CCA units of Asian, 100 units of A-prime, 100 CCA units of PR/8, 100 units of Swine, 200 units of B-Great Lakes, and 100 units of B-Lee. This vaccine showed protective efficacy of 83% when compared with the standard Army influenza vaccine and demonstrated the practicality of combining influenza and adenoviruses in an aqueous vaccine or an emulsified mineral oil vaccine.[67]

Dr. Hennessy reported a protection ratio (VE 38%) in children aged 5 through 12 years of 1.6 to 1 against influenza B. The aqueous vaccine used contained four influenza virus strains, in addition to amounts of JH, 2060, HA1 and 2, CA, CCA , and adenovirus types 1, 2, 3, 4, 5, and 7. No significant reactions were noted. A difference in attack rate was found only during an outbreak of influenza B. This difference was small due to lack of adequate antibody response to the influenza B virus strains.[67]

Dr. Bryon Berlin continued his investigation of adjuvant vaccines. He was unable to find any animal or vegetable oil that was as effective as mineral oil.[60]

Dr. Quilligan noted a protection ratio of approximately 3.7:1 (VE 73%) in children with mental handicaps who had received a monovalent vaccine in 1957 and again in January and May of 1958 and also in 1959. He made the interesting observation that febrile reactions declined with each vaccination.[68]

THE COMMISSION — 1962 TO 1967

During the remainder of the A H2N2 decade, the Asian virus did not create any serious problems in the Armed Services. All personnel were vaccinated each year, and it was not possible to obtain any results from field trials. The alert systems showed that both influenzas A and B were present. In many communities the occurrence of outbreaks of influenza infection affected 20% of the community but did not appear to cause any problems in the Armed Services even though the virus had been repeatedly introduced at the bases.

The Commission maintained its operations much as before, with members and associates of the Commission involved in the following field studies: (*a*) Dr. Rose at Fort Dix in collaboration with the Army group at WRAIR; (*b*) Dr. Chanock at Camp Lejeune and Parris Island with the naval base there; (*c*) Drs. Francis and Davenport at Great Lakes Naval Station cooperating with NAMRU 4; (*d*) Dr. William Mogabgab at Keesler Air Force Base in Louisiana; (*e*) Dr. Meiklejohn at Lowry Air Force Base in Denver; and (*f*) Dr. Loosli with naval and marine units in San Diego.

Adenovirus infections appeared to increase in importance. They had become an even more serious problem than influenza in terms of morbidity from viral respiratory disease.

A number of field studies during this period showed clearly that both inactivated and live oral vaccines were effective in protecting against adenovirus illness and by the end of the period it was clear that the illness caused by adenoviruses types 4 and 7 could be essentially eliminated as a cause of morbidity. With influenza under control and adenoviruses virtually eliminated, research activities turned toward the probable causes of other febrile respiratory illnesses in the military. A number of Commission members began to study the remaining 50% of acute upper respiratory tract infections that occurred in the military and for which the etiology was unknown. The role of other viruses such as parainfluenza viruses, enteroviruses, coronaviruses, rhinoviruses, respiratory synsitial virus, and mycoplasma pneumonia were studied to determine their roles as causes of illness in the Armed Forces. Drs. Lennette and Mogabgab obtained valuable information on the role of rhinoviruses as causes of illness in Army and Air Force personnel.[69, 70]

Influenza Studies

An epidemic of influenza B in 1962 caused considerable mortality in the civilian community but did not cause significant illness in the military. The vaccine at that time contained two influenza B strains, B-Lee/40 and B-Great Lakes/54, which had been added to the vaccine when it appeared that there had been significant antigenic drift away from the B-Lee virus. The Commission considered changing the vaccine composition again but decided it was unnecessary because Captain Lloyd Miller at Great Lakes had observed good protection with a similar vaccine in 1959 against a virus very similar to the one that appeared in 1962.[71]

In the search for vaccine that would provide long lasting immunity and a response adequate to protect against virus strains that had drifted away from the vaccine virus, attention was focused on Dr. Salk's adjuvant vaccine. This preparation was shown by a number of investigators to provide a level of protection that would last for several years. Objections to the use of this adjuvant vaccine in the military were as follows: (*a*) Cysts developed in a certain proportion of recipients 2 to 3 months after administration and some had to be drained surgically. (*b*) There was concern about oncogenecity because of the presence in the adjuvant of components that had been shown to cause tumors in tumor-prone animals. (*c*) There was concern over the risk of hypersensitivity and hyperimmunization. To investigate these risks, a contract was formulated with Dr. Gilbert Beebe to follow, through the Veterans Administration (VA) system, records of 44,459 military personnel who had been vaccinated at Fort Dix in 1962 under the direction of Dr. Salk.[72] Of these, 18,251 had received adjuvant vaccine, 4,317 had received aqueous vaccine, and 21,891 had received formalinized saline.

Dr. Salk believed that the cysts occurred for two reasons: (1) in England, where a large number of individuals had developed cysts, he thought that the lot of vaccine used contained a particularly "toxic" batch of Arlacel, and (2) the injection of the adjuvant vaccine into the subcutaneous tissue rather than intramuscularly accounted for most of the remaining cysts. It was noted that the amount of mineral oil injected into each person was very small, 0.25 mL. Advantages of adjuvant preparations were considered to be more important than the risks. It was recommended that the vaccine be used as a combined influenza adenovirus preparation.[71]

The question of hypersensitivity and hyperimmunization had been raised at Fort Detrick, Frederick, Maryland, and Dr. Leigh Cluff investigated this possibility. Results were essentially negative.[73] Major Haycraft in Omaha, Nebraska, in collaboration with the Ann Arbor group, looked into this question in Strategic Air Command crews, who were regarded as the most intensely immunized group in the Armed Services. Major Haycraft carried out meticulous studies and found no difference when compared to a control group.[71]

The threat of epidemic influenza during this period was very slight. All persons in the Armed Forces were vaccinated. The question was raised whether there was sufficient gain for the military to give multiple annual doses of the influenza vaccine. A collaborative study to look into this question was arranged between Dr. Davenport and Colonel Ralph C. Singer, Chief of Preventive Medicine of the Army. They found that most permanent party members, even though they had received a number of annual revaccinations, lacked antibody to the newly arrived strain that appeared in the following year. It had been noted earlier that these persons almost always responded very well to the booster. An excellent response was almost always observed in recruits who received vaccine for the first time. It was concluded that primary vaccination of recruits was essential and that annual revaccination of seasoned troops might well provide considerable benefit.[74]

Chemoprophylaxis

During this period, a number of observations was made on the tolerance of various population groups to amantadine. The drug was effective against influenza A, but not influenza B. Captain Peckinpaugh found that doses of either 200 mg Amantadine or 300 mg of rimantadine did not produce significant toxicity in training personnel.[74] In Ann Arbor, Drs. Quilligan and J. F. Finklea found the

toxicity of amantadine to be quite low in children.[75] Dr. Hassan Maassab found that rimantadine was slightly more potent than amantadine.[76]

Other Studies

Dr. Edwin D. Kilbourne was interested in determining whether interferon induction could be of use in control of the viral infections. In 1967, Dr. Francis was presented the Outstanding Civilian Service Award by Major General James T. McGibony on behalf of Surgeon General Leonard D. Heaton. A partial record of General McGibony's remarks is as follows:

> No words nor awards can recompense Dr. Francis for the endless sacrifices and contributions he has made. His own words which, with his permission I quote, best describe his own, as well as my evaluation of his service. In August he wrote to General Heaton the following: "I can assure you that (my services to the Army through the Armed Forces Epidemiological Board) have been the most rewarding activity in which I have ever been engaged. It has, in fact, embodied a dedication to the concept that preventive medicine is the key to the development and preservation of vigorous military forces. It has been my pleasure, my pride, and my honor to have served in these activities.

At the November meeting in 1968, the Commission noted the death of Dr. Bell (epidemiologist for the U.S. Public Health Service), who had been with the Commission since its early days. The minute adopted by the Commission was as follows:

> Toward its mission Dr. Joseph A. Bell brought the experience of a career devoted to the prevention and control of acute respiratory disease — he constantly sought new epidemiological approaches to the study of preventive measures. His lively spirit as well as his broad insight were valuable contributions to the Commission's deliberations. He and his constructive judgment will be sorely missed.

THE COMMISSION — 1968 TO 1972

The last 5 years of the Commission proved to be an interesting and exciting period. Influenza A virus had again experienced an antigenic shift with the appearance of Hong Kong-type viruses. The story of how the virus was discovered and how things proceeded from that point is of considerable interest and for that reason is presented in some detail.

In late July 1968, Dr. Francis was traveling from Europe to Tokyo. He stopped for one night in Hong Kong and, reading the local paper, learned of a sharp outbreak of influenza. Dr. E. S. Chang at the WHO laboratory in Hong Kong had isolated a virus in rhesus monkey kidney tissue culture that had been identified as influenza A at the laboratory in England that was the European strain typing center. Dr. Francis proceeded to Tokyo where he conferred with the senior personnel of the 406th Army Laboratory and the South East Asia Treaty Organization laboratory (Bangkok), which happened to be in Tokyo at the time.

He also contacted Dr. Hideo Fukumi, who had conducted research at the Ann Arbor laboratories in the School of Public Health in Michigan. He notified Dr. Davenport, Director of the Commission, that there was an influenza epidemic in Hong Kong. Dr. Davenport immediately contacted Colonel Singer. They discussed the situation and agreed on a program of activities. It seemed likely that the presence of qualified personnel at the 406th laboratory in Tokyo made it unnecessary for Commission personnel to collect specimens for viral isolation. On 20 July and 8 August, samples were received from Hong Kong.

Meanwhile, the Commission and Colonel Singer had met and agreed that monovalent vaccine (A/H3N2) should be given to the troops as soon as possible. The strains that had been received from

the Armed Forces were all isolated in monkey kidneys and were considered unsuitable for vaccine production. The first virus strain, A/Aichi/8/68 (H3N2), isolated in eggs, arrived in the Ann Arbor laboratory on 29 August 1968 from Dr. Fukumi, who had collected specimens from the crew of an Israeli ship that had recently arrived from Hong Kong. The first strains isolated in eggs in a military laboratory in Tokyo arrived in Ann Arbor in September. The A/Aichi/8/68 strain was considered suitable for vaccine production and was forwarded promptly to the Division of Biologic Standards for distribution to manufacturers. As a result of the delay in isolation of virus strains suitable for vaccine production, most Hong Kong vaccine reached the Armed Services after the epidemic had passed its peak.

Despite concern that the new virus might cause a pandemic similar to that observed 10 years before, no serious problems were encountered at the military bases. Field studies had been set up at five bases. In only two of these was there a significant incidence of influenza (Lowry Air Force Base and Keesler Air Force, Basel). Drs. Theodore Eickhoff and Meiklejohn observed that adjuvant vaccines containing A/Taiwan/64 appeared to have roughly 50% effectiveness against Hong Kong influenza.[77] Dr. Mogabgab reported that the aqueous Hong Kong vaccine provided a higher level of protection.[78] The attack rate was very low in both these studies, but nonetheless the trend was there. The rates in civilians were much higher than in the Armed Services. At Lowry Air Force Base, a high rate of serologic conversion was observed in individuals who did not report to sick call, and it was estimated that 72% of the personnel had been infected by the Hong Kong virus during the season. The sparing of the military personnel may have been due, in part, to the fact that neuraminidase was the same in the H3N2 virus as in the H2N2 viruses that had been prevalent during the preceding decade. This was in line with Dr. Kilbourne's observations about neuraminidase antibody.[79]

The standardization of vaccines was greatly improved during this period by Dr. Nicola Tauraso of the Division of Biologic Standards of the NIH. The procedures for vaccine manufacture were much improved and the highly purified vaccines contained pure virus particles. Reactions became far less common than in the past.

The meeting of the Commission in November 1969 was saddened by the report of Dr. Francis' death. The Commission expressed its deep sense of obligation and grief by adopting the following minute:

> The members and associate members of the Commission on Influenza, Armed Forces Epidemiological Board, express their sorrow and deep sense of personal loss on the death of Dr. Thomas Francis, Jr., who was instrumental in organizing the Commission in 1941, served as its Director until 1955, and remained a member until 1 October 1969. Inspired by his leadership and guided by the brilliant example of his own scientific contributions, the Commission led the way in work that laid the foundation of modern research in influenza. In all of this work the Commission was encouraged and fortified by Dr. Francis' unswerving adherence to the principle that the continual acquisition of new information by basic scientific research is essential to any progressive program of development that is intended to solve practical problems.

The retirement of Dr. Francis as Director of the Commission in no way diminished his interest in its affairs. To the very end of his life he continued to give it the benefits of his remarkable wisdom, imaginative foresight, and unerring good judgment. All of the persons who had the privilege of association with him in the activities of the Commission are thankful for his friendship and stimulating presence, and they are mindful of the legacy of challenge he has bequeathed them. Dr. Francis had served as Director of the Commission from its founding in 1940 until 1955. He was replaced at that time by Dr. Davenport, who served until 1971.

Other Studies

A number of research activities of the Commission were continued during this period. Dr. Kilbourne showed that by a recombination procedure, a Hong Kong virus could be made with hemagglutinin

and neuraminidase with the growth characteristics of A/PR/8/34. This procedure was expected to facilitate the rapid production of vaccine.[80]

Dr. Hassan Maassab continued his work on cold adaptation[81] and showed that in humans the live cold-adapted virus did not produce illness but did stimulate the production of antibody. He also compared the relative isolation rate of influenza virus in eggs and chick kidney cultures.

Dr. Rose, in collaboration with Dr. Councilman Morgan, reported on electron microscopic studies of the steps by which influenza virus enters cells and replicates. The sequence of events differed from that observed with adenovirus or parainfluenza viruses.[82]

Dr. Richard Winzler, continuing his studies on virus enzymes, showed that neuraminidase of influenza viruses slowly cleaved sialic acid.[83] Dr. Herbert H. Blough reported his studies of the lipid incorporation into the viral membrane.[84]

Dr. Meiklejohn tested a small number of civilian volunteers with a second live Russian (H2N2) virus vaccine. As in a previous study, this type of vaccine produced antibody only in persons whose previous serum was devoid of antibody.[85] Dr. Julius Younger reported results of the studies on the adjuvant properties of hexadecylamine.[69] He made the interesting observation that use of this adjuvant caused response in some species but not in others. Unfortunately, humans turned out to be one of the species with no adjuvant response.

Adenovirus

During the 1960s, it became clear that adenoviruses were the major cause of morbidity in the recruit population of the three military services. Many studies had shown that most illness were due to either type 4 or type 7 adenovirus, with an occasional case infected with type 3. Inactivated vaccine against each type had provided a high percentage of efficacy in some studies, whereas others had shown relatively poor protection.

Adenovirus infections were a primary interest of the Commission on Acute Respiratory Diseases. Members of the Commission on Influenza became involved in adenovirus research because the technical procedures for the study of influenza provided a unique opportunity to obtain specimens for diagnosis of each type of infection. Dr. Hilleman at WRAIR had been the first to demonstrate the effectiveness of inactivated vaccine at Fort Dix.[86] Colonel Edward Buescher was also interested in testing a live oral adenovirus vaccine that was given by mouth in an enteric capsule.[87] It had been shown to be highly effective against type 4 and type 7. Dr. Chanock first had the clever idea of administering wild live virus in an enteric capsule. He recognized that the virus that propagated for a long time in the gut, like poliomyelitis, might immunize well against the respiratory challenge. The virus was cultured in Wistar Institute human embryonic lung fibroblast 38 cells and was not attenuated.[88]

Early in 1970, a committee was formed consisting of four members of the CARD and Dr. Meiklejohn of the Commission on Influenza. (With the exception of Dr. Harry Ginsberg, the Chairman, all others were also associate members of the Commission on Influenza. These were Dr. Chanock, Dr. George Gee Jackson, and Colonel Buescher [see Appendix 3].)

This committee was expected to make recommendations regarding live adenovirus vaccines. The committee recommended to the AFEB that the Army contract for acquisition of live oral vaccine, type 4, for use in recruits during the 1970 and 1971 influenza season. Further study of live type 7 vaccine, which had been shown to be equally effective, was recommended. When both vaccines were given together simultaneously, the antibody response was equally good for each virus.

The committee also urged further evaluation of capsid or subunit vaccine. There was considerable concern, particularly by Dr. Ginsberg, Director of the Commission on Acute Respiratory Diseases, about the possible onconogenicity of type 7 adenovirus. Previously, it was known that some type 7 strains had hybridized with SV40, an oncogenic virus of simian origin.

The original tests were highly successful. Later lots of vaccine were less effective and it was found that the titer of the virus had to be maintained at a minimum level of 10^{-5} ID 50. The question of possible oncogenicity was a troublesome one. Dr. Ginsberg submitted a minority report stressing his



JOSEPH A. BELL, M.D., D.P.H.

Joseph Bell, a widely recognized epidemiologist, graduated in medicine from the University of Colorado in 1929. He trained in medicine and received his degree in public health from The Johns Hopkins School of Hygiene and Public Health in 1948. He was commissioned Assistant Surgeon General of the U.S. Public Health Service and devoted his entire professional life as a public servant.

Among his many distinguished memberships was the American Public Health Association, the Commission on Influenza of the AFEB, the American Epidemiologic Society (President, 1952), and the Association of Military Surgeons of the United States. His many creative contributions included design of the initial plans for the epidemiologic study of polio myelitis vaccine, membership on the Subcommittee on Control of Communicable Diseases of the American Public Health Association, and the WHO Expert Advisory Panel on International Quarantine.

reluctance to administer live type 7 vaccine to large numbers of recruits.

The majority of the committee believed the very high incidence of upper respiratory tract infection in recruit populations justified the use of the type 4 and type 7 vaccine. Furthermore, it had been clearly shown that almost all recruits not already infected would contact both types of adenoviruses infections during the first year or two of their military service.

The committee also recommended that oral type 14 and 21 vaccines should be developed experimentally. In Europe, sporadic outbreaks in military units had been attributed to these two viruses. It was made clear that virus surveillance should be carried out whenever possible to determine vaccine effectiveness and to determine any ill effects that might be related to the vaccine.

THE END OF THE COMMISSION

From the earliest studies at Fort Dix in the 1940s, there had been uneasiness on the part of Dr. Salk and others because the Department of the Army failed to provide medical officers assigned specifically for work on influenza vaccine field trials. Considerable personnel turnover at a large recruit base such as Fort Dix made it very difficult for any visiting epidemiologist to monitor personnel in vaccinated and control groups in any vaccine trial. Despite repeated requests by the Commission Director, the Army authorities often failed to provide personnel targeted for this type of activity. This experience appeared to differ from other AFEB Commission programs and could have represented a unique local difference. During the 1960s, disagreements continued to occur between Commission members and Army personnel. Frequently, these clashes were over the site of the annual meeting. Department of the Army authorities preferred to hold the meeting at WRAIR because of the convenience for related personnel; this also permitted broader attendance by interested military persons. Members of the Commission on Influenza preferred to hold the meeting at Ann Arbor. Undoubtedly, military travel restrictions and financial constraints influenced this attitude. This issue was compromised by holding two annual meetings: One scientific meeting at Ann Arbor for 3 days and a 1-day meeting at WRAIR, where administrative and pressing scientific problems were discussed. The latter meeting was small and was attended only by members of the Commission and involved military officers.

Dr. Davenport made a consistent effort to bring representatives of the three armed services and civilian groups such as the CDC and the NIH to the annual meetings. All persons holding contracts were invited to attend. Occasionally, directors of the other commissions attended meetings for presentation of interesting data (see Appendix 3)

Further disagreement developed in connection with the Commission's recommendation that the Department of the Army use vaccine prepared with adjuvant. This recommendation was never implemented. The Bureau of Biologics of the NIH did not approve adjuvant vaccine on the grounds that it was potentially oncongenic and would violate the Delaney Amendment. This amendment specified that no material should be injected into humans that was "oncogenic in any animal." "Oncogenicity" was based on injection of relatively large amounts of mineral oil into certain tumor-prone animals. Most Commission members believed that the risk of injecting vaccine that contained very small amounts of mineral oil into humans would be outweighed by elimination of the need for annual immunization against influenza. Also, it was concluded that better protection might be obtained against influenza, adenovirus, and other potential antigens that were to be added to the vaccine. Furthermore, Commission members were favorably influenced by the data collected by Dr. Beebe that showed no harmful effects among 18,000 persons who had received adjuvant vaccine 10 years previously. These data were thought to carry far more weight than the experimental data in animals provided by the Bureau of Biologics of the NIH. Nonetheless, the Army, reinforced by its legal division, accepted the position of the Bureau of Biologics.

The legal unit stressed that placebo studies involving Army volunteers could no longer be employed. Once a vaccine had been accepted for general use, it was held to be unethical to withhold it from any person. The irony of this position was not lost on a number of Commission members. They recalled the reluctance of some medical personnel in higher ranks to take vaccine on the grounds that little protection was provided or there were severe reactions. In addition, legal authorities added fuel to the fire by commenting that the Commission had violated several regulations relating to continued appointments and potential incidents of conflict of interest.

Without question, Army medical scientists and Commission members had drifted apart. Cooperative, favorable working relationships were maintained between the Commission and U.S. Navy and Air Force personnel. However, the Navy Department had begun looking to the National Research Council for technical advice on infectious diseases rather than to the Commission.

The nature of the differences between the regular Army personnel and the Commission remained troublesome. Dr. MacLeod, President of the AFEB in 1966, addressed these differences on the occasion of the 25th anniversary of the formation of the AFEB. His provocative comments included the following:

> The military medical services have always had a difficult struggle to finance and man what they know has to be done to cope with present exigencies and future probabilities. They have known from the time of General Sternberg that they must be strong internally and this is very difficult to achieve when one considers that scientific contributions are not valued as highly in the military services as they should be in this scientific world we live in. Whoever heard of a First Lieutenant being made a full Colonel because he made a scientific discovery!
>
> I am not giving lip service to the need to have high biomedical research competence in the military service. To the contrary, I believe it is absolutely essential that this be so and have consistently worked for it. Without it, the military simply could not take advantage of the scientific advances taking place throughout the scientific world.
>
> At the same time, and based on considerable experience, I know that the day will never come when the military services can be scientifically self-sufficient in medicine any more than NIH in Bethesda can be for civil medicine.
>
> The Armed Forces, therefore, must perfect even this extraordinary mechanism, the AFEB, to add new dimensions to their research toward the control of disease that they themselves through their intramural operations cannot hope to achieve alone.
>
> So today I would like to reaffirm, and hopefully see enlarged, this partnership between the Armed Forces and civilian investigators that has been the envy of agencies throughout the government and I would like to see it explore new means of making this partnership more effective. Let us not be complacent in the face of events which drive us into traditional operating modes.

Despite Dr. MacLeod's urging for better relationships between the two groups, The Surgeon General of the Army appointed a Management Committee in 1971 to review activities of the AFEB. All government civilian agencies were subject to review at this time. This Committee was made up of the following members: Elliott J. William (Chairman), Department of the Army, Civilian Directorate of Plans, Supply and Operation, Office of The Surgeon General, Department of the Army; Phillip E. Winter, M.D., LTC, MC, USA, Directorate of Health and Environment, Office of The Surgeon General, Department of the Army; and Lieutenant Colonel France F. Jordan, MSC, U.S. Army Medical Research and Development Command.

The Committee was instructed to investigate a number of issues, including tenure of appointments and possible conflict of interests. After considering a number of possible alternatives, the Committee recommended that the AFEB continue as such with broader emphasis on chronic diseases. It further recommended that the Commissions be abolished to avoid any possible conflict or interest. The needs of the Army could be met because of the availability of trained medical officers, the emergence of an

"in-house military medical research and development community, and the growing effectiveness of the prevention of disease have materially lessened the requirement for AFEB assistance in both field investigations and the organization of contract research."[90]

A number of Commission members were hurt by the tone of this report. Only one member of the Commission on Influenza was consulted by the Management Committee. All members, during and after World War II, felt that they had fulfilled a national obligation and at the same time had given generously of their time without remuneration. Many members had directed their research efforts entirely in the direction of the scientific needs of the Armed Forces. Their only compensation was a fee of $50 per day during the time of the annual meetings of the Commission. It was fully acknowledged that the Army medical personnel at WRAIR had developed a considerable degree of competence. Many of these persons at WRAIR no longer sought advice from the Commission on Influenza, but had established relations with scientists at the NIH and CDC who they felt would provide guidance. Commission members surmised that WRAIR investigators would not be able to maintain adequate scientific competence, particularly in view of the fact that the physicians' draft would end. It was contemplated that with cessation of the Berry plan and the physicians' draft, the Army would have difficulty recruiting and retaining highly qualified personnel. With considerable regret, it became obvious that a close and effective relationship that had functioned effectively for more than 25 years and had greatly advanced the knowledge of influenza and other respiratory diseases would cease.

Dr. Davenport resigned as Director of the Commission on Influenza in 1971. He was succeeded by Dr. Meiklejohn who served as Director for the final 2 years of the Commission. The Commission ceased to exist on 1 January 1973.

CONCLUSIONS

When the Commission on Influenza was formed, very little was known about influenza or the viruses that caused it. At the time of its formation, the Commission established a comprehensive series of questions. The goals were fairly straightforward and the questions raised had almost been answered by the time World War II ended. The Commission showed that

- inactivated virus vaccine could protect against both influenzas A and B,
- immune serum given via the respiratory route did not protect against challenge with aerosols of the virus,
- the attack rate of influenza varied inversely with the HI antibody titer,
- immunity following natural infections was relatively weak (the fact that immunity was considerably reduced as early as 4.5 months after infection with wild virus made it seem unlikely that live attenuated virus would provide adequate protection; it was also conceived that the reversion of virus to a virulent type during laboratory experimentation with attenuated strains might lead to new outbreaks),
- influenza varied in great severity from the classic influenza in 1918 to an almost subclinical type of illness observed recently with influenza B,
- influenza virus was extremely unpredictable, which made it essential to conduct studies over a number of years to develop an immunity that would be long lasting.

During the years following World War II, much was learned about the virus in all respects. Antigenic shift, when new surface antigens appeared, occurred infrequently. However, repeated observations revealed that vaccine would provide a high level of protection and that it was worthwhile to vaccinate all military personnel annually. There continued to be questions about which virus strain



HAROLD S. GINSBERG, M.D.

After graduation in medicine at Tulane, Harry Ginsberg trained in medicine and pathology for three years on the Harvard Service at the Boston CIty Hospital. Here he established friendships with John Dingle and Bill Jordan. During World War II he was Chief of Medicine at the U.S. Army Hospital, Ft. Bragg, North Carolina, where he showed that adenoviruses, type 4, was a cause of acute respiratory infections. At Ft. Bragg he was again associated with Dr. Dingle who directed the Commission on Acute Respiratory Diseases.

Three productive years were then spent with Frank Horsfall, at the Rockefeller Institute with work on influenza and viral pneumonia. He elucidated the genetics of adenovirus replication and virulence, particularly, type 5. He then joined Bill Jordan in John Dingle's outstanding department of Medicine at Case Western Reserve University. Harry then served with distinction at the University of Pennsylvania and Columbia University College of Physicians and Surgeons as chairman of microbiology. Even today, he arranges annual seminars on infectious disease problems and new vaccines and serves as a visiting scientist with Dr. Chanock at NIH. He rendered wise advice as a member of the Commission on Influenza of the AFEB.



GORDON N. MEIKLEJOHN, M.D.

After graduating in medicine from McGill University in 1937, Dr. Gordon Meiklejohn served his internship and residency in medicine at the Rockefeller Foundation. From 1944 to 1946, he served as a lieutenant in the U.S. Navy. He joined the faculty of the University of California, where he was appointed Professor of Medicine in 1951. From 1951 to 1975, Gordon served as the Distinguished Professor of Medicine and Chairman of the Department of Medicine at the University of Colorado in Denver.

Gordon is one of the most longstanding and devoted contributors to AFEB activities. He served as a member of the Commission on Influenza from 1948 to 1973, and directed that Commission from 1971 to 1973. He has been a pillar of support in conducting the year-to-year surveillance studies on the incidence of and the antigenic changes related to influenza. These continuing serologic observations, many of which are conducted at Lackland Air Force Base and other key laboratories, are closely correlated with those of the Centers for Disease Control in Atlanta, the World Health Organization, and the AFEB. These painstaking observations are of great importance in helping select the particular influenza viruses that are incorporated in new vaccines from year to year.



FALL MEETING OF THE COMMISSION ON INFLUENZA

13 and 14 November 1972
Walter Reed Army Medical Institute of Research

Seated, left to right: Drs. Edwin D. Kilbourne, Frederick M. Davenport, Gordon N. Meiklejohn (Commission Director), Edwin H. Lennette, and Julius S. Younger.

Standing, left to right: Drs. Herbert A. Blough, Calderon Howe, Robert M. Chanock, Jerome L. Schulman, Purnell W. Choppin, and Albert V. Hennessy.

should be incorporated in the vaccine. Some favored a monovalent vaccine prepared from the most recently isolated strain. Others preferred a polyvalent vaccine containing, in addition to the newly isolated virus, representative strains from the earlier years. It was shown in 1957, when the Asian (H2N2) virus appeared, that an antibody was present in the sera of individuals in older age groups. This finding suggested that a similar virus had been present as far back as 1890. This led to the development of the "doctrine of original antigenic sin" proposed by the Ann Arbor group.[91]

Much interest focused on Dr. Salk's mineral oil Arlacel adjuvant that made it possible to obtain very high antibody levels with very small amounts of antigen. Such antibody responses persisted for several years rather than for only 1 to 2 years against influenza A. The most effective protection was obtained with adjuvant vaccine in 1960, at a level of 94%. Adjuvant vaccines were also shown to have the advantage of being able to incorporate many different strains of influenza virus as well as other viruses with a resultant good response to each component in terms of protective antibody.

It became obvious that as influenza came under control, a number of other viral agents were responsible for many of the upper respiratory tract infections. Commission members made these observations at a number of military bases in different parts of the United States. Adenovirus, in particular, caused considerable morbidity in a number of recruit installations. Commission scientists conducted studies of adenovirus vaccines that showed that either injected inactivated or orally administered live vaccines were highly effective in preventing type 4 and type 7 illness. The work in this area was coordinated with activities of the Commission on Acute Respiratory Diseases, which had carried responsibility for that particular project. The Commission also played a role in elucidating the etiology of "viral pneumonia" in inductees and isolation of the Eaton agent, which was shown to be the cause of the common variety of "atypical pneumonia."

During the latter part of the Commission's tenure, influenza was under control with vaccination for all military personnel. New studies on characterization of influenza virus were undertaken. A number of basic scientists were recruited to work with the Commission.

Dr. Maassab continued his work on cold adaptation of both influenzas A and B. Dr. Kilbourne developed a method of recombining a new virus with an old strain. This finding made it possible to combine hemagglutinin and neuraminidase antigens in a new virus with the growth characteristics of an old virus (PR/8). With Dr. Jerome Schulman, Dr. Kilbourne developed a mouse model to study the transmission of influenza by the airborne route.[92] They also acquired much information on the neuraminidases of different strains of influenza viruses.

When the Commission's activities ceased in 1973, its members felt a fully justified sense of pride and satisfaction with the realization that its major responsibilities had been met and that the Armed Forces had been provided the means to control influenza to a very considerable extent. In addition, Commission-oriented research had established an awareness of the important potential of influenza virus. It was obvious that more work was needed and new data developed before there could be full assurances of investigative control of this old scourge in the future. Specifically, certain questions remained regarding the nature of antigenic drift, and the origin of new viruses such as A/H2N2 and A/H3N2. Furthermore, it was patently obvious that many persons escaped influenza infection in spite of low levels of HI antibody. This fact alone made it clear that more data were needed to clarify the nature of immunity.

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SECTION 2—APPENDIX 1

EXPERIMENTAL CHALLENGE OF VACCINATED PERSONS

Influenza A (102 volunteers)
Challenge — Influenza A/Baum/40 (1940) in allantoic fluid
Method — Nebulized 2 mL of virus in each nostril

	No. of persons	Vaccinated	Challenge interval	Persons with temperature over 100°F, %	Persons with temperature over 101°F, %
Gp 1	36	No	—	50	25
Gp 2	28	Yes	4.5 mo.	32	11
Gp 3	21	Yes	2 weeks	14	—
Gp 4	17	Yes	*	18	—

*Boosted 4.5 months later and then challenged 2 weeks after booster.

Comment: Definite evidence of protection at 2 weeks, less at 4.5 months after vaccination.

Influenza B (96 volunteers)
Challenge — Influenza B in allantoic fluid

	No. of persons	Vaccinated	Challenge interval	Persons with temperature over 100°F, %	Persons with temperature over 101°F, %
Gp 1	27	No	—	41	22
Gp 2	27	Yes	4.5 mo.	7	—
Gp 3	23	Yes	4 weeks	13	—
Gp 4	19	Yes	*	11	—

*Boosted at 4.5 months and challenged 4 weeks after booster.

Incubation period = 12 to 24 hours
Comment: Definite evidence of protection against influenza B. In contrast to results with influenza A, no difference was observed in persons vaccinated either 4 weeks or 4.5 months previously.

SECTION 2—APPENDIX 2

INTRANASAL SERUM PROPHYLAXIS

Experiment 1.
To test 1.0 mL of high titer human immune serum given 4 hours before atomized virus via oxygen mask.

	Material sprayed	Challenge virus	Clinical influenza, %
Group 1	Immune serum	Virus	96
Group 2	Normal saline	Virus	89
Group 3	Immune serum	Irradiated virus	0

Comment: No evidence of protection.

Experiment 2.
Because the first challenge may have been too severe, the test was repeated with more serum given before and after virus challenge.
Method — Serum or control material was given in 4-mL amounts: 11, 7, and 5 hours before challenge (23 mL) and 7 and 17 hours after challenge (14 mL) — Total 37 mL.

	Material sprayed	Challenge virus	Clinical influenza
Group 1	Immune serum	Different lot of influenza A	11/15
Group 2	Saline control	Different lot of influenza A	8/15

Comment: No evidence of protection.

Titration of challenge virus

Dilution	Clinical influenza
None	6/6
10^{-2}	2/6
10^{-4}	0/6

Rechallenge after 4 months

Clinical Influenza	
Infected persons	0/18
Controls	7/12

SECTION 2—APPENDIX 3

ATTENDANCE AT 1968 ANNUAL MEETING OF COMMISSION ON INFLUENZA

Annual meeting of the Commission on Influenza held 17, 18, and 19 November 1968 in Ann Arbor, Michigan. Those attending were:

Commission Members
Dr. Frederick M. Davenport
Dr. Edwin D. Kilbourne
Dr. J. Vernon Knight
Dr. Edwin H. Lennette
Dr. Clayton G. Loosli
Dr. Gordon Meiklejohn
Dr. Frederick A. Rasmussen, Jr.
Dr. Harry M. Rose
Dr. Julius S. Younger

Associate Members
Dr. Byron S. Berlin
Dr. Herbert H. Blough
Dr. Robert M. Chanock*
Dr. Purnell W. Choppin
Dr. Walter R. Dowdle
Dr. Theodore C. Eickhoff
Dr. Albert V. Hennessy
Dr. Calderon Howe
Dr. George Gee Jackson*
Dr. Julius A. Kasel
Dr. Albert McKee
Dr. William J. Mogabgab
Captain Robert O. Peckinpaugh
Dr. Jerome L. Schulman
Dr. Nicola M. Tauraso
Dr. Richard J. Winzler

Responsible Investigator
Dr. Gilbert W. Beebe

AFEB
Colonel Bradley W. Prior

Air Force
Lieutenant Colonel Robert J. Brandt

Army
Lieutenant Colonel Raymond L. Coultrip
Major C. D. Smith
Colonel Albert Leibovitz
Major Seymour H. White
Major. R. Edelman
Colonel Robert H. Quinn

Navy
Captain C. H. Miller
Commander W. Beam
Lieutenant D. Lehane
Lieutenant N. Newberg

Guests
Dr. Jack H. Schieble
Dr. Franklin H. Top, Jr.
Dr. Earl Edwards
Dr. Max J. Rosenbaum
Dr. Willard E. Pierce
Dr. Arnold D. Monto
Dr. Edward A. Eckert
Dr. Hassan F. Maassab

Director of the Commission on Influenza: Dr. Frederick M. Davenport, M.D.

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*Members of the Commission on Acute Respiratory Diseases (CARD)

SECTION 3

Commission on Epidemiological Survey

Foreword

The Commission on Epidemiological Survey (CES) was conceived as part of the mission of the original Armed Forces Epidemiological Board (AFEB). Various infectious diseases were considered as threats to any military force. Toward this end, the United States and adjacent countries were divided into sections to evaluate any threat and define the epidemiological significance of various entities within a geographic unit.

For example, coccidioidomycosis seemed to be localized primarily in the western desert areas of the United States. It came under serious consideration and evaluation by Dr. Charles Smith who gave wise advice based on surveillance studies regarding the need to remain alert.

The CES was formulated in 1954 when it became apparent that the threat of use of biological agents as weapons (biological warfare) was a reality and merited constant vigilance involving new studies of pathogenesis and development of effective means of early detection and control. Defense was the key issue and on this basis the new CES became an integral part of the AFEB. The CES was given oversight responsibility for the newly developed Biological Warfare program at Fort Detrick in Frederick, Maryland. The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) unit was a later development at Frederick, with which the CES maintained a close and effective relationship.

Dr. Richard Shope was the first CES Director. He was succeeded by Dr. Theodore E. Woodward. Colonel William Tigertt, MC, Colonel Abram S. Benenson, MC, and Colonel Dan Crozier, MC, were the group of responsible military professionals who, with their capable staff and CES members and the full backing of Walter Reed Army Institute of Research (WRAIR), developed a program that placed our country in an effective and ready posture.

I am grateful to Dr. Crozier for preparing this factual and interpretive history of the CES. It is a fitting tribute to our nation's foresight to accurately predict the rapidly changing future and, at the same time, discharge our responsibilities in an open and forthright manner.

— Theodore E. Woodward, M.D.

History of the Commission on Epidemiological Survey

Dan Crozier, M.D.

THE FIRST COMMISSION ON EPIDEMIOLOGICAL SURVEY (CES)—1941 TO 1945

The Commission on Epidemiological Survey (CES) was one of the eight commissions of the original Board for Investigation of Influenza and other Epidemic Diseases established by the Secretary of the Army in 1941. Its first director was Stanhope Bayne-Jones, M.D., originally of Yale University School of Medicine, New Haven, Connecticut. The first president of the Board was Francis G. Blake, M.D., distinguished Professor of Medicine at Yale. On 12 February 1941, Dr. Blake corresponded with Dr. Bayne-Jones, informing him of the establishment of the Board and its commissions. Dr. Blake, as Board President, asked Dr. Bayne-Jones to accept the position of Director of the CES. He provided a brief summary of a proposed agenda for the CES and requested that Dr. Bayne-Jones develop a program for the four investigative teams that would function under the CES and provide a list of potential members. Dr. Bayne-Jones immediately accepted the appointment and on 21 February transmitted a proposed list of personnel to Dr. Blake and expressed his thoughts regarding the investigative program of the CES. This comprehensive proposal is reproduced in its entirety below because it formed the basis of the CES's program for the next 3 years.

Dear Doctor Blake:

Since receipt of your letter of February 12, I have communicated by telephone and telegraph with the men recommended below as Directors of investigative teams in the designated areas. They are eligible and willing to serve and I understand that this is true also of the persons recommended by them for appointment. There are a few reservations to be considered and releases to be obtained. Therefore, in answer to your letter of the 12th, I submit the following recommendations concerning the initial personnel and outline of programs of the Commission on Epidemiological Survey.

I. Personnel:

1st Corps Area, HQ, Boston, Mass.
Professional staff: J. Howard Mueller, Director, John F. Enders, Emanuel B. Schoenbach.
Technicians: Vincent B. Shields, Pauline A. Miller, William McBrearty.

4th Corps Area, HQ (for Commission), Durham, N.C.
Professional staff: David T. Smith, Director, Wiley D. Forbus, D. F. Milan.
Technicians: Names of 3 to be submitted later.

9th Corps Area, HQ San Francisco, CA.
Professional staff: Edwin W. Schultz, Director, Edward B. Shaw, Charles E. Smith.
Technicians: Names of 3 to be submitted later.

Puerto Rico, Department of, H.Q. San Juan, Puerto Rico
J. Roderiquez Pastor, Manuel A. Perez, Amerigo Pomales Lebron.
Technicians: Names of 3 to be submitted later.

II. Program: The purpose of the Commission on Epidemiological Survey is to assist in the control of epidemic infectious diseases in the Army by the accumulation of data concerning the prevalence of pathogenic organisms in the personnel of selected stations by repeated sampling over a considerable period. Surveys will be designed to acquire information on pre-epidemic and epidemic periods. The stations and camps at which surveys will be made will be in the 1st Corps area, 4th Corps area, 9th Corps area and the Department of Puerto Rico. The investigative teams will carry out work in laboratories of institutions at their headquarters and at available stationary and mobile laboratories at military stations to which the teams may be sent for temporary duty when deemed advisable by the Surgeon General. The headquarters laboratories will be:

1st Corps Area, Department of Bacteriology and Immunology, Harvard Medical School, Boston, MA.
4th Corps Area, Department of Bacteriology and Pathology, Duke University, School of Medicine, Durham, NC.
9th Corps Area, Department of Bacteriology and Experimental Pathology, Stanford University School of Medicine, Stanford University, CA.
School of Tropical Medicine, San Juan, Puerto Rico.

The most important military epidemics to be considered are:

a. Respiratory transmission group: Pneumonias, meningococcus. meningitis, scarlet fever, influenza, diphtheria, colds, measles, mumps and chickenpox(?).
b. Enteric transmission group: Typhoid and paratyphoid fever, dysenteries, simple diarrheas and some types of infectious jaundice.
c. Insect transmission group: Rickettsial infections: Typhus, Rocky Mountain spotted fever; protozoal infections, malaria, chiefly; virus infections, yellow fever, chiefly.

As it is not possible to determine the prevalence of the pathogenic organisms and viruses causing a number of these diseases as each investigative team will be confronted with different problems in the separate areas, and as the teams will not be able to cover the whole field, portions of the study will be selected for concentrated investigation by each team or by combinations of the teams.

The investigative teams of this Commission will be primarily concerned with surveys of prevalence of pathogenic bacteria, but will also study the prevalence of other organisms in certain areas and under conditions to be defined as desirable. These surveys will be coordinated with other surveys, particularly in reference to the prevalence and types of viruses. Furthermore, in order to avoid the wasted efforts consequent upon wholesale bacteriological surveys, the work should be restricted to the amount which can be done accurately. Whenever possible, tests of susceptibilities will be included. The Directors of the teams will agree upon standard methods having as much uniformity as possible and upon uniform methods of keeping records. There must be also a uniform system of prompt reports.

Details of methods to be used, and other matters of technique and procedure have been considered during the past ten days but are not in order at present to be outlined in this report.
I should like to recommend that as soon as the regional Directors have been appointed, authorization be given for their meeting with me on temporary duty status at New Haven to consider plans and decide upon procedures.

It is not possible, at this time, to submit a list of laboratory equipment, supplies and animals that may be required. An estimate will be made after a meeting of the regional directors, but this will, of necessity, be subject to change from time to time.

Sincerely yours,

S. Bayne-Jones

sb-j:mh



STANHOPE BAYNE-JONES, M.D.

Everyone who knew Dr. Stanhope Bayne-Jones, known as B. J., respected him. B. J. accomplished almost everything: chairmanship of a department of bacteriology, dean, chancellor, writer, army general, epidemiologist, and administrator. He was a wise man with unflinching integrity. During World War II, he served as Deputy Director of Preventive Medicine under General Simmons and Director of the USA Typhus Fever Commission. In addition to these responsibilities, he and General Simmons conceived that a board consisting of lay scientists could serve the U.S. Army effectively. This Board was the forerunner of the AFEB. B. J. served as the first administrator for the new Board and also as its president. During his life, he participated actively and effectively in all activities of the Board and its Commissions. A simple example provides insight into his personal qualities. During the heat of World War II, B. J. once went after midnight to the Washington National Airport to receive special hyperimmune pertussis serum for an infant son of a junior officer. When most would have sent an aide, B. J. went.

The most outstanding tribute to B. J. is his productive life and his insistence that a professional person should accept responsibility for any role of benefit to society and to complete the assignment. B. J. was a coordinator of research, a "Godfather," who understood so well the need to maintain and record a sequential record of important events.

At a meeting of the AFEB in the office of The Surgeon General in Washington on 27 February 1941, the proposed investigative program of the CES was approved essentially as presented. On 18 March 1941, after consulting with Drs. A. R. Dochez, Kenneth F. Maxcy, and Blake, Dr. Bayne-Jones presented a budget of $60,000 ($15,000 for each of the four teams) for 1 year. Dr. Maxcy thought that this was an unexpectedly large amount and that the teams could start their programs with somewhat less but did not object to the proposal. He also stated, "It is not entirely clear as to where the functions of this commission terminate and those of the Commissions of Hemolytic Streptococcus infections, Meningococcus Meningitis, Pneumococcus Pneumonia and Influenza begin."

ADMINISTRATION, ORGANIZATION, AND PERSONNEL

The CES program was to be conducted under a contract with Yale University with the four investigative teams to be based at Harvard, Duke, and Stanford Universities and the Department of Puerto Rico School of Tropical Medicine acting as subcontractor.

In the early planning stages of the AFEB, it was decided that commissions would be established as necessary and that each commission would have a director and "such additional consultant personnel, as necessary, for the purposes of the Commission."

The original membership of the CES was as follows:

Director: Dr. Stanhope Bayne-Jones

Consultants:

Dr. J. Howard Mueller
Harvard Medical School, Boston, Massachusetts

Dr. John F. Enders
Harvard Medical School, Boston, Massachusetts

Dr. Emanuel B. Schoenbach
Harvard Medical School, Boston, Massachusetts

Dr. David T. Smith
Duke University School of Medicine, Durham, North Carolina

Dr. Wiley D. Forbus
Duke University School of Medicine, Durham, North Carolina

Dr. D. F. Milam
Duke University School of Medicine, Durham, North Carolina

Dr. Edwin W. Schultz
Stanford University School of Medicine, San Francisco, California

Dr. Edward B. Shaw
University of California Medical School, San Francisco, California

Dr. Charles E. Smith
Stanford University School of Medicine, San Francisco, California

Dr. P. Morales-Otero
School of Tropical Medicine, University of Puerto Rico, San Juan, Puerto Rico

Dr. J. Roderiguez Pastor
San Juan, Puerto Rico

Dr. Manuel A. Perez
San Juan, Puerto Rico

Dr. Amerigo Pomales Lebron
San Juan, Puerto Rico

Considerable delay was encountered working out the contractual details. The final contract with Yale University was not approved until 1 November 1941. This contract was for $34,745 for the remaining 8 months, until 30 June 1942. The investigative program, however, had been underway since early summer. Just how this was handled financially is not clear from the old records, but presumably the

programs at Harvard, Duke, and Stanford Universities were initiated and conducted on a voluntary basis with locally available funds with some assistance from the AFEB.

Although coccidioidal infections were not included in the original agenda of the CES, Dr. Edwin W. Schultz, director of the 9th Corps area group and Dr. Charles E. Smith, a member of that group, wrote to Dr. Bayne-Jones with a recommendation that it be included in their investigative program. In a letter of 21 May 1941, they stated that the Army's major bases for aviation instruction located in the southern San Joaquin valley in California were in a region of maximal incidence of coccidioidal infection. They added that 80% of the school children tested near the Air Corps Basic Training Center at Taft Air Base reacted positively to coccidioidin. It was stressed that coccidioidomycosis would be a significant cause of morbidity in these aviation training centers.

Dr. Bayne-Jones strongly supported this proposal, and shortly thereafter it was included in the 9th Corps area program. It proved to be one of the most productive of the early programs conducted under the CES.

Dr. Bayne-Jones entered active duty as a Lieutenant Colonel, Medical Corps, in February 1942. He wrote to Dr. Blake that he was concerned about the advisability of his holding the position of Director of the CES while serving as a commissioned officer in the Office of The Surgeon General. Dr. Blake requested an opinion from The Surgeon General and prevailed on Dr. Bayne-Jones to continue to serve at least temporarily. On 4 May 1942, however, he submitted his resignation, which was accepted. He was replaced by Dr. Blake who served in this capacity until the CES became inactive in December 1945.

BACTERIOLOGICAL SURVEY: MENINGOCOCCAL, STREPTOCOCCAL, AND OTHERS

The 1st Service Command study was under the direction of Drs. J. Howard Mueller and John F. Enders. Frequent bacteriologic surveys were conducted at Fort Devins and Camp Edwards to determine the prevalence of β-hemolytic streptococci, *H. influenzae*, meningococci, and diphtheria bacillii. It was hoped to use changes in the prevalence of these organisms to predict the onset of epidemics and possibly develop methods for their control. During the first 2 years of this study, objective and critical comments were made by members of the AFEB. Dr. Blake stated his view that "This work should not go on unless it could be reorganized with possibly an investigator commissioned under the Board to take charge of the direction of the experiment." The study, however, was continued. From the spring of 1942 until March 1943, routine meningococcal surveys revealed that carriers of types II, II alpha, and nontypable (X) stains predominated, with type I carriers remaining essentially constant at about 3.5%. In December 1942, the rate of type I carriers doubled, and in January 1943, tripled. At the same time, the number of clinical cases increased significantly at Camp Edwards. Culture isolates from these patients revealed type I meningococcus, except in one case that probably was a type II alpha. It was concluded from these studies that typing should be an essential part of any survey of meningococcal carriers.

In May 1943, Brigadier General Frederick F. Russel, MC, USA (Ret), reported to Dr. Mueller a sharp outbreak of streptococcal disease at an Army school in Massachusett. It was stated that in the previous 3 weeks there had been "several" cases of scarlet fever, a considerable number of streptococcal sore throats with a number of peritonsillar abscesses, and a high rate of respiratory disease in general. In view of the experience in the U.S. Navy with scarlet fever, and after additional consultation with Dr. T. Duckett Jones, it was decided to administer a 3-day course of sulfadiazine or sulfapyridine, 3 g/day. The next day, chemoprophylaxis began for all students, instructors, kitchen employees, and other personnel after initial cultures were performed. Follow-up cultures were performed in all persons on the day after completion of the treatment. In the period after administration of the sulfonamides, the sick rate dropped sharply, but no significant change was noted in the carrier rate. In the 3-week period preceding the administration of the drug, seven cases of scarlet fever occurred. After drug prophylaxis, no new cases were noted except one that appeared on the day after chemoprophylaxis.

Coccidioidomycosis

The 9th Service Command study of coccidioidomycosis was directed by Dr. Charles E. Smith of Stanford University School of Medicine. The study was designed specifically to develop a program to minimize the danger of disseminated coccidioidomycosis and at the same time benefit from the exposure of a large number of troops stationed in the area to evaluate the epidemiology of this fungus infection. Epidemiological evaluation of an early outbreak during maneuvers in Kern County, California, led to significant changes in desert training methods.

The importance of the cocciodiomycosis study extended beyond the significant contributions to the knowledge of diagnosis, treatment, epidemiology, and prevention of this disease. This group directly focused the attention of military authorities on the importance of this disease, particularly as it related to the location of military personnel in a desert environment. Of equal importance was the continuity that was provided in the overall supervision of the program. Area surgeons, laboratory personnel, ward officers, and commanding officers were subject to frequent change. Hence, it was the Stanford group that coordinated the educational, diagnostic, and follow-up programs that were vitally important in controlling the spread of coccidioidomycosis in military personnel.

Survey of Respiratory Pathogens

The 4th Service Command group based at Duke University conducted a survey of respiratory pathogens in troops at Fort Bragg, North Carolina. This was under the supervision of Dr. David T. Smith, assisted by Mr. W. A. Mickle, Jr.

During the period of 1 July 1942 to 1 November 1942, no significant increase occurred in the prevalence of any particular pathogen that could be related to increased incidence of respiratory disease. With the establishment of the Commission on Acute Respiratory Diseases (CARD), this study was transferred to that Commission.

Budgets and Expenditures

The total budget for the CES for 1942 to 1943 was $44,000, with $14,000 allotted to the 1st Service Command study, $10,000 to the 9th Service Command project, and $20,000 for "epidemiological work in other areas and reserve." This last budgetary item, which had been reduced to $16,000, funded the 4th Service Command study. The remainder was transferred to the Commission on Meningococcal Meningitis ($2,000) and to the Commission of Neurotropic Virus Diseases ($10,500). The 1943 and 1944 report stated, "The availability of this fund has been of great value in assisting in the work of other commissions which during the course of the year were found to need additional funds for special projects."

In the annual report of the CES for 1944, the following appears: "In July Major Wilbur G. Downs, MC, AUS, formally of the Rockefeller Institute, New York City, was appointed to the Commission under the allotment of Officers for the Army Epidemiological Board and assigned as Army Medical Liaison Officer with the Naval Medical Research Unit no. 2. As in previous years, this commission has stood ready to assist other commissions and to conduct special investigations for The Surgeon General, as needed."

Proposals for the work of the CES for July 1943 to July 1944 consisted of the continuation of the bacteriologic surveys of troops in the 1st Service Command under Dr. Mueller, now assisted by Dr. Ann Kuttner, and the coccidioidomycosis study in the 9th Service Command. The budget for $44,000 was approve.

The carrier studies in the 1st Service Command were terminated at the end of the 1944 and 1945 study year. The investigators pointed out that the streptococcal, influenza, and diphtheria rates had remained "pre-epidemic," and no significant amount of illness caused by these organisms had been noted among the troop populations studied. The prevalence of meningococcal carriers, particularly

type I, however, showed a pattern paralleling the epidemic curve during the observation period. The coccidioidomycosis study continued to provide valuable data. This group provided skin test antigen to many organizations outside of the War Department, not only in the United States, but to foreign countries. They provided ongoing laboratory diagnostic support for various medical facilities. It became apparent that a number of infections occurred in laboratory personnel from performing animal inoculation at military hospitals. The group recommended that, when laboratory personnel detected a suspicious pathogenic culture, animal inoculation be deferred and the specimen be transmitted to the Stanford University Laboratory for confirmation. This procedure worked well. Significant progress was also made in evaluating various methods of dust control. A representative of the Preventive Medicine Division of the Office of The Army Surgeon General commented at the annual meeting of the AFEB in the fall of 1945 that this 9th Service Command study was the focus of the Army investigative program of coccidioidomycosis.

Influenza Vaccine

Although a 4th Service Command study on influenza vaccine was supported financially by the CES, the results were reported by the Commission on Influenza. The evaluation was carried out at Duke University Hospital from 1 February 1945 to 14 February 1946 under the direction of Dr. Joseph W. Beard.

Studies in Puerto Rico

The 4th Service Command investigative team, which was to have been located in Puerto Rico, with Dr. P. Morales-Otero as Director, never became operational. The allotted funds were diverted to other commissions. It appears, however, that some coordination occurred between the group in Puerto Rico and the CES. In April 1944, a paper entitled, "The Streptococcus Problem in the Tropics. A Throat Culture Survey of Troops stationed in Puerto Rico" by Drs. G. J. Dammin, A. Pomales Lebron, and P. Morales-Otero was approved by The Surgeon General of the Army for publication. A footnote was added to the manuscript by Dr. Bayne-Jones acknowledging association of the authors with the CES. In June 1945, another manuscript entitled, "A Throat Culture Survey of Troops stationed in Puerto Rico" by Drs. A. Pomales Lebron, G. J. Dammin, C. Pons, and P. Morales-Otero was cleared for publication by The Surgeon General of the Army. Correspondence related to this clearance stated that the work being reported was accomplished as a project of the CES. In the annual report of the AFEB for 1943, it was stated: "The Commission has stimulated studies of hemolytic Streptococcal infection in Puerto Rico and has stood ready to aid other commissions."

Termination of First Commission on Epidemiological Survey

Shortly after World War II, the investigative program of the CES underwent a close reevaluation. By the late fall of 1945, it was determined that the program envisioned for that commission could be absorbed into other existing commissions and that the CES was no longer essential. All activities were terminated, funding was discontinued, army-owned equipment in the hands of contractors was disposed of, and the CES became inactive.

THE SECOND COMMISSION ON EPIDEMIOLOGICAL SURVEY (CES)—1954 TO 1973

Early in 1954, Major General George E. Armstrong, The Surgeon General, U.S. Army, reversed a long-standing policy of the Army Medical Service and agreed, in principle, to a joint Army Medical

Service–Chemical Corps study of the problems inherent in biological warfare. Brigadier General John E. Wood, Commandant, Army Medical Service Graduate School, Washington, DC, served as The Surgeon General's representative in the negotiations that followed and continued to serve under Major General Silas B. Hayes, who replaced General Armstrong. Shortly afterward, General Wood requested that the AFEB review this proposal and make recommendations to The Surgeon General. A special meeting of the AFEB was convened in the summer of 1954. After a thorough evaluation and discussion, the AFEB concluded that the Army Medical Service should participate in this proposed joint study.

At the regular meeting of the AFEB in September 1954, this plan was approved and membership of the advisory group, as recommended, was approved. Members of this group were Dr. Richard E. Shope (Chairman) The Rockefeller Institute, New York; Dr. Joseph E. Smadel, Army Medical Service Graduate School, Washington, DC; Dr. Theodore E. Woodward, University of Maryland School of Medicine, Baltimore, Maryland; Dr. John H. Dingle, School of Medicine, Western Reserve University, Cleveland, Ohio; Dr. W. Barry Wood, The Johns Hopkins Hospital, Baltimore, MD. Dr. Colin MacLeod (exofficio) New York University College of Medicine, New York; and Colonel William D. Tigertt, MC, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, DC, who had been named earlier as the project officer.

The stated aims of this group were to assist The Surgeon General and the Chief Chemical Officer in developing a program as quoted below:

a. To obtain a realistic evaluation of biological warfare as a weapon in its present state of development.
b. To define the defensive problems in biological warfare with sufficient clarity and authority to serve as the basis for development of a program of defense against biological warfare.

At the time of this meeting, the subject of biological warfare was extremely controversial. This was true among certain members of the scientific world as well as lay groups. It was suggested that the title, "Commission on Epidemiological Survey," would be a suitable designation for this new advisory group because the title was considered to be vague and noncommittal. This recommendation led to reactivation of the CES.

The CES was unique within the structure of the AFEB in that its responsibility extended into the in-house research program as well as that conducted under contract with nongovernmental institutions. As the Surgeon General's charge to this commission was studied, it was concluded that the research programs should concentrate on three broad categories.

1. The pathogenesis of infectious diseases considered to be important in the medical defense against biological warfare, including susceptibility of man to appropriate potential agents.
2. Prophylaxis and treatment of such diseases.
3. Methods for the early recognition of infection in an exposed population and rapid identification of specific organisms or groups of organisms.

Shortly after the September meeting, Drs. Shope, Smadel, and Tigertt spent several days at Camp Detrick, Frederick, Maryland, with the personnel of the Biological Laboratory reviewing the problems inherent in the defense against biological warfare. They concluded that *Rickettsia burnetii,* the causative agent of Queenstown or Q fever, would be the most acceptable organism to employ in studies proposed to evaluate the potential dangers of a biological attack against a U.S. military and civilian population. These studies were to be conducted as a joint endeavor between the CES , as an agent of The Surgeon General of the Army, and the Medical Subcommittee of the Army Chemical Corps Advisory Council. The objective of these studies was to conduct an open air field test of a virulent organism in volunteers. After long and careful evaluation of the entire program, this approach was approved by the CES and presented to the AFEB. After approval by the AFEB and with concurrence of The Surgeon General, the project known as CD-22 was initiated.

The operating agencies, at this point in the program, were the Army Biological Laboratories, a Chemical Corps research unit at Camp Detrick, and the Special Operations Division, Army Medical Service Graduate School in Washington. The research program was centered at Camp Detrick as a joint

operation. The senior representative of the Army Medical Service was Leutenant Colonel Tigertt, commanding officer of Medical Unit (9901.07) Walter Reed Army Medical Center. This unit was established as a part of WRAIR specifically to conduct the Joint Medical Service–Chemical Corps Project. Medical Service Operations at Camp Detrick were the responsibility of Colonel Abram S. Benenson, MC, and laboratory procedures were supervised by Colonel William S. Gochenour, VC.

As the program progressed, each step was evaluated and approved by the CES and the AFEB. During this phase of the project, the Army Medical Service acted as a contractor for the chemical corps because funding was received from the latter branch of the Army.

In October 1954, 1 month after approval of the joint Surgeon General–Chief Chemical Officer, biological warfare research program, Colonel Tigertt contacted Dr. Theodore R. Flaiz, Secretary of the Medical Department, General Conference of the Seventh-Day Adventist Church, to ascertain the views of that church organization as related to the use of volunteers in medical research. Later that month, a committee of the Seventh-Day Adventist Church met with Colonel Tigertt. He presented a thorough review of the proposed use of volunteers in the studies of the defense against biological warfare. He explained how the program would be conducted, the safety control measures, the scientific supervision of military and civilian personnel to be employed, the potential dangers, and the benefits to be gained. After due consideration, The General Conference of the Seventh-Day Adventist Church approved the program and so informed General Hayes. In January 1955, the Secretary of the Army approved a program for "the conduct of research investigations utilizing volunteers in defense against biological warfare." Thus was born what proved to be one of the largest and most successful military medical volunteer research programs in the history of the Army. This program, known as Project Whitecoat, involved approximately 2,000 young Seventh-Day Adventist soldiers and was in continuous operation from 1955 until the military draft was discontinued in 1973.

Project CD-22

The first research program involving the newly activated CES was entitled CD-22. This project involved a study of Q fever in animals and humans in the laboratory and the field. Q fever is a mild to severe febrile disease resulting from infection with *Rickettsia burnetii*. Q fever responds rapidly to treatment with broad-spectrum antibiotics (eg, chloramphenicol, tetracycline), particularly when treatment is instituted early after the onset of symptoms. The prognosis for complete recovery from an infection with this organism is excellent.

The first requirement for the initiation of the project was the preparation of an adequate amount of egg slurry infected with *R. burnetii* to be used in both the animal and human studies. This material was prepared by the Army Biological Laboratories, Camp Detrick, and it was characterized and safety tested by both the Biological Laboratories and the Walter Reed Medical Unit. Some difficulty was encountered in meeting purity standards for the infected slurry, and the first lots were considered of insufficient purity to be administered to humans. However, after considerable discussion and some recrimination, it was agreed in November 1954 that an entirely new lot would be prepared.

By January 1955, a large amount of infected egg slurry was prepared that was determined to be of sufficient purity for exposure of volunteers. Beginning in January 1955, phase I of the project was initiated. Phase I consisted of a series of studies to determine the infective dose of this material in laboratory animals when administered by the aerosol route. After a careful evaluation of the results of these studies, the CES recommended to The Surgeon General and the Chief Chemical Officer that the project enter phase II, the exposure of human subjects. The first Whitecoat volunteers were exposed on 25 January 1955 with the use of the 1 million-liter sphere (commonly known as the "eight ball") at Fort Detrick. This research device (operated by the Army Biological Laboratories) was designed to allow simultaneous exposure of humans and laboratory animals to carefully controlled numbers of organisms by the aerosol route. Laboratory animals were exposed and aerosol impinger samples were taken at the time of human exposure.

Over the next 2 months, the optimum dosage to be employed in field trials in humans was determined, as was the effectiveness of a Q fever vaccine in protecting humans when exposed under laboratory conditions.

After completion of this phase of the study, preparation for phases III and IV was initiated; phase III was planned as a field study of exposure of animals, and phase IV was the exposure of humans to a typical biological warfare aerosol under field conditions. These studies were to be conducted at Dugway Proving Grounds, Utah.

Beginning in March 1955, trials were conducted to examine the field dosage levels at various downwind distances of infected material from a line source disseminated by aerosol generators; the objective was to determine the sampling and exposure distance to be used in phase IV.

Numerous test trials used noninfected egg slurry to standardize the aerosol-generating equipment, evaluate aerosol response, evaluate various meteorologic conditions, and determine the numerous parameters to be considered in the final studies. Three trials were then conducted with the use of infective whole-egg slurry. These trials involved collection of organisms in all glass impingers and the exposure of guinea pigs at various distance downwind from the source. Fluorescent particles also were aerosolized and collected to provide additional information for determining dosage levels and the path of the aerosol.

Phase IV of this project consisted of one trial in which actual field exposure of human subjects, guinea pigs, and monkeys was conducted; additional sampling with millipore filters and impingers was accomplished. This study used 30 Whitecoat volunteers in groups of 3 (1 immunized and 2 nonimmunized) at 10 different stations. In addition, 75 rhesus monkeys and 300 guinea pigs were exposed to the aerosol. The volunteers were located 3,200 feet downwind from the aerosol generators. This final study was conducted just before dawn on 13 July 1955 under direct supervision of the Walter Reed Unit with members of the CES present. Generation of the infected aerosol and collection of samples for laboratory studies was under the direction of personnel from the Army Biological Laboratories and Dugway Proving Grounds.

The details of this study are still classified, but it was shown beyond any doubt that susceptable humans could be infected under field conditions by exposure to an artificially generated aerosol containing infectious organisms.

After completion of the Q fever field trials, additional experimental work was conducted at Camp Detrick on the effectiveness of Q fever vaccine and the use of oxytetracycline (Terramycin) for postexposure prophylaxis and treatment. Exposure was accomplished by the aerosol route with the use of several different dosage levels and at different time periods after completion of the vaccination series. The Formalin-inactivated vaccine was highly effective in protecting against clinical illness, although an occasional individual did become ill. Terramycin was highly effective in treatment of Q fever under all conditions of infection. Individuals given Terramycin prophylactically after aerosol exposure at different dosages were completely protected if the drug was started late in the incubation period (1 or 2 days before anticipated appearance of clinical disease). If a 6-day course of Terramycin was begun 24 hours after exposure, most individuals developed clinical illness after an incubation period approximately twice as long as anticipated for an unprotected person. All volunteers responded well to readministration of the Terramycin.

When one dose of Q fever vaccine was administered after aerosol exposure, some protection was detected against low dosage exposure but very little protection against higher dosages. All persons who developed clinical illness responded well to Terramycin therapy.

Those volunteers who were reexposed to Q fever *Rickettsia* by the aerosol route, after having recovered from clinical illness caused by this organism showed no evidence of infection. No evidence was noted of person-to-person transmission between those with clinical illness and the unprotected personnel who provided day-to-day medical care.

In 1956, three additional members were appointed to the CES. They were Ivan L. Bennett, Jr., M.D., Associate Professor of Medicine, Biological Division, The Johns Hopkins Hospital, Baltimore, Mary-

land; Geoffrey Edsall, M.D., Director, Communicable Disease Division, WRAIR, Washington, DC; and Colonel Tigertt, MC, Assistant Commandant, WRAIR, Washington, DC.

U.S. ARMY MEDICAL UNIT — FORT DETRICK

During Project CD-22, laboratory facilities available to the Walter Reed Unit at Fort Detrick were almost nonexistant. All aerosol exposures were accomplished by personnel of the Army Biological Laboratories, with the human exposures being conducted under the direct control of the Walter Reed group. After the successful completion of Project CD-22, interest in the medical defense against biological weapons increased significantly among senior officers of the Army Medical Service. These officers recognized the significant contributions that research in biological warfare could contribute to the development of knowledge regarding the pathogenesis, diagnosis, prevention, and treatment of infectious diseases not generally encountered in the United States. Potential biological agents could present serious problems, if military forces were required to operate in global areas where such diseases were naturally prevalent.

With this expanded interest, plans were initiated to establish an independent self-supporting unit at Fort Detrick to replace the Walter Reed Unit. On 20 June 1956, the U.S. Army Medical Unit (USAMU), Fort Detrick (08-9901.07) was activated under the command of Colonel Tigertt. This unit was directed to function jointly with the Division of Special Operations of the WRAIR. Funds were provided to the Medical Service by the Chief Chemical Officer.

Necessary laboratory office and support facilities occupied at the time by Biological Laboratory personnel were to be vacated, renovated, and assigned to the new medical unit. In addition, another laboratory building located at the Forest Glen Annex just outside of Washington was to be made available to the medical unit by WRAIR. This latter facility was designed for studies requiring special equipment for handling highly infectious microorganisms. Unfortunately, the occupants of those facilities were slow to vacate the premises and renovations were delayed. Some buildings specified for medical unit use were not available until late in 1957 and others not until 1958. Colonel Tigertt likened the year as "reminiscent of time spent in a wartime staging area."

Gradually, as professional, administrative, technical, and support personnel were assigned, a number of new projects were initiated despite a shortage of laboratory space. In addition to the space assigned to the medical unit at Fort Detrick, laboratory space was made available for the use of USAMU personnel, on a temporary basis, by the Army Biological Laboratories, the Armed Forces Institute of Pathology in Washington, WRAIR, and Dugway Proving Grounds.

The medical treatment facility operated by USAMU consisted of two wards, each capable of handling about 20 patients. One of these was for the care of minor illnesses and injuries in Fort Detrick military personnel and their dependents, and the other was for the care of occupational infectious illnesses occurring in biological laboratory and medical unit personnel and for the housing of Whitecoat personnel participating in volunteer studies. A fully equipped diagnostic laboratory was available. This facility operated throughout 1957 despite limited equipment. It had no operating room at that time, and all patients requiring surgery were transferred either to Walter Reed General Hospital, Washington, DC, or to Frederick Memorial Hospital, Frederick, Maryland. The hospital staff was headed by the chief of the medical service, USAMU, who had the immediate assistance of the entire USAMU professional staff. The staff also included four nurses and a cadre of trained medical corpsmen. On 1 August 1957, the treatment facility was designated Ward 200 of Walter Reed General Hospital. During the latter half of 1957 and early 1958, a complete operating room, a central supply room, and updated diagnostic radiographic equipment were added. Arrangements were in effect with Walter Reed General Hospital to supply a complete surgical team and necessary special equipment when required.



IVAN L. BENNETT, JR., M.D.

Dr. Ivan Bennett graduated with a degree in medicine from Emory University in 1946 and was a product of the Grady Memorial, Duke, and Johns Hopkins Hospitals, where he trained in medicine and pathology. He was assistant professor of medicine at Yale from 1952 to 1954 under Paul Beeson, his associate and close friend. he then progressed through the ranks at Hopkins from associate professor to professor of medicine and held the Baxter Chair in Pathology there from 1958 to 1966. This was followed by his appointment as acting director of the office of science and technology, executive office of the president from 1966 to 1969. He then became a senior officer at the New York University Medical Center, where he served with distinction as vice president for health affairs, dean, director of the medical center, provost, and acting president.

Few American physicians have contributed so much and so wisely to the public interest as Ivan. He had natural blessings of high intelligence, keen wit, and an impelling desire to tackle difficult problems. The AFEB and its CES profited from his keen sense of uncovering potential threats and devising means to counter them. Throughout his later years, he contributed wisely at all levels of professionalism, including the World Health Organization, on matters pertaining to defense against biological warfare.

The United States Cooperative Medical Science Program Benefitted from his wise and inspired leadership over 18 years. Ivan had good taste and a unique talent for choosing the right people for the proper job. He promoted the welfare of good scholars and found gratification in their career development. His record of public service is endless. He died in Tokyo, Japan, on July 22, 1990, while he was attending the 25th anniversary meeting of the U.S./Japan Program.



GEOFFREY EDSALL, M.D.

Dr. Geoff Edsall graduated from Harvard Medical School in 1934 and served his house officership at the Massachusetts General Hospital from 1934 to 1936. Research fellowships followed at Harvard, and he served as an instructor in bacteriology and immunology at the Harvard Schools of Medicine and Public Health. Dr. Edsall was assistant director of the Division of Biologic Laboratories of the Massachusetts Department of Public Health and its director until 1949. For several years, he was Professor of Microbiology and head of the Department of Microbiology at the Boston University School of Medicine, which was followed by his appointment as Director of the Division of Immunology at WRAIR in 1951.

Geoff served the AFEB in may ways, particularly as the director of the Commission on Immunization from 1952 to 1963. The membership of this Commission was graced with some of the leaders in American medicine in biology and immunology. Under Geoff's direction, the Commission accomplished a vast amount of work and collaborated with the activities of other Commissions. The 3-day meetings of this Commission held at WRAIR were actually reviews of contemporary work in immunology and vaccine development. Geoff also served as a member of the CES, where his advice was put to good use. His research interests were broadly distributed throughout the immunological field and his special contributions related to the purification of toxoids, particularly tetanus and diphtheria.



BRIGADIER GENERAL WILLIAM D. TIGERTT, MC (RET.), M.D.

During Bill Tigertt's distinguished military career, he was closely affiliated with the AFEB and several of its Commissions. With the advantage of a remarkable experience in laboratory medicine and an accurate bibliographic memory, Bill applied this broad capability in pursuit of those many difficult infectious disease problems that confronted him. He gained broad experience in tropical disease problems in New Guinea and the Phillipines as director of the 26th Army Laboratory and the 406th General Laboratory, Tokoyo, where malaria, other parasitic diseases, and enteric infections were rampant. Later, as commanding officer of the USAMU at Fort Detrick (later USAMRIID), many answers to problems of pathogenesis, pathophysiology, and control of important viral and rickettsial diseases were clarified under his guidance.

Bill Tigertt was the principal force behind the new thrust to find a better prophylactic and chemotherapeutic way to control malaria, a dilemma caused by the plasmodia resistance problem.

He collaborated closely with the CES and was a member of the Commissions on Malaria, Viral Diseases, and Parasitic Diseases. He always consulted directly with the AFEB on matters vital to the military services.

In late 1958, construction of a specially designed building to house a 1,000 KVP medical radiographic unit was completed and the unit installed. This facility was designed to study the effect of varying doses of radiation on the course of infection in laboratory animals.

Responsibility of CES

After the successful completion of the joint Medical Service-Chemical Corps Project CD-22, activation and expansion of the USAMU at Fort Detrick, availability of a suitable medical treatment facility at Fort Detrick, and the readily available pool of volunteers, the Army Medical Service and the CES became increasingly involved in medical defense against biological warfare. In April 1958, The Surgeon General issued the statement on the following page outlining his current thinking on this subject.

In 1959, The Surgeon General issued a *Statement of Policy* on control of infectious disease. This statement included the following excerpts:

4. Education:
   a. The education of medical personnel in the identification, control and treatment of infectious disease is a function of the Personnel and Training Division since such training is a part of the overall training of Army Medical Service personnel. The provisions of such training should be divided into that of extensive training of trainers, the establishment of a capability of expansion of training in case of mobilization and the accumulation of a readily available library of training aids kept constantly up to date.
   b. The extensive training of trainers could be accomplished in various ways.
      1. By the assignment of career internists, pediatricians, laboratory officers, veterinarians and Army Nurse Corps officers to the Medical Unit, Fort Detrick.
      2. By the assignment of career medical officers to foreign areas where infectious disease is frequently encountered.
      3. By the development of a course in the diagnosis and control of communicable disease at WRAIR, this course to be short, recurring and on a temporary duty basis.
      7. Research and development:
         The research and development program for the prevention and treatment of infections should be expedited. Such research should include, but not be limited to, expansion of identification efforts and development of more efficient reporting methods and procedures. It is particularly important that new methods of automatic reporting be developed. It is desired that the present agreement with the Chief Chemical Officer ultimately be changed so that the Army Medical Service be assigned mission responsibility for research and development in medical prevention and treatment of disease resulting from biological warfare.

These developments were the result, in part, of increasing recognition of the potential impact of the medical problems that would be faced in the event of biological warfare and the importance of naturally occurring infectious diseases for the Armed Forces, particularly in certain overseas areas. After this, two significant personnel developments occurred. The first was the successful effort by Colonel Tigertt in getting career officers assigned to the medical unit and in obtaining the assignment of young noncareer officers interested in infectious disease research. This effort was immeasurably aided by recommendations from members of the AFEB and particularly from members of the CES.

The second was recognition of the assistance available from the CES. The medical unit had not only the benefit of the general guidance provided by the CES, but also the immediate availability, when necessary, of the knowledge of some of the most highly qualified men in the United States in the field of infectious disease. When a problem arose, it was possible to have a phone consultation in a matter of minutes or convene a panel of experts within a few hours. Just the fact that these nationally and internationally recognized authorities were available for guidance and consultation was a significant factor in developing and executing the research program of the medical unit.

By mid-1958, the medical unit facilities at Fort Detrick and the Hazardous Laboratory at Forest Glen were equipped and operational, and the staff was in place. The CES was now actively involved in both the in-house and contract research programs.

The Surgeon General's Statement Regarding Medical Defense Against Biological Warfare

The Surgeon General is concerned with his responsibilities in the control of infectious diseases in situations wherein appreciable portions of a military population can be expected to become ill from exposure anticipated in future types of operation, regardless of whether an agent was naturally or artificially disseminated. He is currently reviewing his capabilities and obviously this involves consideration of his research program in the infectious disease field. Those areas related to his preexisting research program and to the current research program specifically related to defense against biological warfare are to be reviewed and the advice of the Commission on Epidemiological Survey as to the adequacy of the program will be sought.

When formulated, portions of the program will be assigned to specific AMEDS laboratories, or to the contract effort as appropriate.

Quarterly reports will be required on all in-service research programs which are determined to be pertinent to the defensive aspects of biological warfare.

The Surgeon General desires that the Commission on Epidemiological Survey act, as do other commissions, in stimulating and guiding a contract research program. The AMEDS Research and Development Program will support this effort with funds from AMEDS and Chemical Corps sources as appropriate.

In addition, The Surgeon General desires that the Commission on Epidemiological Survey assume an active role in review of the In-service Research Program related to medical defense against biological warfare. In this regard, they will advise The Surgeon General on the soundness of the entire research program related to medical defense against biological warfare.

With the possible exception of certain sensitive, classified matters, these activities should be carried on as are other AFEB affairs.

The differences that this altered situation will make as regards the activities of the Commission on Epidemiological Survey are as follows:

1. It will become more like other Commissions of the Armed Forces Epidemiological Board in that it will stimulate and be responsible for research in areas of its competence under the aegis and with the approval of the Board.
2. In addition, it will assume responsibilities beyond those of other commissions in that it will advise The Surgeon General on in-service research directly applicable to the defensive aspects of biological warfare.
3. It will aid in the planning and will advise on projects under its cognizance, both in-service and contract, and will follow their progress closely.
4. It will advise on experimental protocols in volunteer studies and recommend their individual approval or disapproval.
5. It will expect periodic reports through The Surgeon General of in-service work under its cognizance.
6. It will, when requested by The Surgeon General, initiate experimental work in sensitive areas.
7. It will periodically review the defensive biological warfare research program and will make recommendations for areas that it feels are inadequately covered.

During that year, Dr. Dingle, School of Medicine, Western Reserve University, Cleveland, Ohio, was appointed to a full membership on the CES and Dr. Smadel declined reappointment. Dr. Woodward was designated Deputy Director. One formal meeting was held. In addition, a number of informal conferences were held at Fort Detrick and in Baltimore and Washington. These meetings resulted in a detailed appraisal of the problems inherent in medical defense against biological warfare, permitting a definition of those areas where research was required and the assignment of relative priorities. This appraisal served as the basis for a presentation by Colonel Tigertt to the Special Panel on Biological Warfare of the President's Scientific Advisory Committee on 10 November 1958. This presentation was a wide review of the subject.

Colonel Tigertt stated that The Surgeon General had a demonstrated competence to handle naturally occurring outbreaks of disease of military importance but did not have the capability to handle the very large-scale outbreaks of illness that theoretically might result from a successful biological warfare attack. He also brought to the attention of this group that The Surgeon General was not directly charged with the execution of a research program that would provide such capability. This latter responsibility had been assigned to the Chief Chemical Officer, but in 1954, at the request of the Chief Chemical Officer, The Surgeon General, in effect, became a contractor to the Chemical Corps to engage in a limited research program on certain phases of medical defense.

This presentation discussed the development and use of vaccines of importance in biological warfare and the employment of chemoprophylaxis and the training of physicians and other medical service personnel in the management of exotic disease of biological warfare. The rapid and accurate reporting of disease outbreaks during wartime were discussed along with the requirement for development of more rapid methods of diagnosis and organism identification.

Colonel Tigertt summarized the problems of medical defense against biological warfare as follows:

> We believe we know in considerable detail the type of medical research program which must be undertaken, if a known satisfactory posture for defense against biological warfare is to be attained. This program is hazardous, time consuming, and must inevitably involve the deliberate risk of human life. It has one real bonus value, however, if properly conducted. The results obtained will be applicable to the control of disease whether or not biological warfare ever becomes a reality.

The Research Program

The research program in 1957 and 1958 was centered chiefly on tularemia, which constituted a significant portion of the program, Venezuelan equine encephalomyelitis (VEE), typhoid fever, Rift Valley fever, anthrax, plague, and Q fever.

It was determined that the respiratory-induced form of tularemia could be adequately controlled by the administration of tetracycline as well as streptomycin. Studies conducted by Dr. S. Saslow at Ohio State University, under a contract with the CES, showed that the infectious dose for humans was of the order of a few organisms when exposure was by the aerosol route. At these low doses, the incubation period averaged about 5 days. The Foshay-type vaccine that had been used at Fort Detrick for the protection of laboratory personnel was determined to be not effective. Extensive studies were conducted on a living vaccine strain obtained from Russian sources by Dr. K. F. Meyer during a trip to that country.

Dr. Henry Eiglesbach of the Army Biological Laboratories confirmed that the vaccine had two bacterial colony types, blue and gray, and that only the blue strain was immunogenic. The vaccine that he prepared from the blue strain was studied extensively at the Biological Laboratories and the medical unit and under contract at the University of Maryland Medical School and at Ohio State University. Aerosol exposure was made possible in the contract studies by the use of portable aerosol-generating equipment developed and operated by Biological Laboratory personnel. In addition, these studies determined that the Larson vaccine was of little value in protecting against aerosol exposure.

Rift Valley fever was studied at the Hazardous Disease Laboratory at the Forest Glen Annex of WRAIR under the direction of Dr. Raymond Randall, DVM. His studies were oriented toward development of an effective vaccine. The vaccines used previously in this country and in Africa had produced limited protection. A Formalin-inactivated vaccine produced from a pantropic strain of virus grown in monkey kidney tissue culture was found to produce significant neutralizing antibody in laboratory animals and in humans.

Studies of VEE also were oriented toward development of an effective vaccine. Inactivated vaccines were of little or no value in protecting against laboratory infections. Studies were in progress to obtain a living attenuated vaccine from the Trinidad strain by serial passage in guinea pig heart cell tissue culture.

Under contract with the University of Maryland Medical School, typhoid fever was studied in volunteers from the Maryland House of Corrections at Jessup, Maryland. These studies were conducted at the University of Maryland Hospital and involved 12 volunteers divided into 3 groups. Infection was produced by ingestion of large numbers of *Salmonella typhosa* propagated on artificial media. All 12 volunteers developed disease. The average incubation period was 5 days, and therapy with chloramphenicol resulted in lysis of fever over a period of several days. Studies by Dr. Sheldon Greisman showed that, during the early febrile period, hyperreactivity to norepinephrine was noted with the use of microscopy of the nailbed fold. This was believed to be caused by endotoxin sensitization.

In response to The Surgeon General's guidelines for the research program of the USAMU, Fort Detrick, and the CES, work on the early and rapid diagnosis of disease and the identification of disease-producing organisms were intensified. A contract with Dr. Paul Fremont-Smith, Harvard Medical School, involved the development of a technique for the rapid growth, identification, and antibiotic sensitivity testing of clinically important bacteria. Bacteria grown on thin agar films on glass slides were studied for colonial morphology cellular pattern and tinctorial characteristics. The application of fluorescent antibody techniques to this procedure also were studied.

During this same period, Dr. Martha K. Ward, U.S. Public Health Service, assigned to the USAMU, Fort Detrick was working on methods for the rapid identification of *Franciella tularensis*. Her work involved the development of a selective culture media that would allow the isolation of this organism directly on plates and eliminate the time and hazard inherent in animal inoculation procedures; methods for obtaining more rapid growth on solid media; and the development of a more satisfactory liquid medium for use in blood culture work and perhaps as an enrichment medium to be used in conjunction with fluorescent antibody technique.

During this period, studies were initiated on plague and anthrax. These two diseases had been under investigation in the Army Biological Laboratories, and some work had been done on development of vaccines. With the availability of the renovated laboratories on hazardous materials at Forest Glen and the medical unit, additional vaccine studies became practical.

Dr. Woodward succeeded Dr. Shope as director of the CES in July 1959. At the same time, Dr. Leighton E. Cluff, The Johns Hopkins Hospital, and Dr. Fred R. McCrumb, University of Maryland Medical School, were appointed to the CES as associate members.

Biological Warfare and the Armed Forces

At the spring meeting of the CES in 1960, Brigadier General Joseph McNinch, commanding general of the U.S. Army Medical Research and Development Command, reviewed the importance being placed, at that time, on medical defense against biological warfare. This feeling extended to the highest levels of the Department of Defense and even to the White House. He stated that The Surgeons General of the Army, Navy, Air Force, and Public Health Service had active research programs in this field. He added that the CES was responsible to The Surgeon General of the Army for advice on planning and guidance pertaining to the scientific program, both in-house and under contract. He emphasized that the CES carried responsibility to review the need, design, and scientific excellence of volunteer studies with power to approve or disapprove a project.

General McNinch noted that funding was derived from the Chemical Corps and that an increase of almost 100% was projected for the following fiscal year. A portion of these additional funds would be expended on a contract with a pharmaceutical firm to develop methods for the large-scale production of vaccines as they were developed in the biological warfare medical defense program.

At the March 1960 CES meeting, it was recommended that two subcommittees be appointed. The first subcommittee was to formulate plans and policy regarding anthrax. The subcommittee staff were Dr. MacLeod, chairman, Dr. John Y. Bennett, member, Colonel Tigertt, member, and Dr. Harold Glassman, advisary member (Deputy Scientific Director of the Army Biological Laboratories, Fort Detrick). The second subcommittee was to study problems relative to reorganization and reorientation of the CES and its role with regard to biological warfare. The staff of this subcommittee were Dr. Shope, chairman, Dr. MacLeod, member, and Dr. Woodward, member.

This latter committee was asked to formulate plans after discussion with General McNinch, The Army Surgeon General, Dr. Bayne-Jones, and others. One of the principal areas to be reviewed was the relationship of the CES and the AFEB with the Medical Advisary Committee to the Chief Chemical Officer and other agencies and committees of the Department of Defense.

In July 1961, Colonel Tigertt was transferred for a 1-year assignment to the Medical School in Shiraz, Iran, and was replaced by Colonel Dan Crozier, MC, as commander of the USAMU , Fort Detrick.

The composition of the CES, at that time, was as follows:

Dr. Theodore E. Woodward, Director
Dr. Ivan L. Bennett, Jr., member
Dr. John H. Dingle, member
Dr. Geoffrey Edsall, member
Dr. Colin M. MacLeod, member
Dr. Richard E. Shope, member
Colonel William D. Tigertt, member
Dr. W. Barry Wood, member
Dr. Leighton E. Cluff, associate member
Colonel Dan Crozier, associate member
Dr. Fred R. McCrumb, associate member

When Colonel Crozier took over command of the medical unit, the research program, under the guidance of the CES, was well-organized and highly productive. The laboratories, located in temporary or semipermanent buildings, were adequate, although limited, and the staff were complete and highly qualified. Each of the research divisions was headed by a career officer as were many of the supporting sections. Many of the other staff members were young, enthusiastic physicians and allied scientists in the biological fields who had asked for the assignment or who had been recommended by medical school and university deans familiar with the research program, particularly members of the CES and other AFEB commissions.

Review of Biological Warfare Research Program

At the 7 September 1961 meeting of the CES, a review of the research program, both in-house and contract, was presented. Studies of tularemia, VEE, anthrax, staphylococcal enterotoxin, plague, typhoid fever, and Rift Valley fever constituted a major portion of the program. These diseases and their causative organisms were studied not only to obtain information relative to the particular disease and its specific organism, but also they served as models to study infectious processes in general, including pathogenesis, diagnosis, and prophylaxis and treatment in laboratory animals and humans.

Typhoid Fever

Extensive studies of typhoid fever were conducted under contract with the University of Maryland under the direction of Dr. Woodward. A 15-bed medical ward for the study of this disease in volunteers was opened at the Maryland House of Correction in 1961. The ward was established at a cost of approximately $10,000, and the cost per day per patient was approximately $8.00. Studies were conducted to evaluate the role of typhoid vaccine in modifying or preventing the disease in humans and to investigate the part played by endotoxin in the pathogenesis of typhoid fever. These studies



RICHARD E. SHOPE, M.D.

Dr. Richard E. Shope accomplished much during his relatively short life (64 years). After qualifying in medicine at the University of Iowa in 1924, he trained in pharmacology, with special work on the chemotherapy of tuberculosis. He joined the Rockefeller Institute at Princeton (ultimately the Rockefeller Foundation). An avid outdoorsman with an interest in animals dating from his youth, his research shifted to hog cholera and virology.

A key observation with Dr. Paul Lewis showed that a mixture of *Haemophilus influenzae suis* and swine flu virus produced typical influenza and severe pneumonia in swine. This clarified the complementary role of virus and bacteria in producing diseases and led to his contribution that swine flu virus might cycle through lung worms, with ova passed on in the feces, then to earthworms, and back to the hog from the earthworm. This novel and controversial notion helped explain the cyclic nature of influenza. His most brilliant contribution was the demonstration that the two viruses that affected wild cottontail rabbits produced either a fibroma or papilloma. These viruses carry his name and have had important implications with respect to the pathogenesis of cancer.

Dick Shope had a very distinguished war record and worked under Dr. Thomas Rivers with the U.S. Navy Medical Research Unit on Guam. After World War II, he was the first director of the CES from its reorganization until 1959. Tireless as a productive scientist, he had the facility to objectively monitor the broad scientific program on biological warfare defense at Fort Detrick (later USAMRIID), which was one of the roles of the CES. Under his direction, many new concepts of pathogenesis and control were elucidated. He had the facility to make it enjoyable for members of the CES and others to work with him, and his sense of humor was infectious.



THEODORE E. WOODWARD, M.D.

Dr. Theodore Woodward was raised in Westminster, Maryland; he graduated from Franklin and Marshall College in 1934 and the University of Maryland School of Medicine in 1938. He entered the Army in 1941, interrupting his internship and residency in medicine. During the war, he served at Fort Meade, Maryland, for a short time, and with the U.S. Army Corps of Engineers in Jamaica, B.W.I. This was followed by research training at the Army Medical School in Washington, D.C., where he attended a course in tropical medicine. He was temporarily assigned to a field laboratory with the initial landing forces in northern Africa. His work, primarily on the typhus fevers, involved research at the various Pasteur Institutes in northern Africa, and he was a member of the U.S.A. Typhus Fever Commisssion. He served in Naples, Cairo, the Aden Protetorate, the European theater (in England and Normandy and elsewhere in France), and the Pacific theater (in northern New Guinea and the Philippine Islands).

After World War II, Dr. Woodward practiced medicine privately in Baltimore for several years. In 1948, he joined Joseph E. Smadel in studying the clinical efficacy of chloromycetin in the treatment of scrub typhus and the typhoid fevers in Kuala Lumpur, Malaya (now Malaysia). After this valuable experience, he joined the faculty of the University of Maryland School of Medicine, where he organized the Division of Infectious Diseases. From 1954 to 1981 he chaired the Department of Medicine there.

He was a member of the CES from 1952 to 1973 and served as its Director from 1959 to 1973. He was a member of the Commission on Rickettsial Diseases from 1955 to 1973, and an associate member of the Commission on Immunization from 1950 to 1973. He served as President of the AFEB from 1976 to 1978 and from 1980 to 1992.

confirmed earlier studies that suggested that infection can be produced regularly when 10 million to 1 billion viable organisms were ingested. It also was found that occasionally as few as 100,000 organisms could produce clinical typhoid fever. Neither the severity of the resulting disease nor the length of the incubation period could be correlated with the size of the inoculum.

A number of different immunizing materials were studied in humans, including purified antigens obtained from the National Institutes of Health (NIH) and WRAIR, and the commercially available vaccine commonly administered to humans, particularly military personnel. When challenged with 1 billion organisms orally, the breakthrough rate was very high.

Studies also were conducted to evaluate critically the physiological alterations occurring during human typhoid fever that could be attributed to the activity of *Salmonella typhosa* endotoxin.

Studies under this contract also were conducted at the Hazardous Operations laboratory at the Forest Glen Annex on plague and Rift Valley fever. The Formalin-inactivated Rift Valley fever vaccine prepared by Dr. Randall was shown to be highly effective in the protection of laboratory personnel working with this virus in the United States and in Africa.

Limited studies were initiated on two anthropod-borne virus diseases commonly found in parts of Africa: Chikungunya fever and O'nyong-nyong fever.

Tularemia

The studies on tularemia during this period were concerned primarily with the aerogenic administration of the vaccine strain to humans and to the study of aged aerosols of infectious material.

The feasibility of the administration of living vaccines to animals and humans by this route had been shown for the protection of fowl against Newcastle disease and children against measles. After extensive studies of the administration of living tularemia vaccine to mice, guinea pigs, and monkeys, a protocol for administration of the vaccine by this route to humans was presented to the CES. The proposal was approved, and the studies were conducted by the medical unit at Fort Detrick with the assistance of the Aerobiology Division of the Army Biological Laboratories.

Volunteers experienced no effects from inhalation of the organism-containing aerosol. In individuals with negative serologic reactions before exposure, the response was variable below 1,300 cells presented but above that level aerogenic exposure was uniformly effective. Individuals with a positive agglutination test experienced a serologic booster response only when exposed to larger numbers (up to 10,000) of organisms.

The second series of studies of tularemia dealt with viability-infectivity relationships of aged aerosols. These studies were conducted at USAMU, the University of Maryland, and Ohio State University and included exposure of both laboratory animals and humans to the vaccine strain and the virulent SCHU-S4 strain. The age of the dynamic aerosols was only a few seconds; that of the aged aerosols, 12 to 30 minutes. Exposure of unprotected volunteers to dynamic or fresh aerosols containing the virulent strain resulted in a very high infection rate to doses as low as 20 organisms. Exposure to a 30-minute aerosol resulted in only a 50% infection rate at 170 to 260 organisms.

Venezuelan Equine Encephalomyelitis

Studies on VEE were continued during this period. Studies of this disease in mice, guinea pigs, and monkeys were extended to burros. This virus causes severe epizootics in equines and occurs commonly in parts of the Caribbean region and in South and Central America, with mortality rates as high as 80%.

Uniformly high mortality rates occurred in burros inoculated with either the Trinidad or Columbian strain. The attenuated strain of the Trinidad virus produced in the virology division of the medical unit at Fort Detrick provided solid protection in burros against challenge with the virulant strains. This vaccine also protected burros when challenged with virulent strains of both Eastern and Western equine encephalitis. The single passage of attenuated virus in burros did not restore virulence of the virus for mice.



COLONEL DAN CROZIER, MC, M.D.

Dr. Dan Crozier was closely affiliated with the AFEB, particularly with the CES, for more than a decade. He served effectively as Deputy Director of this Commission. At his retirement in 1973, I, who was then the Chairman of the CES, said, "You, Dan, have been meticulous in every detail, wise in decision making when it related to important medical science problems, hardworking, and selfess in your performance of the job [he served simultaneously as the commander of the U.S. Army Medical Unit at Fort Detrick], forthright and dogged in spelling things out when the lines were thin, and perfectly refreshing and generous in your consideration of others."

Dan Crozier developed a fine medical research unit at Fort Detrick, whose members, including himself, made scientific contributions of lasting value. A laboratory there, now known as USAMRIID, is an important national resource for the study of the pathogenesis and control of highly virulent agents, and is of inestimable importance to our country. Colonel Crozier died in 1994.

Studies on administration of the attenuated vaccine strain of VEE to animals by the aerosol route were extended. No untoward effects were noted, and satisfactory immunity was attained as determined by the development of hemagglutination-inhibiting antibody and challenge with virulent strains. After extensive studies in mice, guinea pigs, and monkeys, it was believed that immunization of humans by this method was feasible and safe. A protocol to this end was being prepared for presentation to the CES.

Anthrax

Studies of anthrax were receiving increased attention during this period. Early in 1961, Colonel Tigertt wrote, "This disease has appeared on every biological warfare agents list since Pasteur. The basic problem lies in the absence of any significant medical experience with the respiratory disease in man. In rare instances, fatal disease results in man following inhalation of an unknown quantity of anthrax spores."

The CES conducted a review of this disease with personnel from the Army Biological Laboratories and the Chief Chemical Officers Medical Advisory Committee participating as invited guests. At the completion of this review, the CES agreed on the following points:

1. Man can be infected through the respiratory route under unknown circumstances.
2. Man can resist exposure to anthrax in large doses under ordinary circumstances.
3. The circumstances that lead to human respiratory infection are unknown.
4. The regularity with which artificial respiratory infection could be induced in man cannot be estimated.
5. A very logical approach to the solution of this problem is through studies on pathogenesis of anthrax infections.

The research program in the medical unit was centered primarily on pathogenesis and studies of laboratory animals, including monkeys, when infected by the aerosol route and studies of the toxin or toxins and the protective antigen produced by the organism.

Staphylococcal Enterotoxin

Studies of staphylococcal enterotoxin with the use of a partially purified product were directed toward defining an acceptable assay procedure, developing suitable experimental models, and investigating the mechanism of the syndromes produced. Various animal species were employed, and the effective and lethal doses by various routes of administration were determined for the rabbit, pig, dog, sheep, monkey, and chimpanzee. It was found that the aerosol and intravenous effective doses in the monkey were similar.

MEDICAL DEPARTMENT–CHEMICAL CORPS COOPERATION

On 7 September 1960, a joint meeting of members of the CES and the Medical Subcommittee of the Army Chemical Corps Advisory Council met at the University of Maryland Hospital in Baltimore. Representing the CES were Drs. Woodward, Shope, Macleod, and Colonel William D. Tigertt. Representing the Chemical Corps Advisory Council were Drs. Charles L. Wisseman, A. McGehee Harvey, William A. Feirer, Riley Housewright, and Harold Glassman.

This meeting evolved from the increasing awareness of various agencies of the government of the importance of the development of defensive measures against biological warfare. The idea of the joint meeting arose at the spring meeting of the CES, at which time it was suggested that the efforts of all groups interested in biological warfare be coordinated. After a series of preliminary meetings, the joint September meeting was organized.

At this meeting, it was agreed that closer liaison should exist between these two committees and that a mechanism for accomplishing this on a continuing basis should be established. It was decided

that selected members from each group, designated by the chairman, would be invited to each scheduled meeting of the other group, and that joint meeting would be called when requested by either chairman. It also was suggested that a recommendation be made to The Surgeon General and the Chief Chemical Officer that a recommendation be submitted to the Secretary of the Army that a representative of each of these committees be appointed to the Advisory Committee of the Secretary of the Army or the Biological Warfare Panel of the Army Science Committee. It also was suggested that interested members of these latter committees be invited to meetings of the CES and the Chemical Corps Advisory Council when considered appropriate.

COLONEL TIGERTT'S SUMMATION

In June 1961, just before his departure from USAMU, Colonel Tigertt wrote an excellent summary of the mission of the medical unit and its relation to the CES. He stated:

> First, and generally accepted without comment, are its relations to any study under the heading of biological warfare which includes the deliberate exposure of volunteers. This includes passing on the justification for the program, an examination of the background data in man and animals, and concurrence in all phases of the study.

A second area of responsibility of the CES was to recommend a course of action to be taken in the study of any particular organism or the various responses to infection that might be obtained during the study of a particular organism. Colonel Tigertt also suggested that the CES and the AFEB, including its other commissions, were in an excellent position to recommend whether a particular study, which was desirable for the defense against biological warfare, could be conducted most efficiently under the auspices of one of the other commissions, in one of the other in-house laboratories, by a civilian contractor, or by some combination of these facilities.

Colonel Tigertt also included a list of potential biological warfare agents that should be considered in the research program:

Bacterial Diseases
Plague
Tularemia
Typhoid
Anthrax
Pseudo-glanders
Glanders
Tuberculosis
Listeriosis
Brucelosis
Cholera
Dysentery

Toxins
Tetanus
Diphtheria
Botulinum
Staphylococcus
Entertoxin

Rickettsial Diseases
Q fever
Epidemic Typhus
Rocky Mountain Spotted Fever
Scrub Typhus
Psittacosis

Fungus Infections
Coccidiodomycosis
Histoplasmosis

Virus Diseases
Smallpox
Yellow Fever
Influenza
Dengue
Rift Valley Fever
Venezuelan Equine Encephalomyelitis
Russian Tick-Borne Virus Complex
Group C Viruses
Chikungunya Virus
Monkey B. Virus
Eaton Agent
Lymphocytic
Choriomeningitis
Infectious Hemorrhagic Fever
Poliomyelitis
Rabies
Phlebotomus Fever
Hepatitis

Colonel Tigertt also brought to the attention of the CES special areas of research that should be considered in establishing the biological warfare medical defense research program These included:

- The metabolic response to infection.
- Supervoltage radiograph as a diagnostic tool.
- Development of rapid diagnostic methods.
- Aerosol transmission of diseases generally not considered to be transmitted by this route.
- Aerosol immunization.
- Biopsy as a rapid diagnostic tool.
- Use of combined vaccines.
- Stockpiling of vacines.
- Stockpiling of diagnostic antigens and antisera.
- Large-scale production methods for vaccines.
- Studies of radiation and infection.

In August 1962, at the request of the USAMU commander, a special meeting of a small ad hoc committee of the CES was held at Fort Detrick. Drs. Woodward, Shope, and Smadel met with USAMU division chiefs and senior investigators to discuss, in general terms, the content and direction of the research program. No attempt was made to review details of individual projects but rather to discuss areas in which division chiefs desired comments. It was felt by both committee members and USAMU personnel that the meeting was of benefit and that similar small groups, consisting of various members of the CES, should meet once or twice a year. Most members of the USAMU staff felt that to have these knowledgeable researchers review their programs and discuss their concepts, approaches, and directions, whether they agreed with them or not, were worthwhile and desirable.

PLAGUE

The September 1962 meeting of the CES was devoted primarily to a review of plague. In addition to the members of the CES and USAMU staffs, a number of invited guests attended. These included Dr. Marcel Baltazard, Director of the Pasteur Institute, Teheran, Iran; Dr. Meyer, Director Emeritus of the George William Hooper Foundation, San Francisco, California; Dr. R. Pollitzer, Division of Epidemiology and Health Statistical Service, World Health Organization; Dr. Werner Janssen, U.S. Army Biological Laboratories, Fort Detrick, Maryland ; Dr. William Lawton, U.S. Army Biological Laboratories, Fort Detrick.

A review of the research program of plague was presented. Dr. Lawton discussed plague antigens, stressing that V and W antigens can be separated, and that the V fraction rather than the W fraction is protective for mice. Major John Marshall, USAMU, working at the Hazardous Laboratory at Forest Glen, reported on plague vaccine trials in mice, in which a number of killed and attenuated vaccines was studied. Considerable variation in the protection offered by the different vaccines was noted as was the protection provided against different challenge strains. Dr. Randall, also working at the Forest Glen Laboratory, reported on the detection of plague antibodies by micromethods, employing a modified HI tannic acid test that used red blood cells sensitized with purified capsular antigen of the plague bacillus, fraction I. He described a test that used Bentonite particles that might have application for rapid testing under field conditions.

Dr. Meyer, generally considered to be the leading authority on plague at that time, presented the results of systematic observations of immunization procedures carried out at the Hooper Foundation over several years. He stressed the need for booster immunization after the initial basic series.

Dr. Meyer discussed, at some length, some of the historical features of plague, describing pertinent epidemiological, pathological, and clinical manifestation of this age-old disease. He stated that plague had been widely studied throughout many areas of the world for many years but that much was yet to be learned.

Dr. Baltazard described his studies of the ecology of plague that had been conducted in Iran and India over many years He discussed a theory of the epidemiology of plague that had been presented by the staff of the Pasteur Institute of Iran in 1960. This theory stated that any species exterminated by a disease cannot be the reservoir of the disease and that the true reservoir of the disease must be sought among those animals whose natural resistance shows them to be best adapted to the disease. Thus, highly susceptible rodents, such as the rat, were not the reservoir of infection; the true reservoir was the highly resistant rodents that survived the epizootic while the susceptible species died.

In addition to the review of plague, the following papers were presented:

- *Infectivity of Aged Aerosols of Pasteurella Tularensis*, William D. Sawyer, Major, MC, USAMU;
- *Studies on Tularemia Vaccine*, Fred R. McCrumb, M.D., University of Maryland;
- *Volunteer Studies of Typhoid Fever*, Richard B. Hornick, M.D., University of Maryland;
- *The Role of Endotoxin in Typhoid Fever and Tularemia in Man*, Sheldon E. Greisman, M.D., University of Maryland;
- *Review of the Attenuated Strain of Venezuelan Encephalomyelitis Virus*, Robert E. McKinney, Major, MSC, USAMU;
- *Studies of Anthrax Toxin*, Martha K. Ward, Captain, USPHS, USAMU; and
- *Lysine Deficiency and Host Resistance to Anthrax*, Irving Gray, Colonel, MSC, USAMU.

SUGGESTED USAMU STUDIES

At the regular CES meeting in 1963, it was suggested that members make recommendations on subjects to be studied either at USAMU, other in-house laboratories including the Navy and Air Force, or under contract with other governmental or civilian institutions. After some prodding from the Director, a number of replies was received. The wide range of suggestions illustrated the diverse range of interest of CES members. Their suggestions included the following:

- Immunological aspects of the spotted fever group;
- Immunological studies of scrub typhus;
- Live vaccines for Chikungunya and O'nyong-nyong fever;
- Combined antigens;
- Combined infections;
- Irradiation and infection;
- Irradiation and immunity;
- Microculture techniques (possibly combined with electronic scanning);
- Cross-immunity within group A arboviruses;
- Stress and infection;
- Psychological aspects of infection;
- Treatment of viral infections;
- Aerogenic immunization;
- The incubation period — enzyme studies;
- New approaches to rapid diagnosis of infectious disease;
- Commercial diagnostic antigen and antisera production;
- Immunological or vaccine studies of any organism of potential biological warfare importance;
- Leukocytes — relation to immunity and sensitivity;
- Teratogenic effects of living vaccines;
- Host susceptibility to infection as a function of age;
- Role of thymus and thymus products in infection;

- Role of physical environment on susceptibility to infection;
- Study of chronicity of viral infections either from disease or immunization;
- Adventitious agents (eg, lymphoma leucosis, pleuropneumonia-like organisms, and Simian viruses):
  (*a*) Methods of inactivation,
  (*b*) Clearing cultures,
  (c) New and simpler methods for detection, and
  (*d*) Effects of inactivated agent in vaccines or antigens;
- Role of fibrin and fibrinolysis in host defense;
- Role of phagocytes in aerosol-transmitted disease;
- Role of growth hormone in infection;
- Possible use of purified ovine prolactin in therapy of infection;
- Possible use of testosterone and its various analogues in therapy of infection;
- Search for biochemical chemical chemotatic "humor" from host tissue or the invading organism that serves to attract leukocytes to site of invasion;
- Staphylococcal enterotoxin:
  (*a*) Effect on cellular permeability and fluid dynamics, and
  (*b*) Metabolism — distribution as related to animal sensitivity;
- The application of neural sciences (including learning ability and acuity) to understanding of virus action;
- Blood pigment changes in anthrax;
- Phagocytic enzyme activity as related to host resistance;
- Bacterial structure and virulence;
- Differentiation of the effect of fever versus infection on host metabolism; and
- Fluorescence polarization to determine specificity of antigen–fluorescent antibody binding.

Some of the proposals were already under study, although some were not within the responsibility of the CES. All suggestions were considered carefully, and a number were included in future research plans both in-house and in the contract program.

NATIONAL DRUG COMPANY CONTRACT

As a part of the expanded research program in the defense against biological warfare and the proposed increase in the biological warfare defense budget, the commanding general, USAMU, and Development Command had suggested in 1960 that a joint project with an American pharmaceutical company be initiated to develop methods for the large-scale production of vaccines developed in the biological warfare medical defense program. This project came to fruition in 1962 with the ground breaking for a new laboratory building to be constructed by the National Drug Company in Swiftwater, Pennsylvania. This laboratory building was designed with all the necessary safety devices to work with highly infectious organisms. It contained four completely independent units where different organisms could be handled with no danger of cross-contamination. The contract also included a requirement to develop, design, and construct automated equipment for the large-scale production of vaccines in eggs and for freeze-drying large production runs of vaccines.

PERSONNEL

At the meeting of the CES at Walter Reed Army Medical Center in August 1963, personnel changes with significant impact on the composition and direction of the CES were evident. Dr. Smadel, a pio-

neer member of the commission and one of the top scientists in the nation, died on 21 July 1963. In memorial, Dr. Smadel was described as "a painstaking investigator, an inspired leader, a dedicated friend of the Commission and of the Armed Forces Epidemiological Board." An excerpt of a tribute paid Dr. Smadel on 9 December 1963 before the AFEB reads:

> The members of this board knew Joseph E. Smadel as one of its ablest scientifically active contributors extending over two decades. He organized and directed the programs of two commissions: Immunization and Rickettsial Diseases, and stabilized the Commission on Epidemiological Survey during its formulation and expansion. Achievements of these commissions have made mankind healthier and richer and each proudly bears an indelible Smadel mark.

The resignations of Drs. Shope and MacLeod were accepted with great regret. Dr. Shope, a charter member and initial director, inspired and guided a distinguished scientific program. The CES, under his direction, developed a broader understanding of the basic mechanisms of certain infectious diseases and effective means of their control. Dr. Shope took administrative difficulties in stride. He felt that he could not continue to serve as an active member of the CES and fulfill his ever increasing obligation to the scientific program of the Rockefeller Institute. He agreed, however, to be available for advice and help. Dr. MacLeod was forced to resign because of heavy responsibilities as director of the President's Scientific Panel. Through many years, he responded to appeals for advice that made seemingly impossible problems simpler and workable. Unfailing in his ready assent to serve, he did so on short notice without regard to personal inconvenience. Dr. MacLeod's contribution of mature judgment and broad vision were sorely needed by the CES during more than a decade of service. The commission, at that time, was composed as follows:

Members
Ivan L. Bennett, Jr., M.D.
Dan Crozier, M.D.
Thomas Francis, Jr., M.D.
James G. Hirsh, M.D.
Vernon Knight, M.D.
W. Barry Wood, Jr., M.D.
Theodore, E. Woodward, M.D., Director.

Associate Members
Leighton E. Cluff, M.D.
Fred R. McCrumb, Jr., M.D.
William D. Tigertt, M.D.
Charles L. Wisseman, Jr., M.D.

Special guests attending the 1963 meeting included Dr. I. H. Lepow, Western Reserve School of Medicine and Chairman of the Commission on Immunization; Dr. Kenneth Goodner, Professor and Head, Department of Microbiology, Jefferson Medical College; and Dr. J. E. Johnson, Johns Hopkins School of Medicine.

The scientific program included:

- *Recent Progress in Anthrax Studies*, Martha K. Ward, Captain, USPHS, USAMRIID;
- *Effect of Lycine Deficiency on the Leukocyte Response*, Irving Gray, Colonel, MSC, USAMRIID;
- *The Effect of Acute Experimentally Induced Tularemia in Humans on the Metabolism of Nitrogen Electrolytes and Minerals and on Adrenocortical Function*, William R. Beisel, Luetenant Colonel, MC, USAMRIID;
- *Fluorescent Antibody Technique*, Robert F. Jaeger, BA, USAMRIID;
- *Endotoxin in Typhoid Fever and Tularemia in Man*, Sheldon Greisman, M.D., University of Maryland;
- *Current Status of Clinical Typhoid Fever Studies*, Richard B. Hornick, M.D., University of Maryland;
- *Effect of Virus Infection on Host Cell Protein Synthesis*, Jerry R. Mohrig, MSC, USAMRIID;
- *Status of Venezuelan Equine Encephalomyelitis Vaccine*, Thomas J. Smith, Major, MC, USAMRIID;
- *Broad Spectrum Chemoprophylaxis of Typhoid Fever and Tularemia*, Richard B. Hornick, M.D., University of Maryland;

- *Blood-Free Culture Medium for Pasteurella Tularensis*, Hugh B. Tresselt, Ph.D., USAMRIID;
- *Electromicroscopy as a Diagnostic Tool*, Anne Buzzell, Ph.D., USAMRIID;
- *Rift Valley Fever Vaccine*, Raymond Randall, D.V.M., WRAIR; and
- *Report on Plague Antigens*, John D. Marshall, Ph.D., USAMRIID.

At the fall meeting in September 1964, Drs. Cluff and Tigertt were made full members of the CES. Drs.Greisman and Hornick were appointed associate members.

RICKETTSIAL AND VIRAL VACCINE STUDIES

In 1965, a cooperative study of AFEB commissions was set up to include the CES , the Rickettsial Commission, and the Commission on Immunization. An ad hoc committee was appointed with Dr. Wisseman as chairman. The committee's first effort was acting as a consultant group for the evaluation of the infectivity and immunogenicity of phase I and phase II Q fever organisms, conducted at the University of Maryland School of Medicine. The volunteers were from the Maryland House of Corrections. The phase II material was prepared at WRAIR , and the aerosol exposures were conducted at the U.S. Army Biological Laboratories at Fort Detrick. The volunteers were hospitalized at the University of Maryland Research Ward at the Maryland House of Corrections. Individuals receiving phase I vaccine were all protected against aerosol challenge. Individuals receiving the phase II vaccine were protected or not protected depending on dilution of the vaccine. Oral ingestion of challenge material produced no illness.

Additional studies reported 1 year later showed that the protection provided by the phase I vaccine was optimal only for about 1 year and that revaccination produced an unacceptable number of sterile abscesses at the revaccination site. Attempts to reduce the amount of vaccine used for the basic immunization series resulted in a significant decrease in protection. Preliminary studies of a phase II living attenuated strain of Q fever vaccine and a living attenuated strain obtained from Russia were reported. In additional studies of the oral administration of virulent Q fever organisms, it was found that an increase from 10^3 or 10^5 organisms to 3×10^7 produced a high percentage of infections.

This committee also provided consultant services for the evaluation of Rocky Mountain spotted fever vaccine conducted under the University of Maryland contract. The protection afforded by two vaccines, one prepared by a commercial company and the other by the Rocky Mountain Laboratory, were studied. Neither provided any significant amount of protection when the vaccinated volunteers were challenged with either 10 or 1 guinea pig infectious doses ($GPIPID_{50}$) of viable pathogenic rickettsia. Incubation periods for the vaccinees were slightly longer than those of the controls.

COMBINED AND SEQUENTIAL IMMUNIZATION

Another area of interest of the ad hoc committee was an evaluation of the studies conducted at USAMU and The Johns Hopkins School of Hygiene and Public Health on the use of combinations of antigens and sequential immunization with group A and B arboviruses. These studies, which were conducted over several years, were designed to determine whether various combinations of vaccines could be administered simultaneously or sequentially without losing antigenicity or producing untoward reactions. It was also reasoned that such administration of three or four vaccines against closely related viruses might confer some immunity against other viruses of the same group.

In general, group A arboviruses VEE, western equine encephalomyelitis (WEE), and eatern equine encephalomyelitis (EEE) could be administered in various schema without undue interference with immunogenicity or reactogenicity but without significant cross- or extended immunity.

For the group B arboviruses, Dr. Winston H. Price of The Johns Hopkins School of Hygiene and Public Health, working under an Army contract, reported that the sequential administration of attenuated strains of yellow fever, Langot strain of the Russian spring-summer group, dengue II, and Japanese encephalitis virus to spider monkeys gave protection against all known strains of group B arborviruses.

Other combined vaccines administered to animals were attenuated tularemia vaccine and nonviable anthrax protective antigen. This combined administration afforded homologeous protection without enhancement or interference by either strain.

Living tularemia vaccine and the living VEE vaccine also were administered as combined antigens without significant deviations from the results attained when the antigens were administered separately.

METABOLIC RESPONSE TO INFECTION

The metabolic response to infection was of considerable interest to the staff of USAMU from its early days, but not until 1962, with the arrival of Colonel William R. Beisel, MC did that interest expand into a major program. In addition to employing this approach to understand and describe the host response to an infectious agent and of the pathogenesis of certain infectious diseases better, this program searched for new methods and new concepts to permit recognition and etiologic identification of infectious illness during the incubation period.

These studies were enhanced by the studies in volunteers of metabolic changes occurring after the administration of live vaccines and challenge studies with a number of different organisms. If a study in humans was being planned by the medical division for the evaluation of a particular vaccine, a metabolic study would be added. This would require very careful fever determinations, urine and feces collections, and some additional examinations of blood specimens. The metabolic response of the immunized compared with the unimmunized subject to virulent challenge could be studied. Studies of tularemia, Q fever, and sandfly fever were conducted as was the response to bacterial endotoxin and physically induced hyperthermia. Individuals immunized against VEE and challenged with a virulent strain also were studied.

At the 1964 annual meeting of the CES, Dr. Beisel made the first detailed report on the metabolic studies conducted at USAMU. He stated that volunteers infected with the agents of tularemia, Q fever, and sandfly fever showed negative nitrogen balance soon after the onset of active infection.

Anorexia and loss of nitrogen in the urine and stool were largely responsible for such changes in tularemia. Artificial pyrexia induced in humans by the intravenous injection of *Salmonella typhosa* endotoxin provoked negative phases during the hyperthermic stages because of poor food intake, urinary losses, and losses caused by excessive sweating.

In sandfly fever, negative nitrogen balance was attributed to poor intake and urinary nitrogen excretion. Subjects ill with Q fever lost excessive urinary nitrogen when febrile. Rickettsemia and positive cultures of the pleural fluid occurred over 3 weeks in one subject even while under tetracycline therapy; despite the absence of fever, excess nitrogen loss occurred. Hence, fever did not play the only role in such changes.

The interest of the commission in this area increased significantly in the following years and the research program of the medical unit was expanded. In 1967, the fall meeting of the CES, which was held 7 and 8 September at WRAIR , was devoted exclusively to this subject. In addition to CES mem-



CHARLES L. WISSEMAN, JR., M.D.

At Southwestern Medical School, Dr. Charles L. Wisseman was a top scholar, and throughout his life, he conducted himself as a scholarly and productive scientist. After World War II, he worked with Joe Smadel at WRAIR. At the bench and in the fields of Malaya, Borneo, Pakistan, and Africa, he effectively pursued the mysteries of typhus, encephalitis, leptospirosis, and other diseases of military importance.

Foremost as a rickettsiologist and skilled as a microbiologist, Charlie chaired the Department of Microbiology at the University of Maryland for many years. Tireless in his work ethic, Charlie chaired the Commission on Rickettsial Diseases for many years until 1973, when the Commission system of the AFEB ceased. Thereafter, he has consulted with many governmental and international agencies, including the World Health Organization.

bers, the staff of USAMU, and representatives of the U.S. Army, Navy, and Air Force, a number of invited guests attended. These included

Dr. Hilton B. Levy
National Institutes of Health

Dr. Elisha Atkins
Yale University

Dr. Paul M. Newberne
Massachusetts Institute of Technology

Dr. Robert L. Squibb
Rutgers University

Dr. Vernon R. Young
Massachusetts Institute of Technology

Dr. Elliot M. Levine
Albert Einstein College

Dr. John M. Woodward
University of Tennessee

Dr. Paul C. Zamecnik
Harvard University

Dr. Peter F. Benventre
University of Cincinnati

Dr. Morton I. Rappoport
University of Maryland

Dr. Irving Gray
Georgetown University

Dr. Adam J. Rapalski
National Research Council

Dr. Harnish Monro
Massachusetts Institute of Technology

Dr. Sidney H. Ingbar
Thorndike Memorial Laboratory

Dr. Herbert L. DuPont
University of Maryland

Dr. Harold N. Glassman
U.S. Army Biological Laboratories, Fort Detrick

Dr. Joseph E. Johnson
University of Florida

Dr. Bernard duBuy
University of Maryland

Dr. Frank A. Carozza, Jr.
University of Maryland

Dr. Walter W. Kernmener
National Air and Space Administration

Dr. Samuel Bessman
University of Maryland

Dr. Beisel stated in his introductory presentation that this meeting of the CES would provide a critical review of this portion of the USAMU research program, which was then in its 5th year. The meeting brought together, for the first time, a large number of individuals whose research interests were directed toward studies of the host response to infection; other invited guests were asked to participate because of their knowledge in closely related fields. Dr. Beisel concluded with the statement that it was his hope and that of the USAMU staff that the program would provide a platform for open discussion and exchange of ideas and concepts. In this way, new leads and suggestions would guide future investigations. The program was divided into six sections:

Section I — Amino acid and enzyme alterations in the host.
Moderator: Dr. Theodore E. Woodward
Discussant: Dr. Samuel Bessman

Section II — Cellular nucleic acid changes during infection.
Moderator: Dr. W. Barry Wood, Jr.
Discussant: Dr. Hilton Levy

Section III — Immunological aspects.
Moderator: Dr. Wood
Discussant: Dr. James G. Hirsch

Section IV — Infection and generalized host responses.
Moderator: Dr. Leighton E. Cluff
Discussant: Dr. Sidney Ingbar

Section V — Infection and generalized host responses: Whole body responses.
Moderator: Dr. Cluff
Discussant: Dr. C. Wisseman
Section VI — Bacterial toxins.
Moderator: Dr. J. Vernon Knight
Discussant: Dr. Eli Atkins.

Thirty-one formal papers and discussions were presented during this 2-day symposium. The research presented was conducted at the USAMU at Fort Detrick, other Department of Defense laboratories, universities and institutions under contract to the CES , and a number of other research laboratories with programs closely allied to the research presented at this meeting.

Dr. MacLeod was called on to summarize the proceedings. He stated that many good and new observations had been made during the meeting. Dr. MacLeod was particularly pleased at the progress made by the USAMU in developing the comprehensive approach to the study of the metabolic alterations that take place during infection and congratulated Dr. Beisel and the medical unit research staff for their excellent presentations.

In his summary of the enormous amount of information presented, Dr. MacLeod classified the metabolic changes occurring during infection as follows:

> First, as to whether the observed changes are direct responses of cells in tissues to the infectious agents. As examples of this, consider the destruction of cells because microbes are growing within them; damage to the cells by the toxic products of the microbes; or damage suffered by phagocytic cells in the course of the scavenger process. These would be direct effects.
>
> The second set of changes would include those that are associated with the stress reactions, ie, changes that effect the hypothalamic, pituitary, and endocrine systems and lead to alterations that are distinct from those due to direct interaction of the microbe in the host tissue.
>
> The third set would be those deriving from the microbe itself, ie, new enzymes appearing as a consequence of organism multiplication during virus infection, or the products of infectious agents such as extracellular protein or perhaps capsular polysaccharides or related products.
>
> The fourth set of changes, of course, are those associated with the immunological response, the production of immunoglobulins for example.
>
> Fifth, there are those effects described particularly by Dr. Gray that are associated with fever itself.
>
> A sixth group might be the products that are not clearly associated with any one of the others, such as the emergence of C-reactive protein (which was not discussed in the meeting) or possibly the increased glycoproteins.
>
> A seventh category would be a mixture of all of these which is probably what is usually going on in the course of an infectious disease.

In closing, Dr. MacLeod stated that the comprehensive nature of the presentations and discussions should provide anyone interested in this research with information on which new and perhaps different or better approaches aimed at solving some of the mysteries of the host response to infection might be developed.

This meeting stimulated the staff of USAMU into expansion of the metabolism and infection program and resulted in the recruitment of specifically selected staff members. New data from ongoing research fulfilled some of Dr. Macleod's closing observations. In fact, the metabolic, endocrine, febrile, and immunological consequences of acute febrile illness (now termed acute phase response) were shown to be stimulated by hormone-like mediators. These are now termed cytokines and include the interleukins (interleukin-1 to interleukin-8), the interferons, colony-stimulating factors, and tumor necrosis factor (cackectin). These substances are released by certain body cells when activated by micro-

organisms or their toxins. The metabolic responses to infection observed at USAMU by Drs. Beisel, Robert W. Wannemacher, Robert S. Pakarek, and Michael C. Powanda were attributed in 1969 to a factor that they termed leucocytic endogenous mediator (LEM). This substance is now known as interleukin-1 and is identical to endogenous pyrogin (the fever-producing factor studied by Dr. Wood) and to lymphocytic activating factor (LAF), which activates the immune system.

RADIATION AND INFECTION

During the early 1960s, interest in the effects of ionizing radiation on infection and the immune response gained considerable momentum. The Commission on Radiation and Infection (CRI) had been added to the AFEB and plans for representation at meetings of this commission and the CES were formulated. Dr. Victor P. Bond, the Director of the CRI and Dr. Richard D. Stoner, Deputy Director, regularly attended meetings of the CES, and representatives of the CES were invited to meetings of the CRI. In addition, several joint ad hoc meetings were held both at the medical unit in Frederick and the Brookhaven National Laboratory in Upton, New York.

During this period, the CRI undertook a survey of the world literature on radiation and infection, and in 1965, the Medical Research Center, Brookhaven National Laboratory, produced an annotated bibliography containing over 800 abstracts concerning the effects of radiation on infection and the immune response. This endeavor added immeasurably to the research programs in this field.

At the annual meeting of the CES in September 1965, Lieutenant Colonel Nelson R. Blemly, MC, Chief of Radiology Division, USAMU reported on the effect of ionizing radiation on the immune response of mice to VEE. Whole-body radiation was accomplished with the 1 MEV unit at USAMU. The mice were exposed to 500 R of whole-body radiation. Challenge was with the attenuated vaccine strain of virus or the fully virulent Trinidad strain. During normal conditions, the attenuated strain produces no illness in mice and protects fully against later challenge with a virulent strain. Administration of the virulent strain to unprotected mice is 100% fatal. The well-being of the mice did not appear to be altered by the stress of the whole-body irradiation.

When the mice were immunized with a standard dose of the vaccine strain, radiation, either before or after immunization, had no effect on the outcome of challenge with the virulent strain. When the immunizing dose was decreased, the protection afforded the irradiated animals was significantly decreased. It was hypothesized that, in the irradiated animals, replication of the attenuated virus was decreased to the point that protection was not established or that antibody production sites were damaged to a degree that interfered with antibody production.

At the meeting of the AFEB in May 1968, action was taken to combine the CES and the CRI. Members of the CRI were transferred to the CES, and the first meeting of the combined commissions was held on 5 September 1968 at WRAIR. Membership of the newly constituted committee was as follows:

Members
Victor P. Bond, M.D.
Leighton E. Cluff, M.D.
Zanvil A. Cohn, M.D.
Dan Crozier, M.D.
John H. Dingle, M.D.
Sanford S. Elberg, Ph.D.
Thomas Francis, Jr., M.D.
Jacob Furth, M.D.
James G. Hirsch, M.D.
J. Vernon Knight, M.D.
Colin M. MacLeod, M.D.
David E. Rogers, M.D.
Myron S. Silverman, Ph.D.
Richard D. Stoner, Ph.D.
Morris Tager, M.D.
William D. Tigertt, M.D.
W. Barry Wood, Jr., M.D.
Theodore E. Woodward, M.D., Director

Associate Members
Austin M. Brues, M.D.
Sheldon E. Greisman, M.D.
Richard B. Hornick, M.D.
Fred R. McCrumb, M.D.
C. Phillip Miller, M.D.
Charles L. Wisseman, Jr., M.D.

Dr. Bond, Director of the CRI , presented his final report to the new commission. He summarized the mission of the CRI as follows:

1. To review and keep abreast of research and other work and activities that pertain to the effects of ionizing radiation on resistance to infection.
2. To identify deficiencies or voids in our knowledge in this field, particularly as related to problems of potential importance in military operations.
3. To attempt to stimulate and encourage investigative work in this field with particular reference to matters of current or potential military pertinence, recognizing that the information developed would be as pertinent to the understanding of infectious processes as to the effects of ionizing radiation.
4. To apprise the military of newer developments that pertain to the effects of radiation on the resistance to infection of exposed subjects.
5. To review on a continuing basis, immunization and other prophylactic procedures that may be employed by the military in the light of possible atomic and biological warfare.
6. To press, continuously for a more complete realization of the hazards of radiation in nuclear warfare.

Dr. Bond also discussed certain problem areas in the investigation of radiation and infection that should be considered for future research. Final reports of three research projects conducted under contract with the CRI were submitted.

The major portion of that meeting dealt with a classified review of the defense against biological warfare. Papers were presented by Colonel Crozier, Dr. Housewright, Mr. E. K. Wolfe, Dr. Benjamin Warschowsky, Captain Lloyd F. Miller, U.S. Navy, Lieutenant Colonel Dale R. Lindall, U.S. Air Force, Lieutenant Colonel Robert W. McKinney, Captain Charles F. Craig, and Colonel Beisel, USAMRIID. Copies of these presentations can be obtained from the U.S. Army Medical Research and Development Command by those cleared for access to classified information.

At the second meeting of the CES–CRI on 4 and 5 September 1969, Drs. Balish, Myron S. Silverman, and Alvin Volkman reported on their work on the effects of radiation on infection and immunity. The reports included not only studies on laboratory animals, but also studies carried out on three humans accidentally irradiated with doses ranging from 100 to 550 R, and 27 patients that had received whole- or partial-body radiation for therapeutic purposes.

At the 1970 meeting, Dr. Volkman, working under contract on problems of cell-mediated immunity, reported that recovery of hypersensitivity after radiation injury in animals is mediated by macrophages and not lymphocytes.

At the September 1969 meeting of the CES, Dr. Gustave J. Dammin, president of the AFEB, announced that a new category of commission members, advisory members, had been established. These advisory members would consist of commission members who had served over long periods and who felt that they could no longer devote the time and energy required to be a fully active commission member. Advisory members would not be expected to attend meetings on a regular basis but would make themselves available for special consultation and would attend meetings when specifically requested by the Director. Three members of the CES requested placement in this category. They were Drs. Dingle, Wood , and Thomas Francis, Jr. Unfortunately, Dr. Francis died in October that same year, and Dr. Wood died just a year and a half later, in March 1971.

The annual meeting of the CES for 1970 was held at WRAIR on 24 and 25 September. The following CES members attended:

Colonel Dan Crozier, Deputy Director
Dr. James G. Hirsch
Dr. J. V. Knight
Dr. Colin M. MacLeod
Dr. Myron S. Silverman
Dr. Morris Tager
Dr. Theodore E. Woodward, Director
Dr. Sheldon E. Greisman
Dr. Richard B. Hornick
Dr. Charles L. Wisseman

Also present were Dr. Dammin and Colonel Prior representing the AFEB, representatives from the U.S. Army, Navy, and Air Force, contractor personnel, staff members from USAMRIID, and a number of guests, including Dr. Allen L. Forbes from the Office of the Chief of Research and Development of the Department of the Army and Dr. Tov Omland, Director of the Norwegian Defence Microbiology Laboratory, Oslo.

Papers were presented by the following individuals under their affiliation:

USAMRIID
Kenneth A. Woeber
Robert S. Pekarek
Robert W. Wannemacher, Jr.
Robert H. Fiser, Jr.
Michael C. Powanda
William L. Steinhart
Gordon L. Bilbrey
Anne Buzzell
Peter G. Canonico
Neil H. Levitt
Joseph Kaplan
William H. Habig
John D. Marshall
David M. Robinson
Peter J. Bartelloni
William R. Beisel
William J. Caspery
Joseph F. Metzger
Joseph C. Denniston

Trudeau Institute, Saranac Lake, New York
Alvin Volkman
George B. Mackaness

University of Maryland
Sheldon E. Greisman
Celeste L. Woodward
Richard B. Hornick
Herbert L. DuPont
Stanley Music
Joseph Libonati
Richard Wenzel
M. J. Snyder
Theodore E. Woodward

STAPHYLOCOCCAL ENTEROTOXIN

Staphylococcal enterotoxin was of considerable interest to the CES from the late 1950s. Cooperative studies between USAMU (later USAMRIID) and the Chemical Corps Biological Laboratories at Fort Detrick were carried out in the preparation, purification, and analysis of material appropriate for laboratory studies. Most research endeavors were carried on with staphylococcal enterotoxin B (SEB). Considerable difficulty was encountered in producing adequate amounts of so-called purified material.

Dr. Virginia G. McGann (USAMRIID) stated in 1969 that, after several years of intensive effort, the purified lot then being studied (lot 14-30) had at least two enterotoxin B moieties and trace amounts of enterotoxin A, α-hemolysin, β-hemolysin, and polysaccharide. Dr. McGann added that physiological studies must be interpreted in light of these findings because of the high biological activity of many of these trace components and the similarity of some of the effects reported for SEB and such components as α-hemolysin.

The first reports to the CES on this subject were presented at the annual meeting on 9 September 1965. Two of these were presented in open session: *Serologic Studies on Staphylococcal Enterotoxin B* by Dr. McGann and *The Mechanisms of Pyrogenicity of Staphylococcal Enterotoxin B* by Captain Frank A. Carozza, MC (USAMRIID). The following day, in executive session, USAMRIID researchers presented a classified program consisting of the following papers:

- *Pyrogenic Effect of Staphylococcal Enterotoxin B*, Captain Carozza;
- *Clearance and Localization Kinetics of Radioactive Labeled Staphylococcal Enterotoxin B:* Part I. Captain Morton I. Rappoport, MC

Part II. Captain Leland F. Hodoval, VC
Part III. Captain Earl L. Morris, VC

- *Effects of Staphylococcal Enterotoxin B on the Coagulation Mechanism and Leukocyte Response in Beagle Dogs—A Preliminary Study,* Captain Charles F. Gilbert, MC;
- *Serologic Methods of Detection of Staphylococcal B Antibody,* Captain Martha K. Ward, USPHS; and
- *Detection and Measurement of Immunological Responses to Staphylococcal Entertoxin B,* Dr. McGann.

These papers were later declassified and are now available in the open literature.

Papers on SEB were presented in 1966 by Captain Carozza and Dr. McGann and in 1967 by Captain S. J. Norman, MC (USAMRIID). Additional studies were presented to the CES at each annual meeting through 1972.

In 1964 and 1965, preliminary human studies of SEB were conducted in senior staff members of the medical unit at Fort Detrick. The results of these studies combined with a very large amount of animal data, including that conducted in chimpanzees, formed the basis for the first presentation of a proposal to the CES for a human study. This proposal was not approved by the CES, and additional information was requested. Shortly afterward, all requested data were provided, and the proposal was resubmitted to the members by mail. This proposal was unanimously approved, and the first study was conducted the same year in Whitecoat volunteers. During the following 14 months, 14 separate human studies were conducted. Most of these were separate parts of the originally approved protocol, but some were individually approved by the CES. These projects were highly productive, but no addtional human studies were conducted after 1966.

STATEMENT OF MISSION

At the 1969 meeting, Dr. Dammin, President of the AFEB, stated that each commission should have a written statement of mission and that such statements should be constantly evaluated and updated and should be maintained on file in the office of the AFEB. The following mission statement was prepared by the CES and submitted to the AFEB:

1. To advise The Surgeons General of the Armed Forces of the United States on the medical defense against biological warfare and on the effects of radiation on host response as related to infection and immunity.
2. To evaluate the threat to the Armed Forces of biological warfare and to recommend policies, procedures, and methods for providing an adequate defense against such attack.
3. To review the research program of the Army, and when requested, of the Navy and the Air Force, in the medical defense against biological warfare and the effects of radiation on the host response to infection and to advise The Surgeons General on their overall direction.
4. To review the research program of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID, formerly USAMU, renamed in February 1969) and advise The Surgeons General of the Army on the work being accomplished.
5. To advise The Surgeons General on volunteer studies in the medical defense against biological warfare and, when requested, review individual experimental protocols and recommend approval or disapproval.
6. To initiate and direct a contract research program in the medical defense against biological warfare and in the field of radiation and infection.

The mission statement was approved and became the formal basis for CES activities.

1970 ANNUAL MEETING

The 1970 annual meeting of the CES was held on 24 and 25 September at WRAIR and was devoted to a review of the completed work or work in progress at the U.S. Army Medical Research Institute of

Infectious Diseases or by institutions under contract with the AFEB. The varied titles of the papers presented exemplify the wide scientific range of the research program being monitored by the CES.

The following papers were presented:

- *Infection and Thyroid Hormone Economy,* Kenneth A. Woeber, USAMRIID;
- *Trace Metals and Infection,* Robert S. Pekavek, USAMRIID;
- *Lipid Metabolism and Infection,* Robert H. Fiser, Jr., USAMRIID;
- *Amino Acid Metabolism and Infection,* Robert W. Wannemacher, Jr., USAMRIID;
- *Tryptophan Metabolism and Infection,* Michael C. Powanda, USAMRIID;
- *Nucleic Acid Metabolism and Infection,* William L. Steinhart, USAMRIID;
- *Renal Function and Infectious Illness,* Gordon L. Bilbrey, USAMRIID;
- *Pathogenesis and Cellular Membranes,* Anne Buzzell, USAMRIID;
- *Cellular Biology and Exogenous Proteins,* Peter G. Canonico;
- *Rapid Detection of Antibody or Viral Antigens by Cellulose Acetate Electrophoresis,* Neil H. Levitt, USAMRIID;
- *Studies of Cellular Immunity,* Joseph Kaplan, USAMRIID;
- *Cytochromes of Pasteurella Pestis,* William H. Habig, USAMRIID;
- *Mechanisms of Delayed-Type Hypersensitivity and Other Types of Cell Mediated Immunity,* Alvin Volkmann and George B. Mackaness, Trudeau Institute;
- *Plague Vaccine Program,* John D. Marshall, Jr., USAMRIID;
- *Status of M-44 Q-Fever Vaccine Studies,* David M. Robinson, USAMRIID;
- *Recent Arbovirus Vaccine Studies in Man,* Peter J. Bartelloni, USAMRIID;
- *The Role of the Liver in Endotoxin Fever and Tolerance,* Sheldon E. Greisman and Celeste L. Woodward, University of Maryland;
- *Studies of Rocky Mountain Spotted Fever Vaccine,* Richard B. Hornick, University of Maryland;
- *Studies of Oral Enteric Vaccines,* Herbert L. DuPont, University of Maryland;
- *Induced Human Cholera,* Stanley Music, Joseph Libonati, Richard Wenzel, M. J. Snyder, Richard B. Hornick, and T. E. Woodward, University of Maryland;
- *Effects of Acute Infectious Illnesses on Sustained Work Performance in Man,* William R. Beisel, USAMRIID;
- *The Use of Electron Spin Resonance in Infectious Disease Research,* William J. Caspery, USAMRIID;
- *Staphylococcal Toxin Program of the Pathology Division,* Joseph F. Metzger, USAMRIID;
- *Hypersensitivity Reactions to Staphylococal Entertoxin B,* Joseph C. Denniston, Jr., Virginia G. McGann, Donald E. Kahn, and Richard O. Spertzel, USAMRIID; and
- *Effect of In Utero Venezuelan Equine Encephalomyelitis Infection of Fetal and Neonatal Mice,* Richard O. Spertzel, USAMRIID.

One of the projects reported at this meeting was a study of the effects of acute infectious illnesses on sustained work performance in humans. It was postulated that in the event of a successful biological warfare attack on U.S. troops in combat, it would be possible that a high percentage of the military personnel in the target area would become ill. It was felt that in such a situation, some of the infected individuals would be capable of carrying on, to some extent, with their assigned duties. A study was designed under contract with the Psychology Department of the University of Louisville to quantitate these effects. This group was well-known for its work in measuring sustained work performance of individuals under stress.

Studies conducted in 1966 and 1967 were designed to obtain baseline information. Continuing studies in 1969 and 1970 included similar testing in volunteers infected with sandfly fever or tularemia to compare performance decrements during infection with concomitant changes in specific metabolic and clinical parameters and to determine if symptomatic therapy would help to sustain an individual's ability to perform work.

Teams of five members each worked for 4 hours followed by a 4-hour rest and another 4-hour period of work each day. The volunteer started the study period monitoring blinking lights, warming lights, and meters. The work then built in intensity to a high-performance requirement during which



GUSTAVE J. DAMMIN, M.D.

Few among us possess the competence, commitment, wise outlook, and equanimity displayed by Dr. Gustave Dammin. His productive war record was followed by a stellar and remarkable career as an experimental pathologist at Washington University School of Medicine and Harvard. The AFEB was singularly fortunate to have him as a member, an important contributor to several of its Commissions, and its distinguished president from 1960 to 1972.

During this important 12 years of AFEB and CES activities, Gus steered a steady ship. Substance abuse in the military, immunization practices, and change of AFEB function were some of the important problems presented to the AFEB during his tenure.

Gus was always on top of all issues and problems; he took them in his steady hand and saw that the best solution to the problem was reached through wise appointments and choice of consultants. Under his guidance, the AFEB and its stellar commissions flourished. A careful and dedicated scientist, Gus Dammin not only advised able investigators in pursuit of their investigative problems but made major contributions on his own. Gus Dammin's leadership role for the AFEB is a matter of historical significance.

the volunteer was simultaneously performing three monitoring tasks, solving arithmetic problems, and working on code solving by crew effort. This peak of work then tapered off somewhat but again increased when target identification was substituted for the arithmetic calculations. After baseline studies, the volunteers were exposed to the agents of either sandfly fever or tularemia.

The individuals infected with sandfly fever became ill on day 2, while those with tularemia became febrile on day 3 and reached a peak of illness on day 4. With the onset of symptomatic illness, sustained performance began to deteriorate and, in the patients with tularemia, reached group-average nadirs of 27% to 44% below baseline. Recovery in performance followed the initiation of specific therapy. Use of symptomatic therapy (aspirin and Darvon) that began with the onset of symptoms and fever was quite successful in reducing performance decrements.

At this same meeting, some interesting but preliminary studies of cholera conducted in volunteers under contract with the University of Maryland were reported. Dr. Stanley Music reviewed studies of induced human cholera designed to develop a human model for testing cholera vaccines. Oral doses of 10^{11} cholera vibrios were found to be required to produce clinical diseases in a significant percentage of exposed volunteers. By administering 2 g of sodium bicarbonate in 60 mL of water immediately before the challenge dose of vibrio, the number required to infect was reduced to 10^6 organisms. In addtional studies, it was determined that the serologic response of volunteers developing diarrheal disease was similar to that occurring in naturally acquired cholera and that the presence of vibriocidal antibody was highly effective in protecting individuals against rechallenge 4 to 12 months later with a homologous strain of vibrio.

VENEZUELAN EQUINE ENCEPHALOMYELITIS VACCINE

The development of an effective live vaccine against VEE infection in humans occupied an important place in the research program of USAMU from its earliest days. A large amount of information was available on the effectiveness of vaccine for the protection of equines, but the vaccine had never been considered seriously for use in this species as a prophylactic procedure.

When this vaccine had been approved for routine use for the protection of laboratory personnel and other persons at risk of infection, a decision was made to prepare a production amount of vaccine under the contract with the National Drug Company in Swiftwater, Pennsylvania. This was considered practical because the strength of the vaccine as administered to humans was 10^3 to 10^4 of the strength of the original tissue culture material, depending on its titer. This allowed small quantities of the undiluted material to be stored in the frozen state and when needed, diluted and freeze-dried in practical size containers. Thus, a 30-mL vial of original material could produce 30,000 to 300,000 doses of vaccine. Enough of the concentrated material was prepared and stored at the National Drug Company to produce approximately 60,000,000 doses of vaccine.

In 1966, a decision was made to prepare a production lot of this vaccine in 20- and 30-mL vials for use in the protection of at-risk personnel and to study its stability in the freeze-dried state. Approximately 3,000,000 doses were prepared. This decision was made at an ad hoc committee meeting of the CES and senior representatives of the Office of The Surgeon General and USAMU. This was a fortuitous decision because in July 1969 an unexpected request for the vaccine was received.

VEE in horses ordinarily ranges from a mild short-lived respiratory disease to a severe central nervous system infection frequently resulting in death. Outbreaks of the disease had been identified in Central and South America since 1935, but the first severe outbreak north of Panama occurred in 1969. In May 1969, equine deaths were reported in El Salvador and Guatemala. On 4 July 1969, with only a presumptive diagnosis of VEE, a request for the vaccine was submitted by these two countries through State Department channels, to the U.S. Army Medical Research and Development Command. The initial shipment of vaccine was made on 8 July and was accompanied by consultants from the Centers for

Disease Control in Atlanta, Georgia, and USAMU in Frederick, Maryland. Lieutenant Colonel McKinney and Richard O. Spertzel from USAMU spent several months in Central America as consultants.

The host countries organized vaccination teams that, working ahead of the infected areas in the predicted direction of spread, established barrier zones by administration of the vaccine and restriction on the movements of equines. Mosquito control was instituted where feasible. Before the epizootic was brought under control, programs were instituted in Guatamala, El Salvador, Honduras, Nicaragua, Costa Rica, and Mexico.

This campaign represented the first large-scale use of the live attenuated strain of VEE (TC-83) for the protection of equines in an epizootic situation. Because of the urgency of the situation, controlled studies were not feasible, but careful field observation persuaded the U.S. consultants that the vaccine was effective. These observations showed that in isolated areas where the disease had not appeared, immunization provided complete protection. In areas where the disease had already appeared, new cases ceased to appear in 7 to 10 days.

In 1970, additional spread of the epizootic occurred in Mexico, and in October of that year at a meeting of the U.S. Animal Health Association, Lieutenant Colonel Spertzel predicted that the disease would spread into the southern United States, particularly Texas, early the next year. Efforts to gain approval for the commercial manufacture of the vaccine for animal use were unsuccessful, so the CES and the staff of USAMU recommended additional vaccine be prepared for possible use in this country. This was approved, and when the disease appeared in Texas in June 1971, the vaccine was available.

By mid-July 1971, cases were being reported as far north as Houston. In late June, immunization was made available to responsible authorities on a voluntary basis. Several large ranch owners immediately immunized their animals and experienced no cases of VEE. In other areas, immunization was not as complete, and a number of animals contracted the disease. In mid-July, immunization was made compulsory in Texas and shortly afterwards several additional states made vaccination compulsory. Some human cases occurred, but by September, only sporadic cases were being reported, and the epizootic was considered to be under control.

This VEE incident was a situation in which a vaccine never seriously considered for use in animals was called on in an emergency. Considerable information was available from the limited laboratory studies, but the vaccine proved remarkably effective in control of the disease. The availability of the vaccine was the result of the foresight of members of the CES and the staff of USAMU and the U.S. Army Medical Research and Development Command.

1971 JOINT MEETING

The 1971 meeting of the CES was held on 23 and 24 September at WRAIR as a joint meeting with the Commission on Immunization.

Members of the CES who attended were as follows: Drs. Crozier, Elberg, Hirsch, Knight, Silverman, M. Tager, Tigertt, Woodward, Greisman, Hornick, and Wisseman.

The following members of the Commission on Immunization attended : K. F. Austen, Benenson, Edsall, T. J. Gill, III, C. H. Kempe, G. B. MacKaness, R. O. Oseasohn, J. W. Uhr,. F. Verwey, H. B. Dull, Gochenour, Jr., B. B. Levine, Marshall, A. M. Pappenheimer, Jr., F. S. Rosen, E. H. Sadun, J. P. Sanford, A. M. Silverstein, and J. C. Wagner.

In addition, representatives from the AFEB, U.S. Army, Navy, and Air Force, USAMRIID, and a number of invited guests attended.

The death of advisory member Dr. W. Barry Wood on 9 March 1971 was commemorated in a memorial minute presented by Dr. Woodward as follows:

> On March 9, 1971, Dr. W. Barry Wood, Jr. died suddenly in Boston of a heart attack at the age of 60. This premature death ended the career of a distinguished physician who, for almost forty years, set an exceptionally high standard of performance as an investigator and educator. This Board and its family of Com-

missions profited immeasurably from his willingness to become involved in problems of paramount importance to the United States.

There are few thoroughly versatile men in contemporary life. Barry was one. Excellence came naturally to him as a scholar, as a graceful, hard-nosed athlete, as a physician who related to the patient, as a scientist who related to the fundamental issues of problems, as a teacher revered by students, and as an administrator who recognized and solved problems logically.

Harvard graduated him with honors in 1936, and Grantland Rice recognized him as of the all-time athletes. Barry was a Hopkins medical graduate and house officer on the Osler Service. Special research experience in microbiology at Harvard under Hans Zinsser prepared him further, with a strong biomedical foundation, for Chairmanship of the Department of Medicine at Washington University in St. Louis in 1942. He was a superb teacher who stressed that a good physician, to properly care for his patients, must be thoroughly trained in medical science.

Barry Wood was a clinician and a fundamental biologist. Uniquely and with eminence he combined these fields. Perhaps he is best known for studies in the pathogenesis of fever. With colleagues, in seeking the molecular basis of pyrexia, he elucidated the mechanisms whereby an endogenous pyrogen from both rabbit polymorphonuclear leukocytes and mononuclear cells plays a major role in the pathogenesis of fever. Other research interests and contributions which significantly advanced knowledge were in the fields of antibacterial chemotherapy, experimental pneumonia and leukocyte phagocytosis. Medical students still recall that a former All American football player first described "surface phagocytosis."

Dr. Barry Wood gave his time and wise counsel unstintingly to the U.S. Army Surgeon General, to the Board and its Commissions. The "Board for the Investigation and Control of Influenza and Other Epidemic Diseases of the United States Army" and Commissions on Meningococcal Meningitis, Pneumonia, Streptococcal Diseases and Epidemiological Survey profited from his advice for years. Early, Barry recognized the need for special in-depth studies of the relationship of radiation and infection; he organized a new Commission and served productively as a member. For years, he carried his share and more as a full Board member. In spite of failing health, Barry, without flinching, retained membership on the Commission on Epidemiological Survey to lend his mature support, sorely needed in sensitive areas of investigation.

One very satisfying field experience came from his visit to Korea in the fall of 1952. Perceptive as a clinician, he detected the delicate balance between blood volume, shock, and the need for judicious fluid replacement in soldiers seriously ill with epidemic hemorrhagic fever. This was Barry's forte, the ability to perceive a difficult problem and reach the closest possible solution. Unruffled in expression, his word was always respected. His questions were penetrating and often represented the important clues to the answers of puzzles.

Dignity and personal grace were his special gifts. Barry was a devoted husband and father; his family was closely woven. Years ago, a master at the Gilman School in Baltimore was annoyed with a group of awkward grade school kids whose football togs were ill-fitted. One boy volunteered to center the football and asked, "Which knee, right or left?" The ball came back to the proper knee like a bullet. On request, he answered, "My name is Wood, sir." All of the Woods are wonderful persons, a splendid legacy.

Barry Wood will be sorely missed by the medical profession and the scientific community, by every medical and academic institution which bears his mark with pride, by this Board and Commission members, by members of each service of the Department of Defense, and by the countless young men and women stimulated and taught by him. Fittingly, we express sympathy to his family and recall with pride that Barry Wood was a remarkable man.

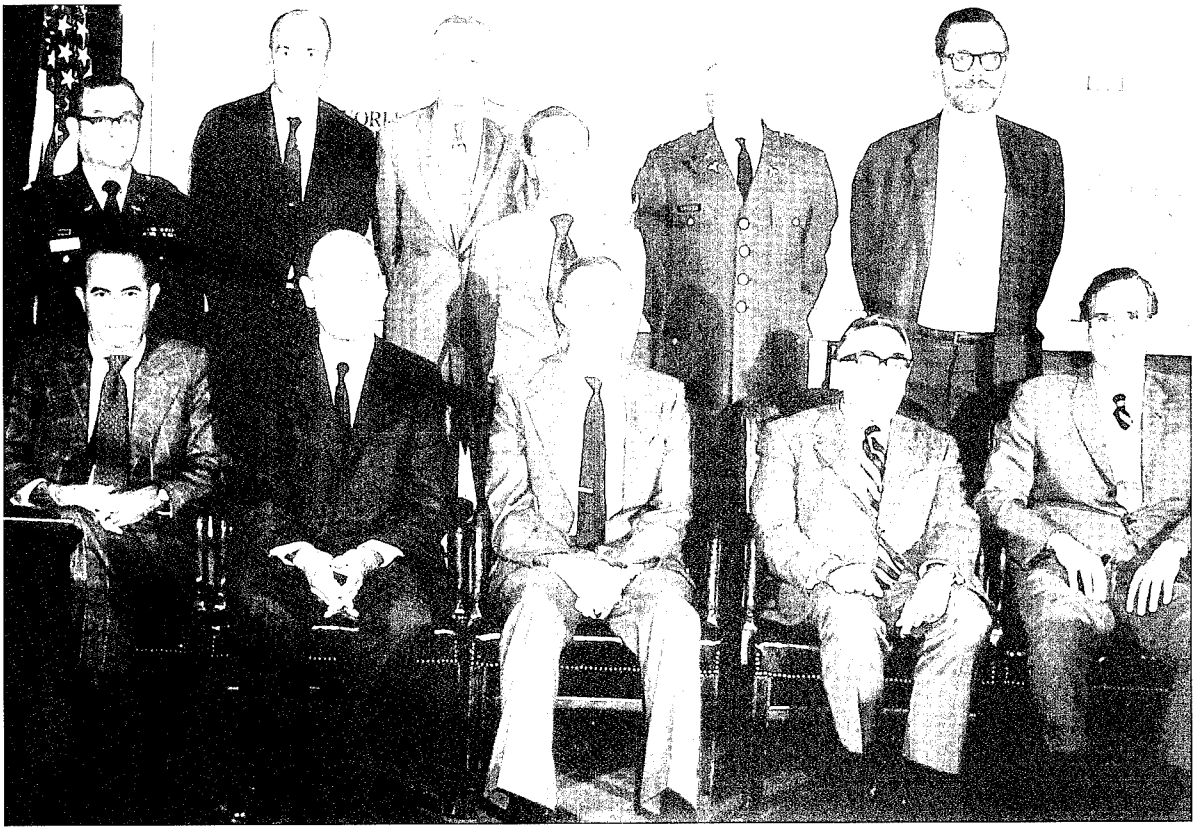
The 2-day joint meeting of the two commissions reviewed the research programs being conducted by AFEB contractors of the commissions and by investigative staff of USAMRIID. Emphasis was placed on the scientific areas of mutual interest to members of both commissions. The scientific program re-



W. BARRY WOOD, JR., M.D.

Dr. W. Barry Wood was a proud alumnus of Harvard and Johns Hopkins. His career was marked by distinction in everything that concerned him. At Washington Unversity, he excelled as an academician and Chairman of the Department of Medicine. One of his major contributions to the field of biology was the demonstration of the phenomenom of "surface phagocytosis." He contributed to the solutions of many infectious disease problems.

Barry was an early member of the AFEB and one of the charter members of the CES. His presence and stature alone were of considerable help to the AFEB and its Commissions.



COMMISSION ON EPIDEMIOLOGICAL SURVEY

Fall meeting, 21 and 22 September 1972
Walter Reed Army Institute of Research
Washington, D.C.

Seated, left to right: Dr. James G. Hirsch, Gustave J. Dammin (President, AFEB), Dr. Theodore E. Woodward (CES Director), Dr. Sanford S. Elberg, Dr. J. Vernon Knight

Standing, left to right: Lieutenant Colonel Norman E. Wilks, (Executive Secretary, AFEB), Dr. Sheldon E. Greisman, Dr. Richard D. Stoner, Dr. Myron S. Silverman, Colonel Dan Crozier, MC (Deputy Director), Dr. Charles L. Wisseman, Jr.

viewed the individual programs and discussed the status of VEE , antibody interaction, antibody formation and methods of assay, biochemical and humeral aspects of cell-mediated immunity and hypersensitivity reactions, development of vaccines for spotted fever, Q fever, gram-negative enteric infections, smallpox, mumps, plague, rabies and tetanus, status of epidemic hemorrhagic fever in Latin America, and the current knowledge of staphylococcal enterotoxoids and metabolic alterations in infection. The two commissions prepared separate annual reports.

Speakers reporting research conducted in programs monitored by the CES were as follows: Drs. Spertzel, Mary H. Wilkie, Stanley G. Rabimowitz, Kaplan, Neil H. Levitt, William H. Adler, Volkman, Canonico, Beisel, Pekerek, Richard H. Kenyon, David M. Robinson, Clarence J. Peters, Joseph F. Metzger, Richard B. Hornick, and Sheldon E. Greisman.

TERMINATION OF CES

In December 1970, Brigadier General Richard R. Taylor, the commanding general, U.S. Army Medical Research and Development Command informed the AFEB of projected changes in the structure and operation of the board and its commissions. This was the result of a congressional directive requiring a review of all consultative boards and commissions of the federal government.

During 1971 and 1972, a detailed examination of the AFEB and its commissions was conducted and at the December 1972 meeting of the board a report was submitted detailing a new advisory system for the Medical Research and Development Command.

In the fall of 1972, when it became apparent that the CES would end shortly, the commander of the USAMRID forwarded a letter to the commanding general, USAMRDC, with copies to the president of the AFEB and the chairman of the CES requesting that an advisory group be appointed to continue the advisory functions of the CES with regard to the in-house research program at USAMRIID. This was approved, and a new advisory group operating independently of the AFEB was appointed. This group, under the chairmanship of Dr. Woodward, was expected to consist of qualified experts in the various fields relating to the research programs of USAMRIID. They would have regularly scheduled meetings at Fort Detrick but, in addition, would have smaller ad hoc groups appointed to advise, when requested, on specific programs and to provide emergency consultations when considered appropriate. The first formal meeting of this group was scheduled to meet at Fort Detrick on 27 and 28 September 1973.

The CES ceased to exist on January 1, 1973. At the close of the last meeting of the CES on 21 and 22 September 1972, Dr. Woodward made the following statement:

> Grateful appreciation is expressed to members of the commission who through many years have given much to the development of new leads useful for control of infectious diseases and who, through their unstinting contributions of time and effort, have helped keep the military service abreast of where the problems are and how they might be solved. The intellectual stimulus and counsel provided by the members are immeasurable in terms of benefit to the Armed Forces.

SECTION 4

Commission on Streptococcal and Staphylococcal Diseases

Foreword

Rheumatic fever ranks historically among the top diseases in terms of causing lingering illness leading to crippling cardiac disability and death. The ability to control and significantly limit the spread of streptococcal infections played a large and important role in the demise of rheumatic fever and nephritis in developed countries. Improved standards of health and the advent of specific chemotherapy were important aspects of this favorable turn of events. When basic guidelines and defined principles of surveillance and application of preventive methods are discarded, streptococcal infections and rheumatic fever are likely to reappear.

The history of the Commission on Streptococcal and Staphylococcal Diseases is a story of heroic success. The Commission began humbly but firmly in 1941 as a part of the Armed Forces Epidemiological Board (AFEB) program mission and, with the exception of 2 years from 1946 to 1948, contributed ceaselessly until its termination in 1973. In the medical community, such persons as Drs. John Dingle, Charles H. Rammelkamp, I. Lowell Rantz, Maclyn McCarty, Rebecca Lancefield, Richard M. Krause, William S. Tillett, Floyd W. Denny, Jr., Lewis W. Wannamaker, Harold B. Houser, Gene H. Stollerman, Armine T. Wilson, and others are really household names.

Drs. Denny and Houser have described the remarkable activities of the Commission that sponsored work on streptococcal and staphylococcal diseases. The record has been one of excellence from its meager beginnings to the Warren Air Force Base, Wyoming, to Cleveland, Ohio; Chapel Hill, North Carolina; Minneapolis, Minnesota; San Francisco, California; and elsewhere, to its termination in 1973.

New knowledge of the means of spread of streptococci and staphylococci, how to detect and classify them, clarification of the mechanisms causing illness and how to control them, particularly streptococci, are all now matters of historical record. Problems remain, but the basic principles are soundly grounded.

The AFEB has always looked with pride toward the contributions of its Commissions, including this one. Denny and Houser have my sincerest thanks and appreciation for bringing this important report to fruition. We are all in their debt, including those dedicated and talented persons who helped make these events possible.

— Theodore E. Woodward, M.D.

History of the Commission on Streptococcal and Staphylococcal Diseases

Floyd W. Denny, Jr., M.D.
and
Harold B. Houser, M.D.

PREFACE

When we were contacted by Dr. Theodore E. Woodward, President of the Armed Forces Epidemiological Board (AFEB), and asked to write the history of the various streptococcus and staphylococcus commissions our first thought was: Why us? On brief reflection, we realized that all of the Commission directors were deceased. Had Charles H. Rammelkamp, Jr., or Lewis W. Wannamaker been alive at the time, it is clear that the task would have been theirs. In their absence, however, we accepted the charge, although with some reluctance because of the enormity of the job.

Writing this history has been truly a "labor of love" and we have enjoyed it thoroughly. At times we had difficulty "keeping our noses to the grindstone" when we met for planning sessions because we kept reminiscing about the "good old days" and our many hours, days, and even weeks of experiences with the Commission. Probably the only thing that allowed us to finish was that we had to return inevitably to our offices in Cleveland, Ohio, and Chapel Hill, North Carolina.

The history of the Streptococcal Disease Laboratory occupies a large portion of this present work. This stems in part from the authors' intimate knowledge of the "strep lab" also from the prominent part the laboratory had in laying the groundwork for much of the streptococcal research supported by the Commission in the 1950s and 1960s. In his recollections of the Commission, Maclyn McCarty refers to the laboratory as "the star in its crown." Because the authors have great respect for Dr. McCarty, we make no efforts to rebut his description in this history.

We did not attempt to follow up on all of the Commission members, both because we thought it not necessary and because of the size of the task. We did try to contact all of the members of the professional staff of the Streptococcal Disease Laboratory. We were able to locate or determine the deaths of all of them. Seven of the staff are now dead: Robert J. Kohen, Earl C. Marple, William D. Perry, Charles H. Rammelkamp, Jr., Alan C. Siegel, Chandler A. Stetson, and Lewis W. Wannamaker. We communicated with the remaining staff; summaries or excerpts from the letters we received are included in Appendices V and VIII.

Almost all of the work of gathering the information for this history and writing the text was done by us. The greatest sources of material were our personal records or those of others involved in the Commission work. We did obtain valuable information from the files of the National Library of Medicine, the Smadel Library at the Walter Reed Army Institute of Research (WRAIR), and the National Archives. Unfortunately, many of the records that would have been helpful have been lost, misplaced, or destroyed. We do want to acknowledge the help given to us by the staff of the AFEB office, especially Jean Ward and Colonel Robert A. Wells. We also want to thank Dr. H. Sherwood Lawrence for writing his reminiscences of the saga of transfer factor and Dr. Fred Robbins for his memorial to Dr. Rammelkamp. Finally, we thank Mary Gardner of Cleveland and Kathy Cheek of Chapel Hill for their excellent help in bringing to light our thoughts and scribbles.

THE COMMISSION ON HEMOLYTIC STREPTOCOCCAL INFECTIONS — 6 FEBRUARY 1941 TO 30 JUNE 1946

The importance of hemolytic streptococcal infections, their complications, and sequelae were not generally recognized by the military services at the start of World War II. The important work of Lancefield[1] and Griffith[2] during the late 1920s and early 1930s resulted in classification schemes for hemolytic streptococci and established the group A β-hemolytic streptococcus as an important human pathogen. The work of Coburn[3] during the same period provided strong epidemiological evidence for a direct association between group A hemolytic streptococcal respiratory infections and subsequent acute rheumatic fever. This information, not widely disseminated to the medical community at large, was not generally known and, when known, was not universally accepted. As late as December 1941 Paul accepted that "... hemolytic streptococcal infections have something to do with rheumatic fever" but still questioned whether the hemolytic streptococcus was the only infectious agent in rheumatic fever.[4]

At the beginning of World War II, the military services had no history to draw on for concern about group A hemolytic streptococcal infections. The streptococcal etiology of scarlet fever was not established until the early 1920s. A brief review by Rantz[5] of the history of streptococcal infection and its sequelae in the military prior to World War II indicates that these infections were a major problem. Erysipelas and acute rheumatism were epidemic in the U.S. Army during the Civil War. Twenty-five thousand cases of acute articular rheumatism occurred during World War I, suggesting epidemic streptococcal disease (rheumatic fever is not mentioned in the official history of the Medical Department of the U.S. Army in World War I). Scarlet fever was 45th on the list of important diseases in the U.S. Army in World War I, based on admission to sick report.[6] Streptococcal respiratory infections without a skin rash were not distinguished from other respiratory infections and any relation to subsequent rheumatic fever was not appreciated. It was against the above backdrop, that Rantz[5] attributes the poor preparations of the Medical Department to cope with the problems of hemolytic streptococcal infections at the start of World War II.

At the time of the first meeting of the newly established Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army in February 1941, the paucity of information about the occurrence of streptococcal infection and sequelae during the prewar mobilization was recognized.[5] Outbreaks of scarlet fever and rheumatic fever at Chanute Field and Scott Field in Illinois and at Fort Knox, Kentucky, in early 1941 emphasized the seriousness of the problem. The Board, at its first meeting, recommended that "'Commissions' of the Board be appointed to deal with important infectious diseases, each 'Commission' to have a 'Director' and such additional consultant personnel as necessary for the purposes of the Commission."[7] The Commission on Hemolytic Streptococcal Infections was one of the seven recommended Commissions. The Board also recommended, as director of the Commission, Dr. Francis F. Schwentker of The Rockefeller Foundation, New York City. Dr. Schwentker declined the directorship because of anticipated absence from the United States. As a result, the Streptococcal Commission was not represented at the second meeting of the Board, 27 and 28 February 1941. At this meeting, Dr. Martin H. Dawson, College of Physicians and Surgeons, Columbia University, New York City, was appointed Director of the Commission.[7] The Commission Director's responsibilities were to appoint an executive committee, arrange for meetings of the committee, and prepare field and interim research programs, budgets, and lists of additional personnel. The committee appointed by Dr. Dawson was comprised of Dr. Chester F. Keefer, Boston University School of Medicine; Dr. David Seegal, Research Division for Chronic Diseases, Welfare Island, New York City; Dr. William S. Tillett, New York University College of Medicine; and Dr. James Trask, Yale University College of Medicine, New Haven, Connecticut.

Dr. Dawson resigned as Director on 14 October 1942 owing to poor health and recommended Dr. Keefer as Director. Dr. Keefer accepted appointment and continued as Director until the Commission

was disbanded in 1946. Dawson remained a member of the Commission until his death in 1945. Dr. Trask died in May 1942. Most of the Commission members served through 1945. Drs. Ann G. Kuttner, John S. Lockwood, Wesley W. Spink, Homer F. Swift, Tillett, and Conrad Wesselhoeft were still members in 1946.

The Commission held its first meeting on 26 April 1941 at Columbia University, New York.[8] All members of the Commission attended. Dr. Swift, Hospital of the Rockefeller Institute for Medical Research, New York, also attended as an unofficial consultant. The Commission's first order of business was to recommend appointment of an additional 13 members, 6 "clinicians" and 7 "bacteriologists":

Clinicians
George F. Dick, Chicago, Illinois
Conrad Wesselhoeft, Boston, Massachusetts
J. D. Lyttle, New York City
Champ Lyons, Boston, Massachusetts
John Lockwood, Philadelphia, Pennsylvania
Frank Meleney, New York City

Bacteriologists
Eleanor Bliss, Baltimore, Maryland
Ann Kuttner, Irvington, New York City
C. V. Seastone, Madison, Wisconsin
Harold Lyall, Albany, New York
Julia Coffey, Albany, New York
Harry Rose, New York City
P. L. Boisvert, New Haven, Connecticut

Dr. Swift and Dr. Rebecca C. Lancefield were to serve in an advisory capacity. Inspection of the geographic place of residence of the executive committee and the proposed 13 new members shows almost exclusively a Boston, New Haven, New York, east coast axis. This, perhaps, led to a recommendation for eight additional members, selected on a national basis. The nominated members who accepted appointment were

Arthur Bloomfield, San Francisco, California
Franklin Top, Detroit, Michigan
Wesley Spink, Minneapolis, Minnesota
Lowell Rantz, San Francisco, California
Jean Cook, St. Louis, Missouri
J. M. Sherman, Ithaca, New York
Lawrence Wells Smith, Philadelphia, Pennsylvania

The Commission made an operational classification of streptococcal infections and assigned primary responsibility for specific disease states as follows:

Scarlet fever: Trask
Upper respiratory tract: Keefer
Lower respiratory tract: Tillett
Rheumatic fever: Swift
Nephritis: Seegal

Not included in this list but in their classification were wound infections, anaerobic infections, and secondary streptococcal infections with measles and influenza. The Commission also emphasized close cooperation with other Commissions, particularly those on Epidemiological Survey, Measles, and Influenza. The functions of the Commission were defined as coordination of knowledge and offering of advice concerning hemolytic streptococcal infections, investigation of problems of an epidemiological nature, and assistance in control of epidemics. The Commission recognized the need to identify group A hemolytic streptococci and the specific types within group A if meaningful epidemiological studies were to be carried out. The initial recommendation was to rely primarily on agglutination typing, reserving the M precipitin method for special circumstances. Dr. Swift agreed to make the facilities at the Rockefeller Institute available for the latter method. The proposed budget of the Commission included $27,500 for 12,500 mL of grouping sera and 15,000 mL of typing sera. (The initial total budget for the Commission was $78,000.) According to Rantz,[9] the slide agglutination method proved to be of little value in the field and the precipitin method of Drs. Swift, Wilson, and Lancefield[10] was used for

the epidemiological studies carried out during the war. The identification of hemolytic streptococci by group and/or type and the study of their distributions and association with illness in large groups of persons were now possible for the first time. (The Board, still reflecting the soon to be outmoded state of knowledge, approved the use of typing sera in the field "provided outbreaks of one hundred to two hundred cases of scarlet fever occur." No record has been found that indicates when the Board accepted the importance of streptococcal sore throat without rash.)

Studies carried out by the Commission established the importance of streptococcal respiratory infections without rash both as a leading cause of morbidity, particularly in training camps, and as directly related to subsequent occurrence of rheumatic fever. The frequency with which rheumatic fever followed streptococcal infections (3.6% in studies at Fort Carson, Colorado) and the absence of rheumatic fever following nonstreptococcal respiratory infections were other seminal observations that solidified the group A hemolytic streptococcus–rheumatic fever relationship. Commission studies, particularly those at Fort Carson (see below), laid the groundwork for the studies by the Streptococcal Disease Laboratory at Warren Air Force Base, Cheyenne, Wyoming, beginning in 1949.

The activities of the Commission following its organization were rather limited for almost 2 years. This may owe in part to the limitation of the Commission activities to assistance in control of epidemics and investigation of problems of an epidemiological nature. The hemolytic streptococcus also was not reserved to the Commission. The Board had charged the Commission on Epidemiological Survey to conduct periodic surveys throughout the year to determine the prevalence of hemolytic streptococci and other bacterial diseases transmitted via the respiratory tract. Other Commissions also included the streptococcus in their investigations. The Commission on Cross-Infection in Hospitals, and its successor, the Commission on Air-borne Infections, evaluated the effect of ultraviolet light and propylene glycol vapor on dust-borne bacteria in hospitals and barracks. The Commission on Acute Respiratory Diseases (CARD) conducted field and laboratory studies of hemolytic streptococcal infections at Fort Bragg, North Carolina.

The first field study of the Commission was a 1-week survey by Drs. Trask, Schwentker, and Dawson in November 1941 at Scott and Chanute Fields and Fort Knox, all camps with large numbers of reported cases of rheumatic fever the previous year. As a result of the survey, a study was established at Chanute Field under the direction of Dr. Schwentker. During the period of 18 December 1941 to 25 March 1942, he conducted illness and carrier surveys at Chanute and also at Scott Field, Fort Knox, and Fort Francis E. Warren, Wyoming. A food-borne outbreak of septic sore throat at Camp Stoneman, California was investigated by Drs. Arthur L. Bloomfield and Rantz in July 1942, and a minor epidemic of scarlet fever at Santa Ana Army Air Base, California, in October 1942 was studied by Dr. Rantz. In the spring of 1943, large numbers of cases of rheumatic fever were reported from Fort Francis E. Warren and at Lowry Field, Buckley Field, and Camp Carson in Colorado. Drs. Keefer and Rantz visited these installations and for the first time the magnitude of the problem of streptococcal infection and rheumatic fever in the Army was acknowledged. (There were 18,339 admissions for acute rheumatic fever in the Army between 1942 and 1945, for a rate of 0.72 per year per 1,000 average strength.[5]) As a result, Dr. Rantz was asked to plan an extensive investigation directed to the natural history and control of the problem.[9] The Commission on Air-borne Infections, Dr. O. H. Robertson, Director, was requested to participate with the Commission on Hemolytic Streptococcal Infections in the planning and conduct of the studies.

Camp Carson was selected as the site for the study that began in January 1944 and continued through the spring. Dr. Rantz was appointed Field Director and Dr. Morton Hamburger, Jr., was in charge of all field activities for the Commission on Air-borne Infection. The active members of the Commission on Hemolytic Streptococcal Infections and their technical and secretarial assistants are listed below with the dates on which they began and ended their service at Camp Carson:

Dr. Lowell A. Rantz, Field Director
29 November 1943 to 22 May 1944

Dr. Wesley W. Spink
1 January 1944 to 15 April 1944

Dr. Paul J. Boisvert
1 February 1944 to 15 April 1944

Miss Elizabeth Randall, Technician
29 November 1943 to 17 May 1944

Miss Loraine Kerr, Technician
30 November 1943 to 17 May 1944

Miss Viola Ferris, Technician
13 December 1943 to 15 May 1944

Mrs. Helen Halm, Technician
25 March 1944 to 30 June 1944

Mrs. Helen Rantz, Secretary
29 November 1943 to 22 May 1944

Without question, the studies at Camp Carson were the most definitive to that time relative to the relationship between the group A hemolytic streptococcus and rheumatic fever, the natural history of streptococcal infections, the effect of treatment with sulfadiazine and penicillin, and the antibody response to infection. The studies at Camp Carson by Dr. Hamburger complemented the work of Dr. Rantz and provided important information on the microepidemiology of streptococcal infections within barracks. The studies by Drs. Rantz and Hamburger served as models for the later studies at the Streptococcal Disease Laboratory. Dr. Rantz summarized the Camp Carson studies in his unpublished history of the Commission on Hemolytic Streptococcal Infections.[9] Excerpts from his history follow:

> The acute phase of hemolytic streptococcal respiratory disease has been demonstrated to be of a more variable nature than had been realized previously. Exudative tonsillitis was shown to be a characteristic manifestation of infection by these organisms, but large numbers of patients were seen in whom streptococcal infection was proved by the development of circulating antibodies and in whom no exudate was observed. Edema of the pharyngeal tissues, redness, and particularly anterior cervical adenitis were useful signs in the diagnosis of hemolytic streptococcal respiratory infection. The most important result was the establishment of the fact that rheumatic fever is invariably preceded by an infection with group A hemolytic streptococci.
>
> Antifibrinolysin, antistreptolysin, and various precipitating antibody responses were determined in a large group of men infected by group A hemolytic streptococci. The results of these studies have not yet been completely analyzed but, as a result of this work and of serial Dick testings, it may be stated to have been proved conclusively that there are very great biological differences between various types or strains of these hemolytic streptococci. Thus, certain types failed to induce rash formation in Dick positive individuals. There were also great differences in the frequency and magnitude of the antistreptolysin and antifibrinolysin responses which followed infection by the various types.
>
> Because the rheumatic state was invariably preceded by infection by hemolytic streptococci, and because evidence was obtained during the study that reinfection by new types of such organisms was likely to initiate the pathological process, it seemed reasonable to suppose that some fraction or product of the hemolytic streptococcus which is common to all types should be responsible for the development of these disorders. It also seemed probable that some immunological process was the immediate cause of the late, nonsuppurative complications of streptococcal disease.
>
> The studies of the Commission have served to stress the fact that hemolytic streptococcal infections were much more prevalent in certain parts of the United States than others. This was especially true of the states on the eastern and western slopes of the Rocky Mountains (Wyoming, Colorado, Idaho, Utah). It was also true that the incidence of scarlet fever could not be relied upon as an index of the prevalence of hemolytic streptococcal infection in the adult population of any area. Outbreaks of hemolytic streptococcal infection only occasionally have their origin in food. The precise mode of the spread of these infections is not yet clear. There are reservoirs of streptococci in the dust, in blankets, in bed linen, in the nose and throat and in the air, and intimate contact between infected persons and susceptible individuals is extremely important, but it is not known at present what the most important factors are in the spread of the disease among the living subjects. These are matters of the greatest importance and must continue to receive attention until the commonest mode of spread is ascertained, if outbreaks are to be adequately controlled.

> It is also plain from the studies of the Commission that if rheumatic fever is to be prevented, hemolytic streptococcal infection must be prevented. Once hemolytic streptococcal infection becomes established there are no clear cut methods available for preventing rheumatic fever and the incidence of the rheumatic state following hemolytic streptococcal infection is far more common than has been fully appreciated in the past. [Rantz had concluded that neither sulfonamide nor penicillin treatment of the acute streptococcal infection prevented subsequent rheumatic fever; his penicillin treatment studies involved relatively small doses of penicillin and a small number of subjects.] It is important that we learn to detect all cases as promptly as possible, so that adequate care may be provided and efforts made to limit the damage caused by the disease. The most urgent studies for the future should be directed toward methods of preventing hemolytic streptococcal infection and determining the manner in which hemolytic streptococci cause the rheumatic state.

Other activities under the auspices of the Commission were rather limited. The support of the laboratory at the Rockefeller Institute as a reference center for grouping and typing of streptococci was critical to the success of the studies at Camp Carson, but these were carried out by the Navy and the Army Air Force. Dr. Paul L. Boisvert at Yale studied erythrogenic toxin production of group A streptococci. Dr. Rantz continued for several years his study of bacteriologic and serum specimens collected at Camp Carson. As mentioned above, both the CARD and the Commission on Air-borne Infections carried out important work on the hemolytic streptococcus. The Navy, under the leadership of Dr. Alvin F. Coburn, made extensive observations on the geographical spread of streptococci and initiated mass chemoprophylaxis programs with sulfonamide that controlled epidemics until sulfonamide resistant strains became prevalent.[11] Commander Armine T. Wilson, who later became a charter member of the new Commission on Streptococcal Diseases in 1948, was in charge of the Navy's streptococcal typing laboratory and developed the method for measuring sulfonamide resistance. The Army Air Force also carried out sulfadiazine prophylaxis studies[12] and, when sulfonamide resistance appeared, requested The Surgeon General to recommend "to the appropriate committee of the Army Epidemiological Board or to the Committee on Medical Research of the Office of Scientific Research and Development that a clinical study be undertaken to determine the prophylactic effectiveness of oral penicillin against strains of hemolytic streptococci demonstrably resistant to the sulfonamides."[13] The Medical Research Board "expressed deep interest" in the proposal and referred it to the Army Epidemiological Board.[14]

The Board considered the request and made the following recommendation:[15]

> 13. Use of Oral Penicillin for Prophylaxis of Streptococcal Infection
>
> In compliance with the request of the Army Medical Research Board the question of the use of oral penicillin for prophylaxis of hemolytic streptococcal infections of the respiratory tract was considered at the Executive Session following earlier discussion at the meeting of Directors of Commissions and members of the Board on 26 April. The proposals contained in the undated letter from The Air Surgeon to The Surgeon General relative to the undertaking of a clinical study to determine the prophylactic effectiveness of oral penicillin against strains of hemolytic streptococci demonstrably resistant to the sulfonamide were discussed at length. In the course of the discussion it was brought out that widespread use of oral penicillin might result in the selection of penicillin resistant strains and that these strains might become the predominant infective organisms in hemolytic streptococci infections. This risk appeared to be so great that it seemed undesirable to undertake a widespread study at this time. On the other hand, as definite information on the value of oral penicillin as a prophylaxis of infection due to sulfonamide resistant streptococci is desired, it was felt that a small well controlled study would be appropriate. The Board did not contemplate setting up such a study by one of its Commissions at this time.
>
> On motion to Dr. Dochez, seconded by Dr. Maxcy, it was voted to submit to The Surgeon General a statement of information and recommendation as indicated above.

This recommendation effectively curtailed studies of penicillin prophylaxis in the military and it was not until 6 years later that studies of penicillin prophylaxis were initiated at Francis E. Warren Air

Force Base by the Streptococcal Disease Laboratory[16] and at Great Lakes Naval Training Station by the Naval Medical Research Unit (NAMRU-4).[17] These studies showed the effectiveness of penicillin in controlling epidemic streptococcal disease without the appearance of penicillin-resistant strains. Mass prophylaxis with penicillin eventually became the cornerstone of rheumatic fever control in the military services as recounted in subsequent sections of this history. One can speculate that if effective penicillin prophylaxis had been demonstrated in 1945 and 1946 there would have been no pressure to create the Streptococcal Disease Laboratory in 1949.

Conspicuous by its absence during the time of the Commission on Hemolytic Streptococcal Infections is any reference to nephritis, except for the first meeting of the Commission when Dr. Seegal was assigned the responsibility for nephritis. The explanation for no mention of nephritis probably lies with the absence of nephritogenic streptococcal strains in the epidemic situations studied during World War II. It is unlikely that epidemics of nephritis would not have been identified even though the paramount interest was rheumatic fever.

The Board, at its annual meeting on 15 and 16 April 1946, reorganized its structure, effective 1 July 1946, and the Commission was not one of the six commissions of the new Board. The CARD subsumed the streptococcus; this Commission also continued to support the work of Dr. Rantz at Stanford University.

COMMISSION ON STREPTOCOCCAL DISEASES — 1948 TO 1960 AND COMMISSION ON STREPTOCOCCAL AND STAPHYLOCOCCAL DISEASES (CSSD) — 1960-1973

The Army Epidemiological Board at its meeting in May 1948, authorized the formation of a new Commission on Streptococcal Diseases. Colin M. MacLeod, MD, President of the Board, recommended for Director, Dr. Tillett, who met MacLeod's requirement that the Director "have a thorough knowledge of bacteriology of streptococci as well as the diseases caused by this species."[18] The reactivation of the CSSD was initiated by the continued problem of a high incidence of rheumatic fever in the Army camps in the Rocky Mountain area. Although the CARD included streptococcal infections in its charge, the magnitude of the problem was thought to require a new initiative. The Respiratory Disease Commission continued to play an important role in relation to streptococcal infections, however. Its joint sponsorship of the Streptococcal Disease Laboratory, the joint annual meetings of the two Commissions, and the sharing of members and associate members between the two illustrate the close association that existed over the years.

The new CSSD met for the first time in New York City, 26 and 27 February 1949. Dr. Tillett had accepted the directorship of the CSSD, whose members were Drs. Oswald T. Avery, C. Phillip Miller, Rammelkamp, and Wilson; Associate members were Drs. Joseph J. Bunim, Harry Eagle, Hamburger and W. Barry Wood. The purpose of the meeting was "to explore lines of study, either directly or indirectly related to the streptococcal field, that might seem profitable to pursue."[19] Invited guests (Drs. David P. Earle, Jr., Seegal, McCarty, Swift, G. E. Murphy, Horace Gezon, Miller, Benedict Massell, and Kuttner) led discussions on active immunity to streptococcal infections, clinical and immunological features of rheumatic fever, and penicillin and the hemolytic streptococcus. Dr. Rammelkamp presented the current status of the new Streptococcal Disease Laboratory. Two research projects were approved. Dr. Avery received $8,800 for experimental studies on active immunity to hemolytic streptococci, and Dr. Tillett, $11,400, for studies of "Passive Transfer in Humans of Cutaneous Reactivity to Hemolytic Streptococci and Their Products." The Tillett studies, under the active direction of Dr. Lawrence, were supported annually during the life of the Commission and the successor CSSD. Dr. Lawrence, out of his deep respect for him, always made certain that Dr. Tillett was designated as the contractor.

The second meeting of the Commission was held jointly with the CARD in Cleveland, Ohio, on 29 and 30 March 1950. The two funded contracts were continued and one new contract was approved for Dr. Hamburger to study the effect of streptokinase and streptodornase on experimental pneumococcal meningitis in monkeys.

The Commission held a special meeting 6 and 7 November 1950 at the Streptococcal Disease Laboratory, where detailed reports of the Laboratory's research activities were presented. Also at this meeting, the Commission awarded a contract to Dr. Lester O. Krampitz, Western Reserve University, Cleveland, Ohio. to study the biosynthesis of streptococcal M protein.

The contract with Dr. Avery ended in 1951, and until 1953 the contracts of Drs. Hamburger, Krampitz, and Tillett were the only work supported directly by the Commission and, of these, only the work of Dr. Krampitz was related directly to the streptococcal problem. A contract was awarded in 1953 to Dr. Floyd Denny for study of type-specific streptococcal antibodies. The only action items of the Commission during this time dealt with the issue of mass prophylaxis of streptococcal infections. Drs. Bunim and Wood were added as members in 1950 and, Dr. Denny, as associate in 1952.

A new era of activity and productivity for the Commission began in 1954 with the appointment of Dr. Rammelkamp as Director. Five new members and seven new associate members were appointed. New members included Drs. Lancefield, Maclyn McCarty, Alan Bernheimer, Wannamaker, and Denny; Tillett and Wilson were reappointed. Associate members were Drs. Samuel S. Barkulis, Albert H. Coons, Melvin H. Kaplan, Krampitz, Chandler A. Stetson, Robert H. Ebert, and Houser.

Dr. Rammelkamp continued as Director until 1968 except for a 2-year period, 1957 to 1959, when he was replaced by Dr. Wilson. Dr. Wannamaker became Director in 1968 and continued in that position until the commission was disbanded in 1973.

The subsequent annual meetings of the Commission had presentations of the highest scientific caliber and were the national forum for clinical, epidemiological, and basic research related to the group A streptococcus. In addition to reports from contractors, invitations were extended to other scientists. In 1957, for example, the Commission sponsored a special symposium on the day following the regular annual meeting. The program of this meeting appears on page 271.

The continued occurrence of epidemic rheumatic fever in the early 1950s resulted in the appointment of an ad hoc Committee of the Commission in October 1953 to make recommendations to the military services for streptococcal prophylaxis programs. Members of the Committee were Drs. Rammelkamp (Chairman), Eagle, Houser, Gene H. Stollerman, Tillett, Wannamaker, and Wilson. The Committee recommended that prophylactic programs of 250,000 units of oral penicillin twice a day for 10 days, or as an alternative, 1.2 million units of benzathine penicillin, be initiated when epidemic streptococcal disease was present. This Committee evolved into the Committee on Prophylaxis of Streptococcal Infections in the Armed Forces (see below), that played a vital role in eventual control of epidemic streptococcal disease in the military. The committee recommendations were formalized in Department of the Army Technical Bulletin, TB Med 259 (NAVMED P-5052-17; AEP 160-5-24), Treatment and Prevention of Streptococcal Disease and its Sequelae.

Acute poststreptococcal nephritis received little attention from the Commission until an epidemic occurred at Bainbridge Naval Training Center, Maryland, in 1951 and 1952. Dr. Rammelkamp investigated this epidemic, which confirmed in his mind that certain types of group A streptococci were nephritogenic. The reports of an unusual clustering of kidney disease in Yugoslavia interested Dr., Rammelkamp, and the Commission supported his studies of Balkan nephropathy. The only other international studies supported by the Commission were penicillin treatment studies of acute rheumatic fever carried out by Dr. Rammelkamp in Chile.

During the mid 1950s, hospital epidemics of staphylococcal infections were common in the United States and created unusual concern. Problems in military hospitals were similar to those reported from civilian hospitals. The Board assigned the responsibility for study of staphylococcal infections to the Commission in 1958. Drs. Rene S. Dubos and David C. Rogers were appointed members and Robert Wise an associate member, in response to the added role of the Commission. Contracts for study of

Program

Symposium on Streptococcal Disease
University of Virginia
Charlottsville, Virginia
27 March 1957

1.	Study of Prophylaxis of Rheumatic Fever	H. Wood
2.	Treatment of Rheumatic Fever with Penicillin Effect on Acute Phase of Illness	T. Mortimer
3.	Further Studies on Streptococcal Infections in Rabbits	R. Glaser
4.	Evidence Supporting an Autoimmune Mechanism in the Pathogenesis of Rheumatic Fever	M. Kaplan
5.	Accessory Factors in Rabbit and Human Blood Involved in the Bactericidal Test for Type-Specific Antibody	G. Stollerman, F. Kantor, and B. Gordon
6.	Studies of L Forms of Group A Streptococci for Polysaccharide Production and Some of the Implications	J. Sharp
7.	Chemical Basis for the Serological Specificity of Group A Carbohydrate	M. McCarty
8.	Streptococcal Bacteriophage; A Lytic Factor in Lysates in Addition to the Phage Particle	R. Krause
9.	Properties of a Streptococcal Enzyme: Occurrence and Possible Significance	A. Kellner and A. Bernheimer
10.	Survival of Streptococci in Leucocytes	A. Wilson and G. Wiley

staphylococcal infections and host reactivity were awarded to Leighton E. Cluff and, for staphylococcal virulence studies, to Richard Ekstedt. Drs. Wannamaker and Rammelkamp also added staphylococcal studies to their contracts.

The Board, at its Spring meeting on 16 and 17 May 1960, based on a recommendation by the Commission, redesignated the Commission as the Commission on Streptococcal and Staphylococcal Diseases (CSSD). Dr. Cluff, who had been appointed an associate member in 1959, was made a full member in 1960, replacing Dr. Dubos. Dr. Rogers remained a member of the CSSD through 1968, and Dr. Cluff through 1972. Drs. Wannamaker and Rammelkamp continued their staphylococcal research. Some research was carried out at an interface of streptococcal and staphylococcal infections, impetigo, by Drs. Cluff, Hugh C. Dillon, and Wannamaker. Other studies concerned the effect of staphylococcal products on group A streptococci. The staphylococcal work of the CSSD did not have the central focus that the streptococcal work had, ie, streptococcal sore throat and its sequelae. The latter were problems of great magnitude to the military and drove much of the effort of the CSSD, particularly in the early years.

The CSSD became somewhat eclectic in its membership and contract support during the second half of its 24 years. Gram-positive bacterial infections, in general, and host responses were represented by Drs. Wood, James G. Hirsch, Lewis Thomas, and Paul G. Quie. The last link to the original Commission on Hemolytic Streptococcal Infections ended in 1966 when Dr. Tillett retired from the Commission. The outstanding accomplishment of the CSSD during the latter years was the work of Drs. Wannamaker and Dillon in elucidating the epidemiology of impetigo and associated acute glomerulonephritis.

The last meeting of the CSSD held jointly, as usual, with the CARD, was at WRAIR 8–10 November 1972. The CSSD now was comprised of 13 members and 13 associate members. Dr. Tillett was still a responsible investigator for one of the eight contracts of the CSSD. The program reflected the shift from studies directly related to the military to studies of the biology of the streptococcus and staphylococcus and epidemiological studies in civilian populations, including those in Trinidad and Egypt. Of the 18 papers presented, 9 were by invited guests. The invited guests and members and associate members represented the major centers and individuals in the United States carrying out research on the group A streptococcus and its diseases. This emphasized the premier role the CSSD played in financial and intellectual support of streptococcal research, not only in the United States, but also to the rest of the world through the personal and scientific ties developed by members of the CSSD.

It seems appropriate to include the last paragraph of the last Annual Report by Dr. Wannamaker in its entirety because it demonstrates so well the milieu of the activities of the CSSD:

> At the fall meeting of the Commission held jointly with the Commission on Acute Respiratory Diseases on Wednesday, 8 November through Friday, 10 November, 1972, reports of contractors and other scientific reports were heard (see agenda attached). Invited outside speakers included Dr. Karakawa, who reported on an unusual capsular antigen obtained from staphylococcal strains associated with infection in a military hospital; Dr. Judy Falk reported on HLA studies in rheumatic families. **The spirit of the Commission was maintained to the end.**

The tradition of the CSSD meetings did not end with the last meeting. An ad hoc committee of the CSSD composed of Drs. Richard M. Krause (Chairman), Dillon, Houser, and Wannamaker discussed ways to continue the tradition. The Committee proposed that a "Streptococcal Club" be formed and that an annual scientific session be held in conjunction with the meeting of the Infectious Diseases Society. The first meeting was held in Washington, D.C. on 16 September 1973. The "Club" became the Lancefield Society in 1978. Annual meetings have continued and membership grew from fewer than 50 persons in 1973 to over 150 in 1990.

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The Commission on Streptococcal and Staphylococcal Diseases (CSSD), November 1972.

8–10 November 1972

Seated, left to right: Harold B. Houser, Richard M. Krause, Lewis W. Wannamaker (Commission director), Rebecca C. Lancefield, Charles H. Rammelkamp, Jr.

Standing, left to right: Edward A. Mortimer, Jr., Bascom F. Anthony, Emil C. Gotschlich, Kenneth L. Vosti, Gene H. Stollerman, John B. Robbins, Hugh C. Dillon, Jr., Elia M. Ayoub, Emanuel Wolinsky, Paul G. Quie, Robert C. Austrian.

THE STREPTOCOCCAL DISEASE LABORATORY

The history of events leading to the establishment of the Streptococcal Disease Laboratory — henceforth called the Strep Lab — began in the late 1940s, probably sometime during 1947 or early 1948. At that time, very little was known about the treatment of streptococcal infections, and nothing was known about the prevention of rheumatic fever by treating streptococcal infections. As already mentioned in the earlier history of the CSSD, it had been demonstrated during World War II that sulfonamide treatment of streptococcal infections had very little effect on the course of the acute disease and did not prevent the subsequent occurrence of rheumatic fever.

When the Strep Lab was opened in January 1949, the effect of treatment with the newer antimicrobials on clinical disease and the prevention of rheumatic fever was largely unknown. The decision was made at that time that the use of untreated controls was not only ethical, it was scientifically necessary if these issues were to be decided conclusively. Several years after the results of the studies done at the Strep Lab appeared in the scientific literature, there was criticism of the use of untreated patients as controls in many of the early studies. This criticism proved to be an annoying problem for several months, but no serious after effects occurred. The authors decided that it would be appropriate to clarify at this stage of this history the ethical issues raised in the studies carried out by the Strep Lab so that the readers would not be confused by this issue. After more than 40 years since these studies began, the authors of this report still feel strongly that our studies were ethically warranted and in good taste. It is our hope that the readers of this report in the 1990s will review this report of the activities of the Strep Lab in the light of this observation.

Background of Formation

The first mention of renewed interest in special studies on streptococcal infections and rheumatic fever in the Armed Services appeared in the AFEB Annual Report of 17 April 1947 to 1 April 1948. Under the general heading of "Field Trips" is a report entitled "Study of a reported outbreak of streptococcal infections at Lowry Field and at Fort Francis E. Warren," which was carried out between 14 and 17 February 1948 by Drs. Rammelkamp, and William S. Jordan, Jr. The report described in detail the problem at Lowry Field and added a short paragraph to the effect that the problem was similar at Fort Warren. The final section of this report is reproduced below because it describes very well the current thinking that set the basis for the establishment of the Strep Lab and its relationship to Western Reserve University (now Case Western Reserve University):

> Proposal for a continuous study of streptococcal infection. Little detailed information is available regarding the pathogenicity of various types of group A streptococci. It seems entirely possible that certain biological or chemical characteristics of specific types of streptococci may be of paramount importance. Thus a clue as to the substance or substances which are responsible for exudate, scarlet fever, rheumatic fever, pneumonia or empyema may be obtained from a long term study of the relation of the specific type to the disease process. Lowry Field would seem to be an ideal location for such a study. In the past, streptococcal infections have been prevalent in this area, and furthermore, some data concerning the types of streptococci in preceding years are available.
>
> The proposed investigation would include epidemiological, clinical and laboratory studies. An attempt would be made to determine the cause for the high rates of streptococcal infections in the population. Records of new recruits would be maintained. At regular intervals culture surveys would be made on the normal population. All patients entering the hospital would be cultured, and those exhibiting beta-hemolytic streptococci would be bled for acute and convalescent serum specimens. Brief clinical records would be maintained on all patients harboring beta-hemolytic streptococci and their clinical manifestations classified. Streptococci isolated would be grouped and typed, and all group A strains forwarded to the laboratories at Western Reserve University for further study.

It is estimated that the personnel required for this project would include two physicians, two enlisted men and three technicians at Lowry Field. Additional technical help would be required at Western Reserve University.

The next mention of this project appears in the AFEB Quarterly Report ending 31 December 1948, with the following short paragraph:

A study of streptococcal infections has been instituted at Fort Francis E. Warren, under the joint auspices of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases. Dr. Charles H. Rammelkamp, Jr. has been appointed as field director of this study. Alterations are being made in a ward building of the Post hospital to house the laboratory which will be ready for operation during January. Three army officers, Lts. William R. Brink, Floyd Denny and Lewis W. Wannamaker, have completed a training period at Western Reserve University and have been transferred to Fort Warren. Training of the technical staff has been started.

The AFEB Annual Report of 1 May 1948 to 1 April 1949 clarifies, at least in part, the choice of Fort Warren as the site for the Strep Lab, instead of Lowry Field as suggested first. It outlines briefly the events leading to the establishment of the Lab and describes the initial staff and early studies. This part of the Report is reproduced in its entirety because it gives the background for the laboratory activities, which are to follow:

Study of streptococcal infections at Fort Warren

In October, 1948, a survey of Fort Francis E. Warren, Lowry Field, and Camp Carson was made by Drs. MacLeod, Tillett, Dingle, Rammelkamp and Colonels Patton and Pleuncke, Major Kossuth, and Lt. Brink. It was decided that Fort Francis E. Warren offered an ideal location for a long term study of streptococcal infections and rheumatic fever because of the high incidence of these diseases and the extreme interest of Col. J.C.B. Elliott, Commanding Officer, and Col. J.K. Cullen, Post Surgeon.

Plans for the laboratory and lists of equipment were prepared and submitted to Col. J.C.B. Elliott by 1 December and by 24 January 1949 the laboratory, which is a renovated W-l hospital ward, was sufficiently completed so that the study was instituted.

The staff consists of Dr. Edward Custer, Lts. Brink, Denny and Wannamaker, 4 technicians, a secretary and 2 dieners. In addition, 2 enlisted men were assigned to the laboratory. The 3 medical corps officers received preliminary training in the Department of Preventive Medicine at Western Reserve University for a period of approximately 6 months.

The various studies now being conducted at Fort Francis E. Warren may be divided into 3 broad categories: Epidemiological, Clinical and Laboratory.

It seems appropriate to elaborate on the events leading to the establishment of the Strep Lab at Fort Warren. Accordingly, three documents will be reproduced in their entirety below and a fourth will be presented in Appendix 2. The first document is a letter from Dr. MacLeod, President of the AFEB, to Colonel Thomas E. Patton, MC, Chief of the Preventive Medicine Division, Office of The Surgeon General, Department of the Army, requesting officially the establishment of the Lab:

Dear Colonel Patton

I am enclosing six copies of a brief report of our recent trip to Camp Carson, Lowry Field and Fort Francis E. Warren, which indicates, I believe, the reasons for choosing Fort Warren as the site for the study of streptococcal diseases and rheumatic fever in the Rocky Mountain area.

Following discussion with Dr. Tillett, Dr. Dingle and Dr. Rammelkamp, Major Kossuth and yourself, the consensus was that Fort Warren is the most suitable of the three posts visited. I wish, therefore, to make formal recommendation that the study be located at Fort Warren.

It is recommended further that the study be set up under the joint auspices of the Commission on Streptococcal Diseases and the Commission on Acute Respiratory Infections, and that the contract be drawn up with Western Reserve University. Details regarding the latter will be supplied by Dr. Dingle, and will require clearance by the Army Epidemiological Board. In the opinion of both Dr. Dingle and myself, it is important that a letter of authority, originating on a high military level, be provided. Our respective experiences during World Ward II at Fort Bragg, N.C. and Sioux Falls Air Base, S.D., have emphasized the importance of such an authorization if a long term study is to be carried out successfully. Copies of these letters of authorization, are available, I believe in the files in Washington. That relating to Fort Bragg should be in the files of the A.E.B.; that relating to Sioux Falls in the Air Surgeon's Office.

It is our hope that this study can be got underway very promptly. Drs. Dingle and Rammelkamp will be responsible for the design and equipment of the laboratory and as soon as final Army and Air Force approval are obtained, sketches will be forwarded to Col. Elliott at Fort Warren, so that the appropriate alterations can be begun. It is our hope that the study will be running smoothly by the time the high epidemicity of streptococcal diseases can be expected.

Sincerely yours,

Colin H. MacLeod, M.D., President

The report to The Surgeon General, Department of the Army (through Preventive Medicine Division), subject: Survey of sites for location of study of streptococcal diseases and rheumatic fever in the Rocky Mountain Area is in Appendix 2 . Two supporting documents from Colonel John K. Cullen, MC Surgeon, Station Hospital Fort Francis E. Warren, and Colonel John C.B. Elliott Commanding Officer, Fort Warren, are as follows:

MEMORANDUM TO: Streptococcal Disease Commission
THRU: Commanding Officer
Fort Francis E. Warren
and
3450th Technical Training Wing
Fort Francis E. Warren, Wyoming

SUBJECT: Factors Pertinent to the Consideration of Establishing a Research Laboratory at this Station.

1. Inasmuch as I will be unable to be present during your visit to this station, I wish to present the following resume of factors which are believed to be pertinent to the consideration of the possibility of establishing a laboratory at this station for basic research in streptococcal infections and respiratory disease:

a. The mission of this station is to train Air Force personnel in various administrative and technical specialties. This involves a continuous flow of personnel through this Base throughout the year. At the present time the military strength at this Base is approximately 9,000 of which approximately 5,200 are "Pipeline" personnel. The remainder are permanent party personnel or members of T/O and E organizations. The average turn-over of student personnel is 3-4 times per year. Thus, it can be seen that with the present personnel set-up the total number of individuals who might be exposed during the course of a year to whatever diseases there may be in this locality will approximate 20,000. If the strength of this Base is raised to approximately 12,500, as is contemplated (with approximately 8,000 of these being "Pipeline"

personnel), the total number of individuals passing through this Base in the course of a year will then be approximately 28,000.

b. This station is separated by natural geographic features into two areas: The permanent party area which is north of Crow Creek, and the student area which is south of Crow Creek. The housing in the permanent party area is, for the most part, composed of permanent type brick structures, while that in the school area is entirely cantonment type in nature.

c. There is available in the Station Hospital area readily convertible space for the housing of any laboratory facilities which it may be desired to set up. This space, which is in a standard type W-l ward, can be readily converted to laboratory needs with a minimum expenditure of money and labor. It is immediately adjacent to the present hospital laboratory.

d. Because of the presence at this station of such specialist schools as the carpenters' school, the electricians' school, the plumbing school and the sheet metal school, it will be possible to carry out such alterations and/or construction as may be required, either initially or later on, at a minimum cost and without delay.

e. A factor which is of prime importance to the successful accomplishment of the mission of such a group as is contemplated is the matter of cooperation and support of the Base Commander. Colonel Elliott, the Commanding Officer of this station, has long been personally interested in the matters of rheumatic fever and streptococcal infections and can be depended upon to give 100% moral and logistic support to any laboratory group which is sent to this station.

f. Another factor which would have a material effect on the work of any research group is the attitude of the medical officers at the station. The group of young medical officers now stationed here are far and away the best group of such young doctors I have had the pleasure of working with during my entire career in the army. Although young and relatively inexperienced, they are all enthusiastic, hardworking, cooperative and have plenty of initiative. This latter quality is illustrated by the proposed program of recording observations in cases of rheumatic fever which have been set up by the medical service in conjunction with Dr. Flett, the medical consultant.

2. Without having any personal knowledge of the situations at either Lowry Air Force Base or Camp Carson, I feel confident that the support which will be given to this research group, if it is established at Fort Warren, cannot be exceeded in any respect at either of the other two stations.

"A True Copy"

F.M. Lunnie
Captain, MSC
Hospital Adjutant

John K. Cullen
Colonel, Medical Corps
Surgeon

1st Ind **CO/JCBE/mjm**
7 Oct 1948

Headquarters Fort F.E. Warren and 3450th Technical Training Wing, Fort F.E. Warren, Wyoming

MEMORANDUM TO: Streptococcal Disease Commission

1. My attitude is that this problem of upper respiratory disease and rheumatic fever must be solved by preventive means - not run away from. There is much conflicting information on this subject, but it has not been proved to my satisfaction that the enlisted man who is susceptible to these infections will not still be so after one, two, or ten years of service if he enters a violent climate. If this is the case, it is better to eliminate this man early, before we have trained and shipped him to a theatre, only to lose his skill in a casualty. Our approach to this problem must be the same as that of malaria - to combat it preventively wherever it may be encountered with the simplest possible means. I also feel that any field problem must be solved by fact finding at that source, not by remote control suppositions. It is for this reason that I am so anxious to have the technicians work with us here.

2. We have here a climate subject to violent and deceptive changes. U.R.I.s starts when the heat is turned on in barracks and appear to follow in intensity the periods of daily maximum changes in temperature. Sixty-seven (67) percent of the time our weather is clear, and on a cold winter day when the wind is low in this dry climate, it is possible to be relatively comfortable. However, when the sun goes down, going out in the same clothing is a severe shock to the resistance of the body which is trying to pump a constant 98.6° temperature, and furthermore the altitude is no great assistance to the heart in this matter. This seems to be the crux of the matter. Of course our type barracks are fine incubators for the bugs who jump on the body of weakened resistance.

3. On the other hand our men must be trained to function efficiently in all climates and altitudes as we must be able to produce more with less men to survive the next conflict. Our engineering schools must be trained to function efficiently throughout the winter by use of proper clothing and clothing discipline if we are to meet this requirement. We work outside throughout the entire winter with some of our schools here, a more violent training requirement than will be found at either Lowry or Carson. Furthermore, we are probably the largest with the largest turnover. I think we are in the area where most can be learned and I am determined to solve this problem if it is humanly possible.

4. For the above reasons, I will throw every resource I can to the assistance of this unit if it will come in here and work with us. What Colonel Cullen says, goes for me — I would like to have you define what you need before you leave here.

/s/ John C.B. Elliott
/t/ Colonel, USAF
Commanding

These documents are important for several reasons. They indicate the choice of Fort Warren as the Strep Lab site, recommend that the Lab be set up under the joint auspices of the Commission on Streptococcal Diseases and the CARD, and request a letter of authority, "originating on a high military level." (A copy of this letter has not been found and it is not known if such a letter ever existed.) They also indicate the strong endorsement of and support for the Lab at Fort Warren. These documents were dated from 5 October through 19 October 1948. Dr. Rammelkamp was named field director, as indicated in the AFEB Quarterly Report ending 31 December 1948.

The Strep Lab began to function officially on 24 January 1949. The following sections will describe more fully the construction of the Lab, its staffing, and the professional personnel participating in the studies. The accomplishments of the Lab will be described in a section on the clinical aspects of streptococcal infections and rheumatic fever and a section on the epidemiology of streptococcal infections. Brief mention will be made of specific laboratory observations, but laboratory studies will more often be described in conjunction with the clinical and epidemiology studies. Short sections will be devoted to the receipt of the Lasker Award by the Strep Lab, its closing in 1955, and a reunion held in Cheyenne in 1974. A complete list of publications generated from studies at the Strep Lab will complete the chapter.

The Laboratory

The decision was made to house the laboratory primarily in a W-l one-story wooden hospital ward that was converted into adequate laboratory space. One such building formed the main laboratory; a few offices and space for some clinical studies were also available in an adjacent ward building. The laboratory was located at what was then Fort Francis E. Warren on the outskirts of Cheyenne, Wyoming. The surrounding country was extremely flat, almost desert-like in its lack of vegetation, and the laboratory overlooked nothing but this desolate plain. The small initial nucleus comprised of Drs. Rammelkamp, William Brink, Denny, and Wannamaker, at that time in the Department of Preventive Medicine at Western Reserve University School of Medicine in Cleveland, Ohio, designed the renovations to be made in the W-l ward. Because Fort Francis E. Warren at that time was a technical training base and had a carpenters' school, students did the construction work. The results were entirely adequate, although not luxurious, but the Cleveland group in their naïveté had omitted the inclusion of any drawer space in the entire laboratory. As it turned out we learned very quickly that a very efficient laboratory could be run without drawers.

It is appropriate that the reader be introduced to the climate in southeastern Wyoming. The army base, Fort Francis E. Warren, subsequently changed to Warren Air Force Base, is located on the outskirts of Cheyenne, Wyoming, at an altitude of slightly over 6,000 feet. This dictated that the weather was never very warm and temperatures of –20°F were common, –25° occasional, and –35° witnessed at least on one occasion by the authors. The air was extremely dry, the wind at times during the winter was fierce, being recorded at above 90 mph on several occasions. The humidity was low.

Administration/Personnel

The technical staff of the laboratory was an interesting assortment of largely untrained individuals. Mary Riner, the daughter of a local supreme court judge and a college graduate in science, although not trained as a laboratory technician, was made the chief technician. This was an extremely fortunate choice because she was the mainstay of the technical staff for several years. Other local civilian and Air Force and Army individuals served as laboratory technicians; most of their training took place after joining the laboratory. The laboratory diener, John Datillo, a Chicago cab driver, was an interesting and colorful addition to the staff. The laboratory was furnished with an official car and a series of drivers. Master Sargent Marple joined the laboratory when it opened and remained the administrator and coordinator for the laboratory until its closure. His remarkable talents and dedication were indicated by

promotion to major and his nomination for a Legion of Merit Award during the last years of the laboratory.

The professional personnel of the Strep Lab during its years of existence are listed alphabetically in the table below; all were members of the Armed Forces, except Drs. Edward A. Custer and Willard C. Schmidt and the student research fellows from Western Reserve University. Special recognition should be given to Dr. Rammelkamp, who was its only director. He was a superb scientist who lead his staff throughout the many studies that will be described subsequently. One of his most notable characteristics was his generosity toward young associates. He was instrumental in the scientific and academic development of many of us who remember him with exceptional fondness. He was a workaholic in the true sense of the word and his consumption of Coca Cola and cigarettes was tremendous. He is remembered with great fondness by those of us whom he termed his "birds." For those whom he regarded with less affection he used the term "drut."

Because Dr. Rammelkamp did not relinquish his duties in the Departments of Preventive Medicine and Internal Medicine at the Western Reserve University School of Medicine, he appointed a series of assistant directors to help him administer the Strep Lab, as listed below:

Professional Staff

William R. Brink	1948–1949
Loring L. Brock	1951–1953
Frank J. Catanzaro, Sr. (Assistant Director 1953–1954)	1952–1954
Robert Chamovitz	1953–1954
Ernest J. Clark*	1951
Edward A. Custer	1949
Floyd W. Denny, Jr. (Assistant Director 1949–1951)	1948–1951
George C. Eckhardt	1950–1952
Edward O. Hahn	1949–1952
Harold B. Houser	1949–1952
Robert J. Kohen†	1953
Richard M. Krause‡	1950–1951
Earl C. Marple§	1949–1955
Alton J. Morris	1953–1955
William D. Perry	1951–1953
Charles H. Rammelkamp, Jr., Director	1948–1955
Willard C. Schmidt	1954–1955
Alan C. Siegel	1952–1953
Chandler A. Stetson (Assistant Director 1952–1953)	1951–1953
Bertrand L. Stolzer	1951–1953
Daniel Stowens	1950–1951
Lewis W. Wannamaker (Assistant Director 1951–1952)	1948–1952
Richard D. Yoder ‡	1949

*Member of hospital staff; assisted in rheumatic fever treatment studies.
† Assisted in nephritis studies at Bainbridge Naval Training Station.
‡ Medical student at Western Reserve University.
§ Laboratory administrator.

MAJOR SCIENTIFIC ACCOMPLISHMENTS

Clinical Studies

Prevention of Acute Rheumatic Fever by Treating Acute Streptococcal Respiratory Infections

Clearly, the most outstanding accomplishment of the Strep Lab staff was the observation that the treatment of an acute streptococcal respiratory infection with an effective antimicrobial prevented the occurrence of rheumatic fever in the great majority of cases. This was reported first in the fall of 1950 before the Midwestern Section of the American Federation for Clinical Research. The report was received without great fanfare and it is of possible historical interest that the Central Society for Clinical Investigation had not accepted the article for presentation. In any event, these seminal observations appeared in the *Journal of the American Medical Association* in 1950 in an article entitled "The prevention of rheumatic fever by treatment of the preceding streptococcic [*sic*] infection." Because of its importance, this article is reproduced in its entirety in Appendix 6. In 1985 it was recognized as a "Landmark Article" by the *Journal of the American Medical Association* and was reproduced in the 26 July issue of that journal. It was accompanied by a commentary (Appendix 6) by Dr. Alan L. Bisno who emphasized its subsequent importance in reducing the occurrence of rheumatic heart disease.

These studies, the brainchild of Dr. Rammelkamp, were unusual in their simplicity and have been recognized as models for prospective, well-controlled clinical trials. Following the initial observation that the treatment of streptococcal infections with various doses of depot penicillin prevented the occurrence of acute rheumatic fever, Dr. Rammelkamp directed the Strep Lab staff in a series of studies to clarify the mechanism of prevention and the details of proper management of acute infections. The following sections describe in some detail these studies.

Effect of procaine penicillin G (suspended in peanut oil containing 2% aluminum monostearate). In this, the first study, airmen with exudative tonsillitis or pharyngitis were observed in the hospital between 24 January and 1 July 1949; 798 patients with even serial numbers received penicillin therapy and 804 with odd serial numbers served as controls. Penicillin was given as soon after admission as possible in two schedules: 278 patients received 300,000 units of penicillin on admission to the study and again in 72 hours; 520 patients received 300,000 units of penicillin on admission and again in 48 hours and 600,000 units 96 hours after the initial dose. Rheumatic fever developed in 2 treated patients and 17 untreated (P=.0006). Penicillin treatment greatly reduced the carriage of streptococci and the antistreptolysin O response was blunted. These preliminary studies set the stage for other studies that confirmed these results and clarified further the details of the treatment of patients with streptococcal pharyngitis and the prevention of rheumatic fever.

These early studies were extended and the final results published in the *American Journal of Medicine* in 1951. The basic format of the study was unchanged. The table at the top of page 283 shows the numbers of patients in the treated and untreated groups and the dosage schedules of penicillin.

Definite rheumatic fever developed within 45 days after the streptococcal infection in 28 untreated patients and 2 treated patients. As in the earlier studies, the carriage of streptococci was reduced and the antistreptolysin O titers blunted in the treated patients.

Effect of chlortetracycline. Between 23 February 1950 and 9 March 1951, 2,004 patients with exudative tonsillitis/pharyngitis were studied; 1,009 received 8 to 11 g chlortetracycline over a period of 4 to 6 days, and 1,035 served as controls. Within 35 days after the onset of infection, definite rheumatic fever occurred in 5 treated patients and 20 controls; within 45 days, there were 11 cases in the treated group and 24 in the untreated group. Thus, chlortetracycline, although effective in reducing the occurrence of

Study Format

Regimen	Treated	Untreated	Totals
I 300,000 units stat 300,000 units 48 hours 600,000 units 96 hours	634	582	1216
II 300,000 units stat 300,000 units 72 hours	254	288	542
III 600,000 units stat	290	292	582
Totals	1178	1162	2340

rheumatic fever, was not as effective as penicillin in the previous studies. This reduced effectiveness was mirrored in less effectiveness in eradication of the streptococcus from the throat and in reducing the antistreptolysin O response.

Effect of oxytetracycline. Between 10 March 1951 and 4 January 1953, 1,409 patients with exudative tonsillitis/pharyngitis were studied; 713 received 10 to 10.5 g oxytetracycline over a 5-day period and 696 served as untreated controls. Definite rheumatic fever occurred in 12 patients in the control group and in 5 in the treated group. As with chlorotetracycline, there was less reduction in the carriage of streptococci and antistreptolysin O in treated patients than was seen with penicillin treatment.

Effect of benzathine penicillin G (Bicillin). From 4 January to 9 July 1953, 257 patients with exudative pharyngitis were treated with 600,000 to 1,200,000 units of injectable benzathine penicillin at the time of hospital admission; 109 patients were untreated and acted as controls. The effect on the eradication of the carriage of streptococci was dramatic and the reduction of antistreptolysin O formation was marked. Rheumatic fever occurred in 2 control patients and in none of the treated.

Effect of sulfadiazine. Between April 1953 and February 1954, 291 patients received sulfadiazine (2 g initially, followed by 1 g every 6 hours for 5 days), and 264 patients served as untreated controls. Sulfadiazine did not eradicate the streptococcus, and rheumatic fever was not prevented in the treated group.

Factors responsible for the failure to prevent rheumatic fever in treated patients. Experience of treatment of 5,198 cases of group A streptococcus pharyngitis showed that rheumatic fever developed in 76. The primary cause of failure to prevent rheumatic fever was that the infecting organism was not eliminated by treatment. Other factors that may have accounted for some therapeutic failure were the acquisition of a new infection after therapy and, of less importance, a history of previous rheumatic fever or recent streptococcal infection.

Effect of delayed treatment on the occurrence of rheumatic fever. In studies on the role of the streptococcus in the pathogenesis of rheumatic fever, it was shown that rheumatic fever was prevented when penicillin therapy was delayed until 9 days after the onset of the streptococcal infection. Rheumatic fever occurred in 3 of 420 patients receiving delayed treatment and in 20 of 450 who were not treated or received sulfadiazine at the onset of illness. Delayed treatment resulted in elimination of the infecting streptococcus, but the development of antistreptolysin O was not significantly affected. In the sulfadiazine-treated patients, the streptococcus was not eradicated, but the antistreptolysin O response was blunted. In contrast, the control patients developed a full antistreptolysin O response and continued to carry the infecting streptococcus. These studies were interpreted to demonstrate that the persistence of the infecting streptococcus in the host's pharynx was more important in the pathogenesis of rheumatic fever than was the development of humoral antibody. A clear spinoff of these results, however, was the demonstration that the clinician caring for a patient with pharyngitis was not obligated to rush the administration of an antistreptococcal drug but could still prevent rheumatic fever by taking sufficient time to establish accurately the diagnosis of a streptococcal infection before treating.

Effect of the Duration of Antibiotic Therapy on the Eradication of the Infecting Streptococcus and on the Occurrence of Rheumatic Fever. The studies described above indicated that it was important to eradicate

the streptococcus from infected patients to effectively prevent rheumatic fever. These studies also indicated that the 5 to 7 days of treatment used in these studies were not always effective in eliminating the streptococcus. Studies were done using oxytetracycline, penicillin, erythromycin, and sulfisoxazole administered in regimens of 5, 8, and 10 days. The convalescent carrier rates were poorest in the 5-day regimens, better in the 8-day regimens, and best of all if penicillin was given for 10 days. The numbers of patients in these studies were too small to evaluate the effectiveness of these drugs in preventing rheumatic fever.

All of these studies provided the information for the modern management of the prevention of rheumatic fever by treating acute streptococcal infections. The various important points established by these studies are as follows.

- Penicillin G is the drug of choice for treating patients with streptococcal pharyngitis.
- Other antimicrobials tested were not as effective as penicillin, though they did prevent some cases of rheumatic fever.
- Sulfonamides were not effective in eradicating the streptococcus or preventing rheumatic fever.
- The effectiveness of an antibiotic in preventing rheumatic fever was related to its effectiveness in eradicating the streptococcus from the pharynx.
- Treatment for 10 days was more effective than shorter regimens in eradicating the streptococcus.
- Antibiotic therapy delayed as long as 9 days after onset of acute pharyngitis was effective in eradicating the streptococcus from the throat and in preventing rheumatic fever.

Effect of Antibiotic Treatment on Electrocardiographic Changes Associated with Acute Rheumatic Fever and Subsequent Valvular Disease

Shortly after the *Journal of the American Medical Association* publication of the rheumatic fever prevention article, Dr. Lewis Weinstein and colleagues, Boston University, published an uncontrolled penicillin treatment study of scarlet fever in children.[20] Their conclusion that penicillin suppressed clinical symptoms of acute rheumatic fever (ARF) but did not prevent carditis gave Dr. Rammelkamp and the personnel of the Strep Lab great concern. The response of the Strep Lab personified one of Dr. Rammelkamp's scientific characteristics — don't argue, but design a study to answer the question. The study designed was an ambitious one that resulted in the collection between November 1950 and March 1952 of approximately 8,000 electrocardiograms (ECGs) from 1,304 airman with treated (729) or untreated (575) streptococcal sore throat. Each man had six ECGs between day 3 and day 21 after onset of sore throat. Dr. Edward O. Hahn had the primary responsibility for carrying out the study, including the reading of the ECGs. Treatment was either with a tetracycline (196 men) or by one of three schedules of penicillin (533 men). There were no differences in the results among the various treatment schedules. Treatment significantly reduced the proportion with PR interval prolongation by 71% and with any abnormality by 56%. PR abnormality after onset of sore throat appeared on or before the 10th day in 65% to 70% of both the treated and the untreated groups. Definite ARF occurred in 8 (1.1%) and possible ARF in 2 (0.3%) of the treated group, whereas in the control group there were 25 (4.3%) with definite and 4 (0.7%) with possible ARF, a reduction in ARF of 73% by treatment.

These studies established that antibiotic treatment of streptococcal sore throat significantly reduced not only the occurrence of symptomatic ARF but also the frequency of ECG changes pathognomonic for ARF, and thus, presumably for valvulitis and subsequent valvular disease. The data are not inconsistent, however, with a possible suppression of clinical symptoms of ARF in a small proportion of patients. The story did not end here, however.

In 1955, Weinstein et al.[21] published a follow-up of the patients and reported that 8 of 10 children with only ECG changes 7 years previously now had rheumatic valvular disease. This report convinced

Dr. Rammelkamp that a long-term follow-up of treated and untreated airmen was necessary to establish finally that treatment prevented not only ARF but also chronic valvular disease.

In 1967, Dr. Rammelkamp initiated a follow-up of 130 airmen from the ECG study who had either ECG changes only or clinical ARF. This proved to be a frustrating undertaking despite the outstanding cooperation of the Veterans Administration. Some records had been destroyed by fire, some men could not be traced, and some men refused examination. Nevertheless, 90 subjects, 31 treated and 59 untreated, eventually were examined by Drs. Louis Rakita and Robert Bahler, colleagues of Dr. Rammelkamp at Metropolitan General Hospital. The follow-up, 19 to 20 years after the observed clinical state, revealed one person with rheumatic heart disease out of 31 treated and 5 with rheumatic heart disease out of 59 untreated. Although this difference was not statistically significant, the relative risk of 0.41 if treated was of the same order of magnitude as for ECG abnormalities, 0.44.

None of the studies described in this section was published in a peer-reviewed journal. Dr. Rammelkamp was saving them for something to do when he retired. He was working diligently on what was to be a series of five papers, at the time of his death in 1981. Sufficient analysis had been completed by that time so that he was secure in his knowledge that antibiotic treatment of streptococcal sore throat did indeed significantly reduce the occurrence of subsequent rheumatic heart disease.

20. Weinstein, L., Bachrach, L., and Boyer, N. H. Observation on the development of rheumatic fever and glomerulonephritis in cases of scarlet fever treated with penicillin. *N. Engl. J. Med.* 1950, 242, 1002–1010
21. Weinstein, L., Boyer, N. H., and Goldfield, M. Rheumatic heart disease in scarlet-fever patients treated with penicillin. *N. Engl. J. Med.* 1955, 253, 1–7.

The Effect of the Treatment on the Natural Course of Streptococcal Pharyngitis

Effect of chlortetracycline and penicillin. The effects of chlortetracycline and penicillin were evaluated in a controlled study of 495 patients with streptococcal tonsillitis and pharyngitis. Chlortetracycline was slightly more effective than penicillin in lowering the fever and causing rapid subsidence of symptoms. Both drugs exhibited slight action on abnormal physical signs. They were equally effective in inhibiting antibody formation. Penicillin usually eradicated the carrier state, whereas chlortetracycline failed to influence the incidence of convalescent carriers.

Effect of cortisone. Eighty-seven treated and 87 control patients were studied to determine the effect of cortisone on the clinical and immunological response to streptococcal respiratory infections. Cortisone exerted no effect on the symptoms or physical signs of patients. Patients who received cortisone exhibited fever for a longer period of time than the control patients. There was no significant effect on antistreptolysin O titers. The numbers of patients studied were too small to evaluate the occurrence of rheumatic fever.

It is of historical interest that these studies, showing clearly the effect of antibiotics on the course of streptococcal respiratory infections in well-controlled studies, were either ignored or interpreted incorrectly as showing no effect. Several studies done in the 1980s showing the same results were interpreted as demonstrating for the first time the beneficial clinical effects of treating patients with streptococcal tonsillitis and pharyngitis.

Relationship of Serological Type of Streptococcus to Acute Disease and Complications

As far as it can be ascertained, no systematic and comprehensive study of this phenomenon was made; certainly there were no published articles on the subject. In the annual report for 1949 and 1950, the following study was summarized:

> Fifty-four patients with type 5 streptococcal infections, 49 with type 14 infections and 37 with type 24 infections, all untreated, were seen daily and their symptoms and signs recorded. Patients with type 24 infections were associated with a mild disease and recovery occurred more rapidly than observed in infections with types 5 and 14. In studies to be described in a later section on type-specific or anti-M protein antibodies it was shown that specific antibodies to types 5, 6, 14 and 24 differed markedly in the time of appearance while antistreptolysin O responses occurred at approximately the same time. Analysis of the occurrence of rheumatic fever following infections with various types of streptococci at Warren Air Force Base showed a rather constant attack rate of 2-3% in untreated patients. This was in marked contrast to the great propensity of type 12 streptococci to be associated with glomerulonephritis.

Susceptibility to Acute Respiratory Infections, Streptococcal Infections, and Rheumatic Fever

One of the original aims of setting up the Strep Lab was to study the reasons why respiratory infections, streptococcal infections, and rheumatic fever occurred so frequently in the mountain areas of the western part of the United States The first annual report from the Laboratory, 1949 to 1950, contains a short section on this subject as follows:

> All men assigned to Francis E. Warren are interviewed to determine the effect, if any, that the state of residence, history of tonsillectomy, personal and family history of rheumatic fever have on the subsequent attack rates of various respiratory infections and rheumatic fever.

We can find no records, nor are there published articles , regarding any studies on the susceptibility to acute nonstreptococcal respiratory infections. A variety of studies was done to elucidate susceptibility to streptococcal infections and rheumatic fever. Factors important in the epidemiology of the spread of streptococci have been included in the section on epidemiology, as has the lack of effect of tonsillectomy and adenoidectomy. Aside from these observations, no further studies were done on susceptibility to the development of streptococcal infections. Observations on 122 airmen with a positive family history of rheumatic fever and 1,359 with a negative history showed similar attack rates for rheumatic fever. In contrast, airmen with a personal history of rheumatic fever, or who had rheumatic heart disease, had attack rates up to 10 times those recorded for airmen with a negative personal history. Extensive studies were done on the relationship of the formation of streptococcal antibodies to the development of rheumatic fever. In studies on patients with untreated streptococcal infections, 0.8% (7 of 856) with rises of 0 to 120 units of antistreptolysin O developed rheumatic fever, 3.6% (19 of 553) with rises of 121 to 250 units, and 5.5% (30 of 545) with rises over 250 units developed acute rheumatic fever. No relationship was found between initial levels of antistreptolysin O and subsequent attacks of rheumatic fever. Studies done in collaboration with Dr. Wilson measuring the response of patients with rheumatic fever to influenza and cholera antigens showed no differences when compared to normal controls.

Treatment of Rheumatic Fever

The staff of the Laboratory, in collaboration with the medical service of the Warren Air Force Base hospital, carried out the first controlled therapeutic trial of steroids in rheumatic fever in young adults. The Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association

began planning in early 1950 for a multicenter clinical trial of aspirin, cortisone, and adrenocorticotropin (ACTH) in treatment of acute rheumatic fever. Dr. Rammelkamp, a member of the Principal Investigators Subcommittee, actively involved the Laboratory in protocol and procedures development. The trial, one of the earliest multicenter clinical trials and the first multinational trial, involved 12 clinical centers in the United States, Canada, and Great Britain. The only center treating adults was the Warren Air Force Base center.

Acquisition of patients began in January 1951 and continued to June 1952. The studies at Warren Air Force Base included the drug 3-hydroxy-2-phenylcinchoninic acid (HPC) as well as aspirin, cortisone, and ACTH. Dr. James G. Hirsch, Chief of the Medical Service at Warren Air Force Base, and Dr. D. M. Flett, civilian consultant, had begun evaluation of HPC when the planning for the multicenter study began. A quid quo pro for agreement of the medical service to participate in the multicenter study was inclusion of HPC as one of the therapeutic agents to be evaluated. The steering committee of the trial agreed to this and the trial at Warren began with one third of the patients assigned to the HPC treatment, one third to aspirin, and one sixth each to cortisone and ACTH. The HPC arm was discontinued in June 1951 after which there was equal allocation to the remaining three groups. One hundred eighty-six men entered the study. This contrasts with the total of 505 children enrolled at the other 12 clinical centers.

The study at Warren Air Force Base, while following the basic protocol, increased the frequency of clinical, ECG, and laboratory observations. The protocol required clinical observations daily during the first week of treatment, once a week for the remaining 5 weeks of treatment, daily for the first 2 weeks posttreatment, and once during the 3rd week posttreatment. Dr. Rammelkamp and the associate investigators, Dr. Houser of the Strep Lab and Captain Ernest J. Clark of the hospital medical service, decided to make daily observations on all patients for the full 9 weeks. It was also decided that each patient would have the same observer through the observation period. Thus, for 18 months, a day off was a rarity for the observer and leave time was not even a subject for discussion. Dr. Bertrand L. Stolzer joined the Strep Lab in 1952 and participated in the later stage of the study. Dr. Walter Pritchard, Western Reserve University, examined 87% of the patients between the 10th and 16th months after start of therapy.

The course of illness by treatment group in the young adult patients (average age was 20 years) was similar to that observed in the children in the study at the other clinical centers. No one drug exhibited any advantage over the others either during the acute illness or in residual valvular disease at 14-month follow-up. A statement is made in the publication describing the 14-month follow-up that longer term follow-up was to be carried out. None of the available records indicates that such a follow-up did occur.

Additional patients were treated with aspirin or cortisone over the next 2 years. In the annual report for years 1955 and 1956, an analysis of 96 aspirin-treated patients and 72 cortisone-treated patients showed a significant difference in murmurs 8 months after the beginning of therapy. Forty-nine (51%) of aspirin-treated patients had clinically significant murmurs in contrast to 20 (26.3%) in the cortisone group. Most of the difference was attributable to the absence of aortic diastolic murmurs in all but one patient in the cortisone group. It was speculated that the failure of the studies in children to show a similar advantage of cortisone over aspirin was due to the earlier treatment in the airmen. Fifty percent of the young adults began treatment during their 1st week of illness in contrast to a median time of 2 weeks in the children. There is no record that these results were published.

The decision to increase the frequency of ECG and laboratory observations over protocol requirements resulted in information about the course of illness of acute rheumatic fever not previously or subsequently observed in a large cohort of acute rheumatic fever patients. Twenty-five percent of patients had prolonged A-V conduction time at the time of diagnosis; however, the daily or every other day frequency of ECG s showed that 50% of patients exhibited prolonged conduction at some time during the 9 weeks after onset. The frequent antistreptolysin O and erythrocyte sedimentation determinations resulted in analyses unique to the Warren studies.

Shortly before the closing of the Strep Lab, a study of the effect on valvular disease of treatment with large doses of penicillin during acute rheumatic fever was initiated. The small number of cases at Warren and in Cleveland, where a similar study was started, resulted in the shifting of these studies to Chile, where they were carried out by Dr. Rammelkamp after the closure of the Strep Lab.

Epidemiological Studies

Occurrence of Respiratory Infections and Rheumatic Fever at Warren Air Force Base

From the opening of the Strep Lab in January 1949 until its closure in September 1955, hospital admissions for acute respiratory infections and rheumatic fever were monitored. The following table shows these results; unfortunately the results after March 1954 cannot be found.

Hospital admissions for respiratory disease and rheumatic fever at Warren Air Force Base, 1949 to 1954

	Respiratory Admissions					Rheumatic Fever
				Streptococcal Type		
Year	Total	Non-Strep	Strep	Predominant	Common	Admissions
1949	3,846	1,640	2,206	14	24,5	117
1950	3,164	1,311	1,853	14	5	54
1951	5,646	2,060	3,586	14	5,1,6	144
1952	4,843	2,008	2,835	30	14,3,18	125
1953	3,459	1,255	2,204	30	19,3,14	136
1954*	157	101	56	—	5,14,19	1

*1 January to 1 March

During the period for which records are available, 12,740 cases of streptococcal tonsillitis/pharyngitis and 577 cases of rheumatic fever were studied. During the 5-year period, two influenza outbreaks occurred, one in January 1950 and another in January 1953; the attack rates for hospitalized patients were 32 and 46/1,000/week, respectively. The table also shows the types of group A streptococci that predominated and those that were common during that time. The rates for hospitalization for airmen with streptococcal disease were low during the warmer months of the year but rose to high levels during the winter and spring months. Rates of 12 to 15/1,000/week, were not unusual and a rate as high as 24/1,000/week was recorded in February 1951. Surveys for the pharyngeal carriage of streptococci were done in several population groups. For airmen already in place on the base, carrier rates were shown to be from 30% to 38%. At the time, the rate was 30% in airmen and the rate in Cheyenne high school students was 11%; the distribution of streptococcal types in the two groups was similar. In contrast, culture surveys of new arrivals on the base showed rates of 5% to 22%, and the distribution of types was different from those prevalent on the base at that time. The clinical studies that were performed on these patients with streptococcal pharyngitis have been described above. In addition to the studies done on hospitalized patients, a variety of studies was performed on individuals who were not admitted to hospital as a necessary part of the study.

The Effect of Environmental, Host, and Bacterial Factors on the Spread of Group A Streptococci

Extensive studies were performed during the entire period of operation of the Strep Lab to elucidate the factors responsible for the spread of group A streptococci from person to person. The effect of climate on recovery from streptococcal infections was evaluated in a special study in which infected airmen were moved to Tyndall Air Force Base, Florida, and compared to a group remaining at Warren Air Force Base . The effect of tonsillectomy and adenoidectomy was studied as a part of the routine investigation of respiratory infections of airmen at Warren Air Force Base. These studies will be outlined in a subsequent section. The remainder of the studies outlined below was done under carefully controlled conditions in special barracks where the spread of streptococci from infected to uninfected airmen was documented.

The role of the organism. The prevalent or "epidemic" types of streptococci spread more readily than did nonprevalent or "nonepidemic" types, but it was not possible to rule out the role of infection outside of the barracks. Also, the presence of viable streptococci in dry dust did not increase the spread of streptococci. This observation was confirmed by volunteer studies that showed that streptococci in dust dried 4 to 8 hours and inoculated into the pharynx in volunteers did not cause infections, whereas "wet" streptococci did.

The role of the host. The presence of type-specific antibody (anti-M-protein) provided protection to infection with homologous-types of streptococci but not to heterologous types. No evidence was found that tonsillectomy and adenoidectomy reduced the risk to acquiring a streptococcal infection or developing acute rheumatic fever. The severity of the course of streptococcal infections was also not altered by tonsillectomy and adenoidectomy.

The role of human reservoirs. These studies, possibly related to the host, showed that the duration of carriage of streptococci following acute infection was related inversely to the infectivity of the organism for contacts. The likelihood of infection in contacts was directly related to the quantity of streptococci in cultures of the infectious "spreader" and also to the number of streptococcus carriers in the barracks. The increased infectiveness of the nasal carriers was also demonstrated, confirming earlier studies by Dr. Hamburger.

Modes of spread. Studies on this facet of the epidemiology of streptococci were done in an attempt to clarify the importance of the airborne route (by droplet nuclei and dust), compared with more direct contact, which includes spread by large droplets. It was found that the spread of infection was indirectly related to the distance of the carrier from the uninfected airman. These studies, and the failure of dry dust containing viable streptococci placed in barracks to cause infection, indicated that the major mode of spread of streptococci is by close contact and large droplets, thus emphasizing the importance of crowding in the epidemiology of streptococcal infections.

Effect of the environment. Already mentioned was the failure of dust containing streptococci to cause infection. Further confirmation of the lesser importance of dry streptococci in the environment was demonstrated by the failure of blankets containing larger numbers of streptococci, and used by airmen, to cause infection. The role of climate was more difficult to evaluate in that it could not be controlled easily. A solution to this problem was sought by moving a group of airmen just recovering from an untreated streptococcal infection to Tyndall Air Force Base, Florida, and comparing the rate of disappearance of the carrier state to a similar group left in Wyoming. Almost all patients continued to harbor group A streptococci for 16 to 19 weeks, at which time the study was terminated. There was no evidence that the change in climate had any effect on the length of the carrier state or the number of organisms isolated from the pharynx, although nontypable variants appeared slightly earlier and streptococci disappeared from the anterior nares sooner in the group transferred to a warmer climate.

Dr. Krause demonstrated that these nontypable variants were less infectious for monkeys than were the typable strains. Furthermore, the monkeys that were infected subsequently shed streptococci of the same M type as the original infecting strains.

These studies, performed primarily by Drs. Rammelkamp and Wannamaker, demonstrated the role of type-specific immunity in streptococcal infections and showed the importance of the acutely infected host in spreading infection by direct contact or large droplets to susceptible hosts. They also showed the lack of importance of streptococci in the environment and helped explain past failures to control the spread of streptococci by aerosols and ultraviolet light.

Studies on Penicillin Prophylaxis

When it was demonstrated that penicillin, in contrast to sulfadiazine, eradicates the streptococcus from the throat of carriers, is relatively nontoxic to the patient, and does not cause the development of resistant streptococcal strains, a series of studies was undertaken to clarify its role in preventing streptococcal infection and rheumatic fever in armed forces personnel. Initial investigations were divided into two parts: (1) studies comparing the effect of several penicillin regimens on the carrier state, and (2) a study evaluating the effect of oral penicillin on streptococcal carrier and disease rates in large groups of airmen.

For studies on the effect on the carrier state, only confirmed, chronic carriers were included. Oral penicillin, procaine penicillin in oil, and intramuscular benzathine penicillin (Bicillin) in various dosage schedules were compared. Oral penicillin in twice daily doses of 500,000 units or 1,000,000 units for 10 days was effective in total eradication of streptococci. If 1,000,000 units was given twice daily for 5 days, the carrier state was reduced effectively while the drug was being administered, but the organism promptly reappeared in the majority of cases. A regimen of 250,000 units once daily for 10 days was only 75% effective in reducing the carrier state, but most eradications persisted for 3 weeks. Penicillin in oil, 600,000 units every other day for 4 doses (8 to 10 days coverage), eradicated streptococci permanently from all carriers, whereas a single injection of 600,000 units (2 to 3 days coverage) rendered carriers culture negative for 48 hours, after which streptococci promptly reappeared. Intramuscular benzathine penicillin given in a single injection of 600,000 units or two simultaneous injections of 900,000 units each (total 1,800,000 units) was effective in eradicating the streptococcus; the larger dose was probably slightly more effective.

These studies showed that two factors were necessary if the group A streptococcus was to be eradicated from carriers: (1) the dose must be adequate, and (2) penicillin should be administered for a relatively long period of time, 10 days being sufficient in these studies.

In the second part of these studies, 1,000,000 units of oral penicillin G was administered twice daily for either 5 or 10 days to entire squadrons of men; approximately 1,300 men were included in each schedule. The longer dosage schedule was more effective in eradication of the streptococcus and in reducing the incidence of streptococcal infections. Following discontinuation of the drug, there was a gradual loss of effect, and after the 4th week, rates again reached control levels.

After the initial studies had shown the effectiveness of penicillin prophylaxis, three subsequent large-scale trials were done to establish appropriate drug regimens, including duration of protection, and occurrence of drug reactions. In the first study, benzathine penicillin was administered as a single intramuscular injection in doses of 1,200,000 and 600,000 units to 960 and 950 young men. Oral penicillin, in doses of 250,000 units twice daily, was given to 845 men for 10 days. These regimens resulted in sensitivity reactions of 5.21, 2.10, and 1.07%, respectively; reactions were mild and consisted of urticarial skin rashes. All three regimens were effective in eliminating the carrier state, but the larger dose of benzathine penicillin was most effective.

In the second study, a single intramuscular injection of benzathine penicillin was given to 2,214 airmen exposed to epidemic streptococcal infections. There was prompt reduction in streptococcal infections in the group receiving prophylaxis compared with an untreated control group. In the third study, benzathine penicillin G was administered as a single intramuscular injection in doses of 1,200,000, 600,000, and 300,000 units to 246, 255, and 240 men, respectively, during an epidemic of streptococcal pharyngitis. The duration of protection provided by each dose as determined by the development of exudative pharyngitis due to group A streptococcus was 6 to 7 weeks, 4 to 5 weeks, and 1 to 2 weeks,

respectively. All three regimens were equally effective in eradicating streptococci from carriers. These studies confirmed the data obtained in the earlier studies and provided the necessary information to recommend to the Armed Services, appropriate prophylactic regimens in military populations.

Studies on Glomerulonephritis

Although the Strep Lab was developed to investigate the relationship between streptococcal respiratory infections and rheumatic fever, one of the notable observations made was the relationship of infections due to specific types of group A streptococci to acute glomerulonephritis. The first mention of this appeared in the annual report of the Laboratory for 1952 and 1953. The section of that report describing the outbreak of nephritis following type 12 streptococci covers completely the initial observations. We believe this section was written by Dr. Rammelkamp. The nephritogenicity of specific types of streptococci was his "brainchild" and this study was "vintage Rammelkamp." The section follows:

Studies on post-streptococcal glomerulonephritis at the U.S. Naval Training Center, Bainbridge, Maryland.

During the years 1949-1952, only 2 cases of acute glomerulonephritis were observed at Warren Air Force Base Hospital, although the streptococcal and rheumatic disease rates were high during this period. This fact suggests that the nephritogenic capacity of the streptococcal strains prevalent in this area during these years was low. In contrast to this situation, acute glomerulonephritis was frequently observed during the winter of 1951-1952 at the Bainbridge Naval Training Center, cases of this disease outnumbering those of rheumatic fever in a ratio of 2 to 1. It was found that nearly half of the cases of exudative pharyngitis at Bainbridge were due to group A type 12 streptococci, and that there was a close association between infections due to this type of streptococcus and the subsequent development of acute nephritis. During a controlled study involving approximately 400 patients, 15 cases of acute nephritis occurred following type 12 streptococcal infections, while no cases were observed after infections with types 3, 6, or 19 streptococci.

Penicillin therapy of acute type 12 streptococcal pharyngitis in 50 cases appeared to be effective in preventing acute nephritis, while large doses of gamma globulin administered early in the course of the acute pharyngitis in 32 patients did not prevent this complication and may indeed have increased the attack rate.

Addis counts performed each day on each patient indicated that there is frequently a mild transient hematuria during the first few days of acute streptococcal infections; type 12 infections did not differ significantly in this respect from infections due to other types studied at Bainbridge and Warren Air Force Base. After the subsidence of this initial microscopic hematuria, fifteen patients with type 12 infections developed albuminuria, cylindruria and hematuria of marked degree, and were considered to have acute glomerulonephritis. The majority of these patients showed a significant elevation in blood pressure, approximately half had headache, nausea, vomiting or other symptoms commonly associated with this disease, while only 3 had edema. The average interval between the onset of streptococcal pharyngitis and the onset of acute nephritis was 10.5 days in these patients. Twenty-four other patients with type 12 infections showed urinary abnormalities (usually consisting only of microscopic hematuria) and may be classified as possible or mild cases of acute nephritis.

Immunologic studies have revealed no striking difference in antibody response to those patients developing acute nephritis as compared to those with uncomplicated streptococcal pharyngitis. The gamma globulin levels in the patients with nephritis appear to show a greater average rise, and may be a reflection of the rather high incidence of suppurative complications in this group.

Several publications by Dr. Rammelkamp and his coworkers appeared before the appearance of the observations made at the Bainbridge Naval Training Center. These summarize other data that suggest that acute glomerulonephritis tends to follow infection with a limited number of streptococcal

types. In addition to these studies, an outbreak of streptococcal infections associated with type 12 streptococci in a kindergarten in Cheyenne was also described. The attack rate for nephritis of children with type 12 streptococci was unusually high, whereas nephritis did not follow infections due to other types. This prospective study allowed the delineation of the clinical spectrum of nephritis following infection with a nephritogenic strain of streptococcus.

Laboratory Studies

The principale focus of the Strep Lab was on clinical and epidemiological studies, with the laboratory furnishing supporting data for these investigations. The magnitude of this support is shown by figures given in the first annual report for 1949 and 1950. In the first year, approximately 20,000 throat cultures were processed and 6,000 strains of streptococci identified! Many representative strains were lyophilized for future study.

Acute and convalescent bloods by the hundreds were collected, processed, and the sera frozen at –20°C. No records exist of the total numbers of routine laboratory tests performed, but the above figures give some idea of the magnitude of this part of the operation. Although specific laboratory studies were not a major effort of the Strep Lab, several deserve mention.

Use of Maxted's Method for Group Classification of Hemolytic Streptococci

W. R. Maxted's method, using an enzyme produced by a strain of *Streptomyces albus* was compared with conventional methods using 1,010 consecutively isolated strains of hemolytic streptococci. Classification by this method was successful in 998 strains; its accuracy was comparable to other methods, and it was easier to perform.

Type-Specific Streptococcal Antibody

A modification of the bacteriostatic assay for demonstration of type-specific streptococcal antibodies described by Dr. Sidney Rothbard was developed. This consisted of the ability of constant dilutions of test serum in the presence of leucocytes to inhibit varying dilutions of specific types of group A streptococci as demonstrated by the presence (no antibody) or absence (antibody present) of hemolysis after adequate incubation. Type-specific antibody developed in the majority of patients following streptococcal infections. In contrast to antistreptolysin O, this antibody developed slowly and showed marked variation in the time of development according to the infecting type of streptococcus. Treatment with penicillin and chlortetracycline inhibited formation of this antibody, with penicillin causing the greater degree of inhibition. The degree of inhibition appeared to be related to the successful elimination of the organism by therapy. This method of demonstrating type-specific antibody was used in the epidemiological studies described previously.

Studies on M Protein

Several questions regarding M protein were addressed during the life of the Strep Lab. The studies on type-specific bacteriostatic antibodies are described in the section above and the role of these antibodies in host protection has been described in a previous section. In the studies on the effect of climate on clinical streptococcal infections, it was shown that the carriage of streptococci persisted for several

months but that the isolated organisms frequently had lost their M protein and thus were nontypable. Efforts were made to quantitate the M protein of specific isolates so that this phenomenon could be investigated further. These studies are described in an earlier section.

Studies were also done on the determination of type 19 M antibody in sera using the quantitative precipitin test, and with the stimulation of type 19 antibody formation in humans following the subcutaneous injection of purified type 19 M protein. The details of the reaction using rabbit antisera were explored and published. Efforts to immunize volunteers were thwarted by the toxicity of the M protein preparation in some individuals and the insensitivity of the method. In the results recorded in the annual reports, only the occasional patient responded with significant antibody formation.

Miscellaneous Studies

Stool Culture Survey

Stool cultures were taken from approximately 400 airmen with streptococcal pharyngitis, 300 of whom were untreated. A total of 63 patients, or 15.8%, had one or more cultures positive for the same type of streptococcus isolated from the throat culture. There was no correlation between the presence of streptococci in the stool and the gastrointestinal manifestations seen in patients with streptococcal pharyngitis. The two cases of rheumatic fever in the observed patients had negative stool cultures.

This study recalls to the authors certain events surrounding its inception and follow-up. The study was arranged by Dr. Rammelkamp because of a conversation he had had with Dr. Maxwell Finland, who had told Dr. Rammelkamp of the importance of the stool carriage in some of his patients with streptococcal disease. At the completion of the study described above it was presented to Dr. Finland at an annual meeting. His response was: "But Rammel, I said staphylococci, not streptococci!"

Blood Culture Survey

In an effort to study the possible role of streptococcal sepsis in streptococcal pharyngitis and rheumatic fever, 2,164 blood cultures were obtained from 364 patients, four of whom developed rheumatic fever. No streptococci were isolated from the blood of these four patients. Of the remaining 360 patients, 4 had single isolates of group A streptococci but these were different types from those isolated from the throats. In addition, 10 to 15 blood cultures were obtained from each of 24 patients with rheumatic fever, 12 treated with cortisone and 12 with aspirin; no streptococci were isolated. None of these observations supported the thesis that streptococcal bacteremia is associated with the development of rheumatic fever.

Steroid Excretion

Extensive efforts were made to study the steroid excretion in patients with streptococcal pharyngitis who did and did not develop rheumatic fever. Twenty-four-hour collections of urine were obtained from 200 patients during the acute phase of illness and 3 to 4 weeks later in control patients and in those developing rheumatic fever. All urine specimens were transported by air to Cleveland for analysis. Technical, logistical, and administrative problems plagued these studies, and no meaningful results were obtained.

Studies by Outside Scientists

Because of the nature of the clinical and epidemiological studies being carried out at the Strep Lab, it provided the opportunity for and the site of a variety of studies by scientists not directly associated with the Lab.

Studies on Influenza

As noted earlier, two epidemics of influenza occurred during the early years. Acute and convalescent sera were collected on several hundred airmen, and respiratory secretions were obtained on selected cases for isolation of viruses. These studies were done in the Department of Preventive Medicine at Western Reserve University or at the WRAIR. In addition, the airforce personnel at Warren Air Force Base were utilized in a field trial of immunization against influenza in cooperation with Dr. Thomas Francis. The final results of these studies have been lost to the authors.

Chlortetracycline Treatment of Atypical Pneumonia

In cooperation with Captain Hirsch and Colonel Cullen at Warren Air Force Base, the effect of chlortetracycline in primary atypical pneumonia was evaluated. All patients had roentgenologic evidence of pneumonia. Although the numbers of patients were rather small, there was no evidence that treated patients cleared their pneumonia more quickly than occurred in control patients.

Studies by visiting scientists

Between 1949 and 1950, visiting scientists spent several weeks in the Strep Lab working on problems of their own interest. Dr. Wilson studied the inhibition of streptococci by substances present in milk, Dr. Stollerman worked on antistreptolysin S responses in rheumatic and nonrheumatic subjects, Dr. Robert Thompson investigated antihyaluronidase responses, and Dr. William Jeffries collaborated on steroid responses in infected airmen.

VISITORS TO THE LABORATORY

The visiting scientists who spent several weeks working in the Laboratory are listed above. In addition, the Commission on Streptococcal Diseases held a meeting at Warren Air Force Base in November 1950. The annual reports record that the following people were visitors to the Laboratory in some capacity:

Dr. George Badger
Dr. Robert Cruickshank
Dr. John Dingle
Colonel Fratis Duff
General Eubanks
Dr. T. Duckett Jones
Colonel F. J. Knoblauch
Dr. Clayton Loosli
Dr. Gordon Meiklejohn
Colonel Donald Preston
Dr. Walter Pritchard
Colonel Hartwin Schilze

CLOSING OF THE LABORATORY

The Laboratory was closed in September 1955. Because of the significance of this event, the paragraph by Dr. Rammelkamp outlining this event is reproduced below in its entirety.

> The studies conducted since 1 January 1949 at Warren Air Force Base under the joint auspices of the Commissions on Acute Respiratory Diseases and Streptococcal Diseases were terminated on 15 September 1955 and the Laboratory closed. The staff included Captain Alton J. Morris and Dr. Williard C. Schmidt. Captain Morris resigned June 1955 and Dr. Schmidt transferred to Cleveland in September 1955. All of the records, serum specimens and cultures were transferred to Cleveland. Captain Earl C. Marple, USAF, who served as administrator of the unit since 1949, was responsible for the transfer of the records, sera, etc. Because of his contributions to the laboratory, epidemiological studies, and volunteer inoculation, he was recommended for a Legion of Merit Award.

The greatest recognition of the accomplishments of the Laboratory came with the receipt of the Lasker Award in 1954. Because of its significance, the Award is presented in its entirety.

American Public Health Association's
Albert Lasker Group Award

1954

to the

Streptococcal Disease Laboratory
Armed Forces Epidemiological Board
Francis E. Warren Air Force Base
Cheyenne, Wyoming

The Streptococcal Disease Laboratory at Francis E. Warren Air Force Base was established in 1949 under the joint auspices of the Commissions on Streptococcal Diseases and Acute Respiratory Diseases of the Armed Forces Epidemiological Board. From its beginning the Laboratory has been directed by Dr. Charles H. Rammelkamp, Jr. The success achieved is due in great measure to his deep originality, brilliant leadership of a group of young medical corps officers and civilian physicians, and keen awareness of the advantages afforded by military populations in epidemiological analyses. The collaboration of the medical departments of all three military services in the work of the Laboratory, with minor exceptions, has been exemplary.

The Laboratory's contributions to knowledge of streptococcal diseases are in the forefront of advances in preventive medicine in this generation and include: significant information on direct spread of streptococci from man to man with deemphasis of the airborne route lately in fashion; the role of specific antibodies in active immunity of man; the efficacy of antibiotics in preventing rheumatic fever when used to treat the antecedent streptococcal infection; controlled studies of therapy of rheumatic fever, rational chemoprophylaxis of streptococcal infections; and the brilliant addition to our knowledge of acute kidney infections through discovery of strains of streptococci which cause kidney lesions.

Lowell J. Reed, Chairman
The Lasker Awards Committee of the American Public Heath Association

Hugh R. Leavell, President
The American Public Health Association

TWENTY-FIFTH REUNION OF THE STREPTOCOCCAL DISEASE LABORATORY IN 1974

To celebrate the 25th anniversary of the opening of the Strep Lab, a reunion of staff and military dignitaries was held at Warren Air Force Base on 3 October 1974. The program of events is reproduced below.

Program of Events at 25th Anniversary of Strep Lab

Twenty-fifth Anniversary Symposium in
Commemoration of the Streptococcal Disease
Laboratory, Warren AFB, Wyoming

A Festschrift for
Charles H. Rammelkamp, M.D.
Mentor, Colleague, Critic

October 3, 1974

Francis E. Warren Air Force Base, Wyoming

H.B. Houser, M.D. Chairman

9:45 am Welcoming Remarks

Col. Christopher S. Adams, Jr.
Commander, 90th Strategic Missile Wing

Colonel (Dr.) G. Douglas Adamson,
Commander, USAF Hospital,
Francis E. Warren Air Force Base
Leroy R. Maki, Ph.D., President,
Wyoming Heart Association

9:00 - 10:25 Richard M. Krause, M.D., Presiding

9:00 - 9:20 Lewis W. Wannamaker, M.D.
A Search for Better Antibody Tests for Group A and Group B Streptococcal Infections

9:25 - 9:55 W.R. Maxted, Honorary Ph.D.
The Evolution of the Typing System for Group A Streptococci

10:00 - 10:20 R.M. Krause, M.D.
On the Ways Antibodies to Streptococcal Carbohydrates Can Substitute for Myeloma Proteins

10:25 - 10:45 Break

10:45 - 12:00 Chandler A. Stetson, M.D., Presiding

10:45 - 11:05 Melvin H. Kaplan, M.D.
Immunopathologic Studies of Rheumatic Heart Valves

11: 10 - 11:30 Paul P. Cleary, Ph.D.
The Genetic Instability of Serum Opacity and Resistance to Phagocytosis of Group A Streptococci

11:35 - 11:55 Jiri Rotta, Ph.D.
Biological Reactions to Peptidoglycan of Group A Streptococcus and Other Bacteria

12:00 - 1:30 Lunch, Officers Open Mess

1:30 - 3:30 Floyd W. Denny, Jr., M.D., Presiding

1:30 - 2:00 Hugh C. Dillon, M.D.
Post-Streptococcal Glomerulonephritis: The Pyoderma Era

2:05 - 2:25 Harold B. Houser, M.D.
Observations on the Epidemiology of Rheumatic Fever

2:30 - 2:50 Gene H. Stollerman, M.D.
The Relative Rheumatogenicity of Group A Streptococcal Strains

2:55 - 3:25 Aziz El Kholy, M.D.
The Pattern of Acquisition and Spread of Group A Streptococci in Families

3:30 - 4:00 Break

4:00 - 5:10 Harold B. Houser, M.D., Presiding

4:00 - 4:20 Loring Brock, M.D.
Recreational and Vocational Evaluation and Planning for the Young Cardiac Patient

4:25 - 4:45 Floyd W. Denny, Jr., M.D.
Mycoplasma pneumoniae Disease: An Immune Paradox

4:50 - 5:10 Chandler A. Stetson, M.D.
Crystal Gazing

6:00 - 7:30 Reception, Officers Open Mess

7:30 p.m. Dinner, Officers Open Mess

Lewis W. Wannamaker, M.D., Presiding
Edward A. Mortimer, M.D.
Frederick C. Robbins, M.D.
Maclyn McCarty, M.D.

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Richard M. Krause, M.D., Professor, The Rockefeller University, New York, New York

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Gene H. Stollerman, M.D., Professor and Chairman, Department of Medicine, University of Tennessee, Memphis, Tennessee

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Acknowledgements

The Organizing Committee thanks Dr. Edwin H. Lennette, President; Lt. Col. Duane G. Erickson, Executive Secretary; and Miss Elizabeth Gilbert, Executive Assistant, of the Armed Forces Epidemiological Board for their support and assistance which made this symposium possible.

The following organizations have generously contributed financial support for the symposium:
Abbott Laboratories, North Chicago, Illinois
Eli Lilly and Company, Indianapolis, Indiana
The Upjohn Company, Kalamazoo, Michigan
Wyeth Laboratories, Philadelphia, Pennsylvania

The Committee acknowledges with thanks the efforts of Colonel Christopher S. Adams, Jr., Colonel Godfrey D. Adamson, Colonel John Brashear and the personnel of Francis E. Warren Air Force Base.

The Committee
H.B. Houser, Chairman
R.M. Krause, Co-Chairman
F.W. Denny
L.W. Wannamaker

Publications

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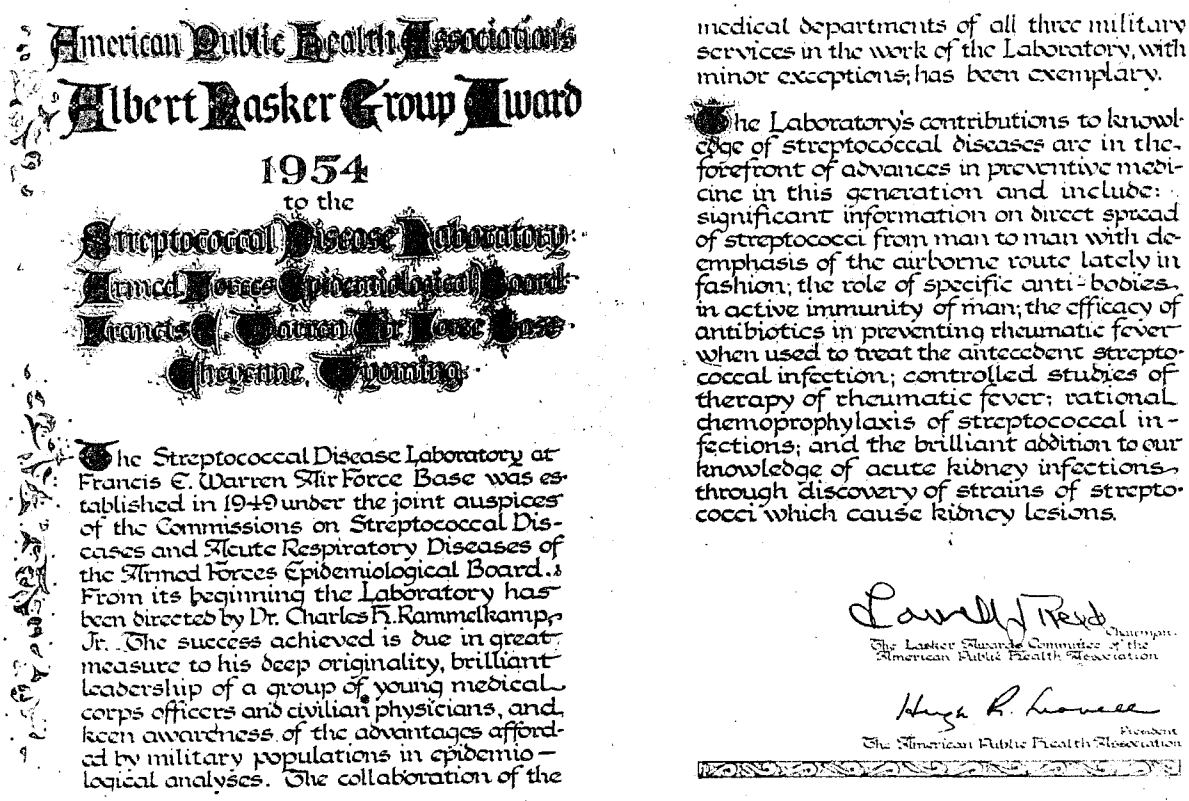
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EFFORTS OF THE CSSD TO CONTROL STREPTOCOCCAL INFECTIONS AND RHEUMATIC FEVER IN THE ARMED FORCES

Treatment of acute streptococcal infections with penicillin, as demonstrated by the Streptococcal Disease Laboratory, prevented rheumatic fever in treated persons; however, this method by itself did not control epidemic rheumatic fever. The majority of military personnel presenting with rheumatic fever had no antecedent clinical infection or did not present to sick call for diagnosis and treatment. The mass penicillin prophylaxis studies initiated in 1951 at the Streptococcal Disease Laboratory and at the Great Lakes Naval Training Station demonstrated conclusively the ability to control epidemic streptococcal disease and rheumatic fever in recruit and trainee populations. These studies led to recommendations from the CSSD for control of rheumatic fever and streptococcal disease. The recommendations were for appropriate laboratory identification of β-hemolytic streptococci, treatment of streptococcal infections, and epidemiological surveillance with guidelines for initiation of targeted mass prophylaxis.

The ad hoc committee organized in 1953 was formalized in 1955 as the Committee on Prophylaxis of Streptococcal Infections in the Armed Forces. The Committee annually reviewed current developments in studies of prophylaxis and transmitted recommendations to the preventive medicine officers of the three services. An initial recommendation for oral penicillin as the first choice for prophylaxis



American Public Health Association's
Albert Lasker Group Award
1954
to the
Streptococcal Disease Laboratory
Armed Forces Epidemiological Board
Francis E. Warren Air Force Base
Cheyenne, Wyoming

The Streptococcal Disease Laboratory at Francis E. Warren Air Force Base was established in 1949 under the joint auspices of the Commissions on Streptococcal Diseases and Acute Respiratory Diseases of the Armed Forces Epidemiological Board. From its beginning the Laboratory has been directed by Dr. Charles H. Rammelkamp, Jr. The success achieved is due in great measure to his deep originality, brilliant leadership of a group of young medical corps officers and civilian physicians, and keen awareness of the advantages afforded by military populations in epidemiological analyses. The collaboration of the medical departments of all three military services in the work of the Laboratory, with minor exceptions, has been exemplary.

The Laboratory's contributions to knowledge of streptococcal diseases are in the forefront of advances in preventive medicine in this generation and include: significant information on direct spread of streptococci from man to man with deemphasis of the airborne route lately in fashion; the role of specific anti-bodies in active immunity of man; the efficacy of antibiotics in preventing rheumatic fever when used to treat the antecedent streptococcal infection; controlled studies of therapy of rheumatic fever; rational chemoprophylaxis of streptococcal infections; and the brilliant addition to our knowledge of acute kidney infections through discovery of strains of streptococci which cause kidney lesions.

Chairman
The Lasker Awards Committee of the
American Public Health Association

President
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was eventually superseded by a recommendation of intramuscular benzathine penicillin as the drug of choice for prophylaxis. The latter recommendation came only after allaying the concern of the military services that there would be an unacceptable level of sensitivity reaction to the injectable penicillin. The issue of sensitivity reactions was debated at the AFEB Board meeting of May, 1957, as the following excerpt from the minutes indicates:

> Dr. Rammelkamp expressed concern over the effect that a TB Med on the importance of the problem of sensitization to penicillin might have on the use of this drug in the prophylaxis and prevention of streptococcal infections. Dr. Rammelkamp stated his belief that prophylactic use would be stopped but that therapeutic use would not be decreased. Dr. Feller agreed and expressed the opinion that streptococcal infections were not being adequately treated at the present time. Dr. Shepard pointed out that the benefits from penicillin outweighed the chances of difficulty at the present time. Dr. Kern suggested the oral administration of penicillin which he believed to be a safer product. Dr. Wood emphasized that the administration of any drug depended on judgment and that a TB Med could not give that. Dr. Eisen stated that Dr. Pillsbury did not have in mind a directive that would jeopardize therapeutic and prophylactic administration of penicillin. Dr. Dingle asked that Dr. Eisen convey to Dr. Pillsbury the sense of the discussion and requested that the Commission on Cutaneous Diseases outline a proposed circular letter or TB Med.

This issue was not settled so far as the military was concerned until the AFEB held a special meeting in early 1959 directed specifically to the question of penicillin reactions and their relation to prophylaxis and treatment of streptococcal infections. The consensus from the meeting was that the risk of anaphylaxis with intramuscular penicillin in a population screened for sensitivity was negligible and that the slightly increased occurrence of other sensitivity reactions did not outweigh the marked advantage of injectable benzathine penicillin over oral penicillin in control of epidemic disease.

The Committee, initially advisory to the preventive medicine offices of the three services, assumed a more active role in 1957. Epidemic streptococcal disease and rheumatic fever continued to occur at recruit and other military bases, and it was apparent that the recommendations for control were not being implemented. At the May 1957 meeting of the Board, Dr. Rammelkamp proposed that an annual seminar be presented for orientation of personnel at the military base level. Dr. Rammelkamp's preamble statements and recommendation follow:

A) The Commission was concerned with reports of epidemics of streptococcal infection and rheumatic fever at several military establishments. It should again be emphasized that the occurrence of multiple cases of rheumatic fever at a single military base indicates failure to apply presently available preventive measures. Every effort should be made to assure adequate reporting, so that immediate control measures can be established without delay.

B) The Commission would like to call to the attention of the Military Services the fact that approximately four percent of men entering the services give a personal history of a previous attack of rheumatic fever. Since the risk of recurrent rheumatic fever following a streptococcal infection in these men is 20 percent, some consideration as to the desirability of prophylaxis should be entertained. Certainly, good preventive medical practices would include prophylaxis for those men assigned to areas where the risk of streptococcal infection is high.

C) In view of the fact that streptococcal infections, nephritis, and initial and recurrent attacks of rheumatic fever may be prevented by prophylactic measures, a vigorous effort should be made to protect military personnel from these diseases. It is therefore recommended that the Surgeons General establish an annual joint orientation seminar for selected medical personnel from those bases where these diseases have been a recurrent problem for the purpose of establishing adequate control measures. The Commission on Streptococcal Diseases would welcome the opportunity to participate in such a program.

The recommendation was accepted and the Committee on Prophylaxis of Streptococcal Infections was charged with the responsibility to organize and conduct the annual seminars. The first seminar was held at Fort Carson in the fall of 1957. Annual seminars continued, with the last at Lowry Air Force Base in 1970 .

The seminars were held on military bases selected by one of the three services on a rotating basis. Attendees were primarily preventive medicine and laboratory officers from Army, Navy, and Air Force bases. The average military attendance per year for the 14 seminars was 42.5 persons with 22.7, 6.9, and 12.9 persons, respectively, from the Army, Navy, and Air Force.

The seminars were usually 1 day in length and consisted of a series of presentations by Committee members and reports from military bases selected by the committee from responses to questionnaires sent to the bases after the prior respiratory disease season. The following program for the seminar at Lackland Air Force Base on 10 October 1961 is illustrative of the content and format of the seminars.

Program for Seminar at Lackland Air Force Base, 10 October 1961

Conference on Prophylaxis of Streptococcal Infections
Lackland Air Force Base, Texas
10 October 1961

0900-0910	Introduction	
0910-0920	Streptococcal Infections and the Armed Forces	Dr. C. H. Rammelkamp
0920-0945	Epidemiology of streptococcal infections in military populations	Dr. H. B. Houser
0945-1005	The clinical diagnosis of streptococcal infection and rheumatic fever	Dr. R. H. Krause
1005-1030	The laboratory diagnosis of streptococcal infection	Mr. P. F. Frank
l030-1100	Theoretical and practical aspects of treatment of streptococcal infection	Dr. E. A. Mortimer, Jr
1115-1130	Methods of prophylaxis of streptococcal infection	Dr. H. F. Wood
1130-1200	Discussion	
1200-1330	Lunch	
1330-1400	The development of streptococcal prophylaxis programs at Great Lakes Naval Training Center	Capt. L. F. Miller
1400-1430	Discussion	
1430-1500	Epidemic streptococcal disease, 1960-61, at Lowry Air Force Base, Colorado	Dr. S. S. Shkolnik Dr. R. B. McFarland
1500-1530	Epidemic streptococcal disease 1960-61, Camp Pendleton and San Diego, California	Capt. R. A. Mount
1530-1700	Discussion	

In subsequent years, the seminars were occasionally 1.5 days in length because other Commissions found the seminars useful for education related to a current problem in the military. For example, the 12th annual seminar at Great Lakes Naval Training Station had formal presentations by Theodore Eickhoff, Committee on Meningococcal Infection, CARD, and Fred Davenport, Director, Commission on Influenza.

The seminars had immediate impact on the control of epidemic rheumatic fever. Lowry Air Force Base, averaging 30 cases of rheumatic fever per year for the 4 years preceding the 1957 seminar, initiated a surveillance and mass prophylaxis program following the 1957 seminar and had only five cases of rheumatic fever in the 1957 and 1958 season. No further cases were identified at Lowry until 1967 and 1968, when a nonhemolytic group A streptococcus became epidemic and seven cases of rheumatic fever occurred before the laboratory at Lowry became alerted to its presence. Amarillo Air Force Base, Texas, also experienced a high rheumatic fever rate, 7/1,000/year, in the 1967 and 1968 season, prob-

ably attributable to the nonhemolytic strain. Recruits from Amarillo sent to Lowry for training are likely to have introduced the strain to Lowry.

Lackland Air Force Base, Texas, also instituted a streptococcal program following the 1957 seminar and, after averaging 33 cases of rheumatic fever for the previous 3 years, reported only three cases in 1957 and 1958. Other Army Air Force and Navy bases with traditionally high rates of rheumatic fever reported small numbers of cases as the surveillance and treatment programs were put in place.

The only installations with continuing problems in the early 1960s were the San Diego Naval Training Center and Marine Corp Recruit Depot and Great Lakes. San Diego averaged 13.8 cases per year between 1961 and 1965, and Great Lakes had 45 cases in the two seasons 1961 to 1962 and 1962 to 63. Although these numbers were nowhere near the hundreds of cases occurring in the late 1940s and early 1950s, the Navy felt it was not achieving the desired results from surveillance and intervention when indicated. Ft. Leonard Wood had initiated routine administration of benzathine penicillin to all incoming recruits rather than relying on the recommended surveillance program. The Navy instituted similar routine prophylaxis programs at Great Lakes and Parris Island in the early 1960s and at San Diego following the 1965 seminar at San Diego. No cases of rheumatic fever were reported by Great Lakes and San Diego in 1966 to 1967 or 1967 to 1968.

Whether the decline in rheumatic fever over the years of the seminars was the result of the control programs rather than a secular change in risk for rheumatic fever was a topic of discussion at each seminar during the mid to late 1960s. A rapidly decreasing incidence of rheumatic fever was also occurring in the civilian population at the same time. The Committee was concerned with the routine administration of benzathine penicillin to incoming recruits with its attendant sensitivity reactions, particularly if there no longer were indications for its use. At the behest of the Committee, Ft. Leonard Wood did abandon its routine prophylaxis program in 1967 to 1968 and 1968 to 1969 and followed the surveillance guidelines. Although there was no evidence that the surveillance program was less effective, the increased amount of time required by the preventive medicine officer and his staff for surveillance prompted the base to return to the routine prophylaxis program. Routine prophylaxis for new recruits became firmly entrenched as a procedure by the Navy and persisted into the 1980s.

After the 1970 seminar at Lowry Air Force Base, the Committee raised the question of continuation of the seminar with the military medical officers in attendance at Lowry. Their consensus was that the annual review of streptococcal disease and its sequelae served a useful purpose for continuing education of military medical officers in the recognition and control of streptococcal diseases. Accordingly, the recommendation of the Committee was to hold the seminar in 1971. The Navy extended an invitation for the meeting to be held at Orlando Naval Training Center, Florida, in the fall of 1971. This announcement at the spring meeting of the CSSD, 11 March 1971, brought a response from the preventive medicine offices of the three services that, before concurring in plans for a 1971 seminar, they planned to examine the need for another seminar.

At the Executive Meeting of the AFEB on 19 May 1971, Lieutenant General H. B. Jennings, Jr., Surgeon General, United States Army, requested that "the symposium (seminar). . . be modified this year by making it a two-sided re-evaluation, ad hoc committee or study group. . . . and to totally reevaluate the streptococcal disease problem, establish its relative priority and plan future requirements."

The Committee accepted this recommendation, cancelled plans for the seminar, and scheduled a meeting for reevaluation on 29 November 1971 at WRAIR.

A planning meeting was held in Washington, DC on 14 July 1971. In attendance at this meeting were Dr. Gustave Dammin, President, AFEB; Dr. Wannamaker, Director, Commission on Streptococcal and Staphylococcal Diseases; Colonel Bradley W. Prior, Executive Secretary, AFEB; Committee members, Dr. Houser, Chairman, and Drs. Dillon, Edward A. Mortimer, Jr., and Krause. Colonel P. Nugent, Captain C. H. Miller, and Colonel J. H. Greenberg represented the Preventive Medicine Offices of the Air Force, Navy, and Army, respectively. Lieutenant Colonel R. E. Winter, and Major C. T. Kaelber accompanied Colonel Greenberg. Colonel D. W. Sample and Major M. A. Moussa represented Headquarters, United States Army Medical Research and Development Command.

The meeting resulted in a memorandum from the AFEB to the three Surgeons General requesting information about streptococcal problems and programs during 1970 and 1971 for discussion at the 19 November meeting. The memorandum also concisely described the purposes of the annual seminar format as follows: Memorandum dated 26 July 1971 from Bradley W. Prior, Colonel USAF, MC, Executive Secretary, AFEB to the Surgeons General of the Army, Navy, and Air Force.

> These include continuing education of the military personnel responsible for control and management of streptococcal disease and its sequelae in populations of recruits or others, translation of research and development activities into application in the field, and exhibition and discussion of field problems with the members of the committee. The last has been an extremely important aspect of the seminars since it has provided an opportunity for annual monitoring of streptococcal experience at the individual military base level.

Military representatives in their presentations emphasized the decreasing and low rates of acute rheumatic fever in the services. The incidence rates per 100,000 military personnel per year for acute rheumatic fever in 1970 were 9, 8, and 3.8 respectively, for the Army, Navy, and Air Force. The Army reported 125 cases in dependents in 1970 and the Air Force in the same period had 44 dependent cases. All three services agreed that continued surveillance of streptococcal infections was indicated but that the seminar was not an effective or efficient way to disseminate information to those people intimately concerned with surveillance. The discussion then centered on alternatives to the seminar that would continue the input of the members of the CSSD and would also permit the CSSD to remain abreast of current problems in the military.

Each preventive medicine officer was requested to submit a specific plan for continuation of the education and information program of the seminar relative to his or her own service. At the executive meeting of the CSSD the next day, the Navy, through Commander Comer, affirmed its stand that the seminar was not necessary and that it did not plan to propose any formal mechanism to replace it. Colonel Nugent stated that the Air Force adopted the Navy position. Colonels Greenberg and Ward stated that the Army planned to submit a specific proposal that would include the appointment of consultants to the preventive medicine officers of eight basic recruit training bases plus two others. The Army followed through on its proposal, and several members of the Committee and CSSD visited selected bases as consultants to The Army Surgeon General for the next 2 to 3 years.

The activities of the Committee on Prophylaxis of Streptococcal Infections resulted in the CSSD having the closest contact with preventive medicine officers in the field of any of the AFEB Commissions. Implementation of streptococcal control programs was hastened by this contact with a resultant savings in morbidity for all the Armed Forces during the late 1950s and early 1960s.

The members of the Committee on Prophylaxis of Streptococcal Infections in the Armed Forces follow:

F. Stephen Chapman, Ph.D.
Floyd W. Denny, M.D., Chairman, 1955 to 1961
Hugh C. Dillon, M.D.
Paul F. Frank, M.S.
Harold B. Houser, M.D., Chairman, 1961 to 1971
Richard M. Krause, M.D.
Robert B. McFarland, M.D.
Edward A. Mortimer, Jr., M.D.
Willard C. Schmidt, M.D.
Gene H. Stollerman, M.D.
Harrison F. Wood, M.D.

MAJOR SCIENTIFIC ACCOMPLISHMENTS OF WORK SUPPORTED BY CONTRACTS OF THE CSSD

The Streptococcus

Epidemiology

The epidemiology of streptococcal throat and skin infections and their relationship to pharyngitis and acute glomerulonephritis. Major observations were made on this subject in the laboratories of Drs. Wannamaker and Dillon. The Wannamaker studies were performed in Minneapolis, with the field observations being made at the Red Lake Indian Reservation in northern Minnesota; Dr. Dillon's observations were made in Birmingham, Alabama. Because the overall results from both sites were quite similar, they will be reported together. Extensive studies at both sites indicated that the epidemiology and bacteriology of throat and skin infections were different and, in general, the two clinical entities were not related. It was shown that group A streptococci were carried on normal skin before onset of pyoderma and that this was not related to throat carriage. The types of group A streptococci isolated from the two sites were different and special, such as the 8/23/Imp.19 and 3/13/B complexes, and were found frequently in pyoderma. Superimposed staphylococcal infection occurred frequently in the pyoderma patients but not in pharyngitis patients. Pyoderma occurred in late summer and early fall, frequently in very young children, whereas pharyngitis occurred more frequently in older children in the winter and early spring. Acute glomerulonephritis followed infection of the skin with special "nephritogenic types" that were different from pharyngitis "nephritogenic types"; rheumatic fever did not occur following streptococcal pyoderma. The latent period of nephritis following pyoderma was much longer, 21 days, than the latent period following pharyngitis, 10 days. Dr. Dillon and his group demonstrated that reduced serum complement was an especially good diagnostic test in poststreptococcal glomerulonephritis. Studies by both groups delineated effective treatment regimens. Following the demonstration by Dr. Wannamaker that anti-deoxyribonuclease (DNase) B was a useful diagnostic test in streptococcal infection, both groups confirmed this usefulness in diagnosing the presence of a previous streptococcal infection in patients with acute glomerulonephritis. This was an especially helpful observation when it was demonstrated that antistreptolysin O responses were poor following pyoderma, probably because of lipids in the skin. These seminal observations, made by investigators working under contracts with the CSSD, provided much of the information regarding streptococcal skin infections that remains valid at this time.

Food-borne epidemic of streptococcal pharyngitis at the Air Force Academy. One of the largest food-borne epidemics of streptococcal infection on record occurred among cadets of the U. S. Air Force Academy in the spring of 1968. Over 1,200 cadets (38.4% of the population) developed symptoms of streptococcal pharyngitis. Drs. Wannamaker and Dillon and their coworkers did an extensive surveillance of 214 convalescent cadets. Most developed antibodies to antistreptolysin O and deoxyribonuclease B. Intramuscular benzathine penicillin was more effective than oral erythromycin in eradicating streptococci; there were 1.5% failures with the penicillin compared with 15% with erythromycin. The infecting streptococcus was a type 12 by T-agglutination but no nephritis occurred, suggesting that the strain was not nephritogenic. No rheumatic fever occurred, suggesting that the antibiotic treatment of all infected personnel was effective prevention.

Streptococcal infections at Loring Air Force Base, Maine. Studies were done at this base by Dr. Krause because of the prevalence of streptococcal infections at an installation that was not a training command — that is, there were few recruits and the personnel resembled civilian populations. It was found that the family was the site of spread of many streptococcal infections; the attack rates of positive cultures in families from a positive index case were five times greater than in families of a negative index case. These studies emphasized the importance of the family in the spread of infections in the military.

Streptococcal infections in Cleveland school children. Studies done by Rammelkamp and his group in conjunction with an extensive rheumatic fever prevention program in northeast Ohio clearly showed the importance of the school as a site of spread of group A streptococci. These studies confirmed the studies at Loring described above and those done in Nashville, Tennessee, and Casper, Wyoming.

Basic Laboratory Observations

Studies on the bacteriolytic properties of streptomyces albus and its action on hemolytic streptococci. These studies reported in a preliminary way in the annual report of 1949 and 1950 are cited only because they are done by Dr. Avery working with Bertram E. Sprofkin at Vanderbilt University after Dr. Avery had retired from the Rockefeller Institute. One of the authors (F. D.), also at Vanderbilt during the 1950s, had many delightful visits with Dr. Avery before his death.

Group A streptococcal M protein. Considerable interest was placed on M protein, and the antibodies formed in response to it following streptococcal infection, because these antibodies protect against subsequent infection due to the same type of streptococcus. Dr. Lancefield showed years before that rabbits and mice injected with whole streptococcal cells developed type-specific, or anti-M-protein antibodies. Studies performed at the Strep Lab showing the protective effects of these antibodies have been described in a previous section. Unfortunately, attempts to develop a vaccine that was suitable for human use were largely unsuccessful. Dr. Krampitz from Western Reserve University had a contract for several years in an effort to purify M protein so that the events leading to its synthesis could be elucidated. Great difficulty was encountered in trying to purify the protein without losing serological activity. It was learned that group A streptococci stripped of their M protein by enzymes were still viable and capable of making new M protein without subsequently dividing.

Dr. Barkulis, University of Illinois, used a cell-wall preparation of group A streptococci in an attempt to develop an effective vaccine. His preparation was effective in rabbits, but when given to volunteers, only 4 of 24 vaccinated subjects developed type-specific antibodies.

Studies by Willard Schmidt of Western Reserve University using an M protein preparation from type 19 streptococci were begun at the Streptococcal Disease Laboratory and have already been described. These were continued in Cleveland after the Strep Lab closed, but were discontinued after only 2 of 22 children developed bactericidal antibodies after vaccination.

Dr. Stollerman, then at Northwestern University, appeared to have more success than others at developing a satisfactory M protein preparation for use in humans. Using type 12 cell-wall vaccines prepared by the method of Dr. Barkulis, he showed that rabbits, and subsequently humans, developed recall responses when vaccinated at a time when antibodies following previous natural infection had fallen to low or undetectable levels. Subsequent use of the vaccine in subjects who failed to develop type-specific antibody following type 12 infection showed antibody conversion in 4 of 5 children. Similar results were shown in children using a type 5 vaccine. Further studies, however, showed very poor responses in individuals who had not been previously infected with the homologous type of streptococcus, even when water-in-oil emulsions were used in the vaccines.

It is of interest that efforts are still being made currently to produce vaccines to group A streptococci, but none have been successful.

The type-specific long-chain formation by group A streptococci. In his studies on M protein and vaccines, Dr. Stollerman made the interesting observation that the most virulent strains of streptococci produced the shortest chains and that these strains, in the presence of type-specific antibodies, produced long chains. He subsequently developed this observation into a test for type-specific antibodies that gave results comparable to those using the bactericidal test.

The relationship of biological to epidemiological characteristics of group A streptococci. This is the title of a long-term contract held by Dr. Wannamaker at the University of Minnesota. Dr. Wannamaker's bril-

liant observations on the epidemiology of streptococcal respiratory infection in airmen at Warren Air Force Base, and the epidemiology of skin and throat infections in Native Americans on the Red Lake Reservation, have already been described. In addition, his laboratory was the center for important observations on the biology of group A streptococci and the relationships of these streptococcal biological products to streptococcal respiratory and skin infections, rheumatic fever, and acute glomerulonephritis.

Possibly the most noteworthy observations concerned the deoxyribonucleases produced by group A streptococci. Dr. Wannamaker and his coworkers described four such enzymes termed A, B, C, and D. All were thoroughly investigated, but DNase B and the antibodies produced to it proved the most useful in the clinical setting. It was shown that anti-DNase antibodies developed as frequently as did antistreptolysin responses in patients with streptococcal pharyngitis. In contrast, patients with streptococcal pyoderma developed anti-DNase antibodies much more frequently than antistreptolysin O. Further studies on streptococcal antibodies compared the responses in patients with uncomplicated pharyngitis to those responses of patients with rheumatic fever and nephritis. The decline of antibodies in these groups was carefully delineated.

In addition to the studies on the deoxyribonucleases, Dr. Wannamaker's group also made observations on diphosphopyridine nuclease (DPNase), the streptokinases, the lipoproteinases, the serum opacity factor, nicotinamide adenine dinucleotidase (NADase), and on the RNA and protein content of cell walls.

This group made some of the first observations on the use of fluorescent antibody to identify group A streptococci in laboratory cultures and in specimens from infected patients. Extensive studies were done on patients in an attempt to identify reliable methods for differentiating patients with an acute streptococcal infection from those with the streptococcal carrier state.

It is appropriate to note here that the Wannamaker laboratory was the site of many more important observations than those cited here and was a haven for the development of a whole new generation of young scientists who now maintain prominent positions throughout the world.

Streptococcal L forms. The possible role of streptococcal cells without walls in the pathogenesis of the complications of streptococcal infections interested several investigators, and the CSSD supported contracts to investigate this phenomenon in several laboratories. In general, these investigations proved fruitless and eventually were discontinued. Dr. Harry Gooder at the University of North Carolina chose the group D streptococcus as a model and did extensive studies on the optimal conditions for the induction, stabilization, and growth of L forms in this group of streptococcus. Dr. Mortimer at the University of New Mexico chose mouse and hamster models for the study of group A L forms and concentrated particularly on hamster skin infections. Preliminary studies on group A L forms were also described from the laboratories of Drs. Dillon and Wannamaker. As with the other studies, these trials provided no new insights into streptococcal infections and their complications.

Streptococcal proteinase. This contract, under the direction of Stanford Moore of the Rockefeller Institute, was of interest to the CSSD because Stuart Elliott had earlier described this enzyme that had the ability to destroy the serologic activity of the type-specific antigen, M protein, of group A streptococci. Dr. Elliott had determined that it could be prepared in gram quantities; it was ideal for studies of the mechanism of its action on streptococcal cells and of the comparative biochemistry of proteins. Over a period of several years, these workers determined the chemical nature of the enzyme, including its amino acid composition, and the portion of the molecule that is the site of immunological specificity.

Streptococcal group carbohydrate. Several investigators explored the chemical nature and immunological response to the group-specific carbohydrates of streptococci. Dr. Krause, working at the Rockefeller Institute, studied the chemical composition of streptococcal cell walls and showed that groups A, B, C, D, and G were similar. He also demonstrated that mice immunized with cell-wall vaccines were protected on challenge. In continuation of these studies, he was able to show that humans developed antibody to group A carbohydrates. He also found that certain rabbits immunized with streptococcal vaccines developed large amounts of electrophoretically uniform gammaglobulin with specificity to the group carbohydrate. Dr. Krause was able to selectively breed rabbits that were exceptionally good antibody producers. Dr. Schmidt, working with Dr. Rammelkamp, studied differ-

ent methods of preparing cell walls and, determining their fate in mice, he was able to detect soluble, serologically active group A carbohydrate in tissue extracts and in urine.

Penicillin Treatment of Acute Rheumatic Fever

Studies to evaluate the effect on acute rheumatic fever of prolonged treatment with large doses of penicillin were carried out in Chile by Dr. Rammelkamp and coworkers Mortimer, Rakita, and Krause. The rationale for these studies was based on indirect evidence — failure to prevent rheumatic fever if the infecting organism is not eradicated by treatment and reduction in risk of rheumatic fever even after delay of streptococcal treatment for 9 days, and on theory — persistence of living streptococci in heart tissues is related to the pathogenesis of valvular disease.

Three studies were conducted in Santiago, Chile, in 1956, 1958, and 1961. Patients admitted to three Santiago hospitals with acute rheumatic fever were randomly assigned to penicillin treatment or no penicillin treatment. All patients were treated with aspirin. Intramuscular aqueous sodium penicillin G, 500,000 units every 4 hours , was administered for 1 week, followed by aqueous procaine penicillin G, 600,000 units every 12 hours , for 2 weeks, and 1,200,000 units of benzathine penicillin G on the 22nd day. Benzathine penicillin prophylaxis was given to all patients on the 43rd day and continued until the time of the 1-year follow-up.

The results of the first study of 66 patients, while not showing significant difference overall in valvular disease at 1 year, did show a favorable effect of penicillin on valvular disease in subjects with "nonfixed" valvular disease at the time of admission. The latter finding led to a rather optimistic reporting of the effectiveness of penicillin treatment. It was decided that the study should be replicated, so an additional 63 patients were studied in Santiago in 1958. No protective effect of penicillin treatment was observed. A third study of an additional 97 patients was carried out in 1961. The results were similar to those of the second study. When all studies were combined, the 122 penicillin-treated patients with 1-year follow-up had no significant difference in valvular disease from the 120 control patients.

Although these studies produced negative results, they further illustrated the methodical approach of Dr. Rammelkamp to defining the role of the streptococcus in the pathogenesis of rheumatic fever.

Nephritis

The studies of Dr. Rammelkamp leading to the definition of nephritogenic types of group A streptococci were discussed above in the section on the Streptococcal Disease Laboratory. In the winter of 1955 and 1956, an outbreak of approximately 6,500 cases of acute nephritis occurred in Japan; Dr. Rammelkamp established that type 12 group A streptococcus was the epidemic strain.

Dr. Rammelkamp felt strongly that poststreptococcal acute glomerulonephritis was a self-limited disease and rarely, if ever, progressed to chronic nephritis. His feeling was based in part on two follow-up studies he carried out. The first was a study of 61 patients with untreated type 12 infections observed during the nephritis epidemic at Bainbridge in 1952. Twelve patients with acute nephritis and 47 without nephritis were studied 15 to 48 months after the type 12 infection. One patient was considered to have chronic nephritis. This patient had had mild poststreptococcal hematuria with occasional systolic pressure above 140 mm Hg. In the second study, Dr. Rammelkamp evaluated 42 persons who had had post–scarlet fever nephritis 5 to 20 years earlier. None of these persons had evidence of chronic nephritis. Also, he and Schmidt were unable to detect type-specific antibody to nephritogenic types in the sera of persons with chronic nephritis. Lively debate between Drs. Rammelkamp and David P. Earle took place over several years around the issue of progression of acute glomerulonephritis to chronic nephritis. The other major studies of poststreptococcal nephritis supported by the CSSD were those of Drs. Wannamaker and Dillon, described above in the epidemiology of skin infections.

In connection with a meeting of the CSSD 3 March 1969, a symposium on "Skin Infections and Nephritis" was held jointly with the Commission on Cutaneous Diseases. Mr. David Taplin, of the

latter Commission, presented the problem of pyogenic skin infections with a potential threat of nephritis in servicemen in Southeast Asia.[22] Reports were also made on the large outbreaks of nephritis following skin infections in Trinidad (Dr. Tom Parker, Central Public Health Laboratory, London, and Drs. David Earle, John Finklea, and Elizabeth Potter, Northwestern University) and the ongoing studies of Drs. Wannamaker in Minnesota and Dillon in Alabama. The peculiar biologic characteristics of cutaneous streptococci were discussed by Maxted, Central Public Health Laboratory, London.

The work of Drs. Rammelkamp, Wannamaker, and Dillon in elucidating the epidemiology, clinical course, and natural history of poststreptococcal acute glomerulonephritis is one of the outstanding achievements of the CSSD.

22. Allen, A. M., Taplin, D., and Twigg, L. Cutaneous streptococcal infections in Vietnam. *Arch. Dermatol.* 1971, 104, 271–280.

Balkan Nephropathy

In 1960, the existence of endemic nephropathy in sharply localized areas in Yugoslavia was brought to Dr. Rammelkamp's attention by a visit from Dr. Jacob Gaon of the medical faculty of the University of Sarajevo.

The high prevalence of chronic renal disease in areas that had high rates of "Trench" nephritis in both world wars was particularly intriguing to Dr. Rammelkamp. Intensive epidemiological, clinical, and laboratory studies were carried out by Drs. Rammelkamp, Robert Griggs, and Philip Hall in cooperation with Yugoslavian epidemiologists and nephrologists. The disease involved thousands of native people living along the tributaries of the Danube River in several Eastern European countries. In Yugoslavia, it was established that the disease was chronic, frequently led to death from uremia, and the initial lesions involved the renal tubules. Epidemiological studies suggested an environmental rather than genetic cause. The disease occurred predominantly in farmers and their children and could be related to the farming of specific fields. Dr. Hall developed a relatively simple and specific diagnostic test that could identify early disease (radio immunodiffusion of β-2 microglobulin in urine). Development of this test took a year longer than anticipated when urine specimens, carefully collected by Dr. Hall in October 1964, were stolen from the luggage compartment of an airport bus in London. He and Dr. Dammin were the first to use biopsy material to describe the histopathology of early stages of the disease. Association of the disease with transitional cell tumors of the renal pelvis and ureters was established.

Based on the epidemiological and pathophysiological observations, hypothetical etiologic agents were investigated. These included lead, cadmium, arsenic, leptospira, plant exotoxin, silica salts, and bacterial infection. None of these agents could be associated with the disease. These studies, supported by the CSSD through 1971, have continued into the 1990s under the direction of Dr. Hall, Case Western Reserve University.

Transfer Factor

Basic studies on transfer factor by Drs. Tillett and Lawrence of New York University were supported through the CSSD from 1949 until it was discontinued. Dr. Tillett remained the principal investigator during this entire time, but it was clear early on that Dr. Lawrence was a prime mover. These studies had their genesis in the observations by Dr. Merrill W. Chase that the cellular transfer of tuberculin was possible in guinea pigs. At Dr. Tillett's suggestion, Dr. Lawrence was able to successfully transfer cutaneous delayed hypersensitivity to tuberculin from immune human donors to nonimmune recipients using blood leucocytes. This then led to the transfer of delayed sensitivity to streptococcal products in humans. This was prompted by interest in rheumatic fever and the possibility that cardiac damage could be the result of inflammatory hypersensitivity reactions of the delayed type. Transfer in humans was readily accomplished using intact streptococci, streptokinase and streptodornase (SK-

SD), and group A streptococcus M protein. Although the role of delayed hypersensitivity in streptococcal infections and rheumatic fever has never been delineated, the studies by Drs. Lawrence and Tillett opened up the scope of the entire field. The perfection of in vitro assays of cellular immunity and the discovery of the lymphokines advanced the field still further and led subsequently to the understanding that cellular immunity was at the core of understanding the mechanisms of allograft rejection; tumor immunity; prevention and recovery from intracellular infections caused by viruses, mycobacteria, and fungi; and some types of autoimmune responses.

It is of interest to note that Drs. Lawrence and Tillett, challenged by doubtfulness of Dr. Charles Smith of the CARD, developed a coccidioidin-specific transfer factor that transferred delayed reactivity and cellular immunity to coccidioidin from immune to nonimmune subjects. This form of therapy was shown to be of benefit in the management of patients with disseminated, amphotericin-resistant coccidioidomycosis.

Dr. Lawrence's reminiscences of the work on transfer factor and the CSSD are recorded in Appendix 7.

THE STAPHYLOCOCCUS

The first contracts for support of staphylococcal research were awarded by the CSSD in 1958 and 1959 to Dr. Cluff, The John Hopkins University, Dr. Ekstedt, Northwestern University, and Dr. Wannamaker. Dr. Rammelkamp incorporated staphylococcal studies in his streptococcal contract at this time also. Dr. Keiichi Goshi, Medical College of Virginia, was supported from 1963 to 1965. Dr. Joseph E. Johnson, University of Florida, assumed responsibility for Dr. Cluff's contract when Dr. Cluff moved to the University of Florida in 1966. In addition, Dr. Dillon's studies of impetigo included definition of the role of staphylococci in impetiginous infections. Research related to the staphylococcus was in three areas: hospital epidemiology, host response to infection, and the biology of the organism.

Hospital Epidemiology

Drs. Rammelkamp, Mortimer, and Emanuel Wolinsky carried out a series of studies at Cleveland Metropolitan General Hospital that provided new and basic knowledge on the mechanisms of transmission of pathogenic staphylococci in the hospital setting. Their initial studies were conducted in a specifically designed newborn nursery unit to determine whether infant-to-infant spread was direct (heavy droplets projected short distances) or indirect (airborne droplet nuclei or dust). (These studies were carried out at a time when almost all newborns in this hospital became colonized by the time of their hospital discharge.) An index infant, known to be a nasal carrier of bacteriophage-typable strain of staphylococcus, was introduced into the unit. Uninfected newborns were admitted to one of six bassinets set at fixed distances from the index baby. Nurses who handled the uninfected infants had no direct contact with the index case. Ninety-five uninfected infants were admitted over an 8-week period. These brilliantly conceived studies showed that infant-to-infant spread was rare but there was a high rate (35%) of acquisition of strains carried by two of the three nurses. This and subsequent studies showed that the major mechanism of transmission was from the hands of personnel both to an infant and among infants. Handwashing by personnel markedly reduced spread but still permitted a significant amount of transmission.

A study of transmission of staphylococci from mothers to their newborn infants indicated that this was an infrequent occurrence during the 4 or 5 days of hospital stay, but that about one third of the infants acquired their mother's organism after returning home. Other studies in the nursery at Cleveland Metropolitan General Hospital indicated that fomites were not important vectors for transmission

unless they were contaminated by large numbers of staphylococci from open draining lesions. Intervention in a nursery epidemic by application of bacitracin ointment to the umbilicus and groin of newborns was demonstrated to control the epidemic with disappearance of the epidemic strain from the nursery.

Dr. Rammelkamp's group also studied the importance of the carrier state as a source of staphylococci in wound sepsis. Two hundred sixty-nine patients in male and female surgical wards were studied over a 2-year period. It was demonstrated that nasal and skin carriage were significant risk factors for wound colonization and wound sepsis. Skin carriage was the most important carrier site for wound colonization, but profuse nasal carriage put patients at increased risk of wound sepsis. The results indicated that measures designed to control the carrier state or to isolate the wound from the external environment should reduce wound sepsis by approximately 50% .

Dr. Cluff and coworkers carried out extensive studies at The John Hopkins Hospital in the epidemiology of staphylococcal infections in hospitalized patients, nursing mothers, pediatric patients, and hospital personnel. One of their interesting but unexplained observations was a seasonal variation in staphylococcal postsurgical wound infections. Over a 4-year period, the rate of infections was highest in January of each year. There was no evidence of similar distribution of infections by season in other hospital patients or in hospital personnel. Their longitudinal studies documented the disappearance of the type 80/81 strain, the "virulent" epidemic strain of the late 1950s, and its replacement in the hospital by the dominance of another strain, type 54. They speculated that increased use of neomycin for preoperative preparation of the bowel was responsible for the emergence of the new type. Occasioned by a marked increase in isolations of *Staphylococcus aureus* from the stools of pediatric patients, Dr. Cluff studied the intestinal flora of 38 children in a Baltimore orphanage. These studies, conducted longitudinally over a 6-month period, showed that *S. aureus* was present in only 4% of the cultures. *S. albus* in combination with a Gram-negative bacillus was present in 72% of the specimens. It was also demonstrated that only 13% of the children had persistence of the same stool flora over a 3-month period.

Host Response to Infection

Dr. Ekstedt studied natural and acquired resistance to the staphylococcus in mice. He showed that mice were protected from infection by immunization with whole cell vaccines from either living or killed cells. Cell walls, crude fractions, teichoic acid, and the Smith surface antigen also offered protection under certain experimental conditions. Germ-free mice were naturally highly resistant to infection. Dr. Ekstedt produced a form of runt disease in neonatal mice by repeated intraperitoneal injection of washed, killed staphylococci during the first 48 hours after birth. (Injection of killed streptococci also caused runt disease.) Germ-free mice were resistant to the runting phenomenon but could be induced to runt by adding homologous antiserum to the vaccine. Dr. Ekstedt also identified a serum antistaphylococcal factor in human, horse, and rabbit sera as a water-soluble globulin; it was not present in bovine serum. This factor had a direct lethal and lytic action on *S. aureus* and certain other bacteria.

Dr. Goshi evaluated the relationship of serum anti-alpha hemolysin to a variety of localized and more general staphylococcal skin infections. He concluded that there was no correlation between the level of anti-alpha hemolysin and either chronicity and healing of infection or phagocytosis and bacterial killing.

Drs. Wannamaker and Quie, using a rabbit model with necrotic skin lesions induced by subcutaneous injection of *S. aureus*, evaluated the effect of rabbit, bovine, and human platelets injected into the lesions. An obvious and consistent enhancement of infection occurred. This enhancement was also present in animals that had recovered from infection with a staphylococcal antibody response. A full-thickness experimental burn model in rabbits was developed by Drs. Wannamaker and Bascom F. Anthony to evaluate bacterial interference in mixed infections. Several strains of staphylococci were equally capable of colonizing and preventing superinfection by other inoculated staphylococci. Cross infection was also prevented. They demonstrated that this resistance was a local phenomenon, because

new burns on an animal could be infected with a second strain of staphylococcus. Heat-killed organisms did not cause interference. Although the mechanism of interference was not established, they concluded it was not by direct antagonism, nor was there any evidence of a humoral or tissue factor. Drs. Wannamaker and Adnan Dajani studied experimental skin infections in the hamster as a model for impetigo. They determined that the inoculum size required for infection was much greater for staphylococci than for group A streptococci and that there was great variation among staphylococcal phage types in their ability to cause infection.

Dr. Cluff and coworkers also used rabbit models for a series of experiments evaluating the effects of endotoxin, nonspecific inflammation, and anti-α-hemolysin immunity. Endotoxin, derived from *Escherichia coli* or *S. flexneri*, transiently increased the infectivity of pathogenic staphylococci but not of nonpathogenic organisms. The endotoxin effect was inhibited by α-hemolysin antibody if the latter was administered within 4 hours of the endotoxin. The increased susceptibility could be transferred to normal recipients via whole blood but not plasma. Transfer could not be made to endotoxin-tolerant animals. Endotoxin also inhibited leucocyte migration into the peritoneum after injection of staphylococci. The effect of endotoxin could be duplicated by the use of benzenes or nitrogen mustard when they caused leukopenia. They attributed the endotoxin effect to the resultant granulocytopenia. Nonspecific skin inflammation caused by thermal, chemical, or bacterial injury; arthus reaction; or tuberculin was more susceptible than normal skin to infection with intracutaneously injected staphylococci. However, if inflammation was present more than 2 to 3 days before injection, there was often increased resistance to infection. Repeated skin infections also enhanced infectivity and the extent and severity of infection. Rabbits immunized against α-hemolysin showed inhibition of necrosis and reduced growth of staphylococci in the experimental skin lesions. Renal abscesses after intrarenal injections of staphylococci were also prevented by α-hemolysin antibody.

Dr. Johnson, at the University of Florida, evaluated the effectiveness of lysostaphin in the rabbit burn model. He demonstrated that intravenous lysostaphin improved staphylococcal infections as effectively as methicillin treatment. Topical ointment was partially effective.

Studies in human hosts were rather limited. Dr. Cluff studied human cutaneous reaction to α-hemolysin or its toxoid. All subjects had demonstrable antibody to α-hemolysin. The skin reaction observed was biphasic, with early wheal and erythema followed by induration. The early response was similar to that elicited with ragweed or timothy antigens, ie, a polymorphonuclear response. The secondary response of induration was histologically not distinguishable from that of tuberculin, ie, a perivascular mononuclear response. The size of the secondary response was inversely related to the magnitude of the anti-α-hemolysin serum titer. Drs. Quie and Wannamaker compared serum levels of α-hemolysin and staphylokinase antibodies in children and adults with staphylococcal lesions, in normal persons and in maternal cord sera. They demonstrated placental transmission of both antibodies, active antibody to both by 2 years of age, and similar antibody responses after either infection or colonization.

Dr. Quie and coworkers identified the inability of polymorphonuclear leucocytes to kill ingested *S. aureus* in patients with chronic granulomatous disease of childhood. This x-linked disease is characterized by recurrent severe infections, hepatosplenomegaly, and eczematoid skin lesions. The leucocytes from these children demonstrated normal in vitro phagocytosis, but the usual degranulation did not occur and the organism persisted intact in the leucocyte. It was subsequently shown that there is a defect within the phagocyte in oxidative metabolism and production of reactive oxygen radicals during phagocytosis.

Biology of the Staphylococcus

Drs. Quie and Wannamaker were curious about the mechanism of the Muller phenomenon, the appearance of numerous discrete satellite areas of clearing around colonies of coagulase positive staphylococci grown on agar plates containing rabbit serum and an indicator such as hemoglobin or whole red cells. They determined that the phenomenon could be duplicated in a sterile system by supernates

of staphylococcal broth cultures. They could also reproduce the phenomenon when purified plasminogen was substituted for whole serum. The Muller factor was demonstrated to be identical with previously described staphylokinase. Their experiments with both rabbit and human sera showed that human sera usually failed to produce (inhibited) the Muller phenomenon in the sterile system. A method for quantitative measurement of the inhibitor was developed. They concluded that the heat-stable inhibitor, in the gammaglobulin fraction of serum, was probably antistaphylokinase.

Drs. Quie and Ralph Williams investigated the antiphagocytic effects of staphylococcal protein A. Strains producing large amounts of protein A tended to be resistant to phagocytosis. Protein A itself inhibited phagocytosis in in vitro systems. They demonstrated that protein A combines nonspecifically to the Fc portion of human immunoglobulin (Ig) G and blocks or alters the opsonic site. Dr. Quie later showed that protein A affects nonspecific heat-labile opsonins as well as specific opsonins. In other work, he also described microcolonies (G variants) of *S. aureus* that were not pathogenic for mice. These organisms were readily engulfed by phagocytes but showed little cytotoxicity. He suggested that the G variants may be persistent in latent infections.

Dr. Dajani, in Wannamaker's laboratory, described a bactericidal staphylococcal product from phage type 71 that was effective against streptococci of groups A, C , and D, pneumococci, and corynebacteria. The product did not lyse organisms, but caused cessation of protein and DNA synthesis, and disintegrated RNA with cytoplasm dissolution, leaving cell-wall ghosts. The product, a heat-resistant and trypsin-sensitive protein of high molecular weight, was considered to be a bacteriocin. Dr. Dajani demonstrated that the bacteriocin could be neutralized by both immune and nonimmune sera. The nonimmune factor was heat labile and present in all human and guinea pig sera tested. The immune serum factor was heat stable.

Although the staphylococcal research sponsored by the CSSD did not have the major impact of its streptococcal research, several fundamental observations in the field were made and are included in current texts. There are the transmission studies by Dr. Rammelkamp and coworkers, the studies of immunity by Dr. Ekstedt, the risk factors for hospital infections described by Dr. Cluff, and the role of staphylococci in bullous impetigo elucidated by Dr. Dillon. The work of Dr. Quie in phagocytosis not only was important relative to staphylococci, but also in launching his outstanding career in the field.

STUDIES ON MISCELLANEOUS SUBJECTS

Dr. Hamburger, of the University of Cincinnati College of Medicine, studied the effect of streptokinase and streptofornase (streptococcal deoxyribonuclease [SK-SD]) in experimental meningitis in monkeys. Early experiments determined the doses of SK-SD that could be tolerated after intrathecal or intracisternal injection. Difficulty was encountered in establishing reproducible infection in monkeys using a variety of bacteria. Pneumonococcus type 1 was too virulent and *Haemophilus influenzae* not virulent enough. *Pseudomonas aeruginosa* proved to be most satisfactory and was used in experiments that demonstrated that SK-SD had some effect in reducing the exudative response in meningitis. Finally, experiments showed the importance of streptodornase in the enzymatic digestion in vitro of experimentally produced meningeal exudates.

Dr. Stetson, of New York University, pursued a variety of studies while under contract to the CSSD. The first of these involved the motility of leucocytes; he showed that the mechanism of movement was due to the alternating formation of crystal masses in pseudopods and then their solution, with resulting locomotion. He then studied the effects of radiation injury on host defenses, including the probable lack of a role of bacterial endotoxins in the illness resulting from whole-body irradiation in mice. Finally, he studied the role of murine isoantigens in homograft rejection.

Dr. Lewis M. Thomas, of New York University, held a contract for several years to study the pathogenesis of rheumatic fever. He elected to do this by investigating connective tissue pathology and

physiology and several experimental models in immunopathology. First, he studied the human placenta as a homograft. This was followed by the demonstration of the similar actions of papain and vitamin A on cartilage matrix, suggesting that vitamin A had its effect by activating proteolytic enzymes. Allergic encephalomyelitis, immune paralysis following excessive doses of pneumococcal polysaccharides, hemotransplantation and phagocytosis, and leukocyte metabolism were also included in his investigations. His studies on the role of lysosomes in tissue injury and the effect of cortisone in stabilizing lysosomes suggested a mechanism for the "antiinflammatory" action of cortisone. These observations were extended to studies of the role of lysosomes in endotoxin shock, traumatic shock, hypersensitivity reactions, streptococcal infection, and Shwartzman and Arthus reactions; all suggested that instability of lysosomes (or their counterparts, the granules of leukocytes), with release of lysosomal hydrolases into tissues or blood, may be important in the pathogenesis of tissue damage. Dr. Thomas also investigated the role of two mycoplasma species, *M. gallisepticum* and *M. neurolyticum*, in the central nervous system diseases of turkeys and mice, respectively, showing that these organisms, without cell walls, produce lesions by damaging blood vessels. Finally, he studied the relationship of the cell-wall carbohydrate of group H streptococci to group A carbohydrate.

Dr. Wood, of Johns Hopkins University, had a contract entitled "Factors influencing the phagocytic capabilities of polymorphonuclear leukocytes." The purpose was to identify the nonspecific phagocytosis-promoting factor (PPF) in rat serum that causes *Streptococcus pneumoniae* and *Streptococcus pyogenes* to be ingested at an accelerated rate by homologous leukocytes and the comparative phagocytic capabilities of granulocytes obtained from normal rats and from rats with chronic alloxan-induced diabetes mellitus. These studies showed that the phagocytosis-promoting effect of normal serum may be due to the combined opsonizing action of low titer antibodies to somatic antigens shared by many bacterial species and to some of the components of the complement system fixed to the bacterial cell surfaces as a result of the somatic antigen-antibody reactions. The studies in diabetic rats suggested that the depression of antibacterial defenses that occurs in the hyperglycemic, nonacidotic, diabetic host is due to the hypersomolarity of the inflammatory exudate, resulting from the hyperglycemia.

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*Listed under publications of the Strep Lab.

SECTION 4—APPENDIX 1

COMMISSION MEMBERSHIP

Commission on Hemolytic Streptococcal Infections (1941 to 1946)
Commission on Streptococcal Diseases (1948 to 1960)
Commission on Streptococcal and Staphylococcal Diseases (CSSD) (1960 to 1973)

Directors

Martin H. Dawson	1941 to 1942
Chester S. Keefer	1942 to 1946
William S. Tillett	1948 to 1954
Charles H. Rammelkamp, Jr.	1954 to 1957; 1959 to 1968
Armine T. Wilson	1957 to 1959
Lewis W. Wannamaker	1968 to 1973

Deputy Directors

Floyd W. Denny, Jr.	1958 to 1963
Lewis W. Wannamaker	1963 to 1968
Richard M. Krause	1968 to 1973

Members and Associate Members

	Member	Associate Member
Anthony, Bascom F., M.D., University of California, Los Angeles		1970 to 1973
Avery, Oswald T., M.D., Vanderbilt University	1948 to 1954	
Ayoub, Elia M., M.D., University of Florida		1971 to 1973
Barkulis, Samuel S., M.D., University of Illinois		1954 to 1959
Bernheimer, Alan W., Ph.D, New York University	1954 to 1966	
Bliss, Eleanor A., Sc.D, John Hopkins University	1941 to 1945	
Bloomfield, Arthur L., M.D., Stanford University	1942 to 1945	
Boisvert, Paul L., M.D., Yale University	1942 to 1944	
Bunim, Joseph J., M.D., New York University	1949 to 1954	

Chapman, S. Stephen, M.D., University of Minnesota		1968 to 1971
Cluff, Leighton E., M.D., John Hopkins Hospital	1960 to 1973	1957 to 1960
Coffey, Julia M. New York State Department of Health	1941 to 1945	
Cooke, Jean V., M.D., Washington University	1941 to 1945	
Coons, Albert H., M.D., Harvard Medical School		1954 to 1959
Dawson, Martin H., M.D., Columbia University	1941 to 1944	
Denny, Floyd W., Jr., M.D., Vanderbilt University	1954 to 1971	1952 to 1954
Dick, George F., M.D., University of Chicago	1941 to 1945	
Dillon, Hugh C., Jr., M.D., University of Alabama	1969 to 1973	1968 and 1969
Dubos, Rene J., M.D., The Rockefeller Institute	1958 to 1960	
Eagle, C. Phillip Harry, M.D., Albert Einstein College of Medicine		1949 to 1954
Ebert, Robert H., M.D., University of Chicago		1954 to 1957
Fox, Eugene N., Ph.D., University of Chicago		1968 to 1973
Glaser, Robert, M.D., University of California		1957 to 1960
Gotschlich, Emil C., M.D., University of Connecticut Medical Center		1971 to 1973
Hamburger, Morton, Jr., M.D., University of Cincinnati		1948 to 1954
Hirsch, James G., M.D., The Rockefeller Institute	1963 to 1970	
Hook, Edward W., M.D., University of Virginia		1962 to 1968
Houser, Harold B., M.D., Western Reserve University	1962 to 1973	1954 to 1957
Kaplan, Melvin H., M.D., Western Reserve University		1954 to 1971
Keefer, Chester S., M.D., Boston University	1941 to 1946	
Koenig, M. Glenn, M.D., Vanderbilt University		1964 to 1973
Krampitz, Lester O., Ph.D., Western Reserve University		1954 to 1957
Krause, Richard M., M.D., The Rockefeller Institute	1963 to 1973	1960 to 1963
Kuttner, Ann G., Ph.D., Irvington House	1941 to 1946	

Lancefield, Rebecca C., Ph.D., The Rockefeller Institute	1954 to 1973	
Lawrence, H. Sherwood, M.D., New York University		1956 to 1973
Lockwood, John S., M.D., University of Pennsylvania	1941 to 1946	
Lyall, Harold W., Ph.D., New York State Department of Health	1941 to 1945	
Lyons, Champ, M.D., Harvard Medical School	1941 to 1945	
Lyttle, John D., M.D., Columbia University	1941 to 1945	
Markowitz, Milton, M.D., University of Connecticut		1971 to 1973
McCarty, Maclyn, M.D., The Rockefeller Institute	1954 to 1973	1950 to 1954
Meleney, Frank L., M.D., Columbia University	1941 to 1945	
Miller, C. Phillip, M.D., The University of Chicago	1948 to 1954	
Moody, Max D., M.D., National Communicable Disease Center		1968 to 1971
Morse, Stephen, M.D., The Rockefeller Institute		1964 to 1968
Mortimer, Edward A., M.D., University of New Mexico	1969 to 1973	1962 to 1969
Quie, Paul G., M.D., University of Minnesota		1964 to 1973
Rammelkamp, Charles H., Jr., MD Western Reserve University	1948 to 1973	
Rantz, Lowell A., M.D., Stanford University	1941 to 1945	
Rogers, David E., M.D., Vanderbilt University	1958 to 1968	
Rose, Harry M., M.D., Columbia University	1941 to 1945	
Schmidt, Willard C., M.D., University of Rochester		1956 to 1972
Schwentker, Francis, F., M.D., The Rockefeller Institute	1941 to 1942	
Seal, John R., M.D., CDR, MSC, USN, Great Lakes Naval Training Center		1956 to 1958
Seastone, Charles V., M.D., University of Wisconsin		1942
Seegal, David, M.D., Columbia University	1941 to 1945	
Sherman, James M., Ph.D., Cornell University	1941 to 1945	
Slade, Hutton D., M.D., Northwestern University		1957 to 1961

Smith, Lawrence W., M.D., Philadelphia, Pennsylvania	1941 to 1944	
Spink, Wesley W., M.D., University of Minnesota	1941 to 1946	
Stetson, Chandler A., M.D., New York University		1954 to 1966
Stollerman, Gene H., M.D., Northwestern University	1970 to 1973	1956 to 1970
Swift, Homer F., M.D., The Rockefeller Institute	1942 to 1946	
Thomas, Lewis, M.D., New York University	1958 to 1963	1963 to 1970
Tillett, William S., M.D., New York University	1941 to 1946 1948 to 1966	
Top, Franklin H., M.D., Wayne State University	1942 to 1945	
Trask, James D., M.D., Yale University	1941 to 42	
Updyke, Elaine L., Sc.D., National Communicable Disease Center	1957 to 1966	
Vosti, Kenneth L., M.D., Stanford University		1970 to 1973
Wannamaker, Lewis W., M.D., University of Minnesota	1954 to 1973	
Wesselhoeft, Conrad, M.D., Boston, Massachusetts	1941 to 1946	
Wiley, Grove G., M.D., Alfred I. duPont Institute		1960 to 1971
Wilson, Armine T., M.D., Alfred I. duPont Institute	1948 to 1964	
Wise, Robert I., M.D., Jefferson Medical College		1958 to 1966
Wolinsky, Emanuel, M.D., Case Western Reserve University	1971 to 1973	1968 to 1971
Wood, Harrison F., M.D., Yale University		1957 to 1963
Wood, W. Barry, M.D., John Hopkins University	1950 to 1954	1948 to 1950

SECTION 4—APPENDIX 2

SURVEY OF SITES TO LOCATE THE STREPTOCOCCAL DISEASE LABORATORY

The choice of Fort Francis E. Warren, Wyoming, as the site for the location of the Streptococcal Disease Laboratory (later Warren Air Force Base) was a very important determinant of the success of the Laboratory. The document describing the survey of sites for that location is included here in its entirety.

10 October 1948

To: The Surgeon General, Department of the Army (through Preventive Medicine Division)
Subject: Survey of sites for location of study of streptococcal diseases and rheumatic fever in the Rocky Mountain Area

1. During World War II, a high incidence of streptococcal infection and rheumatic fever occurred in posts in the Rocky Mountain area. With certain of these posts having been reopened for the training of troops, the probability is very good that streptococcal infections will again occur in epidemic form in them. The experience at Fort Francis E. Warren, Wyoming, during the Spring of 1948, where approximately 45 cases of rheumatic fever occurred in a total student population of about 4500, is a strong indication of what may be expected unless means can be devised for prevention.

It has been considered highly desirable to set up a long term study of streptococcal infections and rheumatic fever at a post in the epidemic area in order to study the reasons why these diseases occur so commonly there, to devise and test possible prophylactic measures, and to make a detailed clinical and epidemiological study of the relationship of streptococcal infection to rheumatic fever.

In order to select the most advantageous site for this study a tour of the following posts in the Rocky Mountain area was made between 9 and 13 October 1948: Fort Francis E. Warren, Wyoming (9, 10 and 11 Oct.); Lowry Field, Colorado (11 and 12 Oct.); Camp Carson, Col. (13 Oct.). The investigating party consisted of the following members: Dr. William S. Tillett, Director, Commission on Streptococcal Diseases, Army Epidemiological Board; Dr. John H. Dingle, Director, Commission on Acute Respiratory Diseases, A.E.B.; Dr. Charles Rammelkamp, Commission on Acute Respiratory Diseases, A.E.B.; Colonel Thomas E. Patton, M.C., Preventive Medicine Division, Office of the Surgeon General; Major Louis Kossuth, M.C., Air Surgeon's Office; Colonel Pluennoko, M.C., Surgeon, Technical Training Command, U.S.A.F.; Lt. William Brink, M.C.; and Dr. Colin M. MacLeod, President, Army Epidemiological Board.

2. Of the three posts visited, it was considered that Fort Francis E. Warren affords certain important advantages not shared by Lowry Field and Camp Carson, which would appear to make it the most suitable site for the study. Fort Warren is used by the Technical Training Command of the Air Force for training in a wide variety of skills. These include the following: administrative courses (stenographers, clerk typists); engineering construction and equipment; engineers (draftsmen and surveyors); automotive maintenance; utilities (plumbers, carpenters). The following is a list of the present courses with load and flow:

Table I

Course No.	Course	Load	Entry	Duration	Site of Training
013	Diesel mechanics	120	4 wks	16 wks	Indoors
050	Carpenter	300	4	12	Outdoors mainly
014	Automotive (Sept.)	1200	1	25	Indoors
059	Construction tech	20 (up to 144)	6	28	60% outdoors
070	Draftsman	300	6	18	Indoors

078	Electrician	120	6	18	Indoors
081	Engineman operator	240	4	16	Outdoors
107	Photolithographer	12	6	12	Indoors
164	Plumber	70–80	4	16	Indoors
166	Powerman	20–42	6	18	70% indoors
201	Sheet metal	120	6	18	Indoors
213	Stenographers	220	2	26	Indoors
227	Surveyors	60	6	18	80% outdoors
256	Welders	20	4	16	Indoors
319	Construction equip mechanics	60	16	32	90% indoors
322	Refrigeration mechanics	20	4	12	Indoors
359	Heavy construction operators	350	4	16	90% outdoors
405	Clerk typist (Aug.)	1850	1	12	Indoors
727	Water supply	12	4	8	90% indoors
4805	Officers — Automotive repair	3	3	10	Indoors

From Table I it can be seen that training takes place both indoors and outside, depending on the course; that certain large classes (e.g., automotive maintenance, stenographers) will be on the post for approximately 6 months, whereas the large clerk typist course lasts for 12 weeks only.

Students coming to Fort Warren derive from Lackland and Shepard Fields, in the main. They have had 13 weeks basic training there. Other students are on detached service from other Air Force installations (seasoned troops), or are the so-called career plan students. The last two groups are relatively small.

Troops are housed in cantonment type barracks, in general close to the school buildings. Floor spacing of 72 sq. ft. per man is in practice now, but with conversion to a 2 shift basis shortly, space per man will be reduced to 60 sq. ft. The present hospital facilities are sufficient for a post population up to 12,000 men which is the maximum projected at present.

Instructors are both military and civilian, there being some 350 of the latter now. Classrooms are either converted barracks or large machine shops. In the latter, the men are widely separated except for certain phases of automotive maintenance, whereas in the barrack school rooms, contact is fairly close, in general.

Adequate laboratory space for the study can be provided in a hospital ward building adjacent to the present laboratory. In addition, alterations, construction of laboratory benches and installation of refrigerating equipment can be carried out with a minimum of delay through use of the classes in drafting, the plumbers and carpenters schools and the school in refrigeration equipment. The study at Fort Warren, therefore, could be got underway promptly.

The acting Commandant (Col. Paul), Director of Training (Col. Lay) and Post Surgeon (Col. Cullen) have all expressed great interest in the study. Colonel J. C. B. Elliott, Commandant was absent from Fort Warren at the time of our survey. His support for the proposed study is given in the 1st Endorsement to "Memo from Surgeon Fort Warren to CO Fort Warren Wyo dtd 5 Oct 48. Subj: Factors Pertinent to the Consideration of Establishing a Research Laboratory at this station." A copy of this endorsement is attached, as well as the original memorandum from Colonel J.K. Cullen.

3. Lowry Field, Col., is divided into 2 training areas designated as Lowry 1 and Lowry 2, separated by about 1 mile, with capacities of 4,000 and 8,000 men, respectively. These 2 areas are fairly well isolated from each other because of distance and type of training. Most of the students in Lowry 1 are drawn from Lackland Field and are recruits who have finished 13 weeks basic training. Two of the largest schools formerly at Lowry Field (automotive mechanics and clerk typists) have been transferred to Fort Warren, and final plans have not yet been put into effect for the new courses and schedules at Lowry Field. Table II shows the projected courses for Lowry Field with load, entry, duration and site of training.

Table II

Course	Load	Entry	Duration	Site of Training
Armament Technician	1496	1 wk	22 wks	Indoors
RCT Technician	620	1 wk	31 wks	Indoors
Comptroller (6 courses)	370	2 wk	12 wks	Indoors
Fire fighting (crash fire)	376	1 wk	8 wks	50% outdoors
Intelligence	506	6 mos		Indoors
Photographers	1244	1 wk	30 wks	30% outdoors
Transportation officers	18			
Radio Operators (now at Scott Field)	1856	1 wk	32 wks	Indoors

The inflow is expected to be 863 men/month beginning 1 January 1949, without the Radio Operator School. The ratio of new recruits to seasoned men is expected to be 2:1. There is a possibility that 2,000 one-year enlistees may be sent to Lowry Field between 1 January 1949 and October 1950. If these come to Lowry, the number of regular students will be correspondingly reduced.

In addition to the school population at Lowry Field, there are approximately 1000 men in "tenant organization," e.g., Air Rescue Units, etc.

Men are housed in cantonment type barracks, with allocation of 72 sq. ft. per man at present. The projected training schedule is not expected to result in overcrowding.

Laboratory facilities could be provided by alterations to a hospital ward building which is available. This would provide adequate space. Alterations would be made from funds regularly allocated to the post for building and maintenance.

At present, hospitalization is being carried out at the Station Hospital of Lowry Field. We were informed, however, that serious attention is being given to a plan to use the facilities of Fitzsimmons General Hospital, Denver, to hospitalize soldiers from Lowry Field. If this plan comes into effect, it would throw serious difficulties in the way of the contemplated study because of the physical separation from Lowry Field.

General Beam, Commandant, and Colonel Neiss, Post Surgeon expressed themselves as being anxious to support a study of streptococcal diseases at Lowry Field. However, because of uncertainties in the hospitalization program it is considered that Lowry Field is at present less advantageous for institution of the study than Fort Warren.

4. Plans for training troops at Camp Carson have not yet reached a stage which permits formulation of plans for the study of streptococcal diseases there. In any case, it appears likely that it would be less advantageous than either Fort Warren or Lowry Field because much of the training of men sent to Camp Carson is carried on at Camp Hale — a considerable distance removed from Camp Carson. The lack of information on projected training, strength, and flow of troops, however, make it impossible at the present time to outline a plan for the study of a streptococcal diseases there. It should be noted that ample laboratory space could be provided in the present hospital building, which is of permanent construction, and that General Sherman, Commandant and Colonel Beringer, Post Surgeon are in full sympathy with the purposes of the study.

Acknowledgement is made to the following officers for their very courteous assistance in carrying out this survey: Colonel J.C.B. Elliott, Commandant, Lt . Col. Paul, Acting Commandant, Lt. Col. Lay, Director of Training and Colonel John Cullen, Post Surgeon, Fort Warren; General Beam, Commandant, Colonel O. K. Neiss, Post Surgeon and Colonel Dixon, Director of Training, Lowry Field; General Sherman, Commandant and Colonel Beringer, Post Surgeon, Camp Carson.

Respectfully submitted,

Colin M. MacLeod, M.D.
Consultant to the Secretary of the Army
President, Army Epidemiological Board

SECTION 4—APPENDIX 3

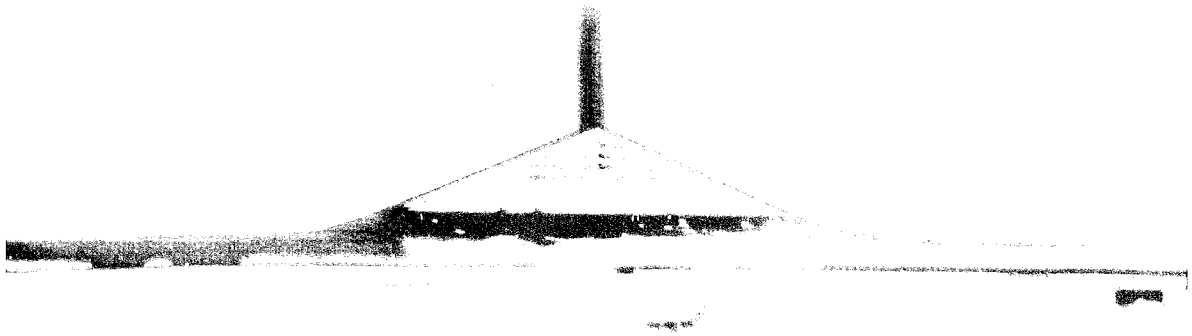
PICTURES OF THE LABORATORY AND PERSONNEL

Few photographs of the Strep Lab were found, so most of those located are included here. The photos on the following pages demonstrate snow drifts several weeks following the large storm of December 1948 and suggest the harsh nature of a Wyoming winter.

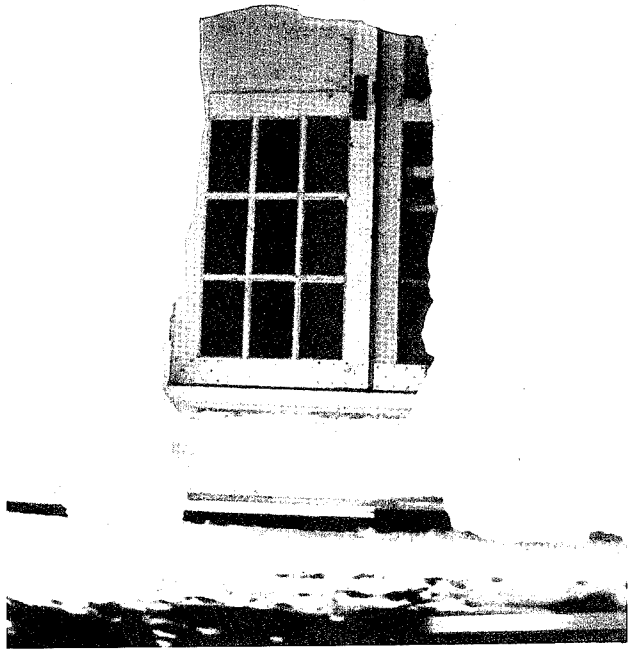


Dr. Rammelkamp's laboratory at Western Reserve University School of Medicine in the fall of 1948.

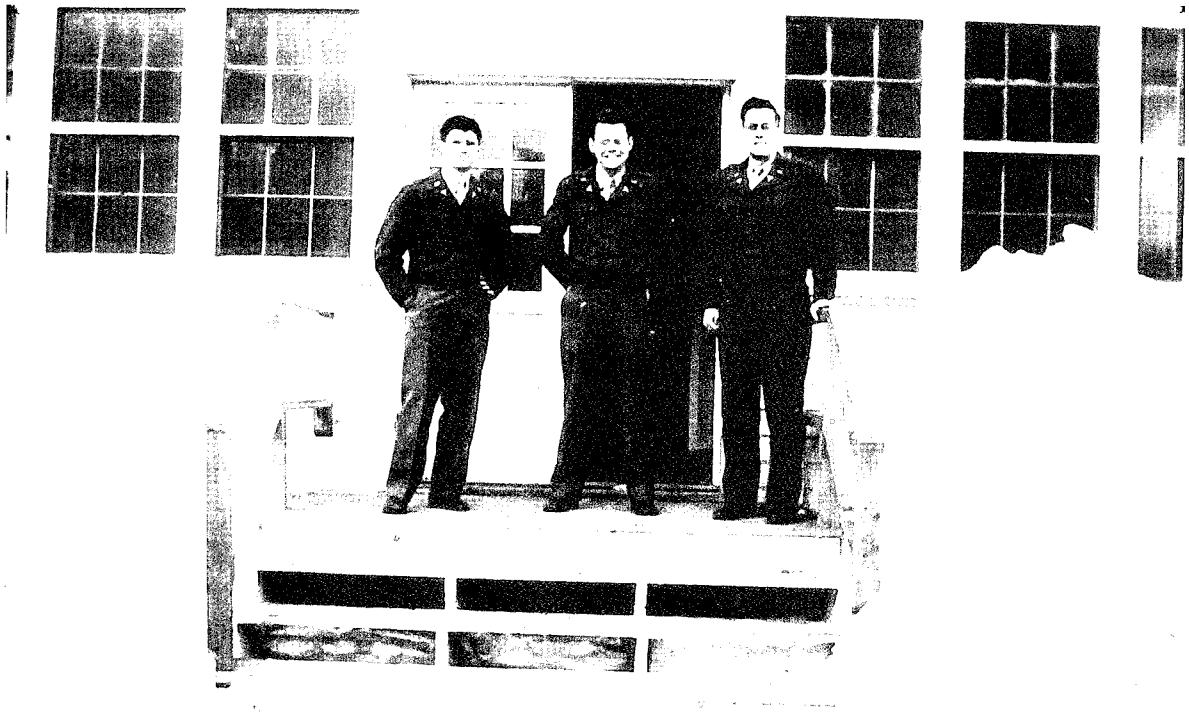
Seated, left to right: Drs. Charles H. Rammelkamp, Jr., and John H. Dingle. Standing: Drs. William R. Brink, Lewis W. Wannamaker, and Floyd W. Denny, Jr., With the exception of Dr. Dingle, these individuals formed the original professional staff of the Streptococcal Disease Laboratory. The three military officers were undergoing training in laboratory procedures before the opening of the Wyoming laboratory.



The appearance of the rear entrance of the laboratory in January 1949, following an unusually severe Wyoming blizzard.

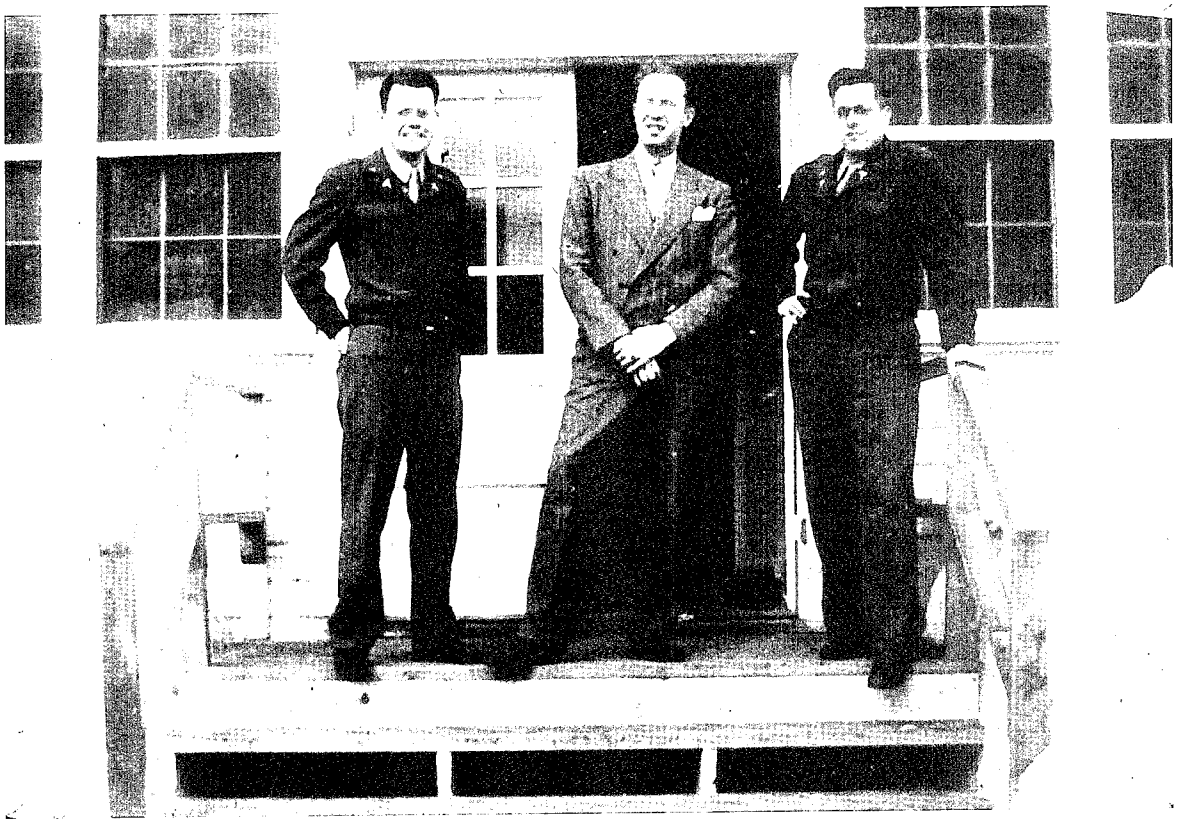


Another view of the doors to the rear entrance to the Laboratory.



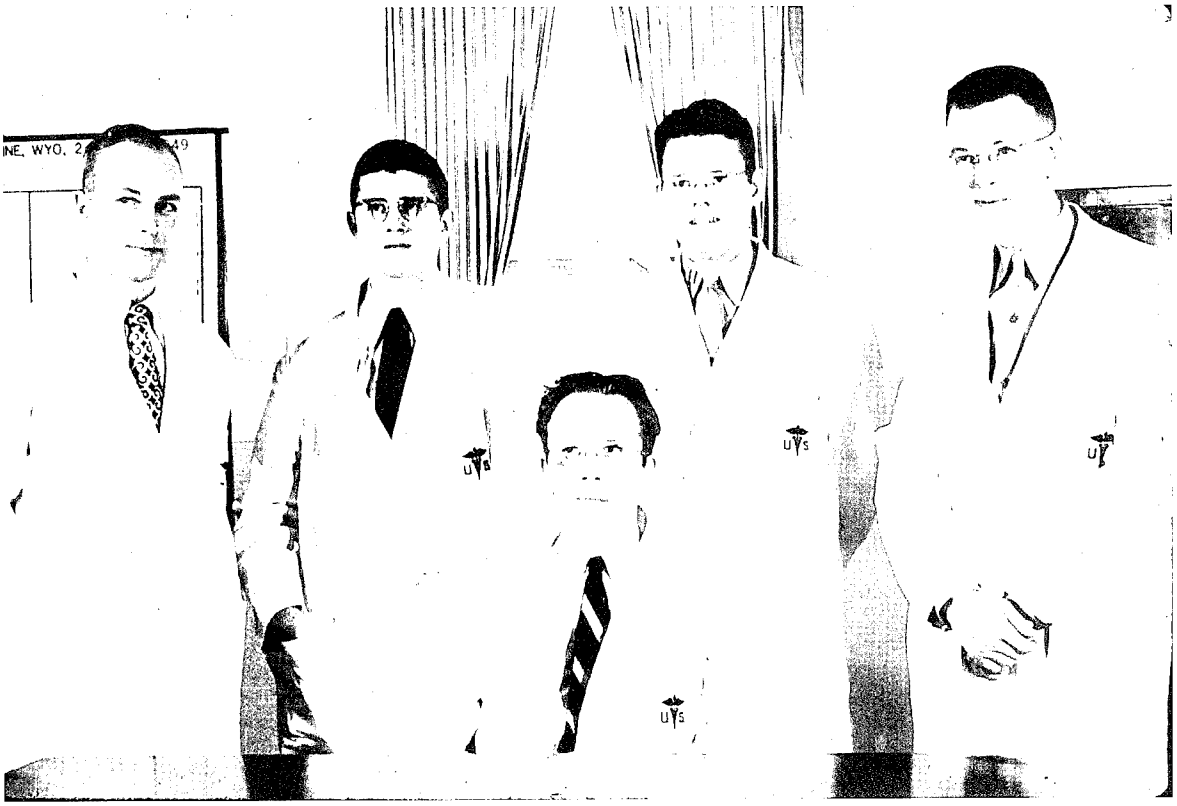
The three original army officers standing
at the front entrance of the Laboratory.

Taken at the same time as the two preceding photos. Left to right: Drs. Floyd W. Denny, Jr., Lewis W. Wannamaker, and William R. Brink.



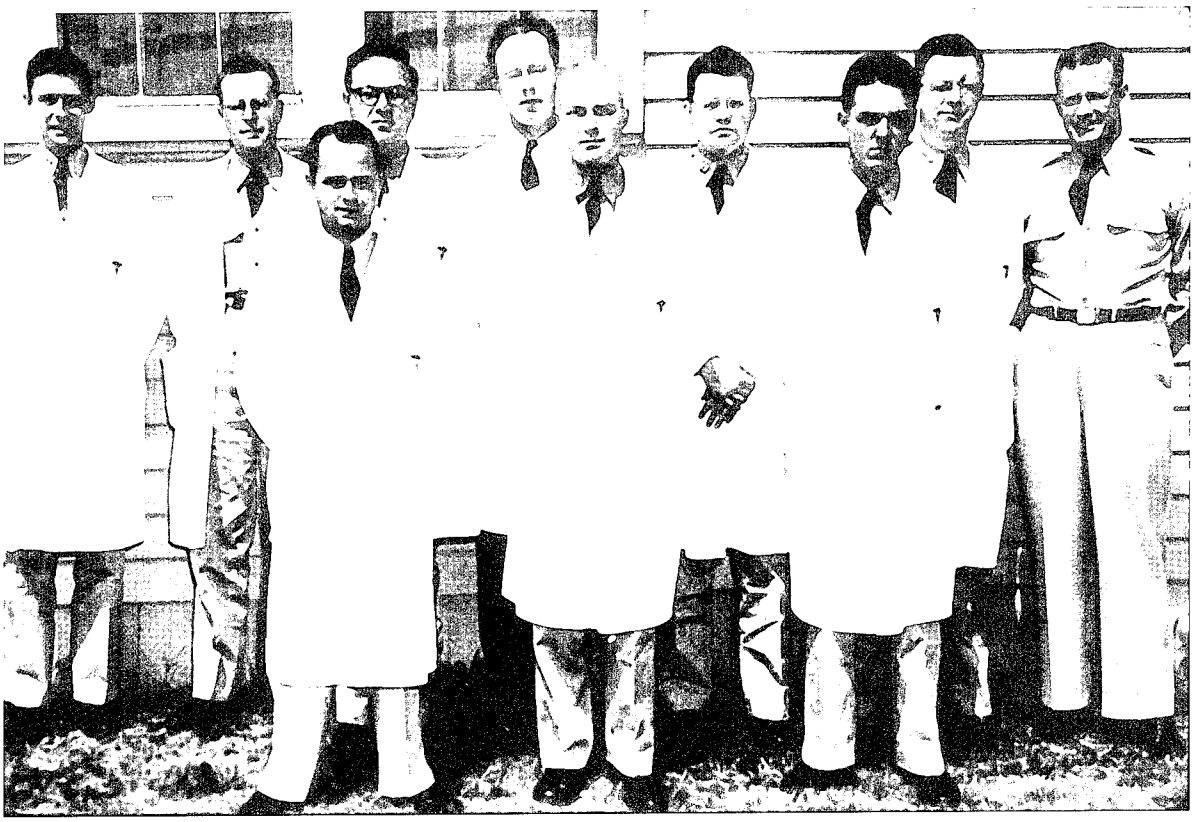
Same setting as prior photo.

Left to right: Drs. Lewis W. Wannamaker, Charles H. Rammelkamp, Jr., and William R. Brink.



The professional staff of the Laboratory in 1950.

Seated: Dr. Charles H. Rammelkamp, Jr. Standing, left to right: Drs. Harold B. Houser, Floyd W. Denny, Jr., Lewis W. Wannamaker, and Edward O. Hahn.



The professional staff of the Laboratory in 1952.

First row, left to right: Drs. L. Loring Brock, Harold B. Houser, and William D. Perry. Back row, left to right: Drs. Chandler A. Stetson, Bertrand L. Stolzer, Alan C. Siegel, Charles H. Rammelkamp, Jr., Lewis W. Wannamaker, Edward O. Hahn, and Earl C. Marple.

SECTION 4—APPENDIX 4

ARTICLE IN CHEYENNE, WYOMING, NEWSPAPER

This article appeared in a Cheyenne, Wyoming, newspaper. Unfortunately, no date accompanies the article but it almost certainly appeared early in 1949. It was accompanied by the first photograph in Appendix 3.

Doctor C.H. Rammelkamp Heads Rheumatic Fever Laboratory

Doctor C.H. Rammelkamp, Associate Professor of Preventive Medicine and Medicine at Western Reserve University Medical School in Cleveland, Ohio, will head the rheumatic fever laboratory at Fort Warren, it was announced recently.

This laboratory is a joint project of the Commission on Acute Respiratory Diseases, Western Reserve University, and the Streptococcal Disease Commission of New York University under the direction of Doctor Tillett, Chairman of the Streptococcal Disease Commission and Professor of Medicine, New York University Medical School.

The purpose of this lab is to determine why streptococcal diseases are prevalent in this area and to take measures to prevent such infectious diseases. The study of these infectious diseases are important for two reasons (1) they will interfere with the training of men during the acute episode, (2) and because a small proportion of such infections are followed by a heart disease.

The lab will be set up for approximately five years. During this period Dr. Rammelkamp's staff expects to conduct research on why heart diseases occur after the infections and try to devise methods to prevent its [sic] occurrence.

Dr. Rammelkamp states "that the staff has received marvelous cooperation from Colonel Elliott, Colonel Cullen and their staff. The laboratory was built and equipped within six weeks after it was decided to have the location here." This post was selected after a survey of a number of Air Force bases and Army posts in this area. It was chosen because of the ideal conditions for study that existed here and the high interest of the hospital personnel.

Doctor Rammelkamp graduated from the University of Chicago Medical School in 1937. Following his graduation he served a year and a half as an intern in Washington University. The doctor has taken courses in surgery at the University of Chicago and chest surgery at Washington University in St. Louis. He attended Harvard University to study infectious streptococcal diseases. After this he spent three and one-half years working with penicillin at Boston University.

The doctor became a consultant of the Secretary of War and was assigned to Fort Bragg, N.C., with the Commission on Acute Respiratory Diseases of the Army Epidemiological Board for the investigation of influenza and streptococcal diseases in the army. He then attended Western Reserve University Medical School where he is now the Associate Professor of Preventive Medicine and Medicine. At the present time Dr. Rammelkamp is again the consultant of the Secretary of War, a member of the Streptococcal Disease Commission and the Director of the Rheumatic Fever Laboratory here at Fort Warren.

The staff includes three army officers, one full time civilian, two enlisted personnel, and six to eight technicians and secretaries. A Doctor Custer will arrive about the first part of the month to take over the duties of acting director in Dr. Rammelkamp's absence.

The three army officers include 1st Lts. William R. Brink, Floyd W. Denny, and Lewis W. Wannamaker.

Lieutenant Brink will cover the clinical aspects of the study. He graduated from Duke University Medical School, Durham, N.C. The lieutenant has had 21 months hospital training at Williamsport Hospital in Pennsylvania. He attended Western Reserve University Medical School to study the particular type of training that he is assigned here to do.

Lieutenant Denny, a graduate of Vanderbilt University in Nashville, Tenn., has had 27 months of hospital training as a civilian at Vanderbilt University. His work is mainly concerned with determining where the men in the service contact influenza and find out whether it is associated with the climate here or not.

Lieutenant Wannamaker, the person in charge of the research laboratory, is a graduate of Duke University Medical School. His 21 months of hospital training are distributed between Duke Hospital and Willard Parker Hospital in the New York City.

A local Cheyenne girl, Mary Riner, will be the chief technician. She received her training in Cleveland, Ohio also. The hospital has assigned personnel to cover the administrative part of the work.

SECTION 4—APPENDIX 5

FOLLOW-UP OF THE PROFESSIONAL STAFF OF THE STREPTOCOCCAL DISEASE LABORATORY

All professional personnel of the Strep Lab were contacted in 1990, except those known to be deceased. Summaries from this correspondence are included below, along with excerpts of letters with comments about the Laboratory experience.

1. William R. Brink, M.D., left the Strep Lab in December of 1949, finished a residency in internal medicine at the Mayo Clinic, and entered private practice in Williamsport, Pennsylvania. He retired in 1987 and now lives in Kitty Hawk, North Carolina, with his wife Margene. In October 1990, he wrote the following reminiscences of the early days of the Strep Lab:

> It's great that you and Hal Houser are writing a history of the Streptococcal Disease Laboratory. I'll be anxiously awaiting a copy of the final monograph.
>
> I thought I might give you a summary of what took place before we decided on establishing the lab at Fort Francis E. Warren. You probably know most of it.
>
> Lewis and I arrived in Cleveland on February 1, 1948. After some preliminary meetings with Drs. Dingle, Rammelkamp, Feller, Hodges and Badger, we met with a group from the Army Epidemiology Board. They decided to set up a commission with Dr. Rammelkamp as the director of the research study. The members of the commission, as I remember them, were Dr. William Tillett and Dr. Colin MacLeod from New York, Dr. Barry Wood from Baltimore, Dr. Rebecca Lancefield from New York, Dr. Wesley Spink from Minneapolis, Dr. Coburn and Dr. Dornberger from Chicago, Dr. Max Finland from Boston, Dr. Dingle and Dr. Rammelkamp from Cleveland and Dr. Morton Hamburger from Cincinnati.
>
> We went to Chicago in April or May of 1948 and visited and went through the labs of Dr. Coburn and Dr. Dornberger. In August or September of 1948, Dr. Dingle, Dr. Rammelkamp, Dr. Tillet, Dr. MacLeod, and a major from the Armed Forces Epidemiology Board, along with Lewis Wannamaker and I went to Lowry Field in Denver. After a day there we went down to Camp Carson and spent a day with General George Sherman III — the commanding officer at Camp Carson. He mistakenly thought we were there to see if the Camp was to be reopened. It had been closed because of a massive strep outbreak the year before with several hundred cases of rheumatic fever. He set us up in a beautiful suite at the Broadmoor Hotel in Colorado Springs. Actually we were there to see if it was a good place to set up the research lab. We then went to Francis E. Warren. This, of course, turned out to be the ideal place to have the lab. It is relatively isolated, had 12,000 personnel, all had been through their basic training, and were going to be there at least six months. In addition, they had a very high incidence of strep infections and rheumatic fever.
>
> While in Cleveland Dr. Rammelkamp asked me to review all the articles I could find that related to strep infections and rheumatic fever. I spent a lot of time in the medical library and reviewed some 2000 articles. Two caught my attention. One was by Dr. Jenesild from Sweden. He had treated a series of strep infections very early in their course with penicillin. He had treated them so soon after onset of their infections that some of them got the same strep type infection again — at a later date.
>
> I wrote him and asked him if any of his first group had gotten rheumatic fever. He wrote back and stated as far as he knew none had gotten rheumatic fever.
>
> The second article was one that was in the *New England Journal of Medicine*. I think it was about 1941 or 1942. They reported on 1002 cases of rheumatic fever. The thing that struck me about the article was that no cases of glomerulonephritis were reported in the group they studied.
>
> I discussed these and other articles I had reviewed with Dr. Dingle, Dr. Rammelkamp and Dr. Feller at a two hour afternoon meeting.
>
> Finally on December 8, 1948 Lewis and I arrived at Cheyenne, Wyoming — in a snow storm. We went to work setting up the lab. As you may remember in early January 1949 we had one of the big blizzards of the

century (Operation Snowlift they called it). A portion of the roof on the North end of the lab collapsed under the weight of the snow. In order to get the lab under way Rammel and I spent a couple of nights cutting up beef hearts and preparing media plates for the strep cultures.

As you may remember in April 1949 Dr. Armine Wilson from the A.I. Dupont Research Institute in Delaware spent a month with us, doing some research work.

In July Margene began working at the lab as a serology technician!!! [Note: Subsequently, she became his wife and the Margene mentioned in his introduction above.]

2. L. Loring Brock, M.D., took fellowships in cardiology at the Universities of Colorado and Washington after leaving the Strep Lab in 1953. He then entered the practice of internal medicine and cardiology in Denver and became interested in health promotion and rehabilitation. He was the Director of the Rehabilitation Unit of the Colorado Heart Association from 1957 to 1978. He subsequently moved to Bigfork, Montana, where he is the Director of the Health Promotion Center in the Flathead Valley.

3. Frank J. Catanzaro, Sr., M.D., entered a practice of cardiology in St. Louis after leaving the Strep Lab in 1955. In 1960 he became Chief of Cardiology at the Cochran Veterans Administration Hospital associated with Washington University. In 1966 he became Director of Medical Education and Chief of Medicine of Missouri Baptist Hospital. He is now Medical Director of that hospital.

4. Robert Chamowitz, M.D., entered a fellowship in gastroenterology after leaving the Strep Lab and has been in a solo practice of gastroenterology in Pittsburgh since that time. In January 1991 he wrote of his great admiration of Dr. Stetson and the benefits he received from working in the Strep Lab. He remains grateful for the contributions to his career made by Dr. Rammelkamp.

5. Ernest J. Clark, M.D., left Warren Air Force Base in 1952 but remained a member of the Air Force until he retired in 1978. He served in military installations in England, Germany, and the United States, including Hawaii. He had several tours in the Office of The Surgeon General of the Air Force. As a Brigadier General, in 1975, he became Director of Professional Services, the post he held until retirement. He now lives in Monument, Colorado.

6. Edward A. Custer, M.D., entered private practice in Palo Alto, California, after a short tour of duty at the Strep Lab. He retired in 1983.

7. Floyd W. Denny, Jr., M.D., left the Strep Lab in 1951 to spend a 2-year fellowship with Dr. Lewis Thomas at the University of Minnesota. He spent 2 years as a junior faculty members in pediatrics at Vanderbilt from 1953 to 1955, when he returned to the Departments of Pediatrics and Preventive Medicine at Western Reserve University. He remained there until the late fall of 1960, when he became Professor and Chairman of Pediatrics at the University of North Carolina. He resigned the chair in 1981 and is now Director of the Program for Health Promotion and Disease Prevention of the University of North Carolina School of Medicine.

8. George C. Eckhardt, M.D., left the Strep Lab in 1952 to enter private pediatric practice in California. He subsequently joined the Permanente Medical Group. He retired in 1982 and now lives in Chico, California.

9. Edward O. Hahn, M.D., entered the solo practice of internal medicine in Cleveland after leaving the Strep Lab. He retired in 1983 and now lives in Thomaston, Maine.

10. Harold B. Houser, M.D., left the Strep Lab in 1952 to start an Arthritis and Rheumatism Foundation Fellowship with Harry Feldman at the State University of New York at Syracuse. In 1954, as Field Director, he established the Laboratory on Housing and Illness, AFEB at Sampson Air Force Base, New York, under the auspices of the CARD. He left Syracuse in 1958 to join the Department of Preventive Medicine at Western Reserve University where he has remained. He was appointed Professor of Epidemiology and Chairman of the Department of Biometry in 1974. Since 1985, he has been Chairman of the Department of Epidemiology and Biostatistics.

11. Robert J. Kohen, M.D., was only tangentially related to the Strep Lab, since he was stationed at the Bainbridge Naval Training Station and assisted Dr. Rammelkamp with studies on glomerulonephritis. We have not been able to locate him, but it is reported that he is deceased.

12. Richard M. Krause, M.D., had an interesting association with the Strep Lab and the Commission. This and excerpts of a letter from him are included in Appendix 7.

13. Earl C. Marple joined the Strep Lab in 1949 as a Master Sergeant and chief administrator and remained with the Lab until it closed. His remarkable talents were indicated by promotion to Major and nomination for a Legion of Merit Award. Major Marple died 19 February 1966.

14. Alton J. Morris, M.D., returned to a medical residency at Barnes Hospital and then to the University of Colorado for a fellowship with Gordon Meiklejohn and Bob Glazer. He then entered the private practice of rheumatology in Springfield, Illinois, following which he developed the hemodialysis program and laboratory at Southern Illinois University School of Medicine, where he was a Professor. Later he went to Eastern Tennessee State University as Program Director, Professor of Medicine, and Chief of Rheumatology. He now practices rheumatology in Kingsport, Tennessee.

15. William D. Perry, M.D., returned to St. Louis, Missouri, in the practice of internal medicine. He died in May 1990.

16. Charles H. Rammelkamp, Jr., M.D., was the primary mover of the Strep Lab and the CSSD during most of its existence. Appendix 10 is devoted in part to the accomplishments of this remarkable man.

17. Willard C. Schmidt, M.D., returned to Western Reserve University School of Medicine where he remained on the faculty until 1973. After entering the private practice of allergy and infectious diseases in Ithaca, New York, for 5 years, he received a Masters of Public Health from Johns Hopkins School of Hygiene and Public Health. In 1979, he became Health Commissioner of Thompkins County, New York. He retired in 1985 and now lives in Ithaca.

18. Alan C. Siegel, M.D., practiced pediatrics in Winnetka, Illinois, after leaving the Strep Lab. He was on the staff of Children's Memorial Hospital where he worked closely with Drs. Stollerman and Eloise Johnson on problems of the streptococcus and rheumatic fever. He died on 8 December 1968.

19. Chandler A. Stetson, M.D., returned to New York University after his tour of duty at the Strep Lab. He subsequently became Professor and Chairman of Pathology there. In 1972, he became Dean of the University of Florida School of Medicine. He died on 25 May 1977.

20. Bertrand L. Stolzer, M.D., entered the practice of rheumatology in Pittsburgh after leaving the Strep Lab. He practices at St. Margaret Memorial Hospital (Doris Palmer Arthritis Center), which is a part of the University of Pittsburgh. In October of 1990, he wrote of the following experience:

> Incidentally, I paid a visit to Warren Air Force Base in September, 1990 and found only a few familiar areas remaining. The old hospital is now an air police station; the Strep Lab is gone; the Officer's Club is about the same and the base is a tranquil missile site. One of the medical officers had no knowledge of the base having been the site for the Streptococcal Disease Laboratory in the past and little knowledge of the role streptococcal disease played in this area.

21. Lewis W. Wannamaker, M.D., was a very important member of the Strep Lab and member of the CSSD. Following his untimely death in 1983, the 86th Ross Conference on pediatric research entitled "Management of Pharyngitis in an Era of Declining Rheumatic Fever" was dedicated to him. The memorial to Dr. Wannamaker in that publication is in Appendix 10.

SECTION 4—APPENDIX 6

LANDMARK ARTICLE

The most notable accomplishment of the Strep Lab was the study demonstrating that the treatment of a streptococcal infection would prevent the subsequent occurrence of rheumatic fever. The first report of the study was published by the *Journal of the American Medical Association* on 13 May 1950. The Journal recognized the significance of this article by designating it as a Landmark Article and reprinted it in its entirety, along with a commentary by Dr. Bisno, both of which are reproduced here, with permission of the journal.

Prevention of Rheumatic Fever
Treatment of the Preceding Streptococcic Infection

Capt. Floyd W. Denny
Capt. Lewis W. Wannamaker
Capt. William R. Brink
Medical Corps, Army of the United States
Charles H. Rammelkamp Jr., M.D.
Cleveland
and
Edward A. Custer, M.D.
Palo Alto, Calif.

The prevention of acute rheumatic fever by the prompt treatment of streptococcic infections with penicillin has been attempted in this study. The results obtained show that this attempt was successful, and, because of their importance, these results are presented here in a preliminary report.

The significance of an adequate means of prevention may be realized when it is considered that rheumatic fever develops in an estimated 200,000 to 250,000 persons in the general population of the United States yearly.[1] Figures for the Armed Services similarly show a high incidence, with an average of 7,300 cases annually for the seven year period from 1942 through 1948.[2] The gravity of the disease itself is emphasized by the estimate of Paul that at least 460,000 persons in the country today have rheumatic heart disease.[3] Not only is rheumatic fever a menace to health, but it is also a serious economic problem. A conservative estimate of the cost of each case that occurs in the Armed Services is $16,000.[2]

DESCRIPTION OF THE STUDY

The study was conducted at Fort Francis E. Warren, in southeastern Wyoming. The Fort is an air force technical training base where approximately 80 per cent of the men are trainees who report after twelve weeks of basic training at a southwestern base. The study began Jan. 24, 1949 and ran continuously until July 1,1949, except for a ten day period in April. Although the average strength of the base during the study was 8,000 men, the actual number exposed to infection was much greater because the men remained in school only eight to thirty-two weeks.

All patients admitted to the hospital for disease of the respiratory tract were seen within a few hours by one of the members of the professional staff of the laboratory. Those having exudate on the tonsils or on the pharyngeal wall were included in the study group. A total of 1,634 such patients were observed.

A total of 798 patients whose Air Force serial numbers ended in an even digit received penicillin treatment, and 804 patients whose serial numbers ended with an odd digit comprised the control group and received no specific treatment. Prior to March 3, 1949 the treatment consisted of 300,000 units of crystalline procaine penicillin G (suspended in peanut oil containing 2 per cent aluminum monostearate) given intramuscularly as soon after admission as possible. This dose was repeated in seventy-two hours. After March 3 the following change was made in the dosage schedule: 300,000 units were administered at the time of admission and again in forty-eight hours, and 600,000 units were given ninety-six hours after the initial dose. Of the 798 patients who received penicillin, 253 were treated before March 3. Eighty-eight per cent of the treated patients received the first penicillin within sixty hours after the onset of the symptoms of the streptococcic illness.

Follow-up studies for the detection of rheumatic fever were performed between the third and fourth weeks after the initial infection, without knowledge of the serial numbers of the patients or of their previous treatment. Those patients suspected of having acute rheumatic fever were hospitalized until a satisfactory diagnosis was established. Rigid criteria for diagnosis were followed. A modification of the classification of Jones[5] was used. This classification may be seen in the following tabulation:

Major Manifestations

Carditis
- a. Definite cardiac enlargement
- b. Appearance of a significant murmur heretofore not present
- c. Friction rub
- d. Heart block or other electrocardiographic findins indicative of carditis
- e. Cardiac failure

Migrating polyarthritis
History of recurrences
Chorea
Subcutaneous nodules

Minor Manifestations

Fever
Abdominal pain
Arthralgia
Skin rash
- a. Erythema marginatum
- b. Erythema multiforme

Epistaxis
Pulmonary changes
Nonspecific electrocardiographic changes
Elevated erythrocyte sedimentation rate (20 or above considered abnormal)
Anemia

For a diagnosis of definite acute rheumatic fever a patient had to have two major manifestations or one major and two minor manifestations. For a diagnosis of probable acute rheumatic fever a patient had to have one major and one minor, one major or two minor manifestations. Instances of abdominal pain, epistaxis, pulmonary changes and anemia were encountered but did not contribute to the classification of these patients. No patient with chorea or subcutaneous nodules was encountered. Only persons in whom acute rheumatic fever developed between ten to thirty-five days after the onset of the observed streptococcic infection are included in this report.

Throat cultures and blood specimens were obtained from the patients on admission and again at the time of the follow-up examination. Strains of beta hemolytic streptococci isolated from cultures

were grouped and typed according to the method of Lancefield.[6] Antistreptolysin O titration was performed on acute and convalescent serums according to a modification of the method of Hodge and Swift.[7]

RESULTS

Of the 798 patients that were treated with penicillin, definite acute rheumatic fever developed in only 2. In contrast, the disease developed in 17 of the untreated patients (table 1), a difference which could be due to chance only 6 times in 10,000. Of the 2 patients in the treated group who became ill with rheumatic fever, 1 was treated within eight hours after the onset of the symptoms of streptococcic disease and the second approximately seventy-two hours after the onset.

Probable acute rheumatic fever developed in 2 patients in the treated group and in 6 patients in the untreated group. Of the 2 patients in the treated group, 1 received penicillin forty-eight hours after the onset of symptoms of streptococcic disease and the second one hundred and eight hours after the onset. Whether the time of treatment of the initial infection is related to the development of poststreptococcic nonsuppurative complications cannot be determined at this time.

The effect of penicillin treatment on the presence of betahemolytic streptococci in cultures of the throat is shown in table 2. In the treated group the number of persons having streptococci was reduced from 78.3 per cent on admission to 18.1 per cent at the time of the follow-up examination. The untreated group showed a reduction from 81.7 per cent to only 52.7 per cent.

The development of antistreptolysin O in the treated and untreated groups was also different. In the treated group only 51 per cent of the patients showed a rise in titer of two or more tubes, while 73 per cent of the untreated patients showed a similar rise. Tests of significance support the validity of these differences.

The prevention of rheumatic fever, the inhibition of antibody and the partial eradication of streptococci in the group of patients treated with penicillin assume more significance when the composition of

Table 1.—*Cases of Rheumatic Fever Found at the Follow-Up Examination in the Treated and Untreated Groups*

	Number of Patients	
	Treated	Untreated
Definite rheumatic fever	2	17*
Probable rheumatic fever	2	6
Total	4	23†

*Test of significance shows that probability is 0.0006.
†Test of significance shows that probability is 0.0002.

Table 2.—*Persistence of Group A Beta Hemolytic Streptococci in the Treated and Untreated Groups*

	Treated (Percentage)	Untreated (Percentage)
Persons with group A beta hemolytic streptococci on admission	78.3	81.7
Persons with group A beta hemolytic streptococci in follow-up examination	18.1	52.7

the treated group and that of the control group are compared. That the two groups were comparable is demonstrated in table 3, in which various features are presented. Moreover, a large proportion of the illnesses in both groups were streptococcic in origin, since group A betahemolytic streptococci were isolated from 80 per cent of all cultures made at admission and since 73 per cent of the untreated patients showed an antistreptolysin response of two or more tubes.

COMMENT

The data presented concerning the incidence of rheumatic fever in the treated and control groups establish the fact that penicillin therapy of acute streptococcic infections will almost completely prevent the subsequent occurrence of rheumatic fever. These results emphasize again the close relationship between streptococcic disease and rheumatic fever.

Attempts to prevent the occurrence or the recurrence of rheumatic fever during the last decade have centered around the streptococcic disease that precedes most cases of acute rheumatic fever. Coburn,[8] Kuttner and Reyersbach[9] and Hodges[10] showed that sulfonamide drugs, given prophylactically, not only reduced the incidence of streptococcic disease but also reduced the occurrence of rheumatic fever. This would seem to be a practical means of prevention in two situations: (a) in closed groups in which the incidence of streptococcic disease is extremely high and (b) in select groups, such as patients with inactive rheumatic fever or rheumatic heart disease, in which the danger of recurrence is great. This method of prevention has not proved to be practical for the general population, however, because of the toxicity of the sulfonamide drugs, the high percentage of sulfonamide-resistant strains of streptococci that develop and the difficulty that is entailed in mass prophylaxis.[8]

Treatment after the development of the streptococcic infection has been another approach to the problem. Sulfonamide drugs have proved to be ineffective when used in this manner.[11] Experience with penicillin has been conflicting. Weinstein, Bachrach and Perrin[12] treated 225 patients with streptococcic disease with penicillin; in 7 of these patients rheumatic fever subsequentlv developed. This observation supports Finland's[13] conclusion, from a review of the literature, that penicillin is not effective when used in this manner for the prevention of rheumatic fever. On the contrary, Massell, Dow and Jones[14] employed penicillin to treat ten clinical and five subclinical hemolytic streptococcic infections in patients hospitalized for rheumatic fever or rheumatic heart disease; the patients failed to exhibit subsequent recurrences. Jersild[15] has shown that poststreptococcic complications, including nephritis,

Table 3.—*Comparability of Treated and Untreated Groups*

	798 Treated Patients (Percentage)	804 Untreated Patients (Percentage)
Age (years):		
17–19	61.0	62.0
20 and over	39.0	38.0
Previous history of rheumatic fever	3.5	4.4
Tonsils present	72.7	70.7
Cervical nodes enlarged or tender	50.1	46.3
Leucocyte count 13,000 or over at admission	54.7	56.3
Persons with group A beta hemolytic streptococci at admission	78.3	81.7
Antistreptolysin O titer of 125 units or less at admission	70.3	69.1
Follow-up obtained	80.7	82.8

are reduced after penicillin treatment of the initial illness, but he makes no statement about the occurrence of rheumatic fever.

The theory has been advanced that rheumatic fever is associated with a peculiar response to an unknown antigen-antibody reaction. Kilbourne and Loge[16] showed that early and intensive pencillin therapy against streptococcic disease suppressed the production of antistreptolysin O. It has been shown here that adequate treatment with penicillin not onlv suppresses the antistreptolysin response but also prevents rheumatic fever. Whether the antibody suppression is only a reflection of the inhibition of some more basic process in the mechanism of rheumatic fever or is in itself the responsibile factor is entirely speculative at this time.

Exudate on the tonsils or oropharynx was used as the sole means of selection of patients to be included in this study because it was a rapid, easily standardized method. It was thought that such a criterion would include the majority of streptococcic infections of the respiratory tract, since various studies have shown that exudative lesions of the throat appear in 60 to 90 per cent of streptococcic infections,[17] particularly in a population experiencing epidemic rates of streptococcic illnesses. The isolation of group A streptococci from 80 per cent of the patients and the demonstration of an increase in the antistreptolysin O titer in 73 per cent of the control group indicate that the majority of the patients actually had streptococcic disease. A few undoubtedly had nonstreptococcic exudative tonsillitis.

If the incidence of rheumatic fever is to be reduced materially by early treatment with penicillin, it becomes necessary that streptococcic infections be diagnosed accurately and early. In some cases the clinical findings alone will permit an almost certain diagnosis of streptococcic infection. Characteristically, such illnesses present a sudden onset of sore throat with pain on swallowing, fever and other constitutional reactions, diffuse redness and edema of the soft palate, tonsils and oropharynx, discrete or confluent exudate and large or tender cervical lymph nodes. Supportive data may be obtained from the laboratory. Many patients will have an elevated total leukocyte count. Cultures of the pharynx will almost always show a predominant growth of beta hemolytic streptococci. Depending on the availability and use of the preceding criteria, a large percentage of streptococcic respiratory infections can be reliably and rapidly diagnosed, particularly during an epidemic period. Treatment with penicillin can thus be instituted immediately.

SUMMARY

Evidence is presented to indicate that rheumatic fever can be prevented by the treatment of streptococcic disease with penicillin. A total of 798 patients with streptococcic infections were treated with penicillin; in only 2 did acute rheumatic fever subsequently develop. Of 804 untreated patients, the disease developed in 17. Penicillin therapy likewise suppresses the antistreptolysin O response and eradicates the streptococci in many cases.

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2. Department of Preventive Medicine, Surgeon General's Office.
3. Paul, J. R. *The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects*. New York: Metropolitan Life Insurance Company, 1943.
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9. Kuttner, A. G., and Reyersbach, G. The prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide. *J. Clin. Invest.* 1943, 22, 77.

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15. Jersild, T. Penicillin therapy in scarlet fever and complicating otitis. *Lancet* 1948, 1, 671.

16. Kilbourne, E. D., and Loge, J. P. The comparative effects of continuous and intermittent penicillin therapy on the formation of antistreptolysin in hemolytic streptococcal pharyngitis. *J. Clin. Invest.* 1948, 27, 418.

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This investigation was supported through the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, Office of the Surgeon General, Washington, D. C.

From the Streptococcal Disease Laboratory, Fort Francis E. Warren, Wyo., and the Department of Preventive Medicine, Western Reserve University School of Medicine, Cleveland.

The Rise and Fall of Rheumatic Fever*

Alan L. Bisno, MD

IN THIS week's issue, the editors of *JAMA* have republished an article that stands clearly as a landmark in modern medical history. The article, which first appeared in The Journal 35 years ago, presents convincing evidence that acute rheumatic fever may be prevented by penicillin therapy for the antecedent streptococcal throat infection. This study and a succeeding one on the same topic published the next year[1] emerged from the famous Streptococcal Disease Laboratory, which functioned at the Fort Warren, Wyo, air force technical training base in the years shortly after the end of World War II. The laboratory, under the leadership of the late Dr Charles H. Rammelkamp, Jr, included among its ranks a number of young investigators destined to make indelible contributions to the field of infectious diseases. Numbered among these were Dr Floyd W. Denny, the senior author of the 1950 *JAMA* article, the late Dr Lewis W. Wannamaker, and other luminaries. Indeed, the meticulous epidemiologic and clinical data that emerged from Fort Warren remain today as the basis for many of our concepts regarding streptococcal pharyngitis and its sequels.

The recognition that acute rheumatic fever is a consequence of preceding group A streptococcal upper respiratory tract infection and that adequate treatment of such infection with penicillin is spectacularly effective in prevention led to development of our current strategies for control of rheumatic fever and rheumatic heart disease. These strategies have been reaffirmed once again by the recent publication of the latest revision of the American Heart Association's recommendations for primary and secondary prevention of rheumatic fever.[2] The now-familiar recommendations relating to primary

prevention call for accurate diagnosis of streptococcal tonsillopharyngitis by use of the throat culture, followed by therapy for a minimum of ten days with penicillin or, in allergic patients, with erythromycin.

Decline of Rheumatic Fever in the United States

In rereading the Fort Warren article, one is struck by the estimates of 200,000 to 250,000 new cases of rheumatic fever developing in the United States annually in the late 1940s, with an average of more than 7,000 new acute rheumatic fever cases annually in the military alone. In those days, whole sanatoriums, such as the famous Irvington House in New York, were devoted to the care of children felled by acute rheumatic fever and severe forms of rheumatic carditis.

The situation in the 1940s contrasts remarkably with that in the 1980s. For many decades, there has been a steady decline in the occurrence of acute rheumatic fever in North America and western Europe. Within the past two decades, this decline has appeared to accelerate, so that in many parts of the United States today, acute rheumatic fever has become a truly rare disorder. Admission of a suspected case to the wards of a major teaching hospital is cause for a grand rounds presentation and for trotting out the more senior clinicians, who regale the house staff with experiences from the bad old days of yore.

The exact incidence of acute rheumatic fever in the United States at this time is difficult to ascertain. Rheumatic fever registries maintained by many states in the past have largely been abandoned.[3] There have, however, been a number of detailed investigative studies carried out in various geographic locales, and the trends they document are most impressive. As recently as two decades ago, careful surveys yielded average annual acute rheumatic fever incidence rates among children and adolescents (aged 5 to 19 years) in Baltimore, Md,[4] and Nashville, Tenn,[5] of approximately 25 per 100,000 population. In the Nashville study, the incidence rate among black children aged 10 to 14 years for the years 1963 to 1969 was 55.5 (all rates expressed per 100,000 population per annum). The acute rheumatic fever incidence among schoolchildren in the borough of Manhattan during 1963 to 1965 was estimated at 61, with rates in the most congested Puerto Rican districts of 78 to 79.[6]

These figures contrast sharply with the most recent survey data. Land and Bisno[7] found an annual acute rheumatic fever incidence rate for schoolchildren in Memphis-Shelby County, Tennessee, during 1977 to 1981 of 1.88. Among white children residing in the suburbs, the rate had fallen to 0.49, ie, one case per 200,000 children per year! These startling figures have been confirmed elsewhere. In his continuing studies of Baltimore, Gordis[8] found the incidence rate of first attacks in children and teenagers had by 1977 to 1981 fallen to 0.5. Similar unprecedentedly low rates have recently been reported for Fairfax County, Virginia,[9] and for the state of Rhode Island.[10]

Possible Reasons for the Waning of Acute Rheumatic Fever

The reasons for the dramatic decline of rheumatic fever incidence in North America, western Europe, and, more recently, in the most highly developed areas of the Far East[11] remain speculative. There is no convincing evidence of a parallel decline in the incidence of group A streptococcal pharyngitis. Indeed, streptococci continue to be isolated in a sizable percentage of children presenting for treatment of simple sore throat.

Continuous antimicrobial prophylaxis has been highly effective in preventing recurrences of acute rheumatic fever in patients with a prior history of the disease. It is difficult, however, to attribute the bulk of the decline in *first attacks* of acute rheumatic fever to antibiotic therapy for strep throat, because the decline appears to antedate the antibiotic era. We know, moreover, that one third or more of acute rheumatic fever cases occur after strep throats that are asymptomatic or at least so mild as to have been overlooked and thus not preventable by antibiotics. Many other relatively mild cases of pharyngitis, particularly those occurring in indigent families, undoubtedly never come to medical attention. In many other cases, failure of compliance with orally prescribed antibiotics makes the efficacy of primary prevention highly problematic.

Although household crowding and other, less well-defined socioeconomic factors appear to influence markedly the incidence of rheumatic fever, it is difficult to see how such factors could explain the precipitous drops in occurrence of the disease that have been observed over the past 20 years in cities such as Baltimore.

Finally, there is considerable epidemiologic evidence to suggest that group A streptococci may vary in their rheumatogenic potential and that currently prevalent streptococcal serotypes may be less apt to initiate the disease. The well-known rheumatogenic serotypes circulating at Fort Warren (eg, types 5, 14, and 24) gave rise to acute rheumatic fever with a relatively constant attack rate approximating 3% in recruits with untreated exudative tonsillopharyngitis.[12] Those serotypes are rarely encountered nowadays in isolates submitted to this writer's laboratory from various areas of the United States, and the types currently causing pharyngitis in many centers have not been strongly epidemiologically related to acute rheumatic fever. Data supporting the concept of relative rheumatogenicity of group A streptococci cannot be summarized here, but the reader is referred to comprehensive reviews published elsewhere.[13,14]

Rheumatic Fever in the Third World

While rheumatic fever has become a rare disease in many parts of the United States, and particularly so in the affluent suburbs, the disease continues to devastate many of the poorer and most densely populated areas of the globe. In the Indian subcontinent, southeast Asia, the Arab world, and in certain areas of Africa and Latin America, rheumatic fever remains one of the leading causes of cardiovascular morbidity and mortality — often the leading cause. To cite only two examples, the annual acute rheumatic fever incidence rate among children in Sri Lanka from 1972 to 1978 averaged 142,[15] while as late as 1980, rheumatic heart disease patients accounted for 40% of all cardiac admissions to a major Indian teaching hospital.[11] Indeed, the incidence of acute rheumatic fever may actually have risen in certain of the tropical Third World countries, because it was widely written and assumed early in this century that rheumatic fever was rare in the tropics.[16]

The duality in the global epidemiology of rheumatic fever raises legitimate questions regarding strategies currently being employed for acute rheumatic fever control in both settings. The strategies employed for management of acute pharyngitis by physicians in this country were developed in the days when acute rheumatic fever was a familiar and ever-present hazard. Are they still valid in an era of declining acute rheumatic fever incidence?

Management of Strep Throat: A Reassessment

The cornerstone of diagnosis of streptococcal pharyngitis for many decades has been the throat culture. This procedure has been advocated by authorities because the broad overlap in signs and symptoms of streptococcal and viral pharyngitis precludes confident distinction between the two on clinical grounds alone in many cases. The throat culture has been roundly criticized, however, on several counts. First and foremost, it cannot differentiate with certainty between acutely affected individuals, who require antibiotic therapy, and asymptomatic carriers, who do not. Second, when a single throat swab is performed (as is conventional), there is an approximate 10% rate of false-negativity.[17] Third, the culture adds expense and time delay to the management of this extremely common clinical problem.

Advocates of the throat culture point out that, even though its use is associated with a modest degree of overtreatment, the throat culture has a negative predictive value in excess of 95%. Thus, a negative culture allows the physician confidently to rule out strep throat and thus withhold antibiotics in the 70% or more of patients with pharyngitis whose cultures are negative. In an era when blunderbuss penicillin use for prevention of acute rheumatic fever is no longer defensible, this is a critical point. The issue of sensitivity has probably been overblown, because the few false-negatives likely represent random sampling errors in patients with weakly positive cultures; the risk of acute rheu-

matic fever ensuing in such patients, most of whom are probably carriers, may well be minuscule. The cost of throat culture, while admittedly a factor, need not be exorbitant if screening is limited to group A streptococci and if determinative bacteriologic procedures and detailed antimicrobial testing on other microbes are avoided. Such cultures can, moreover, be used more sparingly in children younger than 3 and in older adults, because both groups have a relatively low incidence of streptococcal pharyngitis and of rheumatic fever.

Even when throat cultures are performed assiduously, the information obtained is often not used appropriately. A recent survey of Rhode Island physicians and laboratories,[10] for example, revealed that 157,000 throat cultures were performed in 1980 for a population of less than 1 million. Eighty-seven percent of responding primary care physicians stated that they started antimicrobial therapy before culture results were known, and 39% continued antibiotic therapy even if the cultures were negative. Some 44% of respondents indicated that they often did not receive culture results in time to influence therapy. These data are indeed disturbing and raise questions as to the cost-effectiveness of throat cultures as currently employed by many primary care practitioners.

The Fort Warren investigatorsl[18,19] showed that, although prompt penicillin therapy was effective in ameliorating the symptoms of strep throat, such improvement was often not striking, because the disease itself was self-limited within a few days. They also showed[20] that a brief delay in initiation of therapy did not increase appreciably the risk of acute rheumatic fever. Thus, most authorities have felt that immediate treatment was not mandatory except in the minority of children with high fever, significant toxic reaction, or evidence of suppurative complications. Apparently, the profession does not agree.

This dilemma may be resolved with the appearance on the market of kits that allow rapid detection (within minutes to less than an hour) of group A streptococcal antigen and do not require overnight incubation.[21,22] The exact sensitivity of these tests in everyday practice remains to be determined. None is reliable in detecting 1+ cultures (ten colonies or less), but such sensitivity may not be required, given the rarity of acute rheumatic fever and the high proportion of carriers among patients with such weakly positive cultures. If currently available kits or future modifications can be definitely established to have adequate sensitivity for general clinical purposes (and emerging data appear quite favorable), then the physician will be able to make a definitive determination of the need for therapy on the day the patient is seen and even, if desired, before the patient leaves the office.

Once the diagnosis of streptococcal pharyngitis is established, the issue of therapy arises. Because of its demonstrated efficacy (dating back to the landmark report of Denny et al) in prevention of acute rheumatic fever, penicillin is considered the drug of choice. For many years, benzathine penicillin G has been considered the preferred dosage form. The prolonged penicillinemia obtained after a single injection obviates problems of patient compliance and ordinarily results in high rates of eradication of group A streptococci from the pharynx. The injection is painful, however, and parenteral penicillin injections have been associated with fatal hypersensitivity reactions at an estimated frequency of 1.5 deaths per 100,000 administrations.[23] Although the exact data are not available for the risk of fatal anaphylaxis after oral penicillin use, most observers believe that oral penicillin is much less risky in this regard than is a parenteral drug. There is thus the question, given the ubiquity of strep throat and the rarity of acute rheumatic fever, of whether the risk-benefit ratio has now shifted in favor of oral therapy, especially in affluent areas where the acute rheumatic fever risk is particularly low and prospects for patient compliance are (it is hoped) somewhat higher. Indeed, many primary care physicians have already adopted this policy.

A prudent response to the changing epidemiologic scene would suggest that extensive culturing of asymptomatic family contacts of patients with strep throat is no longer necessary, unless there is a rheumatic individual in the family or the epidemiologic situation suggests a high risk of acute rheumatic fever. Moreover, the most recent American Heart Association statement[2] mandates posttreatment cultures only for those patients with strep throat "who are at unusually high risk of rheumatic fever or who remain symptomatic." It goes without saying that repetitive attempts to eradicate asymptomatic throat carriage by multiple repetitive courses of antibiotics are inappropriate and usually futile.

Rheumatic Fever Control in the Third World

The methods of rheumatic fever control pioneered by the Fort Warren investigators and others have marked limitations when applied to the Third World. So-called primary prevention strategies may be foiled by the fact that relatively minor, self-limited illnesses such as sore throat often do not come to medical attention because of extreme poverty, competing family needs, lack of understanding of the potential significance of the illness, and limited access to medical care. Secondary prevention (ie, continuous antibiotic prophylaxis in rheumatic patients to prevent recurrences of acute rheumatic fever and progression of rheumatic heart disease) has been highly effective in selected areas. Unfortunately, organized programs of secondary prophylaxis require monetary resources and well-developed public health infrastructures, which are often lacking in just the areas of greatest need.

While a decline in acute rheumatic fever incidence similar to that observed in the west might be anticipated as socioeconomic conditions improve, such improvement is nowhere to be seen in many of the countries in which the problem is gravest. Meanwhile, untold numbers of individuals will become cardiac cripples or die of rheumatic heart disease. For this reason, the ultimate preventative measure might prove to be not an antibiotic but rather a vaccine.

During the past decade, gratifying progress has been made in purifying and characterizing streptococcal M protein, the antiphagocytic surface substance that confers upon the group A organism its virulence and that elicits type-specific antibodies in the host. These antibodies form the basis of acquired immunity to the group A streptococcus in man. Small peptides contained within the M protein molecule and composed of as few as 35 amino acids have been found to contain antigenic determinants that elicit protective antibodies.[24] Moreover, certain M protein fractions elicit antibodies that opsonize streptococci of several M protein serotypes. These findings suggest that it might be possible to construct vaccines made of pools of peptides that protect against the major rheumatogenic serotypes in a given geographic area.

An exciting recent finding has been the presence of epitopes on the M protein molecule that share antigenic determinants with human heart tissue.[25] Although the relevance of such antigens to the pathogenesis of rheumatic fever is unknown, it is interesting that they have been identified on streptococci belonging to serotypes known to be strongly epidemiologically associated with acute rheumatic fever. In addition to providing a possible theoretical explanation for the concept of relative rheumatogenicity of group A streptococci, identification of these cross-reactive antigens will make it possible to exclude them from future vaccine preparations, thus providing an immunizing agent of maximal safety to the host.

Only time will tell how soon the combination of antimicrobials, socioeconomic changes, and, perhaps, vaccines will finally bring rheumatic fever under ultimate control. That such a prospect is even conceivable, however, is due in large part to the pioneering efforts, only a few decades ago, of the denizens of Fort Warren, Irvington House, and the other great staging areas for a war on rheumatic fever that had some of its earliest beginnings, appropriately enough, in a camp for military recruits.

This work was supported in part by grant 84-996 from the American Heart Association and grant AI-10085 from the National Institutes of Health.

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*A commentary on Denny FW, Wannamaker LW, Brink WR, et al: Prevention of rheumatic tever: Treatment of the preceding streptococcic infection. *JAMA* 1950;143:51-163.

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SECTION 4—APPENDIX 7

TRANSFER FACTOR

The commissions on streptococcal and staphylococcal infections supported parts of the work on transfer factor in the laboratories of Drs. Lawrence and Tillett of the New York University Medical Center. A section on these accomplishments is in the body of the history. Some reminiscences by Dr. Lawrence of his experiences with the commissions are included here.

Recollections of a Streptococcal Watcher
(with apologies to Lewis Thomas)
H.S. Lawrence, NYU Medical Center

What I remember chiefly about the Streptococcal Commission of the AFEB was the stimulating intellectual climate and the impressive scientific achievements of its members who at the same time comprised such a genial, friendly group strongly supportive of young investigators, such as myself. I had the good fortune to be introduced to the Strep Commission by my illustrious teacher and staunch friend, William S. Tillett, who had served as former Chairman of the Commission.

My connections to the streptococcus seemed rather tenuous at the time and limited to getting Rammelkamp's advice on treatment of my son Geoffrey's tonsillitis and yet it all began simply enough. Tillett had read of Chase's cellular transfer of tuberculin sensitivity in guinea pigs and with characteristic insight suggested that I might see if such a transfer of immunity could be brought about in humans as well. The transfer of cutaneous delayed type hypersensitivity from immune human donors to non-immune recipients was readily accomplished using blood leukocytes.

We then moved onto the transfer of delayed sensitivity to streptococcal products in humans. This adaptation arose out of our interest in rheumatic fever and the suspicion that the "altered tissue reactivity" (Tillett's apt phrase) which resulted in cardiac damage following streptococcal infection was more likely to be a result of inflammatory hypersensitivity reactions of the delayed type and cell mediated immune responses to streptococcal products rather than arising from the intercession of the serum antibodies detected in this disease.

The subsequent transfers of delayed cutaneous reactivity to intact streptococci, to SK-SD, an extracellular product close to Tillett's heart, and to streptococcal M-substance were also readily accomplished in humans. This study was supported by the Streptococcal Commission of the AFEB. It was my first research grant award and what a boost in morale it was.

The award was renewed on a yearly basis and I continued to acknowledge with gratitude AFEB support in publications from 1952 up through my Harvey Lecture in 1974, and although other federal and private foundation support ensued, the Streptococcal Commission grant always held a special place in my memory.

Following the transfer of delayed reactivity to streptococcal products, I presented our results to the annual commission meeting in Washington and met O. T. Avery. He was on the same program and closed his presentation with the modest disclaimer that he feared that he had accomplished very little in the preceding year — an unbelievable suggestion which prompted vociferous disagreement from the audience. At dinner that evening I chanced to be seated opposite Avery. He confided to me that he could not understand the full meaning of our results but that he found the whole idea intriguing and was convinced that we were on to something important and should keep at it. To me this was high praise indeed, particularly since Tillett had been trained by Avery and I had been trained by Tillett, it was reassuring that I had not let my teacher down. Parenthetically, I should have told Avery, that I could not understand the full meaning of our results either, but it took me a while longer to fully realize it.

It was about this time that I met Lewis Thomas at one of the annual AFEB meetings, which I have described on the occasion of the presentation of his Kober Medal award by the Association of American Physicians, and from which I quote:

'I first met Lew while he was still at Minnesota when we served together on the Streptococcal Commission of the Armed Services Epidemiological Board along with many of the distinguished members of the Association here today. He had just presented his progress report on the Shwartzman reaction and the place of endotoxin as the cornerstone and central focus of all biological transactions, speaking in a flawless dialect of English and making incisive and witty good sense. The audience was at first rapt and then galvanized into thinking. That is to say thinking as Lew thinks and revelling in the sensation. Colin MacLeod was sitting nearby, and I could see in his enthusiastic reaction, reflected as well in the rest of us, that instant impact of a winner. I knew then that Lew was not long for Minnesota. Indeed, I should have had the courtesy to tell him to start packing then.

For pack he did and came to NYU as Chairman of Pathology in 1954 through the lure of Colin MacLeod, Homer Smith, Alwin Pappenheimer, Severo Ochoa, William Tillett, Bernard Davis, and Saul Farber. And with all due respect to his many friends at Minnesota, it was an offer that he couldn't refuse.' (Lawrence, H.S. Presentation of the George M. Kober Medal to Lewis Thomas, *Trans. Assoc. Am. Physicians* 1983, XCVI, 118–133. Reprinted with permission.)

Those were the Minnesota days with Lew Thomas and his gallant crew Bob Good, Dick Smith, Floyd Denny and our late, beloved Lew Wannamaker.

Although I enjoyed the intellectual simulation of the meetings and the good fellowship of the members greatly, I still felt a bit out of it scientifically — probably because I was studying Delayed Type Hypersensitivity, a sort of nondescript occupation at that time — out of the mainstream and unlikely to lead anywhere. Then suddenly the scope and tempo of the whole field was transformed with the perfection of in vitro assays of cellular immunity and the discovery and exploitation of the lymphokines — events that led to liberation from an indolent red spot in the skin as the sole endpoint of the transaction. These advances coupled with the realization that cellular immunity was at the core of understanding mechanisms of allograft rejection, tumor immunity, prevention and recovery from intracellular infections caused by viruses, mycobacteria and fungi and certain types of autoimmune responses added to the attractiveness and prestige of the field that was to evolve into Cellular Immunology.

Yet in those early days I don't think we really convinced Chuck Smith, our late and beloved doyen of coccidioidomycosis, nor other members of the Commission that serum antibody was only the signal that an intracellular infection had occurred and that cell-mediated immunity was at the heart of the mechanism of resistance to and indispensable for recovery from that disease.

Of course this idea had been in contention since Ehrlich and Metchinkoff squared off and sent it whirling down the labyrinthine corridors of time. Nevertheless, we made our report to the Commission that coccidioidin-specific Transfer Factor did indeed transfer delayed reactivity and cellular immunity to coccidioidin from immune to non-immune individuals. Subsequently several other groups went on to show that Transfer Factor immunotherapy of patients with disseminated, amphotericin-resistant coccidioidomycosis resulted in their clinical, immunological and microbiological recovery.

Surely the collective scientific contributions of the Commission members have had a most favorable impact on the health of military and civilian populations alike, however it is the imprint of the people that lingers long after the parade has passed — so many friends Lew Thomas, Gus Dammin, Floyd Denny, MacLyn McCarty, Dick Krause, Paul Beeson, Ted Woodward, and of course our late stalwarts Colin MacLeod, Rammel, John Dingle, Al Stetson, Armine Wilson and Lew Wannamaker among a host of others over the years — truly scientific gentlemen who won the grateful admiration of us all.

SECTION 4—APPENDIX 8

CORRESPONDENCE WITH COMMISSION MEMBERS

Recollections of associations with the CSSD were sought from several former members. Excerpts from letters received from Drs. McCarty, Krause, and Stollerman are included below.

Dr. McCarty was an Associate Member of the CSSD from 1950 to 1954 and a Member from 1954 to 1973. When asked to record in November 1990 some of his memories of the CSSD, Dr. McCarty wrote the following:

> I don't know how much I can contribute to the history of the Strep Commission. I still regret that all of my files on the subject, which may have served as something of a mnemonic, seem to have been discarded as out of date by an overzealous secretary many years ago.
>
> One memory that comes back to me in thinking about the Commission has to do with the period shortly after the war when Bill Tillett was about to become chairman. He called me to ask if I would act as his deputy while he was serving in this capacity. I had just taken over the strep lab at Rockefeller on the retirement of Homer Swift, after five years of having no responsibilities other than working at the bench, and I was fixed on the idea that I ought to avoid extracurricular activities until I had this new job well in hand. I was further motivated in this idea by the fact that I considered myself on trial in this job, having not received a promotion to member or even associate member. Taking on an active department, with Rebecca Lancefield as one of the members, and the rheumatic fever service in the hospital seemed like a big challenge to me.
>
> In any event, I felt that I had to decline Tillett's invitation. I tried to do this diplomatically, but it was immediately evident that he was annoyed with me. In retrospect, I think it is clear that I was being overcautious and could have easily managed to take on this activity. The upshot was that I did not become a member of the Commission until a few years later (I think in 1951 or 1952). Tillett never mentioned the matter to me again, and we ultimately resumed our friendly relations.
>
> With regard to the contributions of the Commission and its members to science and to the military, I don't believe that I have anything new or unique to offer. Beginning with the star in its crown, the Fort Warren Laboratory, it played a major role in the study of streptococcal infections and their sequelae, which had its impact on our general knowledge of the organism and its diseases as well as on their control in both military and civilian populations. From the point of view of providing a forum for the exchange of ideas and new information, it is clear how the members of the Commission in 1973 lost no time in organizing a "Streptococcal Club" to replace at least that function. Now appropriately renamed the "Lancefield Club," it continues to do this successfully.
>
> While writing this letter it occurred to me to look at the list of Commission members in the recent AFEB anniversary volume to confirm some of the dates. Aside from a number of howlers in the affiliations given (Jim Hirsch and Steve Morse are credited to the Rockefeller Foundation, for example), the list is informative. My dates are given as 1951-1973, more or less confirming what I wrote above. From 1971 I had the title of Advisory Member, which was the compromise reached when I proposed to resign, since with Dick Krause and Becca also members I felt that Rockefeller representation needed to be deemphasized. (I at least have the correspondence on this point, and don't have to rely on memory.)
>
> With so little that is concrete to contribute, I've probably gone on too long already — so I'll close with warm regards.

Dr. Krause had an unusual relationship with the CSSD. While still a medical student at the Western Reserve University (as it was then called) School of Medicine, he spent a year at the Streptococcal Disease Laboratory working primarily on the quantitation of M protein. The impetus for these studies was the apparent loss of M protein from strains of streptococci that were carried in the pharynx for long

periods following acute infections. After graduating from medical school and finishing his residency training in internal medicine, he went to the Rockefeller Institute for Medical Research to study with Drs. Lancefield and McCarty. He subsequently was Professor and Chairman of the Department of Epidemiology at Washington University. After returning to the Rockefeller for several years, he became Director of the Institute of Allergy and Infectious Disease of the National Institutes of Health. Dr. Krause was an Associate Member of the CSSD from 1960 to 1963. He was a member from 1963 to 1973 and the CSSD's Deputy Director from 1968 to 1973. His work was supported in part by the CSSD. He writes in November 1990 of some of his recollections of this work as follows:

> You have asked about the work from my laboratory which was supported in part by the AFEB (in particular Loring Air Force Base). There were two papers published. One, the lead article in *The New England Journal of Medicine*. volume 270, pages 1205-1212, 1964, was entitled 'Prevention of Streptococcal Pharyngitis Among Military Personnel and Their Civilian Dependents by Mass Prophylaxis.'
>
> The spread of streptococcal disease in a population such as Loring Air Force Base was more typical of a civilian community than a military population such as a recruit training command. In the case of Loring Air Force Base the health of the military personnel is influenced in large measure by the health of members of the family as evidenced by the fact that the control of streptococcal pharyngitis among the dependents was an important feature in the control of the disease among the military. Because of the relatively high incidence of streptococcal pharyngitis, penicillin prophylaxis was administered to the children during the third week of February. Targeting this population had a remarkable impact on the subsequent decrease in streptococcal pharyngitis in the military personnel even though they had not received penicillin prophylaxis.
>
> The next study, in many ways, was more interesting. It was published in the *Journal of Laboratory and Clinical Medicine*, volume 56, pages 483-494, 1966. This was entitled 'Studies on the Transmission Within Families of Group A Hemolytic Streptococci.' As noted above, epidemiologic research on group A hemolytic streptococci at Loring Air Force Base had directed attention to the role of interfamilial transmission of the organism in the persistence and spread of streptococcal disease in the community. The personnel at Loring Air Force Base, unlike that at a large recruit training center, consisted predominantly of married military personnel and their dependents. Group A hemolytic streptococcal prevalence was determined for the family contacts of index cases of streptococcal associated respiratory disease and the family contacts of index cases of non-streptococcal respiratory disease. Prevalence percentage of A-positive contacts was at least five times higher for streptococcal index cases than that for the non-streptococcal index cases. This suggests that the home was the major locus and the school the secondary locus for the spread of streptococcal disease in this community. These studies emphasize that patients with streptococcal disease are a potential hazard to other members of the family including the military personnel. Under certain circumstances the identification of streptococcal pharyngitis in one member of the family may warrant bacteriologic procedures to prevent possible spread to other family members.
>
> From 1962 until 1975 I was receiving support for various studies from the Streptococcal/Staphylococcal Diseases Commission [CSSD]. The emphasis of the work was the immune response in rabbits and mice to the polysaccharide antigens of the hemolytic streptococci. When I started this line of investigation, at the time I moved my laboratory to St. Louis, it was my intention to look at the immune response to streptococcal vaccines in rabbits using all the new methods of immunology, moving away, in other words, from the antistreptolysin O and the other long tried and true tests as well as the quantitative perceipitin test. As part of this strategy I recruited people into the laboratory in St. Louis who had been trained in the new immunology, such as Kirk Osterland and Eng Tan who came from Henry Kunkel's laboratory, and Julian Fleishman who came from Rodney Porter's laboratory. The confluence of these new people in the lab and their assistance at looking at the immune response with the new methodologies of the sixties resulted in the end in the use of streptococcal antigens to examine mechanisms of immunity. An unexpected opportunity for this effort was the chance observation that certain rabbits produced 20-50 mg/ml of serum of homogeneous antibody to the group specific polysaccharides. Further studies using rabbits of known pedigree revealed that this response was an inherited trait.

With a plentiful supply of homogeneous antibodies it was possible for the first time to perform structural studies on induced antibodies rather than the myeloma proteins, the only source of homogeneous gamma globulin prior to this time.

Most important for immunogenetics, these antibodies to the streptococcal carbohydrates were used as probes for examining the inheritance of idiotypes. The concept of idiotype emerged from Oudin's studies on the use of specific antibodies as antigens. The unique antigenic element of a specific antibody is the antigen binding site. When the antibody is used as an antigen the anti-antibody is directed against this antigen binding site, and in serologic terms this is called the idiotype.

There were a number of attempts in various laboratories to show the possible inheritance of idiotypes as genetic markers but these were inconclusive. At this juncture it would require a special experimental system and probably a good ration of luck to demonstrate unequivocally that there was genetic inheritance of the idiotype, and by implication, the genes coding for the binding site. Such, in fact, proved to be the case with extensive studies published in a number of papers from the laboratory. In a study of over 133 closely related rabbits and a comparison to 97 unrelated rabbits, there was a clear familial clustering of the idiotype of the proband antibody.

A number of laboratories, after I withdrew from the field in 1975, extended the work to use idiotypy to show the regulation and modulation of immunity. For example, the idiotypic antibody (streptococcal) was used successfully to suppress specific antibody production and it was shown that it was possible to induce T and B cell immunity by anti-idiotypic antibody. These and other observations were part of the background against which Neils Jerne developed his antibody network hypothesis for immune regulation.

Another line of investigation concerned the biological properties of peptidoglycan. This was the work of Jiri Rotta and was published in the *JEM*. He came to the laboratory in 1963 having made the prior observation that streptococcal cell walls would increase nonspecific resistance of mice to subsequent challenge by streptococci. The problem was to determine which component of the cell wall was responsible for this enhanced non-specific resistance. He conclusively showed that this was due to peptidoglycan and not to other cell wall components. He also showed that the peptidoglycan had a number of properties that were similar to endotoxin but he proved beyond doubt that the biological activities of the peptidoglycan fraction was not due to endotoxin contamination.

These were important studies because they contributed to a growing body of evidence of the importance of peptidoglycan components as possible adjuvants. As you know, there has been much done on the smallest component of peptidoglycan that serves as a powerful adjuvant. Muramic acid with several amino acids attached (muramyl dipeptide) is the smallest molecule, and several different compounds using different amino acids are now in clinical trials for adjuvant activity.

This is probably much more than you want to know, Floyd, but it did give me a chance to reminisce over a long period of support by the Commission. It was all great fun and it was the best of times, of course, at Warren Air Force Base.

Dr. Stollerman spent a short period of time at the Streptococcal Disease Laboratory to collect streptococcal strains for some of his studies at Irvington House. In later years some of his work with streptococcal M protein was supported through a contract with the CSSD. He was an Associate Member of the CSSD from 1956 to 1970 and a Member from 1970 to 1973. When asked in December 1990 to record the impact of the CSSD on his work he wrote the following:

Your letter of October 10, 1990, conjures up some of the most poignant memories of my research career. It was, in part, with the timely and valued support of the AFEB Commission on Streptococcal and Staphylococcal Diseases that I was able to focus on the problem of type specific immunity to strep M serotypes in the late 50's and early 60's while I was a Northwestern University.

I had just arrived there from Irvington House where I had become fascinated with the bactericidal test of Todd, refined by Sid Rothbard and Rebecca Lancefield, as a test-tube microcosm of the contest between group A streptococci and the phagocytes of the human host. Dr. Lancefield herself supervised my grasp of

that test and taught me the critical importance of the phase of virulence in which the organism had to be maintained to retain their remarkable resistance to phagocytosis, and that this phase could usually be maintained by repeated mouse passage or passage through fresh human blood.

Armine Wilson was also very helpful in supplying me with strain variants of M serotypes that either had lost the characteristic large capsules (and thus suffered some decline in resistance to phagocytosis), or had retained encapsulation but lost M protein, thus also suffering an anti-phagocytic decline.

It was while making Giemsa stains of the blood-strep mixtures at time intervals during the incubation period of the bactericidal tests that I first observed the inverse relationship of virulence and encapsulation to chain length. In the first hour of growth in either blood or plasma, chain-length shortened dramatically. In contrast, growth in the presence of homologous M antibody caused a spectacular extension of chain length, and this reaction proved to be exquisitely M type specific.

What soon became apparent to me, however, was that this chain reaction to homologous M antibody was not applicable to most strains isolated from throat cultures in community studies (made with Alan Siegel and Eloise Johnson at Childrens Memorial Hospital in Chicago). Strep throat strains rapidly lost virulence during convalescent carriage, and therefore these strains were often unencapsulated, poor in M protein content (though often still typable) and tended to grow spontaneously in longer chains. Moreover, we were beginning to recognize that only a few freshly isolated strains from children with endemic pharyngitis in civilian settings were fully developed in capsular, M protein and antiphagocytic properties when rheumatic fever was rapidly declining in prevalence.

One of these fully virulent variants still haunts me because it was an encapsulated M type 5 that caused acute rheumatic fever within 10 days in a 10 year old boy leading to mitral and aortic regurgitation, despite the treatment of the child on the tenth day with intensive penicillin therapy! A truly rheumatogenic strain was that one and it subsequently fortified my bias toward the essential role of virulence properties in the rheumatogenicity of group A strep. Strains with such properties caused epidemics of rheumatic fever at Great Lakes Naval Training Center (my studies with Paul Frank) whereas rheumatic fever became scarce and then virtually disappeared at the Childrens Memorial Hospital clinic (studies with Alan and Eloise) coincident with the disappearance of these strains. I could not help being impressed with this epidemiologic contrast. The dissociation of ARF and AGN in the subsequent Memphis studies with Alan Bisno further strengthened the conviction of strain "rheumatogenicity." Some eminent future investigators were in my lab as medical students during my sojourn at Northwestern University such as Fred Kantor (now Beeson Professor of Medicine at Yale) and Irun Cohen (now Head of the Department of Cell Biology at the Weizmann Institute), but most particularly the late Edwin Beachey who was my patient when he developed rheumatic fever as a medical student. Dick Ekstedt and I were then studying the effects of removal of the capsule with hyaluronidase. By such treatment we released into the supernate very small quantities of the most spectacularly type-specific inhibitor of the long chain reaction we had ever encountered. It turned out to be highly purified M protein but present in such small quantities as to be undetectable except by biologic tests. But the experiments reinforced my suspicions that the purest M protein could be split off from the strep surface and subsequent vaccine development might depend on such gentle enzymatic treatment.

Our studies of purification of M protein at that time were made from hot acid extracts of M protein as crude starting material. This purified preparation , though M-antigenic (with incomplete Fruend adjuvant) was still strikingly reactogenic. When Ed Beachey joined me in Memphis, we struggled to remove this toxicity by further purification until 1976 when we finally gave up and concluded (*J.C.I.* and *J. Immunol*) that the toxic moiety was an inherent part of the same molecule that contained the type specific antigen (TSA) and that this toxic component could be removed only by splitting TSA off the outermost surface of the organism.

These studies led Ed Beachey to use dilute pepsin at suboptimal pH to prepare "Pep-M." Rebecca Lancefield had tried a pepsin approach in her early studies, but at the time the methodology for protein purification was not sufficiently advanced for much success. The arrival in my lab in Memphis in the early 70's of Itzhak Ofek from Jerusalem changed our approach. Itzhak brought with him from Issac Ginsberg's lab (at the Hadassah Dental School) purified lipoteichoic acid. Ed and I had been awed by Gibbon's studies on adherence of salivary strep to the teeth as a cause of caries. We were convinced that at the very end of the M protein molecule of group A strep would be the adherence lectin. To our astonishment, splitting off pep

M allowed the strep to adhere more avidly to oral membrane receptors. Moreover, the specific blocker of adherence turned out to be lipoteichoic acid! The avalanche of subsequent adherence studies is now history. Meanwhile, we had removed from the surface a piece of M protein of great purity and very little reactogenicity.

When I could get Ed Beachey to return to the "pep M" protein, he identified its molecular primary amino acid structure with the help of Jerry Seyer at the Memphis VA labs. The small peptide epitopes of the M molecule that were protective were molecularly defined and were separate from the non-type specific moieties that Ed and Jim Dale were sorting out as cardiac tissue cross reactants. Ed and I almost had a shot at organizing a vaccine study in the Soweto section of Johannesberg, South Africa in 1972 at the invitation of the South African Medical Council. All that went up in smoke in the political upheavals of that poor ghetto where the prevalence of acute rheumatic fever had reached unprecedented rates. The responsible strep strains were there for the study but vaccine plans went up in smoke in the political turmoil of that civil rights revolution.

Finally, the recent focal outbreaks of acute rheumatic fever in the U.S.A. occurred just before Ed's death, but in time for Ed's work on the molecular structure of rheumatogenic strep to be confirmed by Vince Fischetti and his group in their painstaking studies of the extended M molecule in the rheumatogenic strains collected at the Rockefeller University. The issue of a strep vaccine for selected strains of strep may still be alive. Some people are still asking surviving old-timers like me to discuss its prospects. The latest wrinkle to add is that the toxic property of M protein may be that of a "superantigen" that attaches directly to the T cell receptor! Malak Kotb, the Egyptian lady transplant immunologist who was working with Ed Beachey when he developed cancer, has been in touch with me to review my early experience with the toxicity of M protein. The old studies of the toxicity of streptococcal hemolysins and especially of cell-bound streptolysin S as well as the M protein have been reviewed. M protein, part of which is antiphagocytic and part of which may react nonspecifically with autoimmunity-regulating T lymphocytes now offer fascinating new possibilities about the pathogenesis of rheumatic fever. Stimulation and dysregulation of the strep immune response may be another ploy in the effect of M-rich strains of strep on human tonsillar tissues.

It was great to be part of the great tussle with the strep since the 40's. I will always be grateful to Colin MacLeod and to the Commission for allowing me to enter the fray.

SECTION 4—APPENDIX 9

COMMISSION DIRECTORS DURING WORLD WAR II

The Commission on Hemolytic Streptococcal Infections had two directors during World War II: Dr. Martin H. Dawson, College of Physicians and Surgeons, Columbia University, 1941 and 1942 and Dr. Chester S. Keefer, Boston University School of Medicine, 1942 to 1946. We do not have a picture of Dr. Dawson but the picture below was kindly furnished by Dr. Theodore Woodward.



CHESTER F. KEEFER, M.D.

SECTION 4—APPENDIX 10

COMMISSION DIRECTORS AFTER WORLD WAR II

William S. Tillett
Director, 1948 to 1954

Dr. Tillett had a long and distinguished career as one of the leaders of American academic medicine. His service to the military as adviser and consultant in streptococcal diseases spanned 25 years. He was a member of the Commission on Hemolytic Streptococcal Infections from 1941 to 1946 and was the first director of the Commission on Streptococcal Diseases; he remained a member until 1966. He died in 1974 at the age of 81 years.

The memorial that follows was written by Dr. Lawrence, Dr. Tillet's long-time student and colleague, and is reprinted with the permission of the *Journal of Infectious Diseases*.

Obituaries

It was with great sadness that I learned of Dr. William Smith Tillett's death on April 4, 1974 after a brief illness. He was a fine man, an outstanding scientist, and a beloved physician who is sorely missed by his family, his friends, his colleagues and his students.

Dr. Tillett was a gentleman of the old school: courtly, urbane, witty, and possessed of a grace and softness that was most cherished by the patients at Bellevue Hospital, to whom he was devoted. At the same time he had a common touch for humanity and its foibles, and he could put his finger on the crux of any situation in the laboratory, in the drawing room, or at meetings, for he had little patience with sham or pretence. His forthright and outspoken resolution of a problem at issue could be humorous or sober, and, being incapable of subterfuge, he cleared the air.

Dr. Tillett received his bachelor's degree from the University of North Carolina, where he was a good scholar and an All-American quarterback. After receiving his medical degree at Johns Hopkins, he enlisted in the army and saw action during World War I in France as the captain of a battalion of engineers in the Army Medical Corps.

After the war Dr. Tillett came to Rockefeller University under the aegis of Dr. O. T. Avery, whom he affectionately called "Fess" and whom he admired and revered both as a man and as a scientist. This was the beginning of a long and fruitful relationship that changed the course of Dr. Tillett's career.

He moved back to Johns Hopkins to become Director of Laboratories, and, stimulated by his observation of the lysis of clots by cultures of streptococcus that had been left standing, he began the pursuit of an idea that was to lead to the discovery of streptokinase and streptodornase.

Dr. Tillett came to New York University in 1938 as Professor and Chairman of the Department of Bacteriology and became Professor and Chairman of the Department of Medicine at Bellevue Hospital in 1939; he remained there until his retirement as Professor Emeritus in 1958. He was active in investigative programs until the age of 79.

During the period he was at New York University, Dr. Tillett's greatest achievements came to fruition; particularly outstanding were the isolation, identification and partial purification of streptokinase-streptodornase from streptococcal filtrates with Dr. Sol Sherry and the application of the principle of enzymatic debridement to purulent and thromboembolic disorders. It was also at this time that Dr. Tillett explored the use of the new drug penicillin in the treatment of pneumococcal infections. He combined his newly found enzymatic therapy with penicillin therapy to eliminate the need for surgery in the treatment of empyema.

Dr. Tillett received many honors and awards (including the Lasker and the Borden Awards) for his discovery of streptokinase-streptodornase and the application of enzymatic therapy to disease. The esteem of his colleagues was reflected in the various phases of his career; he was president of the American Society of

Clinical Investigation, of the Association of American Physicians, and of the Harvey Society. He was also a member of the National Academy of Sciences and chairman of the Streptococcal Commission of the Armed Forces Epidemiological Board.

After his retirement in 1958, Dr. Tillett continued to be active in the investigative academic life he loved so well and was the director of a training program in allergy and infectious diseases sponsored by the U.S. Public Health Service. He was happiest when advising a series of young investigators on their research problems.

Upon his retirement, the Department of Medicine had constructed and dedicated a suite of laboratories in Bellevue Hospital, designated the William Smith Tillett Laboratories. These laboratories and the research they foster were his pride and the only regret he was ever heard to express was that we had usurped for laboratory space a room he had set aside for "thinking."

We all miss him deeply — his humor, his gusto, his incisive mind, and his great heart. A generous and gallant man, he helped to raise those brought low by disease and left his signature on the progress of science and humanity.

Lawrence, H. Sherwood. Obituaries: William Smith Tillett 1892–1974

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WILLIAM SMITH TILLETT, M.D.

Charles H. Rammelkamp, Jr.
Director, 1954 to 1957
1959 to 1968

Dr Rammelkamp, was the Director and scientific leader of the Strep Lab during its entire existence and clearly the most important contributor to the CSSD for over 25 years. This exceptional role in the CSSD is recognized in the following memorial prepared by Dr. Robbins.

Charles H. Rammelkamp, Jr., 1911 to 1981

Charles H. Rammelkamp, Jr. died suddenly on December 6, 1981 of a ruptured abdominal aortic aneurysm at the age of 70. On the night before his death he awakened with abdominal pain and suspected what the diagnosis might be. However, with his characteristic concern for others, he did not bother anyone and waited several hours until his wife awakened at 7:00 am, her usual time. His remark to her was, "I think you had better take me to the hospital, I believe I am going into shock." At the hospital he was indeed in shock, and although surgery was done promptly, he did not recover. At the time of his premature death he had just become emeritus professor and was looking forward to a new and exciting career of scholarly activities. During his career he made exceptional contributions to clinical research, teaching and patient care. His scientific contributions were largely in the field of infectious disease, most notably early studies on the clinical application and mechanism of action of antimicrobials, i.e., sulfonamides and penicillin, and the epidemiology of streptococcal infections, the non-suppurative complications of streptococcal infections such as rheumatic fever and acute glomerulonephritis and the prevention of rheumatic fever by treatment of the streptococcal infection with penicillin.

Dr. Rammelkamp, who was known to all his friends and acquaintances as Rammel, was born in Jacksonville, Illinois, on May 24, 1911. He grew up in a family with a sister and two brothers. The environment was a scholarly one with a father who was president of Illinois College. Rammel obtained his A.B. degree (1933) at his father's college and upon graduation chose a medical career with the intention to become a general practitioner. He attended medical school at the University of Chicago (1937) after which he served as an intern in medicine at the Barnes Hospital in St. Louis (1937-1938). After one year at Barnes he returned to Chicago as an intern in surgery at the Billings Memorial Hospitals of the University of Chicago (1938-1939). His foray into surgery lasted only one year and he returned to Barnes as an Assistant Resident in Medicine (1939). It was never quite clear why he chose to spend a year as a surgical resident because he had few of the attributes usually associated with a surgeon but he seems to have enjoyed it and would often comment upon how valuable he found the experience. The course of his career was really determined in 1939 when he went to the Thorndike Memorial Laboratory of Boston City Hospital as Resident Physician. The Thorndike was an exciting place intellectually. At the time, it was populated by such luminaries as George Minot, hematologist and Nobel laureate noted for his work on pernicious anemia; Soma Weiss, teacher "extraordinaire" and cardiovascular investigator; Maxwell Finland and Chester Keefer, both of whom were distinguished infectious disease investigators. In addition there was a group of young physician-scientists who were to become leaders in academic medicine. Fortunately for the field of infectious diseases Rammel accepted a position with Chester Keefer rather than Soma Weiss. Had he joined Weiss cardiology undoubtedly would have benefited greatly.

Rammel's first task in Keefer's laboratory was to group and type beta hemolytic streptococci, a task that he found tedious and uninspiring. Nevertheless, this was the beginning of a lifelong fascination with the streptococcus and the diseases it causes. Next he chose to study an antibiotic, gramicidin, that had been discovered by Rene Dubos. Although effective in the test tube, gramicidin did not prove very useful in vivo because of its poor solubility. Along with these studies Rammel was involved in experiments with sulfonamides that were just beginning to be used clinically. His first publication dealt with sulfathiazole, the first sulfonamide to be introduced in this country. Most of his early work concerned the pharmacology and clinical application of sulfonamides and the bacterial products, gramicidin and tyrothricin.

In 1940 Dr. Keefer moved to the Evans Memorial Laboratory to establish a Department of Medicine at Boston University. Rammel joined him there and soon was engaged in exploring the use of the new and exciting antibiotic, penicillin. The studies done by Rammel, Keefer, and associates on the pharmacokinetics and clinical effectiveness of penicillin were critical in providing the basis for its rational clinical use. Penicillin was a precious commodity at that time and Keefer was given responsibility for its allocation nationally. Thus, Rammel was strategically placed to be kept informed about all studies being conducted throughout the country. One of Rammel's more significant contributions was to devise a procedure for quantitating penicillin levels in blood and other biological fluids, a method that became universally used.

Rammel's tenure in Keefer's department was highly productive but did not last long. The United States had entered the World War II and the military was experiencing serious problems with acute respiratory disease. A Commission on Acute Respiratory Diseases had been established at Fort Bragg, North Carolina, with Dr. John Dingle as its head. Dr. Dingle recruited Rammel along with a fine group of clinical investigators and epidemiologists to conduct studies directed at elucidating the cause of acute respiratory diseases and to develop methods for their control. Rammel's special assignment was streptococcal disease but he was also involved with studies on primary atypical pneumonia (now known to be due to mycoplasma infection), influenza and other respiratory diseases. During its five year existence, the Commission published extensively on these topics. One of the more significant papers described the relationship of epidemics of influenza with the frequency of pneumonia. This has provided the basis for the influenza surveillance by the Centers for Disease Control which follows pneumonia prevalence as a surrogate for influenza. The Commission adopted a policy of communal authorship of papers; the recorded author was the Commission with only a listing of the members, so that a portion of Rammel's bibliography is not identified under his name.

With the war over, Dr. Dingle moved to Cleveland in 1946 along with several members of the Commission, including Rammel, in order to establish a Department of Preventive Medicine at Western Reserve University School of Medicine. The department made many important contributions over the years but is best known for the landmark ten year Family Study program. This careful study provided a gold mine of information about the common illnesses in families and the population at large. Although Rammel was very much involved in the design and conduct of the Family Study he became intrigued with the high prevalence of streptococcal infection and rheumatic fever in troops serving in the Rocky Mountain area. In 1949 he became the director of the Streptococcal Disease Laboratory at Warren Air Force Base in Wyoming. It was here, in a period of six years, that he and his associates conducted the classical studies on the epidemiology and clinical features of streptococcal infection that demonstrated that rheumatic fever could be prevented if the acute streptococcal infection was treated adequately with penicillin. These studies not only made it possible to prevent rheumatic fever but also provided the clinching evidence of the role of the streptococcus in its etiology. The Ft. Warren laboratory was highly productive scientifically but also served as a training ground for an unusually talented group of young physicians among whom where Lewis Wannamaker, Richard Krause, Chandler Stetson, Harold Houser, and Floyd Denny, all of whom went on to distinguished careers. The significance of their work was recognized when, in 1954, the Albert Lasker Group Award was presented to the Streptococcal Disease Laboratory.

Rammel had been puzzled by the fact that only a single case of acute glomerulonephritis had occurred among the more than 1000 cases of streptococcal infection that had been observed at the Warren Air Force Base. The organism recovered from that case was type 12. This observation he put together with earlier findings from a family outbreak of type 12 infection in which five members displayed evidence of acute kidney disease and proposed the hypothesis that type 12, and possibly others, was a nephritogenic strain of streptococcus. This hypothesis on further study did indeed prove to be correct and type 12 and a few other types are now recognized as having the peculiar capability of producing acute nephritis. He and his coworkers were interested in why some strains were nephritogenic and others were not but several lines of investigation did not yield the answer to this intriguing question.

In 1950 Rammel was asked by Dr. Joseph Wearn, then Dean of the Western Reserve Medical School, to help develop an academic program at Cleveland City Hospital (later to become Cleveland Metropolitan Gen-



CHARLES H. RAMMELKAMP, M.D.

eral Hospital [CMGH], and now MetroHealth Medical Center). Dean Wearn had negotiated with the Mayor of Cleveland a new agreement that gave the medical school appointment power for the staff and provided for new facilities including a research building. Rammel was given the titles of Professor of Medicine, Associate Director of Medicine, and Director of Research Laboratories at City Hospital. He was able to recruit a number of outstanding research oriented staff and new directors of Pediatrics and Surgery. The model he had in mind was the Thorndike Memorial Laboratory at Boston City Hospital but, as it turned out, his influence and that of the new recruits affected all aspects of the hospital's functions. Largely through his efforts the City Hospital became the fine academic institution that it is today.

Rammel continued his interest in streptococcal disease and among other activities developed, with his associates, a mail-in system for the rapid diagnosis of streptococcal pharyngitis that allowed the physician to delay treatment until there was evidence that it was indicated, thus forestalling much unnecessary treatment. He also engaged in a series of studies in Chile on the use of penicillin treatment of acute rheumatic fever and valvulitis.

In addition to the streptococcus, Rammel was interested in the staphylococcus. Along with A.J. Gonzaga, Edward A. Mortimer, Jr., and Emanuel Wolinsky, he conducted a series of classical studies on the epidemiology of staphylococcal infections in newborn nurseries. At the time, epidemics of staphylococcal infections were occurring frequently with considerable morbidity and mortality. Their studies showed, quite conclusively, that infection was transmitted on the hands of the caretakers and that simple handwashing was an effective control measure.

Although Rammel's principal scientific interests were in the field of infectious diseases and streptococcal and staphylococcal infections in particular, he brought the same degree of curiosity and scientific analysis to whatever he was concerned with. He was a strong advocate for the application of basic science to clinical problems and was concerned that basic principles were not being taught adequately in the ambulatory or outpatient setting. He devised and put into effect an ambulatory unit where students and their instructors could investigate their patients in more depth than was usual in the clinic. This became an effective and unique teaching unit in which ambulatory patients received exceptionally fine care.

Another example of Rammel's ability to combine a scientific approach with his great concern for teaching and patient care was the "Firm" system of organizing medical care. He had been impressed with the advantages of the "Firm" system as practiced in Great Britain. This consists of a group headed by a senior physician and including registrars (the equivalent of residents and fellows in the U.S.) and students who are responsible for the total care, on a continuing basis, of a group of patients in the hospital and the ambulatory care. This provides for a degree of continuity of care and teaching that does not occur in the usual U.S. system. Although at first he was primarily interested in improving patient care and teaching, he immediately saw its research potential. One can introduce a certain procedure or behavior into one or more firm[s] and not the others and compare the outcome. A key feature of the program is the random assignment of patients to the firms. Since Rammel's death, this unique technique of health care research has been continued at Metro by a cadre of young physicians. Their studies have evoked interest around the country.

Rammel had a profound interest in education. His inquiring mind was always searching for more effective ways to teach. He was a major force in the construction of the innovative curriculum at Western Reserve. His particular interests were better ways of integrating basic science with clinical teaching and the application of epidemiologic principles. He was one of the architects of the so-called "basic" clerkship which was a four month period on either a medical or pediatric service and constituted the student's first intensive clinical experience. It was a long enough period so that the student could experience some continuity of patient care and contact with one group of faculty. It also provided the opportunity to do special projects and to give greater attention than is usually the case to biomedical and psychosocial processes underlying disease.

Rammel's concern for the education of his resident staff was great and, as already mentioned, in large part motivated the introduction of the firm system which proved so successful. He was always available to his house staff and fellows and was much concerned with their education and their personal welfare as well. As a result he was much admired and even loved by most of them.

Rammel was married to Helen Chisholm who was Chester Keefer's secretary and they had three children: Charles H., III, Colin C. and Anne K. Davies. Rammel was devoted to his family although he did not spend as much time with them as he might have because of his heavy schedule and tremendous devotion to his work. However, they had a cottage on the shore of Lake Michigan and he always found some time each year to spend there. The Rammelkamp family was close but not particularly interested in the social life of the community or faculty.

Rammel very much enjoyed association with his faculty, house staff and fellows and his colleagues throughout the country. Typically, with a cigarette in his mouth (in spite of many efforts, he never succeeded in kicking the habit), he would often be found deep in discourse with a group of colleagues that would continue to all hours. The topics discussed would deal with science, education, or intellectual subjects, to a limited extent the usual academic gossip. Although Rammel was actively engaged in many professional societies and served as an officer including being president of many, he had little interest in professional politics. Indeed, among his outstanding attributes were a lack of personal ambition for power or prestige and an unselfish concern for his colleagues no matter what their rank or position. He was a warm, enthusiastic man who evoked respect and admiration from his colleagues and peers and exceptional loyalty from those who worked with or for him.

This biography was written for the *Biographical Memoirs* of the National Academy of Sciences and appeared in Volume 64 of the series. It is reproduced here with permission of the National Academy of Sciences.

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Armine Taylor Wilson
Director, 1957 to 1959

Dr. Wilson, clinically trained as a pediatrician, joined Dr. Lancefield's laboratory at the Rockefeller Institute for Medical Research in 1940 and began a lifelong career as a preeminent streptococcal microbiologist. As director of the Navy's streptococcal typing laboratory, he was closely involved with streptococcal problems in the military during World War II. After discharge from the Navy, he directed the Microbiology Laboratory at the Alfred I. DuPont Institute of the Nemours Foundation in Wilmington, Delaware. He was a charter member of the reorganized CSSD in 1948 and remained a member until his death.

In 1964, because of his importance to the CSSD and their affection for Dr. Wilson, Drs. Wannamaker and Denny wrote the following article, which is reproduced with permission from Mosby-Year Book, Inc.*

An Effective Career Off the Mainstream

The field of pediatrics is so complex and encompasses such a broad area that oftentimes individuals working unobtrusively may make contributions of unusual significance which in large part go unnoticed by the mainstream of pediatrics. Dr. Armine T. Wilson, whose untimely death occurred on Dec. 7, 1964, is a distinguished example of a man trained in pediatrics and dedicated to its principles who found that he could contribute most abundantly through laboratory observations.

Dr. Wilson was first attracted to pediatrics by his association with Dr. A. Graeme Mitchell, head of pediatrics at the University of Cincinnati College of Medicine. He served as chief resident at Children's Hospital in Cincinnati, 1939 to 1940. While with Dr. Mitchell, Dr. Wilson developed an interest in bacterial pheumonia in children and published data on its treatment with sulfapyridine. Dr. Oswald T. Avery, who was on the board of the Children's Hospital at that time, recognized Dr. Wilson's potential for investigation and lured him to the Rockefeller Institute for Medical Research. At this time he worked side by side with Dr. Rebecca C. Lancefield and began the association with hemolytic streptococcus which lasted his entire lifetime.

Dr. Wilson was intimately involved with Dr. Lancefield in the classical work of typing group A streptococci. Much of his subsequent investigation was directed toward elucidation of the intricate biologic properties of hemolytic streptococci, including sulfonamide resistance, antigenic structure, colonial characteristics, and properties related to phagocytosis. A contribution of unique interest to pediatricians was his investigation of the antistreptococcal properties of milk.

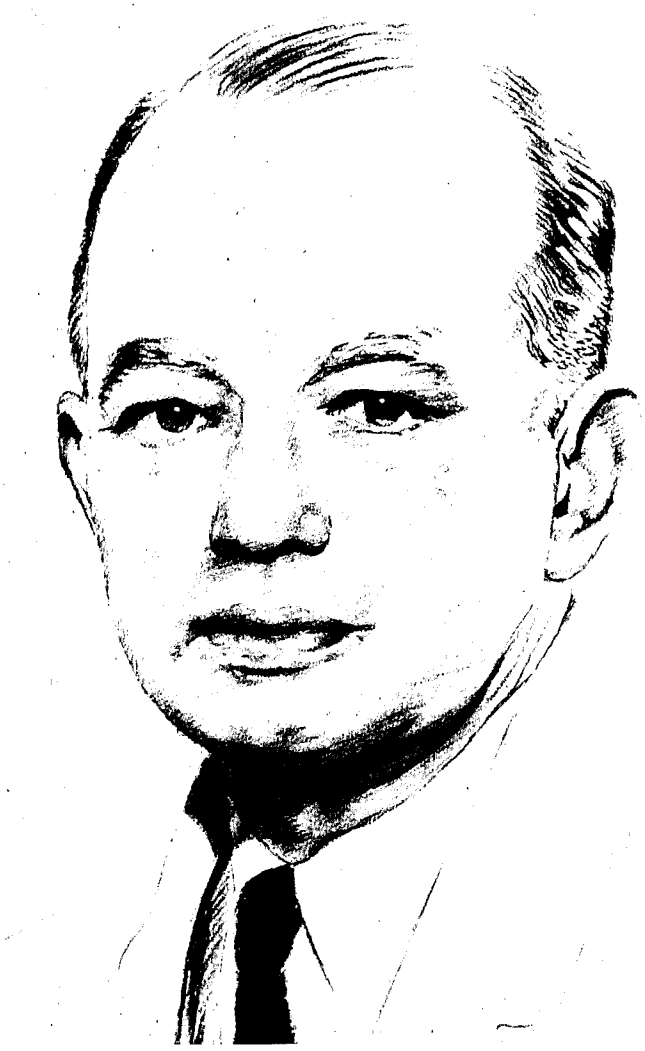
Evidence of his motivation to share his knowledge with students of pediatrics can be found in his concise but comprehensive section on streptococcal infections which first appeared in the 1950 edition of the Mitchell-Nelson standard *Textbook of Pediatrics*, with subsequent revisions until 1964. Although his natural bent was more toward investigation than formal teaching, a suppressed desire to contribute to student education also emerged in an unusual form in his production of a professional teaching film on the dynamics of phagocytosis. This meticulously prepared film has received wide acclaim and use and was officially recognized by receiving the Biological Photographic Association's "Award of Excellence, First Place" on Sept. 3, 1959.

Dr. Wilson's curiosity extended beyond the confines of streptococcus and included observations on the problems of cholera, which took him to various parts of the Near and Far East, and investigations of new methods of sterilization by ethylene oxide.

Beginning with his tour of duty in the Navy during World War II, Dr. Wilson had a continuing concern about problems of epidemiology and military medicine, and served as a member of the Commission on Streptococcal and Staphylococcal Diseases of the Armed Forces Epidemiological Board from January, 1949, until his death. He was director of this Commission from May, 1957, to May, 1959, and was instrumental in broadening its objectives to include staphylococcal diseases.

From the time of his discharge from active duty with the Navy, Dr. Wilson's microbiology laboratory at the Alfred I. DuPont Institute of the Nemours Foundation in Wilmington, Delaware, was an unsurpassed mecca for those whose interests touched his own. Armine Taylor Wilson was a man of quiet wisdom and sound judgment, who in his unhurried and controlled approach to life found time to discuss problems at length and in depth. His unique contributions and his personal dedication to medicine and scientific investigation will enrich the field of pediatrics for many years to come.

*Reprinted with permission from Wannamaker, L. W., and Denny, F. W. An effective career off the mainstream. *J. Pediatr.* 1966, 69, 851–852.



ARMINE T. WILSON, M.D.

Lewis W. Wannamaker
Director, 1968 to 1973

Dr. Wannamaker, one of the most outstanding products of the Strep Lab, had a long association with the CSSD. He was a member of the CSSD from 1954 to 1973, its Deputy Director from 1963 to 1968, and its Director from 1968 to 1973. Lewis died on 24 March 1983 at the age of 59 years. Shortly before his death, he participated in a Ross Conference, entitled the "Management of Pharyngitis in a Era of Declining Rheumatic Fever." This conference was dedicated to his memory.

The memorial to Lewis by Dr. Denny accompanying the conference proceedings is reprinted below, with permission of Ross Laboratories.

I first met Lewis Wannamaker in 1948 in Cleveland, Ohio, where we had been assigned by the Army to study streptococcal infections and rheumatic fever under the direction of John Dingle and Charles Rammelkamp in what was then the Department of Preventive Medicine at Western Reserve University School of Medicine. We remained close friends thereafter until his untimely death on March 24, 1983. It is a privilege for me to write this memorial about this man whom I admired and respected very much.

Under the direction of and in collaboration with Rammelkamp, Lewis began to develop as a scientist. After a period of indoctrination in Cleveland, he joined "Rammel" and others in establishing the Streptococcal Disease Laboratory at Warren Air Force Base, Wyoming. There he developed expertise in and love for clinical and epidemiologic research, an affection that permeated his future investigations. He was instrumental in the many accomplishments of the Strep Lab, including the elucidation of many aspects of the epidemiology of group A streptococcal pharyngitis and the demonstration that the treatment of streptococcal pharyngitis with penicillin and other effective antimicrobial agents prevents rheumatic fever — a feat that earned the Lasker Award in 1954. I suspect it was also at the Strep Lab working with Rammelkamp that Lew developed some of the drive that helped him accomplish difficult tasks in his future career.

In 1952, Lewis joined the faculty of the University of Minnesota, where he subsequently became Professor of Pediatrics and Microbiology and Chief of the Division of Pediatric Infectious Diseases. Between 1955 and 1957 he worked with Maclyn McCarty at what was then the Rockefeller Institute for Medical Research. Laboratory skills were added to his clinical and epidemiologic armamentarium, and the stage was set for a brilliant career. This was recognized by the American Heart Association in 1958 when he was appointed a Career Investigator, a position he held until his death.

Lewis received many awards and honors, including the John Simon Guggenheim Memorial Fellowship, Helen Hay Whitney Fellowship, Outstanding Civilian Service Medal from the Army, Alexander Von Humbolt Award, Duke University Distinguished Alumnus Award, and the Josiah Macy, Jr., Foundation Faculty Scholar Award. In 1980 he received the Robert Koch prize and medal and in 1982 was elected to the Institute of Medicine, National Academy of Sciences. He was a member of many distinguished scientific societies and served on the editorial boards of several medical journals. He was a consultant to The Surgeons General of the Public Health Service and the Army. His special interest in streptococcal infections in the military was evidenced by his longtime membership on the Commission on Streptococcal and Staphylococcal Diseases of the Armed Forces Epidemiological Board; he served as director of this group for many years. Lewis was especially devoted to the American Heart Association and served as the Chairman of its Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis; in 1972, he delivered the T. Duckett Jones Memorial Lecture at the annual meeting of the Association.

Lewis' laboratory at the University of Minnesota Medical School was a mecca for all who had an interest in streptococci and the diseases they cause and an international resource for characterizing streptococci. Lewis was one of the world's authorities on the biology of group A streptococci and the clinical and epidemiologic aspects of streptococcal infections. Examples of his work include the identification of several nucleases of group A streptococci and discovery of a consistent antibody response to one of these nucleases in patients with streptococcal infections; this test has become a standard laboratory method for diagnosis of streptococcal infections. He and his colleagues published classic epidemiologic studies that showed biologic differences in host response when group A streptococci infect the skin or the pharynx. Lewis' laboratory



LEWIS W. WANNAMAKER, M.D.

contributions also include new knowledge about the genetic behavior of streptococci and the role of surface factors and extracellular products in disease.

Lewis was mentor for scores of trainees now in positions of scientific leadership throughout the world. He taught by example and a quiet, determined insistence on the best efforts in research and in writing. His judgment was sought constantly by students and colleagues at Minnesota, and his door was always open. Investigators from England, Germany, Egypt, Poland, New Zealand, India, Scandinavia, and the Orient spent time in his laboratory and were in frequent communication, since Lew shared his knowledge, counsel, and judgment with scientists throughout the world.

As much as Lewis accomplished as an investigator and as a clinician, he may have been appreciated most for his qualities as a human being. He was soft spoken, kind, deliberate in his actions, and slow to anger, but in matters of principle he could be extremely obstinate. He also possessed a rich sense of humor. Some of these qualities were brought home to me by two incidents following his death. I called a mutual friend to tell him that Lew had died and his response included, among other things, "He was some kinda guy." Another mutual friend told me that, in spite of Lew's national and international prominence and influence, he had never heard one derogatory word about Lewis Wannamaker — a remarkable accomplishment indeed. I have never known a finer man.

Lewis is survived by his wife, Hallie; four children: Julie, Ann, Libby, and Whit; his mother; and two brothers. His family was his first priority, and Hallie was a true partner in all of his activities. Those of us who knew Lew well realized his great dependence on Hallie in everything he did; she certainly deserves much credit for his many accomplishments.

Lew participated in this Ross Conference only a month before his death and he contributed greatly to its success. We all turned repeatedly to him for counsel and guidance, which he gave in his quiet and unassuming manner. It is so very appropriate that this publication is dedicated to Lewis Wannamaker. My life was enriched immensely by my friendship with him. I join all of his many friends in paying tribute to this gentle and remarkable man.

SECTION 5

Commission on Enteric Infections

Foreword

The diarrheal diseases have accounted for rates of morbidity and mortality equal to those of enemy action. One has only to recall such disasters during the American Revolution, the Civil War, the western colonization of the United States, the Spanish American War, the war with Mexico, and World War I to realize the impact of dysentery disorders and typhoid fever as two very disabling intestinal infections.

The Commission of Enteric Diseases was founded on rock and blessed during its history with such capable and enthusiastic directors as Drs. James Watt, Albert Hardy, Francis Cheever, Horace Gezon, and Tom Hendrix who guided the Commission's activities from its inception in 1949 until its termination in 1973.

Mary Jane Wood and Dr. Richard B. Hornick, in their very informative and interesting history describe the events and contributions that led to understanding of pathogenesis and control of bacterial and amoebic dysentery better, including cholera and *Escherichia coli* infections, the salmonelloses, particularly typhoid fever, and the various forms of viral gastroenteritis, a new field to which much needed knowledge was added. Commission members were stars in their own right, and their contributions helped clarify the roles of normal and pathogenic enteric agents. In addition, the importance of clean water and noncontaminated food, as well as the impact of control by newly developed vaccines, were recognized.

Many Commission members made personal sacrifices by traveling abroad during active medical military circumstances to observe and survey alongside their medical military counterparts. They not only helped to assess the magnitude of the problem, but also advised on the best practical way to reach a desirable solution.

To Dick Hornick, I am indebted for his part in preparation of this chapter. Not only does he have my grateful thanks, but also congratulations for his important contributions, along with his associates, to the development of knowledge in the important field of intestinal diseases. We regret, despite efforts to obtain them, that photographs of some of the key contributors are not available for inclusion in the section.

— *Theodore E. Woodward, M.D.*

History of the Commission on Enteric Infections

Mary Jane Wood, B.S., R.N.
and
Richard B. Hornick, M.D.

THE COMMISSION ON ENTERIC INFECTIONS

Drs. Colin M. MacLeod and Thomas Francis, Jr., recognized the need to include diarrheal diseases, which are common military problems, in the spectrum of illnesses to be evaluated by the Armed Forces Epidemiological Board (AFEB). They developed plans for the Commission on Enteric Infections. Subsequently, they met with Dr. James Watt and decided on the formation of the Commission during the 1948 annual meeting of the American Public Health Association. The organizational meeting was held 29 January 1949, and was attended by Dr. MacLeod, as President of the AFEB, Dr. Watt, first Director of the Commission, and members William W. Frye, Albert V. Hardy, and Myron E. Wegman. The meeting was held in New Orleans at Louisiana State University (LSU) as a convenience for Drs. Watt, Frye, and Wegman, who were faculty members at LSU or Tulane University. Dr. Hardy, a member of the Florida State Board of Health was associated with LSU faculty personnel on studies of diarrheal diseases as early as 1936.

At the initial meeting, the group decided that the Commission would comprise five members and direct its studies in five major categories: bacteriologic, parasitological, virological, epidemiological planning, and specific investigation. Drs. Hardy and Watt were asked to monitor parasitological work and clinical studies by Dr. Wegman. Virological activities were assigned at a later date. These five categories and responsibilities were consistently addressed during the 23 years of the Commission's function.

Commission members decided to advance the knowledge on bacterial infections as the first priority. Salmonella and shigella also were selected as agents of the highest priority. Dr. Hardy proposed to survey and evaluate the pertinent problems and determine the relevance of current activities and suggest where additional support was needed to expand the knowledge base.

At the second meeting of the Commission, held in New Orleans on 3 April 1949, five areas of potential research on salmonellae were outlined and served as guidelines for studies in subsequent years. (1) Support was needed for a diagnostic center capable of obtaining accurate diagnoses of salmonella infections. It was noted that the Centers for Disease Control (CDC) could and would provide this service and provide necessary typing sera for specified laboratories. The Commission was expected to distribute the sera based on reliable clinical case reports. (2) Field studies were planned to obtain information on prevalence and incidence of human illness: These were expected to provide relevant data and to collect information on the relationship of human infections and those that occurred in animals. (3) The role of coproantibodies was to be evaluated as an investigative tool. (4) New methods of vaccination, especially those given by the oral route, were to be assessed. (5) New antibiotics were to be evaluated for use in the treatment of bacterial infections caused by salmonella and shigella.

Two grants were approved that were related to the salmonella initiative. One supported analysis of data collected on the epidemiology of salmonella and shigella infections and their control. The second supported an animal model of salmonella infections designed to evaluate various antibiotics.

At the annual meeting of the Commission on 14 April 1950, progress on data analysis was reported with the use of standard key punch machines. The Commission believed that such data analysis would



JAMES WATT, M.D.



WILLIAM W. FRYE, M.D.



ALBERT V. HARDY, M.D.

establish major points of difference in the epidemiological characteristics of shigella and salmonella infections.

Dr. Morris F. Shaffer of Tulane University reported his evaluation of various antibiotics for treatment of salmonellosis in baby chicks. He found that none of the available antibiotics, oxytetracycline (Terramycin), neomycin, polymyxin B and D, or chloramphenicol, were particularly effective in the treatment of salmonella infections. However, certain drug combinations and varying dosage schedules offered promising leads that prompted additional study.

At this meeting, it was recommended that Dr. Frye apply for funding to assess the need to find a single, simple, and reliable diagnostic tool, which was the most important issue in the field of amebiasis, and that Armed Forces representatives who work in the field of diarrheal disease be appointed as members of the Commission. It was conceived that individual research projects could be monitored and coordinated for the ultimate benefit of everyone.

The annual meeting of the Commission on Enteric Infections was held on 26 and 27 March 1951 at LSU. (From this meeting forward, the Enteric Disease Commission was called the Commission on Enteric Infections.) Those who worked in the field of enteric diseases accepted that progress on the fundamental biology of organisms that caused enteric infection had been conspicuously lacking for years. A consensus existed that those techniques that had been successfully applied to enhance knowledge of how bacteria and viral agents affect the respiratory tract had not been applied to the enteric group. Field investigations then used had not provided any completely effective methods of salmonella and shigella control. Commission members stressed that emphasis be placed on clarifying the fundamental biological characteristics of shigella and salmonella.

At this meeting, three groups were working on salmonellosis — Dr. Hardy in Florida, Dr. Watt in Georgia, and Dr. Shaffer in Louisiana. Jointly, they decided to coordinate their activity toward standardizing laboratory techniques and the use of culture medium.

The Committee reported on its consultative participation with the Department of the Army in preparation of a training film on the diagnosis, treatment, and prevention of shigellosis. Research on other films dealing with salmonellosis and typhoid fever was initiated.

The Commission, in association with the Public Health Service and the California Department of Health, conducted a 6-month study of a diarrheal outbreak that occurred in the central valley of California—Fresno and Hildago Counties. Studies were conducted in farm labor camps and fringe areas where housing and sanitary conditions were substandard. A control site consisted of a housing project where improved environmental conditions prevailed. Preliminary findings implicated bacteria of the Shigella group as causative agents in 70% of the cases studied.[1]

A severe outbreak of diarrheal disease among prisoners of war in Korea was reported to the Commission. A group was organized to travel to the Orient to perform field studies. Colonel Richard P. Mason, M.D., Department of the Army, and Dr. Hardy preceded the rest of the group to Korea to assess conditions for the proposed investigation. It was planned to treat the infections with differing combinations of sulfadiazine and chloramphenicol, as well as chlortetracycline (Aureomycin), Terramycin, and streptomycin. Pharmaceutical firms contributed large quantities of drugs for some of these studies. To initiate studies and to ensure having these drugs immediately available, Dr. Hardy carried a 5-gallon container of medications on the airplane to Korea.

Work continued in the United States, with Drs. Watt, Quentin M. Geiman, R. S. Benham, and James N. DeLamater separately investigating the chemical composition and metabolism of *Entamoeba histolytica*. Progress was reported in design and the adaptation of equipment needed to provide large, pure quantities of *E. histolytica* for experimental purposes. Despite some progress, production of ameba in the absence of bacteria in culture media was unsuccessful.

By 1952 and 1953, clinical and laboratory data collected during the Korean study, conducted between April 1951 and January 1952, were interpreted, trended, and published. Five papers were published, two as lead articles in the *Journal of the American Medical Association*.[2,3] Drs. Hardy and Colonel Mason (MC, Director, 406th Medical General Laboratory, Tokyo, Japan) published "The Dysenteries in the Armed Forces" in the *American Journal of Tropical Medicine and Hygiene*.[4] The team of investigators in



MORRIS F. SHAFFER, M.D.



COLONEL RICHARD P. MASON, M.D.

Korea accurately diagnosed the cause with the use of rectal cultures and proctoscopic evaluations in addition to clinical data.[5] A total of 142 examinations was performed in 1 day by two physicians and their assistants! Between 300 and 400 rectal cultures were performed daily. The largest identifiable group of pathogens causing the diarrheal epidemic was shigella, although clinical and laboratory findings differed vastly from shigella infections in the United States. Clearly, the diarrheal infections manifested themselves differently from place to place and time to time. The fly was excluded as the prime disseminator of enteric disease because this particular epidemic occurred in the winter months and the military services had excellent insect control. Mass contamination of food was eliminated as a cause. It was apparent that multiple routes of transmission existed. Presumably, shigella survived in a symbiotic relationship until the environment was changed.[4]

Twenty-four different therapeutic or dosage schedules were studied in the treatment of amoebic dysentery; 18 different modalities were used for treatment of bacillary dysentery. In the case of amebiasis, the best therapy for patients with acute disease was a combination of drugs, e.g., oxytetracycline or Aureomycin plus emetine or chloroquine diphosphate or other less commonly used drugs such as carbarsone, chiniofon, and bismuth glycoloylarsanilate.[2]

In the 1940s and early 1950s, sulfonamide therapy was established as a highly effective treatment for shigellosis. Resistant strains became very common during the Korean conflict. The studies conducted on prisoners of war were designed, in part, to evaluate other antibiotics to replace sulfonamides. The tetracyclines and chloramphenicol were very effective in effecting a clinical and bacteriologic cure.

Dr. Shaffer, at Tulane, continued his work on the pathogenesis of salmonella infections. His studies with chicks showed a correlation between salmonellosis in animals and humans. The work of Drs. Shaffer and Hardy, who studied salmonella in greyhounds and hogs and at various abattoirs, clarified several points: (a) salmonellae are relatively hardy organisms capable of withstanding environmental stresses; (b) very large doses of salmonella are necessary to produce illness; and, (c) in epidemics, a propagation of salmonella in food is an almost universal finding.

The diagnostic value of the complement-fixation test in acute amoebic dysentery was studied by Dr. Marion Brooke, who concluded that the test was of little value. He also evaluated the Moan Precipitation Test. The latter was judged to be of no value.

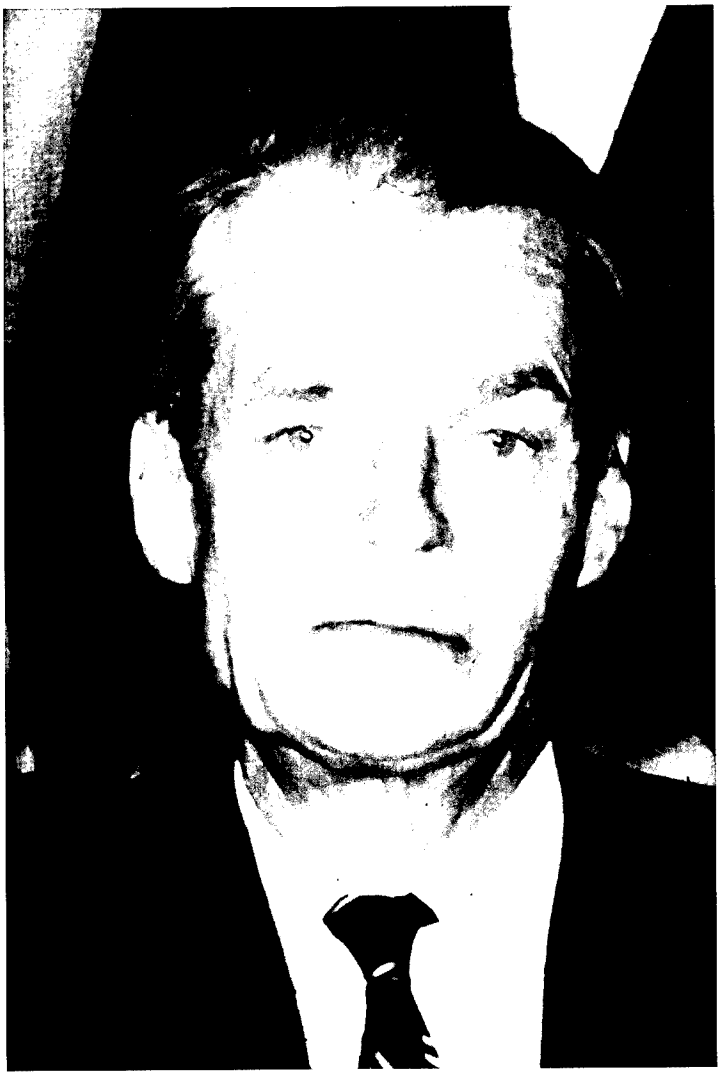
The Commission on Enteric Infections decided to coordinate its activities with the Commission on Immunization with regard to possible field studies to evaluate the efficacy of typhoid vaccines.

Several changes in Commission membership occurred during this period: Dr. Watt resigned his position with the Commission to become Director of the National Heart Institute; Dr. Wegman resigned to devote more time to work with the World Health Organization (WHO); and Dr. Francis S. Cheever, Professor of Microbiology at the University of Pittsburgh, School of Public Health, became a new member.

The spring meeting of the Commission was held jointly with the Commission on Environmental Hygiene in Boston in April 1954. The subjects discussed included (a) amebiasis (Frye), (b) environmental factors related to the dissemination of enteric pathogens (Smith), (c) the control of diarrheal diseases in areas and in population groups with high prevalence (Hardy), and, (d) the pathogenesis of bacillary enteric infections (Dammin).

The Subcommittee on Amebiasis met before this meeting at the laboratory of Dr. DeLamater, School of Medicine, University of Southern California. Drs. Geiman, Frye, and William Balamuth attended. An outcome of their visit was the suggestion that the strains of *E. histolytica* (DKB and HK-9) be used for all studies to ensure consistency. Work on antibody production and the study of immunity was slow and somewhat discouraging.

The Commission on Enteric Infections continued to divide its work into two fields: studies of amebiasis, under the direction of Dr. Frye; and nonamebic enteric infections, under the auspices of Dr. Hardy. The possible role of viral agents as a cause of enteric diseases began and was reported in the annual report of the Commission in March of 1955. Dr. Cheever (University of Pittsburgh), Lieutenant Colonel R. Linberg, M.D. (Army Medical Service Graduate School), and Drs. Irving Gordon and Sonja



FRANCIS S. CHEEVER, M.D.

Buckley (New York State Department of Health) conducted virological studies to explore the relationship between viruses and disease.

In the continuing quest for a significant breakthrough, Dr. Gustave Dammin (Harvard Medical School) undertook a large-scale study on primates at the Okatie Farms (South Carolina). Broad-spectrum antibiotics, administered intramuscularly, yielded superior results to oral administration in altering the course of shigellosis.

The work of Dr. Shaffer continued at Tulane, using wet chicks as experimental hosts. *Salmonella typhi* were used as the major test organism; hyperimmune sera were prepared, and the effect of passive immunity in prevention of enteric infections was studied.

The annual meeting in 1955 comprised those well-qualified investigators who worked in this common field. This stimulating exchange of information, plans, and opinions represented one of the most important aspects of the Commission's work. Because of limited opportunity to study amebic infections in the United States, it was recommended that members of the Commission participate, whenever possible, in studies underway in South and Central America. In addition, the Commission recommended that additional immunological and chemical research in the field of amebiasis be suspended until a sufficient quantity of amebic organisms was obtained in a purified state.

Dr. Cheever, University of Pittsburgh, School of Public Health, continued work on his grant, entitled "An Investigation of the Possible Role of Viruses in Enteric Infections with Particular Reference to Bacillary Dysentery." His studies characterized and identified those agents that might play a role in the pathogenesis of bacillary dysentery.

By 1956, Drs. Frye and Henry E. Meleney had made considerable progress toward discovering information about factors affecting the growth of *E. histolytica*. They produced an agar-free Shaffer–Frye medium in which all of their strains of *E. histolytica* multiplied satisfactorily. Attempts to eliminate the streptobacilli met with failure; the presence of small numbers of whole bacilli was required to permit multiplication of ameba. They concluded that multiplication of amoebae may occur in the absence of demonstrable bacterial growth, but not in the absence of the bacteria themselves.

Studies conducted at the Okatie Farms by Drs. Dammin and Cheever provided new and advanced knowledge in the field of enteric diseases. The epidemiological project of Dr. Hardy focused on determining whether there was a correlation between infection and mortality in monkeys. He found that no appreciable drop occurred in mortality rates after antibiotic therapy, even when the specific organism was largely eliminated. Overcrowding and excessive handling appeared to be the most important factors in increasing mortality rates.

Dr. Dammin's research centered on the development of new media for the isolation and transportation of bacterial enteric pathogens. A new specimen preservative showed promise of being significantly superior to the standard buffered glycerol-saline broth. A new enrichment broth that contained sodium deoxycholate, sodium citrate, and mannitol was developed. In addition, work was carried out on development of a more effective tetrathionate broth and two new plating media.

Dr. Cheever continued his attempt to isolate, identify, and classify viral agents from cases of bacillary dysentery and other diarrheal diseases that occurred in humans and monkeys.[6] The object was to determine what, if any, role these viruses played in the pathogenesis of enteric diseases. Possibly, they were a direct cause or a contributing factor in a synergistic type of relationship with a bacterial agent. The evidence reported indicated no advances despite exhaustive efforts by Drs. Hardy, Cheever, Shaffer, and Geiman to clarify the relationship of the viruses to clinical illness.

Slow but appreciable progress was made in providing a sufficiently large, pure source of *E. histolytica* for the purpose of studying immunological, chemical, and metabolic properties of this organism. In pursuit of this goal, considerable information was acquired relative to the fundamental biological activities of *E. histolytica*.

An article on the history of the Commission written in 1956 in the *Medical Service Digest*, observed that the chain of dysentery transmission was "still poorly understood, but progress has been made in treatment and prophylaxis using the newer antibiotics. Immunization does not seem, at this time, to aid in the control of diarrheal diseases."[7]



HENRY E. MELENEY, M.D.

The control of enteric diseases was aided by sanitary developments through water purification and sewage and waste disposal. In those areas of the world with poor sanitary standards, diarrheal diseases persisted as a major problem. In addition, many disorders were thought to be caused by viruses and not subject to control by vaccines or antibiotic drugs.

The Commission concentrated its efforts toward understanding the metabolic processes of organisms responsible for causing diarrheal infections — salmonella, shigella, ameba, and other bacterial and protozoan organisms. Efforts were intensified to isolate and categorize many viruses as they related to recognizable clinical syndromes. Of these, the enteric cytopathogenic human organ (ECHO) viruses were soon identified as etiologic agents.

In 1957, 1958, and 1959, the Commission on Enteric Infections met jointly with the Commission on Environmental Hygiene to discuss issues of mutual interest. In 1957, the annual meeting was devoted to reports on Arctic epidemiology, Arctic health problems, and field observations on Alaskan maneuvers. A discussion of Environmental Hygiene in the Arctic was conducted by personnel from the Arctic Health Research Center, Public Health Service. These reports indicated that a high incidence (72%) of intestinal parasites occurred among persons in Arctic Greenland. This percentage was higher than that found among Alaskan Eskimos and persons in Arctic Scandinavian countries. The incidence of diarrheal disease and parasites paralleled those of persons in the tropics.[8]

Research grant applications submitted by members of the Commission included the following:

- *The Chemical Composition and Metabolism of* Entamoeba histolytica, Quentin M. Geiman, Ph.D., Stanford University;
- *Effect of Antimetabolites on Growth of* Entamoeba histolytica, Mitsuru Nakamura, Ph.D., Montana State University;
- *An Investigation of the Possible Role of Viruses in Enteric Infections, with Particular Reference to Bacillary Dysentery,* Francis S. Cheever, M.D., University of Pittsburgh;
- *Host Tissue Reactions in Experimental and Naturally-Acquired Enteric Infections,* Gustave J. Dammin, M.D., Harvard University;
- *Growth Requirements of* Entamoeba histolytica, William W. Frye, M.D., Louisiana State University; and
- *Factors Controlling Encystation of* Entamoeba histolytica *In Vitro,* William Balamuth, Ph.D., University of California, Berkeley.

Documentation contained in the 1959 Director's Report written by Dr. Cheever revealed that there had been significant changes in the Commission's program. One project that dealt with the serologic aspects of amebiasis was terminated because of difficulties in obtaining a relatively pure and effective antigen from the parasite. Two biochemical studies that dealt with the composition and metabolic activities of *E. histolytica* were phased out because of lack of significant progress in this difficult field. One project in this area, under the auspices of Drs. Frye and Richard E. Reeves, continued because of favorable progress. Their work showed that *Bacteroides symbioses* inactivated by exposure to cobalt 60 still retained the ability to support the multiplication of *E. histolytica* as well or better than penicillin-inhibited but viable cells. With the use of a three-amino acid medium, ferrous iron was an essential growth requirement for *E. histolytica*. The mechanism by which iron exerts its effect was not clear.

Dr. Balamuth transferred his sponsored studies on factors that controlled encystment of the parasite from the AFEB to the National Institutes of Health (NIH) as part of the NIH program in cellular biology. Dr. Balamuth continued as Deputy Director of the Commission on Enteric Infections, a post that permitted a continued close working liaison between interested members.

Dr. Geiman implemented a new approach on biological factors that governed occurrence of amoebic infections. The biochemical and biological aspects of *E. histolytica* in relation to amebiasis were concentrated in fewer projects. Dr. Horace Gezon continued his studies on the metabolism of shigella, with the goal to determine the mechanism of development of drug resistance.

Those projects dealing with the virological aspects of enteric infections yielded few positive results. No evidence was noted that viral agents played a significant role in the pathogenesis of "bacillary dysentery." The need to actively pursue this problem was stressed.

The Commission increased its interest and work on cholera. It maintained a close liaison with the NIH Cholera Advisory Committee and the Southeast Asia Treaty Organization (SEATO) cholera research program.

Small working meetings became very productive, particularly among the amebiasis group. Joint meetings with the Commission on Environmental Hygiene lagged and ultimately ceased because of obvious divergent areas of mutual interest.

Unfortunately, in the United States in the late 1950s, little interest existed in diarrheal diseases, even though these infections were of great practical importance to the Armed Forces during war. One of the greatest challenges to the Commission was to maintain a vigorous, active, and critical program devoted to diarrheal diseases. It was obviously essential to acquire new knowledge and train competent professional personnel. Both components were necessary if progress was to be made toward control and eradication of diarrheal disease and other enteric infections. The Commission was concerned with a relative lack of achievement in this important field.

In 1961, Dr. Geiman continued his work on amebiasis but shifted emphasis from biochemical to basic biological aspects, which seemed to be the key to pathogenesis. In his report to the Commission, he decried the lack of meaningful results commensurate with the amount of effort expended. He expressed considerable difficulty in recruiting and holding qualified biochemists because of insufficient funds. Furthermore, he emphasized the need to consistently mass produce the quantities of amoebae needed to carry out the appropriate studies.

At the annual meeting of the Commission on Enteric Infections, held 6 and 7 March 1961, it was recommended that the Commission meet with the Commission on Parasitic Diseases because of mutual interests in amebic diseases. Drs. Hoffert, Cheever, and Abraham reported their findings on establishing a possible link between viral agents and diarrheal disease. In their work, the viral isolation rate was low, with little evidence to suggest that these viral agents played a significant role in pathogenesis of diarrheal disease. Generally, all efforts to incriminate viral agents in the etiology of diarrheal disease of unknown origin were disappointing. The Commission recommended that such investigation be suspended until new techniques were established.

Drs. Gezon and Robert B. Yee described their continuing studies on protein and nucleic acid synthesis and the energy-producing pathways in shigella, including the effects of antibiotics on these mechanisms. Chloramphenicol was associated with an increase in soluble RNA but not ribosomal RNA. This increase in RNA was shown to be the result rather than the cause of the inhibition of protein synthesis. It was concluded that these biochemical studies on the nature of antibiotic activity against shigella, and especially the effect in resistant strains, were of potential importance and could lead to better antibacterial agents.[9]

Rudolph Hugh, Ph.D., George Washington University, Washington, D.C., reported his studies on the identification of the *Vibrio* group and related organisms. The significant revival of interest in cholera as a result of the outbreaks of the disease in Thailand, and the establishment of the SEATO laboratory in Dacca in East Pakistan (now Bangladesh), gave particular pertinence to these definitive taxonomic studies.

Drs. Reeves, Bragg, and Frye continued their investigations of factors of importance in the growth and multiplication of *E. histolytica*. It had been possible to propagate nine strains of *E. histolytica* in MS-F medium containing bacterial cells inactivated by exposure to cobalt-60 irradiation. The bacterial cells, after such irradiation exposure, were able to metabolize carbohydrates, although they lost the ability to reproduce themselves by cell division.

Dr. Geiman initiated his work on the pathogenesis of *E. histolytica* at the Porterville State Hospital, California; because of illness, he was unable to submit a progress report.

Dr. Dammin continued his work at Harvard University on the pathogenesis of diarrheal disease. These important microbiological and pathological examinations of Guatemalan children, who died with or because of diarrheal disease, led to what are now basic concepts of the pathogenesis of these common infections. His work confirmed the importance of malnutrition as a predisposing cause of diarrhea. These children were shown to have large numbers of bacteria like *E. coli* in the jejunum. This



HORACE GEZON, M.D.



RICHARD REEVES, M.D.

led to the concept that bacteria in the upper small intestine in such children could act as the stimulus for fluid production. He clearly showed the pathological differences between illnesses caused by invasive versus noninvasive organisms. This work served as a stimulus for the ultimate identification of enterotoxins. In addition, Dr. Dammin continued to work on the production of diarrheal disease in experimental animals. The ultimate aim of these studies was to clarify those major factors responsible for the production of diarrheal disease.

Dr. Dammin, as President of the AFEB, informed Commission members that the entire budgetary allowance to the U.S. Army Medical Research and Development Command was $15 million, $2 million of which was allocated to the AFEB. The projected needs of the AFEB greatly exceeded this sum! Colonel John Rizzolo spoke of the public relations programs planned in recognition of the 20th anniversary of the founding of the AFEB. He stated the *Journal of Military Medicine* was now the outlet for AFEB publications. Editors of the *Journal of Military Medicine* had expressed their interest in publication of AFEB-sponsored scientific articles.

Reports were presented by various members of the U.S. Army, Navy, and Air Force. The incidence of enteric disease had fallen among military personnel but risen among dependents who lived "on the economy." The incidence of infectious hepatitis increased significantly. Fluoridation of domestic water supplies was recommended and approved. Aerospray programs for mosquito control were being evaluated.

The amebiasis research program effort was critically reviewed — unpromising approaches were abandoned and those with potential were continued. Similarly, the virology program was assessed. Because the extensive virological studies had failed to reveal causal relationships in the pathogenesis of diarrheal disease, it was recommended that current studies be concluded and suspended until new techniques were developed or new leads discovered. It was further recommended that greater emphasis be made on investigation of possible host factors related to development of diarrheal disease.

The annual meeting of the Commission on Enteric Infections was held in conjunction with the Commission on Parasitic Diseases in 1962 and 1963. At the annual meeting in 1962, Drs. Hoffert, Cheever, and Abraham reported on their continuing virological and bacteriological studies. Although a variety of viral agents were isolated from cases of diarrheal disease, no clear-cut evidence was produced to link them to pathogenesis. These results represented the preliminary summary of the final report of this group.

Drs. Gezon and Yee reported on protein and nucleic acid synthesis and energy-yielding pathways in shigella, including the effects of antibiotics on these mechanisms. They developed an effective technique for the isolation of soluble and ribosomal ribonucleic acid for *Shigella flexneri 3*. Preliminary studies with chlortetracycline showed that low concentrations of this drug inhibit both protein and RNA synthesis.

Dr. R. Hugh continued his taxonomic studies on *Vibrio comma (cholerae)*, chiefly including the *El tor* biotype. The clinical disease manifestations with the presence of the *El tor vibrio* appeared to be classical cholera.

Drs. Reeves and Frye continued their biochemical investigation of *E. histolytica*.

Dr. Cheever presented Dr. Geiman's report on studies conducted at the Porterville State Hospital. The population group studied was in an endemic area of amebiasis. Clinical, parasitological, and chemotherapeutic studies were undertaken in an attempt to explain a morbidity rate of approximately 60% among infected individuals. Frequent recurrences were noted in a small group of amebiasis-prone individuals.

Dr. Dammin continued work on the pathological changes of host tissue reactions in experimental and naturally acquired enteric disease. Malnutrition did not produce intestinal lesions with any degree of consistency. In bacterial infections, *V. comma (cholerae)* produced no significant pathological changes. *E. coli* caused superficial lesions in most instances, whereas the various members of the shigella and salmonella groups produced gross ulcerative lesions. Dr. Dammin stated at the meeting that new research money was available and commented that fresh and more dynamic research approaches were needed.

The incidence of amebic disease in the military appeared to be slowly declining, whereas the incidence of enteric disease remained constant. Nine outbreaks of bacillary dysentery among U.S. Navy personnel were reported. Diarrheal disease continued to be a problem to the Armed Forces overseas.

The emphasis of the Commission shifted from the study of individual infecting organisms to considerations of host and other environmental factors that might condition the ability of the potentially pathogenic organism to multiply and cause illness. The studies of Drs. Hoffert, Cheever, Hugh, and Gezon, as summarized above, were near completion. Dr. Gezon planned to outline a fresh approach for study of diarrheal disorders. Dr. Reeves planned to continue work on the metabolic requirements of *E. histolytica*. Dr. J. P. Ransom's work would remain focused on the role of cellular interaction in open systems, mechanisms of resistance, or susceptibility to disease. The etiology and pathogenesis of diarrheal disease in several carefully selected population groups in Florida would be evaluated by Dr. Martin H. Kalser. It was hoped that Dr. Hoffert would initiate his investigations of the prophylactic and therapeutic use of *Lactobacillus acidophilus* in enteric disease, whereas Dr. Rolf Freter would focus on the protective role of coproantibody in humans and its induction by oral vaccination of volunteers.

Commission members concurred that the application of traditional study methods had not been productive and that new and bold measures were needed to provide answers to current problems. A noticeable lack of interest in such problems by the public sector simply emphasized the need for the Commission members working in collaboration with military scientists to take the lead. Highlights of the previous year's research activities were reported at the annual meeting of the Commission on Enteric Infections, held at the Walter Reed Army Institute of Research (WRAIR) in Washington in March of 1963.[10]

Drs. Cheever and Abraham, working at the Detention Home of the Juvenile Court of Allegheny County, Pennsylvania, completed studies on the possible relationship of enteroviruses to outbreaks of diarrheal disease. Although no direct evidence was found to support the viral hypothesis, numerous enterovirus-like agents (apparently unrelated to any of the then recognized types) were isolated from various population groups. Significant progress was made in the characterization and classification of these agents.

Dr. Hoffert gave a final report on studies of viral and bacteriological examinations involving control and autopsy specimens obtained during a Guatemalan outbreak. The viral isolation rate yielded no etiologic relationship to diarrheal disease observed during the outbreak; antibody studies led to the same conclusion. Concurrently, Dr. Hoffert began his investigation of the prophylactic and therapeutic use of *L. acidophilus* in enteric disease.

Dr. Dammin (who worked in conjunction with Dr. Hoffert) continued his evaluation of host tissue reactions in experimental and naturally acquired infections. Emphasis was placed on the correlation of the clinical, pathological, and microbiological data accumulated from severe and fatal diarrheal illnesses that occurred in Guatemalan children. He concluded the following:

- Viral agents do not play a significant role in the diarrheal disease observed.
- Malnutrition itself is not the basis for diarrheal disease.
- Fatal diarrheal disease occurs in the absence of recognized enteric pathogens. However, the presence of abnormally high numbers of "normal" bacteria in parts of the intestine usually characterized by scanty bacterial flora. Inflammatory lesions of the bowel are usually associated with the presence of recognized enteric pathogens such as members of the genus *Shigella*.

In presenting their data, Drs. Gezon and Yee reported that the action of chlortetracycline, as with chloramphenicol, resulted in the inhibition of protein synthesis when administered in low concentration.

Dr. Martin H. Kalser, who worked in collaboration with Dr. Hoffert, reported on their first 10 months of data on host factors in relation to the pathogenesis of diarrheal disease of infectious origins. Their subjects were migrant farm laborers, Cuban civilian refugees, and some Bay of Pigs prisoners. The Seminole Indian population was not available for study. The thorough evaluation of patients included bacteriological, viral, and parasitological study of the gastric, jejunal, ileal, and colonic contents. Bacterial counts were higher in the ileum than in the jejunum.

Dr. Ransom gave his annual report on the interaction of representatives of the normal intestinal flora with enteric pathogens in continuously fed cultures. Much of his work was on the design and

construction of equipment necessary for the operation of continuous cultures. This preliminary work allowed him to explore the factors that govern interactions of organisms such as *Salmonella typhimurium* and *Candida albicans* and *S. typhimurium* and *Saccharomyces cerevesiae.*

Dr. Freter reported the results of human coproantibody studies with particular reference to its induction by oral immunization and its protective role in enteric disease. His study vaccine was a suspension of heat-killed *Vibrio cholerae* ingested by medical student volunteers. The optimal schedule for the induction and maintenance of human coproantibody included a primary course of one dose daily for 4 weeks, followed by a weekly dose of this oral vaccine as long as a significant level of coproantibody should be maintained. The definitive test to evaluate vaccine efficacy for prevention of illness would obviously require a controlled field study. Available evidence suggested that coproantibody was not formed in the stomach but in the duodenum and probably in the jejunum, ileum, and large intestines. Dr. Freter believed that antibody response after oral vaccination was caused principally, if not entirely, by the formation of antibodies by the gut itself. In comparison, after parenteral immunization, antibodies were developed from many sites, probably including the gut. He felt that coproantibody was produced throughout the small and large intestines.

Dr. Hugh, The George Washington University Cancer Clinic, Washington, D.C., completed his work on identification of the *Vibrio* group and related organisms. He concluded that the *El Tor vibrio* represented a biotype (or physiological type) of *V. cholerae.* Dr. Reeves reported that cholesterol was an essential growth requirement for *E. histolytica.*

Dr. Geiman gave his final report on studies of the pathogenicity of *E. histolytica.* He described comparative studies of eight reputedly amebicidal drugs in a population group at the Porterville State Hospital in Porterville, California. None was found to be universally effective.

Colonel Robert W. Sherwood of the U.S. Army reported on three promising chemotherapeutic agents, Humatin (paromomycin), Entero-Vioform (iodocholorhydroxyquin), and Furoxone (furazolidone). Commander Jack W. Millar of the U.S. Navy described his experience as medical officer who made a 3-week global tour with a group of high-ranking medical officers. Each took prophylactic Furoxone twice daily, whereas the crew of the plane took no medication. The first group escaped diarrheal disease until the closing days of the trip, when the drug was taken less regularly by some officers. The crew experienced numerous bouts of diarrheal disease during the first few days of the trip when they requested that chemoprophylaxis be made available to them. Commander Millar described an annoying side reaction of flushing. The promising results reported may possibly have been achieved by the prohibition of eating raw vegetables and fruits and drinking nonpotable water.

Dr. Geiman described his use of Entero-Vioform in the Sonoma State Hospital for retarded individuals. The drug successfully cleared the clinical manifestations and eradicated amoebae. The incidence of bacillary dysentery (*Shigella sonnei*) was markedly reduced. No effect on the course of salmonella infections was noted.

The Commission concluded that additional information was needed to define the properties of these drugs and to determine their toxicity for humans, before any recommendation could be made regarding their prophylactic use.

Dr. Dammin, as President of the AFEB, described a proposal to expand the scope of the Berry Plan to include the deferment of young investigators for conduct of research in the three military services and where facilities were available and where investigations conducted under the auspices of the AFEB. "There is a need for the Commission to stimulate interest on the part of young and talented investigators in the epidemiological problems of enteric disease... the need for new blood within the Commission is obvious."[10]

In 1964, The WHO published the *Report of a WHO Expert Committee, Enteric Infections* chaired by Dr. Dammin.[11] Many findings and recommendations presented in the areas of pathology, prevalence, prevention, and, especially, control were based on work that had been performed by members of the Commission on Enteric Infections. Pertinent findings were:

- In the treatment of diarrheal diseases, the identification of the causative agent is important, but prompt assessment and treatment of fluid and electrolyte deficiency are essential for pa-



CAPTAIN JACK W. MILLAR, MC, USN



ROLF FRETER, M.D.

tient survival. Because of abuse of antibiotic treatment and progressive resistance of enteropathogens to antibiotics, it was strongly recommended that knowledge of susceptibility of enteropathogens to antibiotics was necessary for successful control of infection in individual patients. This knowledge would be particularly important for curtailing the duration of the convalescent carrier stage and for the control of infection within a group or community.

- Studies by Dr. Dammin et al on germ-free guinea pigs led to the finding that oral introduction of *E. coli* into germ-free guinea pigs caused no illness. Rather, it gave protection against a subsequent challenge of shigella, despite shigella and *E. coli* differing antigenically.
- Understanding of the significance of a pure water supply, effective excreta disposal, and methods of food handling is fundamental to the prevention of enteric infections.
- The effectiveness of enteric vaccines, at the time of this publication, had been substantiated only for typhoid vaccine.

By 1964, Drs. Cheever and Abraham had completed their studies on enteric viruses associated with diarrhea. In general, they reported little evidence, either serologic or epidemiological, to incriminate any virus as an agent in the etiology of diarrhea. Other investigators reported statistical and serologic evidence that diarrheal disease was frequently associated with specific viral agents, including adenoviruses. It was recommended that efforts to find virus agents in diarrheal illnesses be encouraged, especially as new viral techniques (interference phenomena) might reveal agents etiologically related to diarrhea.

Drs. Gezon and Yee concluded their studies on protein and nucleic acid synthesis and energy-yielding pathways in shigella and the effects of antibiotics upon these mechanisms. It was concluded that the stimulation of RNA synthesis by chloramphenicol was a *result*, rather than the *cause* of inhibition of protein synthesis by shigella; the mode of action of the drug may involve interference with peptide-bonding of amino acids.

Dr. Ransom reported his continued work on the role of cellular interaction in open systems in the mechanism of resistance or susceptibility to disease (*Candida albicans.*) Dr. Freter described the protective role of human coproantibody in enteric diseases and its induction by oral vaccination of volunteers. Sufficient evidence was now available to justify a field trial that compared oral and parenteral enteric vaccines; the objective was to determine whether coproantibodies were as effective in humans as in experimental animals. Field trials for cholera vaccine were initiated by military groups working with SEATO. WHO planned a study that used attenuated oral vaccine to be conducted in Calcutta, India, during the summer of 1965. At first a pilot evaluation would be conducted, then the study would be extended to involve between 100,000 and 200,000 individuals.

Dr. Kalser covered the first 2 years of his project on host factors in relation to the pathogenesis of diarrheal disease of infectious origin. He reported continuing difficulty in obtaining suitable subjects. Only 40 subjects had been studied thus far. All members agreed that basic studies on bowel physiology and changes of bacterial and viral flora in the normal and abnormal gut were essential to develop an understanding of the pathogenesis of diarrheal illness.

Dr. Dammin updated the group on his continuing studies on the host tissue reactions in experimental and naturally acquired infections of military importance. The studies on fatal diarrheal cases in Guatemalan children were completed. Dr. Dammin shared his specimens and pathological data with several other investigators and commissions: Dr. Hoffert used the marmoset as an experimental animal for shigella infection in his exploratory studies. Drs. Goodwin and Wanner of the Phoenix branch of the CDC conducted similar studies.

Dr. Reeves reported his success in culturing *E. histolytica* in very large quantities by using a field sterilizing autoclave that he had converted into an anaerobic incubator. The amoebae were grown with *Bacteroides symbiosus* in a shallow broth layer in Petri dishes. Stock cultures were often contaminated with pleuropneumonia-like organisms (PPLO). Some of his biochemical studies had to be discontinued because of the contamination. Later it was found that ameba culture could be grown free of PPLO if kanamycin and/or chlortetracycline (Aureomycin) were added to the culture medium.

Dr. Geiman gave a sequel to his prior report on the pathogenicity of *E. histolytica*. He treated 2,200 patients at the Porterville State Hospital with 750 mg of iodochlorhydroxyquin (Entero-Vioform). Amebiasis and shigellosis were prevented in this hospital population over a period of 4 years.

In the discussion that followed Dr. Geiman's presentation, Dr. Millar emphasized that a prophylactic drug for military use was urgently needed. Preferably, a drug for short-term, quick protection in individuals with unrestricted activity was desired. There was much discussion about a suitable test population and the need for proper control studies. Colonel Franklin L. Bowling of the U.S. Air Force stated that there was a need for the Commission to make specific recommendation regarding a useful prophylactic regimen. Diarrheal disease was so common at Reamy Air Force Base, Puerto Rico, that it was known as the "Reamy plague."

Samuel B. Formal, Ph.D., of WRAIR described his recent studies of an oral-attenuated shigella vaccine. A vaccine strain of *Shigella flexneri 2* that was streptomycin-dependent was given orally in doses of 10^9 to 10^{11} cells to 20 volunteers. There were no untoward effects. *Shigella* was isolated from their stools up to 5 days after ingestion. Field trials in Yugoslavia were conducted involving 700 persons. They were given five doses of *Shigella flexneri 2* oral vaccine in doses of 3×10^{10} to 5×10^{11} cells, spaced 3 days apart. There was a reaction rate involving mild diarrhea of 4% compared with 3% in those who received the control. An epidemic of *Shigella flexneri 2* occurred later that year. No persons previously given the vaccine became symptomatic, but 21 persons who received the control developed diarrhea. More field trials were planned.

A new draft of TB MED 119 entitled, "Shigellosis (Bacillary Disease)" was prepared by Commission members to replace the outdated bulletin.[12] The problem of further chemoprophylactic field trials for prevention of *Shigellosis* was discussed under unfinished business. Selection of a suitable population for testing was discussed thoroughly.

The need for continued recruitment of competent investigators and new approaches was actively rediscussed. An important move was the appointment of Dr. Formal to the Commission; his appointment as a commission member was accepted with enthusiasm.

In 1965, there was noticeable improvement in the volume and caliber of activities of the Commission. Renewed interest and vigor during meetings led to productive discussions and active interplay with each of the military services. The Navy Department's request for an effective serological test for the detection of amebiasis was fulfilled. To locate a suitable field site for a chemoprophylaxis trial, Drs. Gezon and Hardy visited the LSU International Center for Medical Research and Training site in Costa Rica. Dr. Fred Payne, director of that facility, submitted an application to conduct trials using one or more chemosuppressive agents to prevent amebiasis. Dr. Dammin continued to render valuable assistance to numerous overseas military service laboratories.

The Commanding Officer of Naval Medical Research Unit (NAMRU) 3 requested several members visit for advice regarding additional studies on diarrheal diseases. There was considerable discussion regarding development of new knowledge aimed at determining the causes and indicating control of diarrheal diseases in Armed Forces personnel stationed in the Far East. The resources of the Commission were made available, provided its efforts were not in conflict with studies performed intramurally within the military services. Various Commission members offered to visit Korea or elsewhere on request.

The 1965 Annual Meeting of the Commission on Enteric Infections was held jointly with the Commission on Parasitic Diseases. Six authorities in immunological and serologic testing attended.

Drs. John Kessel (University of Southern California), Irving Kagan (CDC), and Iris Krupp (Tulane University) described their work on the use of hemagglutination test (HA) for diagnosis of amebiasis. Their findings are summarized:

- The HA test and the CF test (complement fixation) are quite specific in separating amebic from nonamebic liver disease.
- There is good correlation between clinical intestinal varieties of amebiasis and a positive HA titer.



SAMUEL B. FORMAL, PH.D.

- The exact diagnostic antibody titer is unclear. Moreover, the initial serum dilution, whether 1:50, 1:4, or 1:2 needed clarification.
- The HA test should be considered to be under development and unready for routine use. More work should be concentrated on making the test more specific and better able to maintain its current level of sensitivity.

Dr. Francesco Biagi (University of Mexico) described an immobilization test for amebiasis. Further experience was needed to clarify specificity of the test. Dr. Morris Goldman described the fluorescent antibody test (FA) for amebiasis. Despite his pessimism, his peers believed that the test had not been fully evaluated and deserved further investigation.

Dr. Shirley Maddison reported studies employing the gel-diffusion technique. She found a 97% correlation between a positive gel-diffusion test and the presence of amebic liver abscess. The test was negative in all cases of ulcerative colitis. The diagnostic fog seemed to be clearing, and two or three useful tests were now available for applied research and epidemiological investigators. For diagnosis of acute amebic liver involvement, the hemagglutination, complement-fixation, gel-diffusion, and immobilization tests all correlated well with clinical findings. For acute amebic dysentery, the complement fixation test appeared to be the best available procedure.

For more chronic amoebic infections and epidemiological surveillance, the hemagglutination and/or gel-diffusion tests were regarded as most likely to provide reliable information. Despite excellent progress, further standardization of the tests and evaluation of specificity were regarded as essential before their broad diagnostic application.

Representatives from the three Armed Forces presented data on the incidence of diarrheal diseases in the military services, particularly in Vietnam. Detailed reports were given. It was concluded that the precise magnitude and specific nature of the problem could not be determined because the majority of troops involved were self-treated. Patients were often not reported through any medical channels.

The first day of the spring meeting of the Commission on Enteric Infections, 28 February 1966, was devoted entirely to discussion of the relationship of the gut flora to pathogenesis and therapy; military representatives made their reports on the second day.

Dr. René Dubos (The Rockefeller Foundation, New York) discussed the ecology of the gut flora using pathogen-free NCS mice of the CFW strain; lactobacilli were established early in the gut and persisted at a high level throughout life. Anaerobic streptococci and bacteroides were established somewhat later and also persisted throughout life. Enterococci and coliforms normally reached a high level by the 10th day of life and then declined rapidly. Clostridia were the last to be established and persisted throughout life.

Dr. Dubos discussed the localization of flora in various regions of the gut. Streptococci and lactobacilli persisted principally in the stomach, small intestine, and caecum. They were adsorbed on to the surface mucosa and in the nonsecretory gastric mucosa. By contrast, bacteroides were localized only in the caecum; coliforms and enterococci were present principally in the caecum and large intestine.

The flora of the mouse gut could be altered by giving penicillin orally for 1 week. Lactobacilli, bacteroides, and coliforms disappeared within 1 day and were replaced by *Candida*, enterococci, and especially clostridia. Mice treated with penicillin showed weight loss and poor food consumption. These findings persisted until the symbiotic flora returned.

Dr. Dubos demonstrated an example of bacteria interference by feeding mice an artificial diet of casein and such bacterial contaminants as slow-lactose-fermenting coliforms and *E. coli*. When each of the latter was fed simultaneously, they multiplied throughout the intestine. When the coliforms were given first and *E. coli* fed 2 days later, only the slow-lactose-fermenting organisms propagated.

Dr. Russell Schaedler (Jefferson Medical School, Thomas Jefferson University, Philadelphia, Pennsylvania) discussed his research on the reestablishment of gut flora in germ-free mice. When lactobacilli, streptococci, bacteroides, and coliforms were fed separately or in combination, normal reestablishment of gut flora developed.

Dr. Edward Kass (Channing Laboratory, Harvard University, Cambridge, Massachusetts) discussed the importance of the bowel flora in various types of clinical infections. Specifically, colonic *E. coli* were

The Agenda of the Spring Meeting of the Commission on Enteric Infections of the Armed Forces Epidemiological Board
Symposium on the Relation of the Gut Flora to Disease and Therapy
Monday, 28 February 1966

Conference Room 341
Walter Reed Army Institute of Research
Washington, D.C.

Moderator: Director of Commission

0900	Opening Remarks	Dr. Horace Gezon
0910	Ecology of the Gastrointestinal Tract	Dr. René Dubos
	Discussant	Colonel Sprinz
	Reestablishment of the Gut Flora in Germ-Free Animals	Dr. Russell Schaedler
	Discussant	Dr. Rolf Freter
	Studies on Clinical Significance of Alteration in Bowel Flora	Dr. Edward Kass
	Discussant	Dr. Ingelfinger
1230	LUNCH	
1345	Bacterial Overgrowth in the Blind Loop Syndrome	Dr. Robert Donaldson
	Discussant	Dr. Martin H. Kalser
	Therapy of Salmonellosis	Dr. Richard B. Hornick
	Discussant	Dr. Edward Kass
	Antibiotic Resistance and RTF in Enteric Organisms	Dr. Stanley Falkow
1730	Social Hour — Officers' Club All members of the Commission and guests are invited.	

The Agenda of the Spring Meeting of the Commission on Enteric Infections of the Armed Forces Epidemiological Board Tuesday, 1 March 1966

Conference Room 341
Walter Reed Army Institute of Research
Washington, D.C.

Moderator: Director of Commission

0900	Opening Remarks By	Commission Director President, AFEB Executive Secretary	Dr. Horace Gezon Dr. Gustave Dammin Captain Britten
0915	Research and Development Command		General Vorder Bruegge
0930	Reports of Preventive Medicine Officers—Air Force, Army, Navy		
1030	BREAK		
1045	Coproantibody in Man		Dr. Rolf Freter
1120	Antitoxin Immunity in Cholera		Dr. William Burrows
1155	Host Studies of Heterogenous Infectious Diarrhea		Dr. Martin H. Kalser
1230	LUNCH		
1330	Host Tissue Reactions		Dr. Gustave J. Dammin
1405	Comparative Biochemistry of *E. histolytica*		Dr. Richard Reeves
1440	Report on Visit to Cali, Columbia, and Guatemala		Dr. Horace Gezon
1515	ADJOURNMENT OF OPEN MEETING		
1530	Executive Session (Full Members and Military Representatives)		

etiologically implicated to urinary tract infections. These organisms contaminate the vagina and then ascend the urethrae to cause cystitis. Urinary tract infections could be controlled by feeding cranberry juice, which contains quinic acid. Intestinal bacteria convert this compound to hippuric acid, an antibacterial agent that is excreted in the urine. The hippuric acid involves altering the urinary pH. Dr. Kass demonstrated that a urine pH of 5 or less would inhibit bacterial growth. He also speculated that manipulation of the gut flora may have therapeutic possibilities. For example, the administration of lactose to a lactating mother replaced staphylococci in an infant's stool with lactobacilli. However, manipulation of the gut flora can have deleterious effects; the implantation of *E. coli* into the intestine of rabbits caused endotoxin production.

Dr. Robert Donaldson, Boston University School of Medicine (Massachusetts), reported on bacterial overgrowth in the blind-loop syndrome. He made an analogy to tropical sprue. Both conditions may be associated with an increased level of fecal fat, a decrease in Vitamin B_{12} absorption, and bile salt abnormality. In each, the low concentration of normal bile salts causes steatorrhea in contrast to abnormal bile salt metabolites that are produced by the bacteria.

Dr. Richard B. Hornick, University of Maryland School of Medicine, Baltimore, Maryland, presented work on experimental typhoid infection in volunteers and its prevention with vaccines and chemotherapeutic agents. The Quailes strain of *Salmonella typhi* was used for producing experimental human infections. Varying numbers of organisms were placed in milk and ingested by healthy fasting volunteers. The infectious doses and attack rages were 10^9 organisms, 98%; 10^8, 94%; 10^7, 68%; and 10^5, 24%. None were infected with 10^3 organisms. The aerosol method of inoculation was attempted unsuccessfully, which suggests that the respiratory tract is not a normal portal of entry. Localization of the typhoid bacillus in the gut was studied at various time intervals after ingestion. Jejunal biopsies were performed after infection of 10^9 *Salmonella typhi*. There was marked evidence of inflammatory responses in the mucosa as early as 2 to 3 days prior to clinical illness.

Chloramphenicol, streptomycin, and neomycin were used as chemoprophylactic agents before and after ingestion of *Salmonella typhi*. None prevented infection. Those who received long-term chloramphenicol therapy remained afebrile, but demonstrated evidence of bacteremia and a rise in antibody titers.

Evaluation of three typhoid vaccines (acetone-extracted K, phenol-extracted L, and purified Vi antigen) were made on volunteers using the Quailes strain of *Salmonella typhi*. When challenged with 10^9 cells, no volunteers were protected; practically all became ill. Lower challenge doses were used subsequently, and protection was demonstrated against a challenge of 10^5 organisms. It was concluded by Dr. Hornick that large numbers of *Salmonella* were required to produce typhoid fever in healthy adults who resided in a nonendemic area. He commented that heavy bacterial contamination and/or the opportunity for *Salmonella typhi* to multiply would create the proper environment for causing illness.[11]

The final presentation of the day was by Dr. Stanley Falkow, who discussed multiple drug resistance of enteric bacteria. Enteric bacteria with multiple drug resistance are prevalent worldwide. The Japanese investigators showed that this resistance was carried by a composite nonchromosomal resistance transfer factor, the "R factor." The R factor is present in *Shigella, E. coli, Salmonella, Klebsiella, Serratia, Arizona, Vibrios, Pasteurella pestis, Pasteurella pseudotuberculosis, Pseudomonas aeruginosa, Proteus,* and *Citrobacter*.

Dr. William Burrows and his coworkers at the University of Chicago, continued to investigate the role of antitoxic immunity as a prophylaxis against cholera. Their experimental model was the ileal loop of the adult rabbit.[14]

Dr. Freter, of the University of Michigan, described two hypotheses that could explain the paradoxical situation by which coproantibodies protect animals from illness without reducing the total number of vibrios in the gut. He found that antibody does not inhibit the production of toxin, but it does interfere with the adherence of vibrios to epithelial cells. With the use of the fluorescent antibody technique, he showed that cholera vibrios were absent on the mucosal surface in the presence of antibodies.



RUSSELL SCHAEDLER, M.D.



RENÉ J. DUBOS, PH.D.



RICHARD B. HORNICK, M.D.

The Agenda for the Symposium on Shigella Vaccines, Killed and Living — Immunologic Considerations
Ad Hoc Meeting of the Commission on Enteric Infections
of the Armed Forces Epidemiological Board
Monday, 27 February 1967

Conference Room 341
Walter Reed Army Institute for Research
Washington, D.C.

Moderator: Director of Commission

0900	Introduction of Topic	Dr. Horace Gezon Dr. Gustave J. Dammin
0915	Killed Shigella Vaccines	Dr. Albert V. Hardy Captain Thomas Floyd
	Discussant	Dr. William Ewing
	Gut Immunity and Antibody Formation	Dr. Rolf Freter
	Antibody and Secretions	Dr. Joseph Bellanti
	Discussant	Dr. William Burrows
1330	Living Attentuated Shigella Vaccines	Dr. Samuel Formal
	Testing in Primates	Dr. Robert C. Good
	Safety Testing in Human Volunteers	Dr. Richard B. Hornick
	Field Testing	Dr. Eugene Gangarosa
	Discussion of Role of Commission in Further Developmental Studies and Military Application	
1700	ADJOURNMENT	
1730	Social hour at Georgian Motel, Silver Spring, MD All members, Military Representatives, and guests are invited. Army bus will furnish transportation from WRAIR to motel.	
2000	Executive Meeting — Commission Members and Executive Secretary	

At the University of Miami, Dr. Kalser completed his investigations on the bacterial flora of the small intestine in normal subjects and in those with diarrheal diseases. He described the effects of antibiotic therapy on the intestinal flora, particularly in patients with malabsorption syndrome. Clinical improvement in these patients, after antibiotic therapy, generally preceded the restoration of a normal intestinal bacterial pattern. He studied electrolyte changes and water loss associated with diarrhea. In patients with steatorrhea or diabetic diarrhea, there was usually little loss of sodium and potassium ions in the stool. In patients with diarrhea associated with a hypermotility, there was a marked loss of these two ions.

Dr. Carlos Ramirez of the New England Institute for Medical Research, completed work initiated by Dr. Ransom on interactions in gut. Inhibition of *Salmonella typhimurium* by *Candida albicans* appeared not to be a result of a metabolic product of the yeast but probably of a competition between the organisms for nutrients.

Drs. Reeves and Lionel G. Warren from Louisiana State University described their biochemical characterization of strains of *Entamoeba histolytica.* An attempt is being made to distinguish those with differing pathogenic properties.

In 1966, the Commission proposed that an investigation be conducted under its auspices to evaluate the etiology, physiological alterations, and control of diarrhea in newly arrived troops in Vietnam. The proposal was not approved by the Research and Development Command; malaria and problems of trauma were higher priority issues. General Vorder Bruegge, of the Research and Development Command, described the fiscal problems faced by the Command that significantly reduced the availability of funds for extramural-sponsored research.

Colonel Adam Rapalski, Chief of Army Preventive Medicine Division, reported that enteric diseases were second only to venereal diseases in prevalence in Vietnam. Captain Townsend of the Air Force described the annual spring diarrhea epidemic at Clark Air Force Base. The Air Force expressed interest in the development of an effective shigella vaccine. Captain Millar of the Navy described nine outbreaks of enteric disease involving over 800 personnel, mostly in Vietnam. Three outbreaks were caused by shigella, with the largest number caused by *Shigella flexneri 2a.* In each of these three outbreaks, sulfa and tetracycline-sensitive strains were the cause. Patients responded well to tetracycline therapy. Nonpotable water and defects in sewage disposal were the apparent sources.

Dr. Gezon, Director of the Commission, opened the Annual Meeting on 27 February 1967. The entire day was spent discussing shigella vaccine developments. Dr. Hardy and Captain Thomas Floyd described the effects of the killed shigella vaccine on humans. Data were obtained from vaccine trials in retarded children and prisoner volunteers. Parenteral inactivated shigella vaccines did *not* provide protection against illness and infection. Apparently, there is strict specificity to an immune response (an attack of one serotype of shigella confers a degree of immunity to that serotype for a certain period of time but not to others). Hence, information is needed regarding the number and various serotypes prevalent in a geographic area where a vaccine is to be used.

The work helped clarify the pathogenesis of shigella infection. It was found that pathogens penetrate the intestinal epithelial cells and invade the lamina propria. It was suggested that intestinal antibodies (coproantibodies), which are short-lived, probably prevented adherence to the epithelial cells. Conceivably, oral vaccination could help prevent bacterial penetration if shigella contained an antigen responsible for invasion. There was little evidence to support this concept. Cellular immunity could possibly help by enabling phagocytic cells to inactivate pathogens intracellularly. If immune mechanisms proved effective against shigella, the mechanism was thought to be specific in action rather than nonspecific. Researchers concluded that live attenuated suspensions of bacteria would be needed to induce immunity.

Dr. Formal presented his group's data on living attenuated shigella vaccines. Virulent strains of shigella were shown to penetrate intestinal epithelial cells, enter the lamina propria, and multiply. Avirulent mutants did not penetrate, whereas attenuated shigella-escherichia hybrids did penetrate but were unable to survive in the lamina propria. Dr. Robert Good, from the Primate Center in Davis, California, confirmed Dr. Formal's findings on the effectiveness of the living oral vaccines in monkeys.

Dr. Hornick reported on the safety testing of lyophilized mutant *Shigella flexneri* at the Maryland House of Corrections. No significant adverse problems were reported. *Shigella sonnei* and a few *Shigella flexneri* serotypes (*Shigella flexneri 2a*) account for essentially all the shigella infections that occur in low socio-economic and confined populations. Another study site, the Wisconsin Southern Colony for mentally defective children, has been selected for field testing. Recurring problems with shigella infections have been reported there. Before the testing could begin, safety had to be ensured and the study required approval by authorities at the CDC. Dr. Hornick was assigned responsibility for conducting these safety studies.[15]

Research applications submitted by members of the Commission in 1967 included

- DA-49-193-MD-2492 W. Burrows. "Antitoxic Immunity to Cholera." University of Chicago.
- DA-49-193-MD-2530 G. J. Dammin. "Host Tissue Reactions in Experimental and Naturally Acquired Infections of Military Importance." Harvard University.
- DA-49-193-MD-2840 R. Freter, Ph.D. "Coproantibody in Man: Its Protective Role in Enteric Diseases and its Induction by Oral Vaccination of Volunteers." University of Michigan, Ann Arbor. Postulation: The principal effect of coproantibody may be in preventing absorption of the intestinal pathogens to the epithelial surfaces and, therefore, interfering with their entrance into the cell.
- DA-49-193-MD-2254 (APR 62 – DEC 66) M. H. Kalser, M.D., Ph.D. "Systemic Reaction to Heterogeneous Diarrhea and Evaluation of Therapy." University of Miami.

Dr. Kalser performed one of the largest studies of microflora of the human gut. The intestinal microbiological environment was determined in about 200 adult individuals. Gastric, jejunal, ileal, and/or fecal specimens were cultured for evidence of viral, bacterial, or microflora growth. A striking finding was the absence of any viral isolates in 450 specimens from normal persons and patients with acute or chronic diarrheal disease. He evaluated several patients with tropical sprue and malabsorption syndrome before, during, and after completion of a several-month course of therapy with tetracycline. There was clinical and functional improvement and a modest decrease in intestinal bacteria. After the antibiotic was discontinued, the bacteria count rose but the clinical improvement persisted.[16]

- DA-49-193-MD-2620 R. E. Reeves, Ph.D. "Comparative Biochemistry of Strains of *Entamoeba histolytica*." Louisiana State University.

With the use of enzymatic techniques, Dr. Reeves attempted to identify the difference between strains of *Entamoeba histolytica* derived from various global areas and of varying degrees of pathogenicity. The specified goal was to identify those strains that are human pathogens through their chemical properties.

At the 1967 fall meeting, Commission members discussed in depth those areas where the military continued to have problems, especially problems with enteric diseases. Acute amebiasis remained a significant problem among Marines in Vietnam. Specific measures were taken to ensure potable water and adequate sewage disposal in an attempt to prevent illness.

Commander Millar, the newly appointed Director of the Preventive Medicine Division of the Navy Department, reported 53 diarrheal outbreaks in Southeast Asia involving 5,800 persons. The pathogen was only identified in 16 of the outbreaks: 4, *Shigella flexneri*; 2, *Shigella sonnei*; 6, staphylococcal food poisoning; and 4, *Salmonella*. A Preventive Medicine Unit was established in Da Nang to help deal with diarrheal problems.

Representing the U.S. Army, Colonel Irvin C. Plough reported that to derive funds for research from the Medical Research and Development Command, the Commission must clearly verify that programmed investigative studies directly supported the military services, and most particularly, those personnel stationed in the field. Presumably, studies of enteric disease in the field received a relatively small percentage of the total research money available.

The Agenda for the Spring Meeting of the Commission on Enteric Infections of the Armed Forces Epidemiological Board
Symposium on Malabsorption
Monday, 18 March 1968

Conference Room 341
Walter Reed Army Institute of Research
Washington, D.C.
Moderator: Director of Commission

0900	Introductory Remarks	Dr. Horace Gezon Dr. Gustave Dammin
0915	Reports of Preventive Medicine Officers — Air Force, Army, Navy Research and Development Command	
1030	COFFEE BREAK	
1045	Normal Gut Architecture and Changes Associated with Celiac Syndrome	Dr. J. Trier
	Diarrhea and Malabsorption in Vietnam	Major L. Legters
	Tropical Sprue in Vietnam	Dr. T. Sheehy
1245	LUNCH	
1400	Clinical Aspects of Tropical Sprue in Puerto Rico	Dr. T Bayless
	Flora Changes Associated with Malabsorption	Dr. F. Goldstein
	Folic Conjugase Enzyme of the Intestine	Dr. I. Rosenberg
	Effect of Wheat Protein and Its Digestive Products in Celiac Disease	Dr. O. Knowlessar
	Recapitulation and Critique	Dr. F. Ingelfinger
1700	ADJOURN	

The Commission on Enteric Infections held its spring symposium on 18 March 1968. The topic of discussion was "Malabsorption and Its Relation to Non-Specific Diarrhea." An impressive cadre of knowledgeable clinical investigators attended. (See the 1968 agenda.) Little additional information was presented on pathogenesis of bacterial diarrhea in military personnel in Vietnam. New knowledge of the etiologic role of *Cholera vibrio* toxin in production of watery diarrhea in infected persons was discussed. It became apparent that studies of enteric toxins would provide new knowledge on the cause of nonspecific diarrhea and the role played by enterotoxin produced by *Escherichia coli* and other species. During the executive session, the Commission learned it would now receive grant proposals and contracts for review. Formerly, such reviews were conducted by the Research and Development Command and its Committee on Enteric Infections. That committee was disbanded; hence, the transfer of the review system to the Commission.

The Commission made the following recommendation to the AFEB concerning boiling water to make it potable: "Any method of boiling water that would make it potable in terms of inactivating infectious hepatitis, would make it free from other infectious agents as well. Boiling water for one minute followed by gradual cooling to ambient temperatures would yield potable drinking water. (At altitudes where water boils at 98°C, boiling is required for five to ten minutes)."[17] By 1969, the Commission became increasingly interested in clarifying the problem of nonspecific types of diarrhea. It was clear that many intestinal infections involving military personnel result from agents currently unknown and that a specific microbe might be the cause.

The 1-day spring meeting was devoted to the subject, "Symposium on Gut Physiology," presented by the gastroenterology group from Walter Reed (see the 1969 Agenda).

The overall objective for the Symposium on Gut Physiology was to elucidate those physiologic abnormalities associated with diarrheal disorders, including the various chemical or physiologic stimuli responsible for such changes. With that basic concept in mind, Commission members enhanced their knowledge of gastrointestinal physiology.

The Commission activities were directed to the problem of experimental infections in an attempt to establish appropriate model systems aimed at clarifying relevant human problems. The need to reexamine the issues of viral etiology and conduct of field trials with chemotherapeutic agents, vaccines, and environmental control measures was reaffirmed.

Dr. Victor M. Villarejos, Louisiana State University ICMRT, San José, Costa Rica, submitted a long and interesting addendum to his project request for virologic studies of stools of patients in Honduras then being evaluated in chemoprophylactic studies. It was his view that in spite of previous negative findings, sophisticated virological studies needed to be repeated in a tropical or semitropical area with poor health standards.

In his earlier work, Dr. Villarejos obtained fecal specimens from patients with acute diarrhea (less than 24 hours between time of onset and that of specimen collection). His collection included fecal specimens from patients whose illness had occurred 48, 72 and 96 hours earlier. Virological studies were conducted on the two groups. He observed an inverse relationship between the rates of isolation of *Enterovirus coxsackie* B types as compared with the noncoxsackie B types in each diarrhea group. The maximum isolation rates of coxsackie B types were derived from patients with acute diarrhea (less than 24 hours between onset and that of specimen collection). This indicated to him the need for the collection of fecal specimens for virologic study as early after the onset of the disease as possible.

The agents belonging to this virus group were ubiquitous. There was abundant clinical evidence describing the diarrhea-producing potential as a result of infection by numbers of this virus group. There were reports of limited epidemics of diarrhea in which members of the virus group were the only pathogenic agents isolated.

Dr. Villarejos concluded that the etiologic role of coxsackie B type toxins should be confirmed as a common cause of enteritis, the possibility of developing a suitable vaccine for prevention was obvious. A vaccine of this type would be useful for new, unexposed persons who travel into a known endemic area.

The Agenda of the Spring Meeting of the Commission on Enteric Infections of the Armed Forces Epidemiological Board
Symposium on Gut Physiology
Monday and Tuesday, 17 and 18 March 1969

Conference Room 341
Walter Reed Army Institute of Research
Washington, D.C.
Moderator: Director of Commission

Monday, 17 March 1969

0900	Introductory Remarks	Dr. Horace Gezon Dr. Gustave Dammin
	Neuromuscular Physiology and Gut Motility Introduction to an Integrated Study of the Pathophysiology of Diarrheal Disease	Major D.G. Reynolds
	Effects of Salmonella Infections on Autonomic Receptor Mechanisms	Major D.G. Reynolds
	COFFEE BREAK	
	Interactions between Blood Flow and Motility The Role of Sphincters in Bowel Function Résumé and Critique	Dr. E.D. Jacobson Dr. L.V. Harris
1245	LUNCH	
1345	Transport Mechanisms Biochemical Approaches to Diarrheal Diseases	Dr. P. Curran
	Electrochemical Parameters in the Study of Diarrheal Disease	Dr. M. Field
	Effect of Salmonella Infections on Intestinal Fluid and Electrolyte Dynamics	Captain G. Plotkin
	Experimental Approach to the Study of Human Diarrhea	Dr. K. Soergel
	Résumé and Critique	Dr. F. Ingelfinger
	ADJOURNMENT	

Tuesday, 18 March 1969

0900	Executive Session — Full members only	
1200	ADJOURNMENT	

The annual spring meeting of the Commission on Enteric Infections was held on 20 March 1970 at the WRAIR, Washington, D.C. Cholera and cholera-like diseases were discussed.

Several publications by Dr. Burrows, Department of Microbiology, University of Chicago, on cholera enterotoxin were completed under Commission sponsorship. In one article entitled, "The Extractable Lipid of the Cholera Enterotoxin," Dr. Burrows examined extracted lipid from *Vibrio cholerae* by thin layer chromatography and gas liquid chromatography. Previously observed inactivation of the toxic activity by chloroform-methanol extraction but not by ethanol-ether precipitation was not associated with demonstrable differences in the nature of extractable lipid. He concluded that extractable lipid was not associated with toxicity.[18]

In another article published later the same year, "Towards an Effective Prophylactic Immunity to Cholera," Dr. Burrows reported that potent antigens capable of eliciting antibacterial and antitoxin immune responses were now available. It remained unclear whether such agents provided an effective level of vibriocidal antibody.[19] I n July, 1970, President Richard M. Nixon appointed a panel to investigate the research programs of the Department of Defense to determine whether a possible conflict of interest existed between the AFEB and its Commissions (*vide infra*). This review and its subsequent effect on the AFEB Commission system is well-covered on pages 119 through 133 in *The Armed Forces Epidemiological Board—Its First Fifty Years: 1940–1990.*[20]

On 5 March 1971, the Commission convened its annual meeting. The principal topic of discussion was "Local Immunity: Is it a Factor in Determining the Response to Enteric Infections." There is no report available for this meeting (see the 1971 agenda).

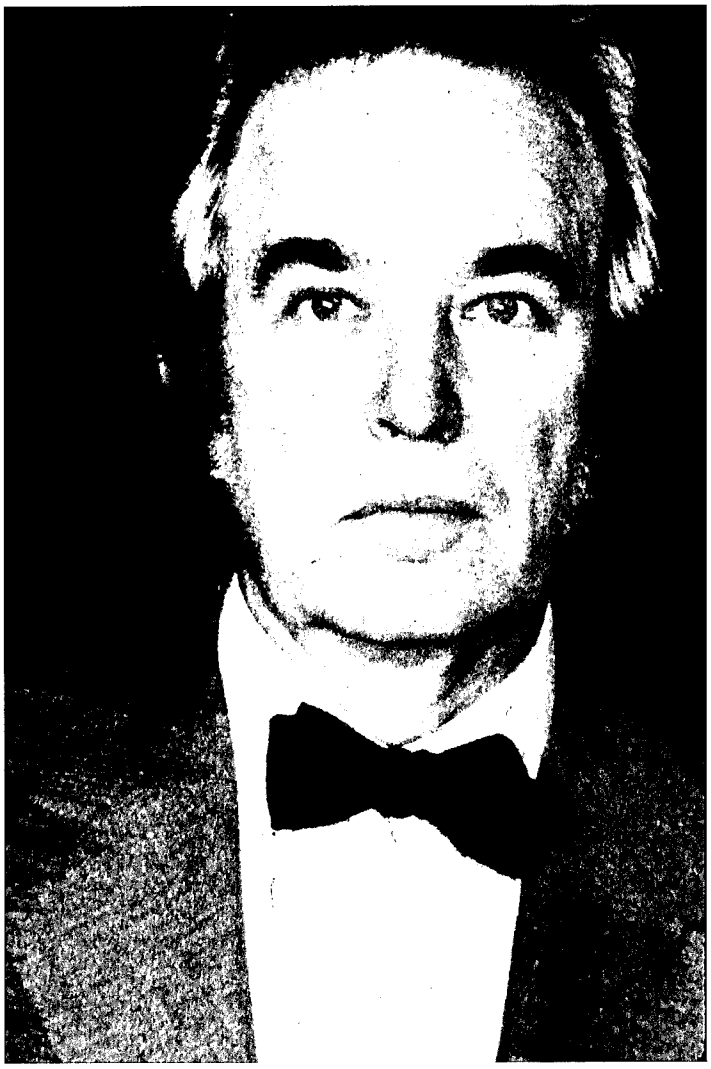
The spring meeting of the Commission on Enteric Disease was convened by its new Director, Dr. Thomas R. Hendrix, of The Johns Hopkins University on 3 March 1972. The meeting was devoted to the subject of shigellosis. A summary of the research accomplishments of the year follows:

- In his final report, Local Immunity to Infectious Diarrheal Disease, Dr. Burrows reported that immunization of rabbits by parenteral and intraluminal routes was followed by the appearance of antibody in serum and intestinal contents. Resistance to toxin challenge more closely paralleled serum titers than coproantibody titers. The toxin-neutralizing antibody identified was IgA.[21]
- Lawrence M. Corwin, Ph.D., Associate Professor of Microbiology, Boston University School of Medicine, spoke on Factors Affecting Virulence of *Shigella flexneri 2a*. He found that immunologically identical strains of *Shigella flexneri 2a* have differences in their cell envelopes. The altered configuration of the cell wall, rather than its chemical composition, accounted for its lack of penetration of the intestinal epithelial cell and the resulting loss of virulence.[22]
- Dr. Dammin, et al, reported on "Host Tissue Reaction in Experimental and Naturally acquired Infections of Military Importance." These studies revealed that only invasive *Salmonella typhimurium* caused rabbit ileal loop to secrete fluid. Fluid accumulation that occurred before invasion was demonstrable, accompanied by discharge of the goblet cells of the villi. Unlike the response associated by the toxigenic bacteria, *Vibrio cholerae* and *Escherichia coli*, no exotoxin had been identified.
- Dr. Falkow, Georgetown University, presented his work, "Infectious Multiple Drug Resistance in the *Enterobacteriaceae*." He also described the genetic and molecular nature of enterotoxic plasmids.
- Dr. Freter reported on his research, "Coproantibody: Its Protective Role in Enteric Diseases and Its Induction by Oral Vaccination of Volunteers." In conventional mice, germ-free mice, and rabbits, such antibodies appeared as a result of local synthesis or possibly derived from serum antibody. Serum antibody was degraded in the intestine in both types of mice. In germ-free mice, the degradation was so rapid that no serum antibody was detectable in the intestine. Therefore, the presence and probably the quality of intestinal flora was shown to affect host resistance by a new mechanism: the sparing of intestinal antibody.
- Dr. Sherwood L. Gorbach reported his studies," The Role of Intestinal Bacteria in Acute Diarrheal Disease." He indicated that there was a need for a rapid and simple method for identifying toxin-producing *Escherichia coli*.

The Agenda for the Spring Meeting of the Commission on Enteric Infections of the Armed Forces Epidemiological Board
"Local Immunity: Is It a Factor in Determining the Response to Enteric Infections"
Friday, 5 March 1971

Conference Room 341
Walter Reed Army Institute of Research
Washington, D.C.

0900	Introduction	Dr. T. R. Hendrix Dr. G. J. Dammin
	Mechanism of Local Immunity	Dr. Arthur M. Silverstein Johns Hopkins University
	Production of Secretory Antibodies	Dr. Andrew G. Plaut State University of New York, Buffalo
1045	COFFEE BREAK	
1100	Studies on Protective Function of Secretory Antibodies; Lessons from the Respiratory Epithelium	Joseph E. Bellanti Georgetown University
	Developmental and Functional Aspects of Local Immunity to Viral Infections	Dr. Pearay L. Ogra State University of New York, Buffalo
1245	LUNCH	
1345	The Role of Antigens in the Development of Immunologic Defense; Lessons from Antigen-Free Diet in Germ-Free Animals	Dr. Bernard S. Wostmann Notre Dame University
	Cellular Immunity in Determining Defense Against Enteric Infections	Dr. Frank M. Collins Trudeau Institute
1530	COFFEE BREAK	
1545	Symposium on Management of Diarrhea	Dr. Herbert L. DuPont University of Maryland
	Management of Fluid and Electrolyte Problems in Diarrhea	Dr. Charles C. J.Carpenter Johns Hopkins University
1700	ADJOURNMENT	



THOMAS R. HENDRIX, M.D.

- Drs. Hornick and Herbert Dupont reported on their work on Shigella vaccines in humans. Although some protection was achieved with oral shigella vaccines, it was not at a level they desired. They initiated a new series of human studies with *Escherichia coli,* combined with shigella group and type antigens. All vaccines were produced in Dr. Formal's laboratory at WRAIR. They evaluated filterable agents that caused "viral gastroenteritis" and, at the time of their presentation, had identified three separate viruses involved in recent outbreaks. The researchers performed their work at the University of Maryland School of Medicine and Hospital. They planned to determine the duration of homologous immunity and degree of heterologous immunity.
- Drs. Kurt J. Isselbacher, W. Allan Walker, David A. Shafritz, and Joseph L. Perrotto reported on the "Pathophysiology of Acute Non-Specific Diarrhea: Uptake of Exotoxins and other Macromolecules and Their Effect on the Intestines." They extended their observations that immunization interferes with antigen uptake by the intestine. They speculated that this effect may be produced by oral or parenteral immunization and is dependent on local (intestinal) antibody. Because cholera toxin must first bind to the mucosa to exert an effect on secretion, comparisons were conducted of the binding of cholera toxin and bovine serum albumin (BSA) in vitro, using sections of rat intestine brush borders. It was found that binding of BSA was enhanced by specific antibody at physiological, but not higher, concentrations. The in vitro model demonstrated that cholera toxin and bovine serum albumin exhibited greater binding in the ileum than in the jejunum. Cholera toxin was able to bind by a factor of 10 compared with BSA. Their studies were developed to provide a rational basis for immunization against enterotoxins.
- Dr. Yee presented a final report, "Laboratory Studies on Shigella Pathogenesis and Immunity." Oral immunization of guinea pigs with an attenuated hybrid *Escherichia coli* and *Shigella flexneri 2a* elicited both cellular and humoral immune response. Peritoneal macrophages from immunized animals were resistant to the lethal action of virulent *Shigella flexneri 2a.*

SUMMARY

In mid-1970, in response to charges of flagrant conflict of interest practices in the government and to a general atmosphere of suspicion and unrest, President Nixon embarked on a thorough governmental housecleaning. He created a panel to investigate the Department of Defense. An ad hoc committee was established to perform a management survey of the AFEB. This panel completed its management survey and presented it to the AFEB in May 1971. The management report cast suspicion that the Board had shown a conflict of interest in the practice of awarding research grants and in its failure to be "responsive to the changes in missions and priorities of the military medical departments."[20] The panel's report continued, questioning whether the function of the AFEB was a duplicate of, and in conflict with, the research activities of the NIH.

A response to the findings of this panel may be found in an impassioned speech to the AFEB on the occasion of its 30th anniversary, given by Dr. Colin MacLeod, Director of the AFEB from 1947 to 1955.[20] He answered the charges point by point, emphasizing that the AFEB provided the "real continuity in military preventive medicine" and that "excellent science...has always been the hallmark of...the AFEB." [23] Anger and bruised feelings were prevalent among the AFEB members; the AFEB, as it had been known, could easily have been dissolved save the efforts of Dr. Dammin. Through his leadership and mediation skills, the AFEB was reorganized; the Commission system was abolished and a new committee structure was adopted.

A new mission was established for the AFEB and its designated committees. They were chartered to function solely as advisors to the Armed Forces when specific problems arose. (A complete account



COMMISSION ON ENTERIC INFECTIONS

Fall Meeting, 18–20 October 1972
Walter Reed Army Institute of Research
Washington, D.C.

Seated, left to right: Dr. Francis S. Cheever, Dr. Horace M. Gezon, Dr. Thomas R. Hendrix (Com. Dir.), Dr. Albert V. Hardy

Standing, left to right: Dr. Eugene J. Gangarosa, Dr. Rolf Freter, Dr. Samuel B. Formal, Dr. Gustave J. Dammin (Pres. AFEB), Dr. Charles C. J. Carpenter, Dr. Marion M. Brooke, Dr. Richard B. Hornick, Dr. Russell W. Schaedler

of the restructuring of the AFEB is contained in *The Armed Forces Epidemiological Board—Its First Fifty Years: 1940–1990* by T. E. Woodward).[20]

This action formally ended the Commission on Enteric Infections, established in 1948. In the 23 years since the inception of the Commission, it had provided the means of controlling and preventing the ravages of many of the acute diarrheal diseases and their subsequent deleterious impact on military effectiveness through its research stimulus and recommendations. The work was not only germane to the Armed Forces but to the general public throughout the world.

The Commission on Enteric Infections served an important leadership role during a period when great advances were made in the understanding of the pathogenesis of diarrheal diseases. The original group wisely chose and clearly defined its objectives. These initiatives kept the Commission focused

on those areas critical to expansion of knowledge on pathogenesis, the use of this information to support measures to develop diagnostic tests to obtain epidemiological data, and to implement preventive measures. Such control measures included the use of, and enlightened methods of, treatment. This critical period featured the new discoveries of enterotoxins and the methods by which they invoke secretory activity of the epithelial cells of the small bowel. No longer was it necessary to implicate differences in water or jet lag or even unculturable viruses as the cause of nonspecific diarrhea, often called travelers' diarrhea. *Escherichia coli*, and other common enteropathogens were found to be clear offenders, responsible for the ubiquitous watery diarrhea that had plagued military personnel for years. Oral replacement fluids were shown to greatly simplify treatment. Oral attenuated typhoid vaccine was shown to be effective in prevention and gave credence to the potential for development of similar vaccines for shigella, salmonella, and *Escherichia coli*. As the knowledge of R-factor plasmids unfolded, antibiotic treatment was found to have significant limitations. Difficulties in the use of antibiotics for established enteric infections remain.

Previously, little was known regarding the control, treatment, and diagnosis of amebiasis. The Commission on Enteric Infections was instrumental in sponsoring key studies that resulted in the successful growth of such organisms on new synthetic media. The availability of pure strains led to sensitive and specific diagnostic tests; this was a major advance in the field of parasitology.

These milestone advances fully justify the time, effort, and financial expenditures of the Commission on Enteric Disease. The financial support and inspired direction of the Commission was critical to the success that the investigators so fully provided. The mission of fulfilling combat readiness and better health was realized in full measure. These military achievements were of equal benefit to the general public.

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Contract No. W-49-007-MD-480 Shigellosis Studies (1951–1956),

Contract No. W-49-007-MD-481 and DA-49-007-MD-22 Salmonellosis Studies (1955–1956). Dr. Albert V. Hardy, Bureau of Laboratories, Florida State Board of Health.

Contract No. W-49-007-MD-112 Enzyme Systems of *Entamoeba histolytica* (1951–1955). Dr. James N. DeLamater, University of Southern California.

Contract No. DA-49-007-MD-113 & 639 Chemical Composition and Metabolism of *Entamoeba histolytica* (1951–1956 and 1958–1959). Dr. Quentin M. Geiman, Harvard School of Public Health.

Contract No. DA-49-007-MD-158 Antigen Analysis of *Entamoeba histolytica* (1951–1952). Dr. Richard J. Porter, University of Michigan, School of Public Health.

Contract No. DA-49-007-MD-202 Study of Immunological Relationships of *Entamoeba histolytica* (1951–1956). Studies on the Entozoic Amoebae (1954–1956). Dr. Ross S. Benham and Dr. Joseph G. Otero, University of Chicago.

Contract No. W-49-007-MD-480 Epidemiology of Shigella and Salmonella Infection and Their Control (1949). Dr. William W. Frye, Louisiana State University, School of Medicine.

Contract No. DA-49-007-MD-756 Identification of Intestinal Parasites Found in Korean and Chinese Prisoners of War and Their Relationship to Diarrheal Diseases (1951–1952). Studies of the Growth Requirements and Mass Cultivation of *Entamoeba histolytica* (1958–1961). Dr. William W. Frye, Louisiana State University, School of Medicine.

Contract No. W-49-007-MD-481 Evaluation of Various Antibiotics in the Treatment of Salmonellosis in Animals (1950–1952 and 1954–1956). Dr. Morris Shaffer, Tulane University.

Contract No. DA-49-007-MD-547 An Investigation of the Possible Role of Viruses in Enteric Infections with particular Reference to Bacillary Dysentery (1954–1956 and 1958–1961). Dr. Francis S. Cheever, University of Pittsburgh.

Contract No. DA-49-007-MD-498 Studies of Non-Bacterial Gastroenteritis (1954–1956). Dr. Irving Gordon, New York State Department of Health.

Contract No. DA-49-007-MD-603 Pathogenesis of Bacterial Protozoan and Metazoan Infections of the Intestinal Tract in the Experimental Animal (1954–1956 and 1958–1959), Contract No. Da-49-007-MD-2530 Host Tissue Reactions in Experimental and Naturally Acquired Enteric Infections of Man and Laboratory Animals (1959–1961, 1966–1967 and 1969–1970). Dr. Gustave J. Dammin, Harvard Medical School.

Contract No. DA-49-007-MD-515 Factors Controlling Encystation of *Entamoeba histolytica in vitro* (1954–1956, 1958–1959). William Balamuth, Ph.D., University of California.

Contact No. AF 18(600)-1251 The Development of New Transportation, Enrichment and Plating Media for the More Rapid Recovery of Enteric Pathogens by Conventional Methods and by Use of the

Membrane Filter (1955–1956). Samuel R. Damon, Ph.D., Bureau of Laboratories, Indiana State Board of Health.

Contract No. DA-49-007-586 Transmission of Intestinal Pathogens in Polar Climates (1954–1956). Dr. John E. Gordon, Howard University.

Contract No. DA-49-007-MD-202 Immunological Relationships of *Entamoeba histolytica* (1951–1955) Studies on the Entozoic Amoebae *Entamoeba histolytica* (1954–1956). Dr. Isabelle Havens, University of Chicago.

Contract No. DA-49-007-MD-965 Protein and Nucleic Acid Synthesis and Energy-Yielding Pathways in *Shigella* and the Effects of Antibiotics on These Mechanisms (1958–1961). Dr. Horace M. Gezon, University of Pittsburgh.

Contract No. DA-49-007-MD-1003 Investigation of the Possible Link Between Viral Agents and Diarrheal Disease (1958–1961).

Contract No. DA-49-193-MD-2353 An Investigation of the Prophylactic and Therapeutic Use of *Lactobacillus acidophilus* in Enteric Disease (1962–1964). Dr. Warren R. Hoffert, Florida State Board of Health.

Contract No. DA-49-007-MD-2044 (1959–1961) Studies on the Identification of the *Vibrio* Group and Related Organisms. Dr. Rudolf Hugh, George Washington University.

Contract No. DA-49-007-MD-891 Effects of Antimetabolites on the Growth of *Entamoeba histolytica* (1958–1960) Dr. Mitsuru Nakamura, Montana State University.

Contract No. DA-49-193-MD-2254 Systemic Reaction to Heterogeneous Infectious Diarrhea and Evaluation of Therapy (1964). Dr. Martin H. Kalser, University of Miami School of Medicine.

Contract No. DA-49-007-MD-771 Intercerebral *Salmonella typhosa* Infection in Chicks: Passive Protection by Chicken Antisera of Differing Specificities (1964). Dr. Inn Soo Suh, So Do Medical School, Seoul, Korea and Dr. Morris F. Shaffer, Tulane University School of Medicine.

Contract No. DA-49-193-MD-64-G112 The Role of Cellular Interaction in Open Systems in Mechanisms of Resistance or Susceptibility to Disease (1965). Dr. Carlos Ramirez and Dr. J. P. Ransom, New England Institute for Medical Research.

Contract No. DA-49-007-MD-2620 Comparative Biochemistry of Strains of *Entamoeba histolytica* (1966–1967). Dr. Richard E. Reeves, Louisiana State University.

Contract No. DA-49-193-MD-2492 Antitoxin Immunity to Cholera (1966–1967). Dr. William Burrows, University of Chicago.

Contract No. DA-49-193-MD-2307 Coproantibody in Man: Its Protective Role in Enteric Diseases and Its Induction by Oral Vaccination of Volunteers (1966–1967, 1970). Dr. Rolf Freter, University of Michigan.

Contract No. DA-17-67-C-7057 Study of Shigella Vaccines in Man (1972). Dr. Richard B. Hornick and Dr. Herbert L. DuPont, University of Maryland School of Medicine.

Contract No. DADA 17-67-C-7061 Infectious Multiple Drug Resistance in the Enterobacteriaceae (1972). Dr. Stanley Falkow, University of Washington.

Contract No. DADA 17-68-C-8146 Factors Affecting Virulence of *Shigella flexneri* (1972). Dr. Lawrence M. Corwin, Boston University School of Medicine.

Contract No. DADA 17-70-C-0110 The Role of Intestinal Bacteria in Acute Diarrheal Disease (1972). Dr. Sherwood L. Gorbach, The Hektoen Institute of Medical Research, Chicago, Illinois.

Contract No. DA-49-139-MD-2707 Diarrhea from Bacterial Enterotoxins (1972). Dr. George F. Grady, Tufts University School of Medicine.

Contract No. DADA 17-68-C-8162 The Role of the Normal Intestinal Flora in *Shigella* Infections (1972). Dr. David J. Hentges, University of Missouri School of Medicine.

Contract No. DADA 17-70-C-0113 Pathophysiology of Acute Non-Specific Diarrhea: Uptake of Exotoxins and other Macromolecules and Their Effect on the Intestine (1972). Dr. Kurt J. Isselbacher, et al, Harvard Medical School.

Contract No. DADA 71-C-1042 The Role of Shigella Enterotoxin in Shigellosis (1972). Dr. Gerald T. Keusch, Mount Sinai School of Medicine.

Contract No. DADA 17-70-C-0111 Intestinal Enzyme Adaptation in Health and Disease (1972). Dr. Norton S. Rosenweig, St. Luke's Hospital Center.

Contract No. DADA 17-69-C-9071 Gut Mucosal Effect of Bacterial Exotoxins (1972). Dr. Craig K. Wallace, The Johns Hopkins University.

Contract No. DADA 17-69-C-9157 Laboratory Studies on *Shigella* Pathogenesis and Immunity: Final Report (1972). Dr. Robert B. Yee, University of Pittsburgh School of Public Health.

Contract No. DADA 17-72-C-2071 The Etiology of Acute Infectious Non-Bacterial Gastroenteritis (1972). Dr. Neil R. Blacklow, University Hospital, Boston, Massachusetts.

SECTION 5—APPENDIX

COMMISSION ON ENTERIC INFECTIONS

1949
Director
James Watt, M.D. (1949–1954)

Members
William W. Frye
Albert V. Hardy
Myron E. Wegman

Associates:
NO INFORMATION AVAILABLE

1950
Members
William W. Frye
Albert V. Hardy
Myron E. Wegman

Associates:
NO INFORMATION AVAILABLE

1951–1952
Members
Gustave J. Dammin
William W. Frye
Albert V. Hardy
Myron E. Wegman

Associates:
James N. DeLamater
Quentin M. Geiman
Richard J. Porter
Morris F. Shaffer

1953
Members:
Justin M. Andrews
Francis S. Cheever
Gustave J. Dammin
William W. Frye
Albert V. Hardy
James Watt

Associates:
Ross S. Benham
James N. DeLamater
Quentin M. Geiman
Henry E. Meleney
Richard J. Porter
Morris F. Shaffer

1954
Director:
Albert V. Hardy (1954–1956)

Members:
Justin M. Andrews
Francis S. Cheever
Gustave J. Dammin
William W. Ferguson
William W. Frye
Quentin M. Geiman
Morris F. Shaffer
James Watt

Associates:
William B. Balamuth
Theodore Bauer
Ross S. Benham
Marion M. Brooke
Irving Gordon
Henry E. Meleney
Richard J. Porter

1955
Members:
Justin M. Andrews
Francis S. Cheever
Gustave J. Dammin
William W. Ferguson
William W. Frye
Quentin M. Geiman
Morris F. Shaffer
James Watt

Associates:
William B. Balamuth
Theodore Bauer
Ross S. Benham
Marion M. Brooke
Irving Gordon
Henry E. Meleney
Richard J. Porter

1956
Director:
Francis S. Cheever (1956–1963)

1956–1958
Members:
Justin M. Andrews
Gustave J. Dammin
William W. Ferguson
William W. Frye
Quentin Geiman
Albert V. Hardy
Morris F. Shaffer

Associates:
William B. Balamuth
Theodore Bauer
Ross S. Benham
Marion M. Brooke
Horace M. Gezon
Irving Gordon
Richard J. Porter
William H. Stewart
James Watt

1959–1961
Members:
Justin M. Andrews
William B. Balamuth
Gustave J. Dammin
William W. Ferguson
William W. Frye
Quentin Geiman
Horace M. Gezon
Albert V. Hardy
Morris F. Shaffer

Associates:
Theodore Bauer
Marion M. Brooke
Harry Eagle
Irving Gordon
Franz J. Ingelfinger
George W. Kidder
Henry E. Meleney
William H. Stewart
Jerome T. Syverton
William Trager
James Watt

1962
Members:

Justin M. Andrews
William B. Balamuth
Gustave J. Dammin
William W. Ferguson
William W. Frye
Quentin M. Geiman
Horace M. Gezon

Associates:
Marion M. Brooke
Harry Eagle
Albert V. Hardy
Franz J. Ingelfinger
George Kidder

1963
Director:
Horace M. Gezon (1963–1970)

Members:
William B. Balamuth
Francis S. Cheever
Gustave J. Dammin
William W. Ferguson
William W. Frye
Quentin M. Geiman

Associates:
Marion M. Brooke
Harry Eagle
Samuel B. Formal
Albert V. Hardy
Franz J. Ingelfinger

1964
Members:
William B. Balamuth
Francis S. Cheever
Gustave J. Dammin
William W. Ferguson
William W. Frye
Quentin M. Geiman

Associates:
Marion M. Brooke
Harry Eagle
Samuel B. Formal
Rolf Freter
Albert V. Hardy
Franz J. Ingelfinger

1965
Members:
William B. Balamuth
Francis S. Cheever
Gustave J. Dammin
William W. Ferguson
Samuel B. Formal
William W. Frye
Quentin M. Geiman
Albert V. Hardy
Franz J. Ingelfinger

Associates:
Marion M. Brooke
Harry Eagle
Rolf Freter

1966–1967
Members:
William B. Balamuth
Francis S. Cheever
Gustave J. Dammin
William W. Ferguson
Samuel B. Formal
William W. Frye
Quentin M. Geiman
Horace M. Gezon
Albert V. Hardy
Franz J. Ingelfinger

Associates:
Marion M. Brooke
Rolf Freter
Russell W. Schaedler

1968–1969
Members:
William B. Balamuth
Francis S. Cheever
Gustave J. Dammin
Samuel B. Formal
Rolf Freter
William W. Frye
Albert B. Hardy
Thomas R. Hendrix
Franz J. Ingelfinger

Associates:
Marion M. Brooke
Eugene J. Gangarosa
Richard B. Hornick
Russell W. Schaedler

1970
Director:
Thomas R. Hendrix (1970–1973)

Members:
Francis S. Cheever
Gustave J. Dammin
Samuel B. Formal
Rolf Freter
Albert V. Hardy
Franz J. Ingelfinger

Associates:
Marion M. Brooke
Robert M. Donaldson, Jr.
Eugene J. Gangarosa
Richard B. Hornick
Russell W. Schaedler

1971–1973
Members:
Charles C. J. Carpenter
Francis S. Cheever
Gustave J. Dammin
Samuel B. Formal
Rolf Freter
Horace M. Gezon
Albert V. Hardy

Associates:
Marion M. Brooke
Eugene J. Gangarosa
Richard B. Hornick
Russell W. Schaedler

SECTION 6

Commission on Parasitic Diseases

Preparation of this history of the Armed Forces Epidemiological Board (AFEB) Commission on Parasitic Diseases was made possible through the help of Colonel Robert A. Wells, Executive Secretary, and Jean P. Ward, Staff Assistant, who assembled essential documents and compiled some of the essential data, and by Helen Day, Editorial Assistant, Department of Tropical Medicine, School of Public Health and Tropical Medicine, Tulane University, whose assistance in numerous ways was essential.

Foreword

Throughout the annals of military medicine, parasites have relentlessly afflicted combat personnel. Exposure in terrain marked with marshes, streams, rivers, rain forests, and remote villages brought combat troops in direct contact with mosquitoes, plasmodia, microfilariae, snails, schistosomes, and all types of parasites. The realization of their importance sparked the formation of the Commission on Parasitic Diseases of the Armed Forces Epidemiological Board (AFEB). The Commission's innovative work and the contributions of many professionals, who worked on parasite detection, prevention, and ultimate control, are a breath of fresh air in the history of military medicine.

From its beginnings in 1953, the Commission has been blessed with quality leadership. The contributions of its members have represented the best advice and wisest direction available anywhere.

Commission Directors Tom Weller, Gustave J. Dammin, Harry Most, and Paul Beaver were the best of all possible choices. They and their stellar associates worked in consort with their medical military professional counterparts to establish a remarkable program of fundamental research and preventive measures covering the years 1953 to 1973. Paul Beaver prepared this history of the AFEB Commission on Parasitic Diseases at a considerable sacrifice. He completed this work despite his failing health. It should better the cause of medicine everywhere and be of lasting value to the Military Medical Services. Unfortunately, Dr. Beaver died in 1993 before having the opportunity to read and enjoy this historical record of the Commission, which is really a tribute to him.

—Theodore E. Woodward, M.D.

History of the Commission on Parasitic Diseases

Paul C. Beaver, Ph.D.

INTRODUCTION

During World War II and in earlier years, whenever a parasitic disease problem was encountered by a military mission and civilian assistance to search for a solution was needed, a special commission of appropriate experts was formed to deal with it. For example, when the campaign to retake the Philippines was affected by large numbers of casualties due to schistosomiasis, a special commission consisting of selected military and civilian parasitologists was formed to determine the nature and extent of the problem and to take appropriate actions to deal with the problem. The Armed Forces Epidemiological Board (AFEB) established a permanent Commission on Parasitic Diseases in order to anticipate or prevent the outbreak of parasitic diseases. In the fall of 1952, Dr. Colin MacLeod, President of the AFEB, asked Dr. Thomas Weller to organize a Commission on Parasitic Diseases. On 13 January 1953, a preliminary meeting was held at the Army Medical School. Five of the original members of the Commission were in attendance, namely, Drs. Paul Beaver, Gustave J. Dammin, Harry Most, Lloyd Rozeboom, and Weller.

MISSION

The first formal meeting of the Commission was held on 2 October 1953 at the Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C. The following notes were taken from the minutes of the meeting. Those in attendance are listed below.

Members of the Commission

Dr. Thomas H. Weller, Director
Dr. Paul C. Beaver
Dr. Ernest B. Bueding
Dr. Gustave J. Dammin
Dr. Harry Most
Dr. Gilbert F. Otto
Dr. Lloyd E. Rozeboom

Representing the Army

Dr. Stanhope Bayne-Jones
Technical Director of Research, Medical Research and Development Board, Office of The Surgeon General
Colonel Arthur P. Long, MC
Assistant Chief, Preventive Medicine Division, Office of The Surgeon General, Department of the Army
Dr. Donald B. McMullen
Chief, Department of Medical Zoology, Army Medical Service Graduate School

Representing the Navy

Commander S. A. Britten, MC, USN
Head, Epidemiology Branch and Communicable Disease Section, Preventive Medicine Division, Bureau of Medicine and Surgery, Department of the Navy

Representing the Air Force

Major Gerald J. Schipper, MC, USAF
Communicable Disease Control Officer, Preventive Medicine Division, Office of The Surgeon General, Department of the Air Force

Representing the National Research Council

Dr. Leon H. Warren
Associate, Division on Medical Sciences

Outline of Meeting
Armed Forces Epidemiology Board
Commission on Parasitic Diseases
Walter Reed Army Medical Center
2 October 1953

9:30	Remarks by Commission Director	Thomas H. Weller
	Commission's Expected Program	Dr. S. Bayne-Jones, Director of Research, Medical Research and Development Board

Remarks by:
- Colonel Arthur P. Long, Department of the Army
- Commander S. A. Britten, Department of the Navy
- Major Gerald J. Schipper, Department of the Air Force
- Dr. Leon H. Warren, National Research Council
- Lieutenant Colonel William R. West-Watson, British Joint Services Mission
- Lieutenant Colonel R. D. Barron, Canadian Joint Staff Mission

General Discussion

Consideration of applications of:
- S. H. Hutner of Haskins Laboratories
- Irving G. Kagan, Zoological Laboratory of the University of Pennsylvania
- Bruce W. Halstead and associates of College of Medical Evangelists
- J. Allen Scott of University of Texas
- R. M. Lewert of University of Chicago
- Gustave J. Dammin of Harvard Medical School

Executive Session

17:30 Adjournment

When he opened the meeting, Dr. Weller emphasized the need felt by the new Commission for information about policies, procedures, funds, and relationships among various organizations and suggested that the Commission should do what it could to remedy the deficiency of workers in parasitology and parasitic diseases. He then introduced Dr. Stanhope Bayne-Jones and asked him to speak about several critical matters. Dr. Bayne-Jones explained that he was serving in his present role as a staff member for the Commission because both the President of the AFEB (Dr. MacLeod) and its Administrator (Colonel Adam Rapalski) were in the Far East. He explained further that he was very new in his position as Technical Director of Research of the Medical Research and Development Board in the Office of The Surgeon General of the Army. He conveyed a welcome from Colonel John Wood and said that he also felt that he was permitted to express his appreciation and welcome on behalf of the three Surgeons General.

Questions and discussions lasted about an hour and recurred often later. The following sections summarize the replies made by Dr. Bayne-Jones during the course of the meeting.

The Board and Commissions

It was noted that the AFEB was an agency of the Department of Defense; under the Secretary of Defense, the Secretary of the Army acted as managing agent, responsible for the main administrative affairs of the AFEB and commissions. The Secretary of the Army delegated authority and responsibilities to and through the command divisions (medical departments) of the three services: Army, Navy,

Outline of Meeting
Commission on Parasitic Diseases
Hotel Peabody, Memphis, Tennessee
2 November 1954

9:30	Introductory Remarks by Commission Director	Thomas H. Weller
	Remarks by:	
	Colonel Whayne, Department of the Army	
	Captain Sapero, Department of the Navy	
	Lieutenant Colonel Townsend, Department of the Air Force	
	Colonel Adam Rapalski, Armed Forces Epidemiological Board	
	Summary of Research in Progress at the 406th General Medical Laboratory	Dr. Lawrence S. Ritchie
	Progress report on work done under contract DA-49-007-MD-516	Dr. R. M. Lewert
	Review of status of revision of TB-MEDS	
13:00	Executive session	
	Discussion of renewal of Contract DA-49-007-MD-516	Dr. Robert M. Lewert
	Consideration of applications of:	
	Dr. Paul C. Beaver, Tulane University	
	Dr. Henry van der Schalie	
	Dr. M. G. Lysenko, University of Wisconsin	
14:30	Meeting adjourned	
19:30	Meeting reconvened in general session	
	Report of work in parasitology at the Naval Medical Research Institute	Dr. Clay Huff
	Informal presentation by Dr. Dammin on certain parasitological findings in monkeys	
21:15	Executive session	
	Discussion of:	
	Research in the field of malaria	
	Interest of the Commission in amebiasis	
	Public health problem posed by groups of individuals infected with intestinal helminths	
	Problem of hydatid disease in the Alaskan theater	
22:15	Meeting adjourned	

and Air Force. Most of the funds available to the AFEB and commissions were supplied by the Army through the Medical Research and Development Board of the Office of the Surgeon General, Department of the Army. Dr. Bayne-Jones said that the Commission on Parasitic Diseases might be in an especially favorable position to develop projects of joint concern among the three Services.

Special Functions

In research, the commissions had operated in two main ways, namely (1) conducting field investigations, and (2) conducting investigations in the home laboratories of members of the commissions or persons associated with the commissions (Associate Members). The Commission would consider research proposals referred to it by the Medical Research and Development Board.

Dr. Bayne-Jones said that

- The proposals from outside would be considered in relation to the program or activity of the Commission.
- If a proposal was approved and a contract executed, the project would then become an integral part of the program of the Commission and would be "monitored" by the Commission.
- The investigators supported by such a contract would not need to be made either members or associates of the Commission.
- As a corollary to the first two statements above, the Commission was not an agency for recommending the dispensing of funds on a grant-in-aid basis; rather it was an agency recommending action on contracts for research or related work connected with the missions of the Armed Forces.

Financing

The Commission on Parasitic Diseases could count on having a total budget allocation of approximately $110,000 for FY 54 (1 July 1953 to 30 June 1954) and probably the same amount for FY 55. This was exclusive of any amount provided through the Medical Research and Development Board for investigations on parasitic diseases by the Army Medical Service Graduate School.

Relationships and Research Programs

Relationships among commissions, research and operating sections in the Office of The Surgeon General, or in Class II Installations of The Surgeon General's Office, research organizations and programs of the Navy and Air Force, and civilian organizations were described by Dr. Bayne-Jones as extensive and complicated. This new Commission would have to find its way through a maze of activities, vested interests, and appeals. It was Dr. Bayne-Jones' advice to the Commission to deal with questions as they arose and to develop some special lines of activity. It was again suggested that the Commission's program should include as many projects of mutual interest to the Army, Navy, and Air Force as possible.

Recruitment

With regard to training and recruitment in the field of parasitology and tropical medicine, Dr. Bayne-Jones offered his opinion on the following matters:

- The Commission could not use its funds for fellowships. According to an opinion from the Department of Defense, under the present appropriation acts, it would be illegal to use money from the Defense Department for fellowship stipends.
- He believed that the Commission could employ investigators and hire contractors with various levels of skill and experience to do research that they and the AFEB wanted done.
- To make the need for more trained parasitologists more widely known, he suggested that the Commission could draw up a statement about the deficiencies of "manpower," skills, and knowledge in this field and have it published in appropriate scientific journals, could circularize various organizations, and could mention the subject in connection with the presentation of papers, presidential addresses, or other discourses.
- Furthermore, the Commission could stimulate interest and attract new workers by outlining interesting and important areas of research and by looking for persons who would be interested in working on problems in those areas.

Basic and Applied Research

From time to time during the session, questions were raised by members of the Commission and some of the guests relating to basic research compared to applied research. Dr. Bayne-Jones said that

although there were many complexities, one simplifying general rule that had been observed from the first was that the research conducted by the AFEB and its commissions must be reasonably related to the mission of the Armed Forces. This mission was, of course, very broad. Although the mission statement was not quoted at the meeting, the following statement of the mission of the Army is quoted from Section II, Paragraph 6, of S.R. 10-5-1, dated 11 April 1950, and entered for the record as follows:

> *Mission.* To provide support for national and international policy, and the security of the United States by planning, directing, and reviewing the military and civil operations of the Army Establishment, to include the organization, training, and equipping of land forces of the United States for the conduct of prompt and sustained combat operations on land in accordance with plans for national security.

In this context, the main point is the breadth of the mission statement, allowing scope for both basic and applied research. The provision that all such research should be reasonably related to the mission of a military service was not so restrictive that it had interfered with the traditional activities of the AFEB and commissions. In this connection, Colonel Arthur P. Long and others pointed out that the research work of the AFEB and commissions was carried out under contracts. Such research contracts did not necessarily have an "end item" in view, but were definitely concerned with work that was expected to be of benefit to the Armed Forces. The commissions and AFEB did not function merely as agencies for dissemination of grants in aid.

Finally, Dr. Bayne-Jones suggested that the question of basic versus applied research should be dealt with in a common-sense manner in direct relation to a research program or research project that might be formulated by the Commission or submitted to it. If it was something that competent investigators wanted to do and could do, and if it was within the broad missions of the Services, there would probably be no serious problems in the way of supporting it if funds were available.

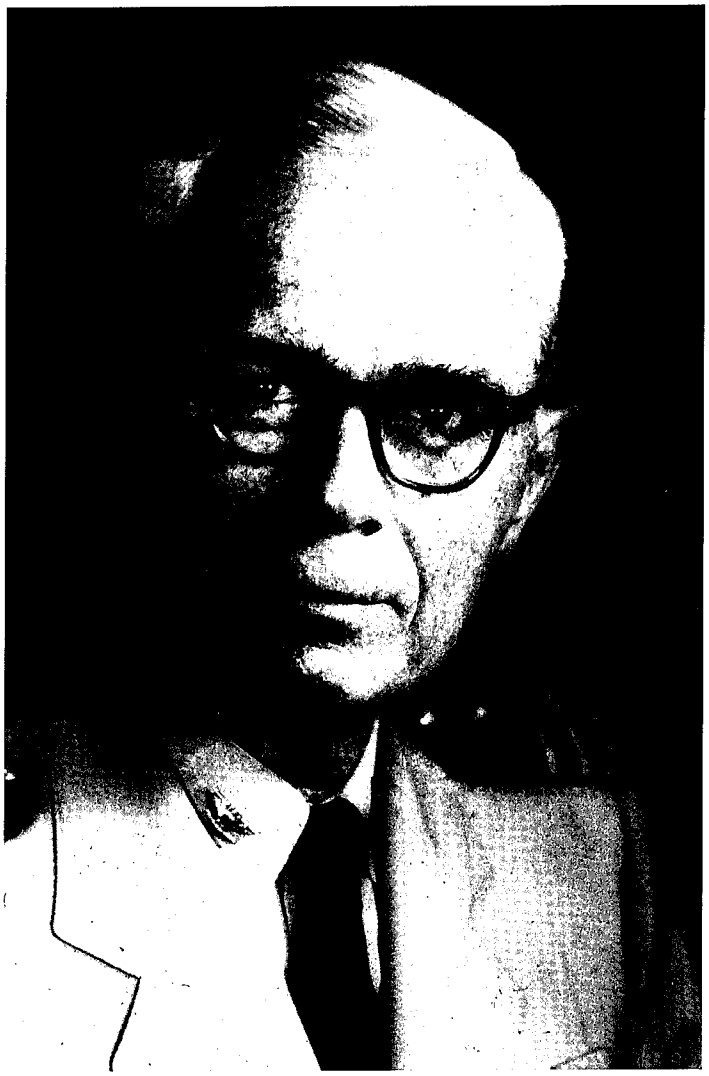
Colonel Long presented information and comments from the Division of Preventive Medicine, Office of The Surgeon General of the Army. He said that the representatives of the Services felt that their place in these meetings was to help the group to understand problems of the Services and to help them evaluate their work as far as the Services were concerned. He said that at that time the military forces were not faced with serious problems of parasitic diseases, but no doubt would have far more extensive problems in case of global war.

Dr. Weller asked what assistance would be requested in connection with revisions of TB–MEDS. Colonel Long said that the staff of the Preventive Medicine Division had sent Dr. MacLeod a stack of TB-MEDS with a request to the AFEB and its commissions to furnish advice and new material for revisions, and for revisions of some other publications.

Captain Sidney A. Britten presented statistics from the Preventive Medicine Division of the Bureau of Medicine and Surgery of the Navy. He said that the Navy was concerned with certain parasitic diseases that caused its personnel loss of time and had an adverse effect on their morale. He quoted a series of figures on schistosomiasis, filariasis, amebiasis, and malaria and referred to the work on schistosomiasis and other diseases being done by the staff of the Navy Medical Research Unit (NAMRU #3) in Cairo, Egypt. Expressing his personal opinion, Commander Britten said that he had considerable interest in prophylaxis against African sleeping sickness (trypanosomiasis) by the use of pentamidine and other compounds. He suggested that the Commission could be of assistance by taking an interest in this subject.

Information from the Preventive Medicine Division of the Office of The Surgeon General of the Air Force was presented by Major Gerald J. Schipper. After discussing some statistics, he pointed out that most of the Air Force personnel were "ground personnel" and, like the other services, the Air Force was concerned about problems of parasitic diseases. Diarrheal disease was one of the major factors interfering with flying duty.

Dr. Leon Warren reviewed the long-standing interest of the National Research Council, Division of Medical Sciences, in the field of parasitology and tropical medicine. He referred to the current committees and subcommittees that were dealing with work in this field and outlined some of their main activities.



CAPTAIN SIDNEY A. BRITTEN, MC, USN

Executive Secretary
1963–1968

The Commission then considered the applications that had been submitted to it. Only one application was from a member of the Commission (Dr. Dammin's application). All of the applications had been referred by the Medical Research and Development Board. The Director had already assigned each application to a member of the Commission for study.

Six applications were considered. Two were regarded as unsuitable for sponsorship. Two were thought to be meritorious but more appropriate for support elsewhere (National Institutes of Health [NIH]) or more appropriate for sponsorship by the Commission on Immunization (including Dr. Dammin's application) and two were approved and recommended to the Board for funding. The approved applications were submitted by Dr. Robert M. Lewert on "The Inhibition of Cercarial Penetration" and by Drs. Bruce Halstead and Edward Wagner on "The Biology of the Snail Host of *Schistosoma japonicum*." (Dr. Lewert later became a member of the Commission.)

In executive session, the Commission considered some matters of policy and the formation of a committee to summarize deficiencies in the supply of trained personnel in the field of parasitic diseases. No action was recorded.

MEMBERSHIP

Commission Directors

Thomas H. Weller, M.D., Harvard School of Public Health, 1953–1959

Gustave J. Dammin, M.D., Harvard Medical School, 1959–1960

Harry Most, M.D., New York University School of Medicine, 1960–1967

Paul C. Beaver, Ph.D., Tulane University School of Public Health and Tropical Medicine, 1967–1972

Deputy Directors

Gustave J. Dammin, M.D., Harvard Medical School, 1957–1959

Elvio H. Sadun, Sc.D., Walter Reed Army Institute of Research, 1969–1972

Members

The number of full members of the Commission varied from 8 or 9 (usually 9) up to 1965, to 12 to 14 thereafter. Listed below are all full members with their academic degrees, affiliations, terms of appointment, and fields of special interest:

William B. Balamuth, Ph.D., University of California, 1969–1972—Amebiasis

Paul C. Beaver, Ph.D., Tulane University, 1953–1972—Filariasis, Amebiasis

Ernest Bueding, M.D., Louisiana State University, 1953–1972—Pharmacology, Anthelmintics

G. Robert Coatney, Ph.D., National Institutes of Health, 1965–1968—Malaria

Gustave J. Dammin, M.D., Harvard University, 1953–1968—Pathology, Tropical Diseases

William W. Frye, Ph.D., M.D., Louisiana State University, 1970–1972—Amebiasis

Clay G. Huff, Sc.D., National Naval Medical Center, 1965–1967—Malaria

Rodney C. Jung, M.D., Ph.D., Tulane University, 1968–1972—Clinical Tropical Medicine

Robert M. Lewert, Sc.D., University of Chicago, 1958–1972—Biochemistry, Immunology, Schistosomiasis

Donald B. McMullen, Sc.D., Walter Reed Army Institute of Research, 1965–1967—Schistosomiasis

Harry Most, M.D., New York University, 1953–1972—Clinical Tropical Medicine, Malaria

Franklin A. Neva, M.D., Harvard School of Public Health, 1965–1968—Leishmaniasis

Gilbert F. Otto, Sc.D., Abbott Laboratories, 1953–1958—Filariasis

Lloyd E. Rozeboom, Sc.D., The Johns Hopkins University, 1953–1972—Medical Entomology

Elvio H. Sadun, Sc.D., Walter Reed Army Institute of Research, 1961–1972—Malaria, Schistosomiasis
Leslie A. Stauber, Sc.D., Rutgers University, 1968–1972—Leishmaniasis
Henry Van der Schalie, Ph.D., University of Michigan, 1953–1972—Malacology
Franz C. von Lichtenberg, M.D., Peter Bent Brigham Hospital, 1965–1968—Pathology, Schistosomiasis
Thomas H. Weller, M.D., Harvard University, 1953–1972—Tropical Diseases, Schistosomiasis
Willard H. Wright, D.V.M., Ph.D., National Institutes of Health, 1953–1972—Helminthology
Martin D. Young, Sc.D., Gorgas Memorial Laboratory, 1968–1972—Malaria

Associate Members

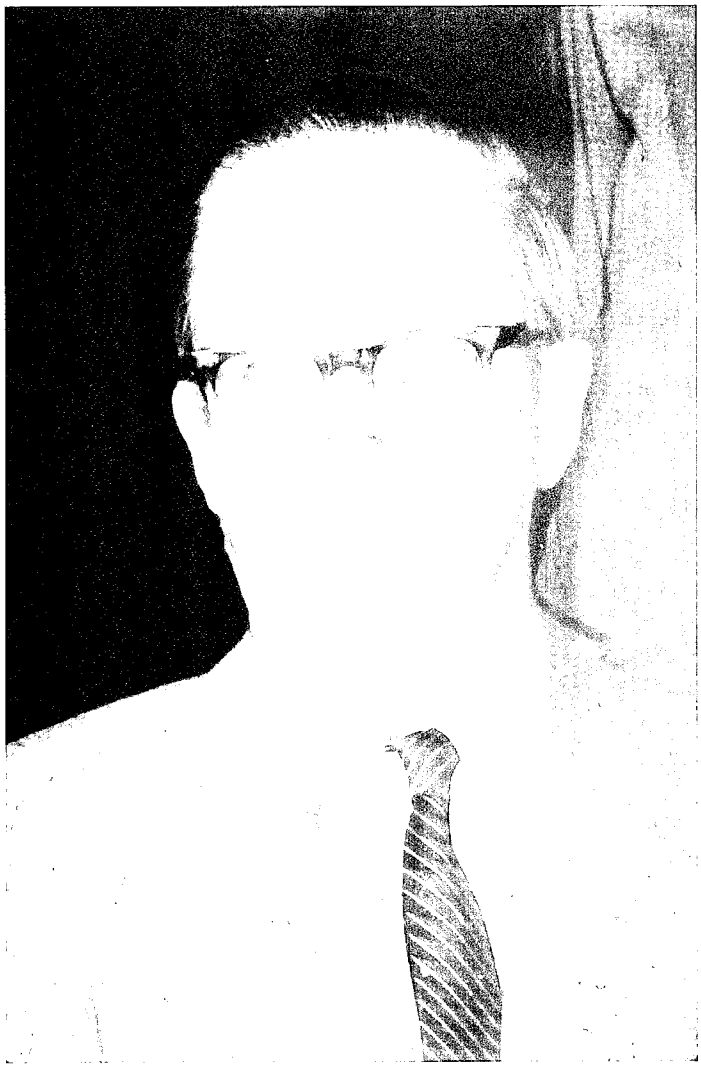
The number of associate members varied from none for the first 2 years to 12 for the years 1963–1964, when chloroquine resistance of *Plasmodium falciparum* was demanding special attention prior to the establishment of a separate Commission on Malaria. Members who were appointed associate members and later appointed full members were Drs. G. Robert Coatney (1959–1964), Clay G. Huff (1955–1965), Rodney Jung (1967–1968), Lewert (1957–1958), Donald R. McMullen (1955–1965), Franklin A. Neva (1961–1965), Elvio H. Sadun (1963–1965), Leslie A. Stauber (1963–1968), Franz von Lichtenberg (1959–1965), and Martin D. Young (1967–1968).

Those who served on the Commission as associate members only include the following:

Robert Altman, M.D., Walter Reed Army Medical Center, 1967–1970—Malaria
Alf S. Alving, M.D., University of Chicago, 1963–1964—Malaria
Ralph W. Bunn, M.D., Walter Reed Army Medical Center, 1959–1960—Malaria
Daniel H. Connor, M.D., Armed Forces Institute of Pathology, 1968–1972—Filariasis
V. G. Dethler, University of Pennsylvania, 1961–1962—Malaria
Robert C. Elderfield, Ph.D., University of Michigan, 1963–1964—Malaria
John M. Geary, M.D., Walter Reed Army Medical Center, Washington, D.C., 1963–1967—Malaria
R. J. Holoway, MSC, USM, Walter Reed Army Medical Center, Washington, D.C.—Pest Control
John Scanlon, Ph.D., University of Texas, 1968–1972—Medical Entomology
Leon H. Schmidt, Ph.D., University of California, 1963–1964—Malaria
William Trager, Ph.D., Rockefeller Institute of Medical Research, 1963–1964—Malaria, Trypanosomiasis

COMMISSION ACTIVITIES

After the first meetings in the fall of 1953 and 1954, fall and spring meetings were held annually (usually in October or November and March or April). Annual reports were submitted by the Director of the Commission to the President of the AFEB. The annual report consisted of the proceedings of the two previous meetings, a summary of Commission activities, and reports from responsible investigators on studies, including those in progress or those completed during the year under sponsorship of the Commission. Frequently, a spring or fall meeting extended over 2 days and included a symposium covering a topic of special military interest. Usually, at both meetings, a regular agenda item included formal reports or comments from representatives of the Army, Navy, and Air Force on the current status of parasitic diseases, or on a special problem such as prophylaxis failure in malaria or the question of risk of hydatid infection for the military personnel stationed in Alaska. Fall meetings occasion-



THOMAS H. WELLER, M.D.

Dr. Thomas H. Weller always conducted himself as a meticulous student of medicine, thoroughly schooled in the fundamentals of the scientific method. Trained as a clinical and laboratory-oriented pediatrician, he extended his capabilities into the fields of virology and parasitology. With his mentor, John Enders, and his associate, Fred Robbins, he received the Nobel Prize for the cultivation of poliomyelitis virus in tissue cultures.

Tom willingly responded to military medical problems; he served with distinction on the Commission on Parasitology and directed its activities from 1953 to 1959, while concurrently engaged at the Harvard School of Public Health. The AFEB Commissions on Malaria and Virus Diseases profited greatly from Tom Weller's wise counsel, teaching ability, and scientific contributions.



GUSTAVE J. DAMMIN, M.D.

There are few among us who possess the competence, commitment, wisdom, and equanimity that Dr. Gustave J. Dammin displayed. His productive war record was followed by a stellar career as an experimental pathologist at Washington University School of Medicine in St. Louis and at Harvard Medical School. Gus was an active contributor to several commissions of the AFEB. Parasitology was one of his favorite fields of interest to which speciality he contributed so importantly. He was Deputy Director of the Commission on Parasitic Diseases from 1957 to 1959 and its Director from 1959 to 1960.

In 1960, he was very appropriately elevated to the Presidency of the AFEB, where he served with great distinction until 1972. During this 12-year period, the AFEB and its commissions dealt with substance abuse in the military, immunization practices, and changes in the organization of the AFEB. Gus steered a steady ship. He saw issues and problems through to their best solutions by his appointments of consultants; the AFEB and its commissions flourished under his guiding hand. A careful and dedicated scientist, Gus Dammin not only advised other investigators, but he also made major contributions of his own. His leadership of the AFEB was of unquestioned historical significance.



HARRY MOST, M.D.

Dr. Harry Most was born in New York City and was a proud product of the New York City University educational system (B.S., 1927; Medicine, 1931; and D.Sc., 1938). He was a Research Fellow of the International Health Division of the Rockefeller Foundation and DTM, London School of Tropical Medicine. At New York University School of Medicine, he was assistant professor of medicine and clinical pathology from 1941 to 1946, associate professor of preventive medicine from 1946 to 1949, professor of tropical medicine from 1949 to 1954, and the Hermann M. Biggs Professor and chairman of the Department of Preventive Medicine from 1954 to 1976; he served as professor of medicine beginning in 1976.

Harry Most was an important member of the New York State Department of Health and held consultant and visiting professorships at Harvard, various hospitals in New York, and the Centers for Disease Control in Atlanta. He served with distinction as a major in the Army of the United States and received the Legion of Merit for special contributions to the military service. Various leading societies awarded him memberships and officerships, including the New York Society of Tropical Medicine, of which he was president in 1963 and 1964; the American Society of Clinical Investigation; the American Medical Association; the American Association for the Advancement of Science; and the Phi Beta Kappa and Alpha Omega Alpha.

For many years, Dr. Most was a member of the Commission on Parasitic Diseases and served as its director in 1950. Truly, he was one our country's leading authorities in tropical medicine and parasitic diseases.



PAUL C. BEAVER, PH.D.

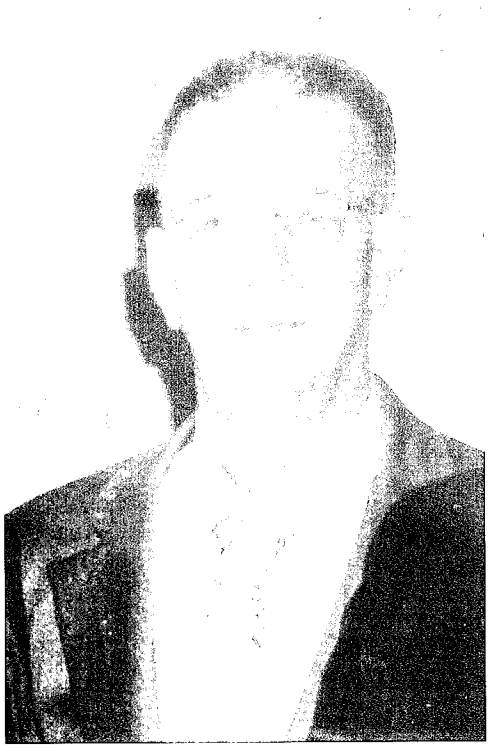
Paul C. Beaver graduated from Wabash College in 1928 and received his doctoral degree from the University of Illinois in 1935. His alma mater awarded him an honorary degree of D.Sc. in 1963. During his early career, Dr. Beaver held academic positions at the University of Wyoming, Lawrence College, and University of Michigan. Between 1942 and 1945, Dr. Beaver was a member of the Georgia Department of Health. He then joined the faculty of the Tulane University Medical School as Assistant Professor of Parasitology between 1945 and 1947. He progressed through the ranks and became Associate Professor in 1947, Professor in 1952, and chaired the department between 1956 and 1971. In 1976, he was made Professor Emeritus.

Faithful and productive as an outstanding parasitologist, he was an important contributing member of the Commission on Parasitic Diseases from 1960 to 1967, and served as its director from 1967 to 1973, at which time the Commission's activities were terminated by executive order.

Dr. Beaver served as a member, councilor, and officer of numerous academic societies, both domestic and abroad. He was vice president of the American Society of Tropical Medicine and Hygiene in 1958 and its president in 1969. The American Society of Parasitology honored him with its presidency in 1968. Two high posts were his membership in the Royal Society of Tropical Medicine and Hygiene and NIH membership of the Parasitic Diseases Panel of the U.S./Japan Cooperative Medical Science Program. Editorial boards of leading parasitological and tropical medicine journals profited from his scholarly capabilities. The AFEB is in his debt for having prepared the history of the Commission on Parasitic Diseases.



RODNEY C. JUNG, M.D., PH.D.



LESLIE A. STAUBER, SC.D.



WILLIAM TRAGER, PH.D.



MARTIN D. YOUNG, SC.D.

ally were held at the site of, and just before or immediately following, the annual meetings of the American Society of Tropical Medicine and Hygiene. This practice was discontinued after the 1967 fall meeting.

Malaria Committee

At the 1957 spring meeting of the Commission, the need for research in the field of malaria was discussed at length. The Commission decided to consider areas where investigative work needed to be performed, with particular reference to the present and potential requirements of the Armed Forces. This decision came after a long discussion, in which it was noted that the National Research Council had disbanded its Panel on Malaria at a time when chloroquine-resistant strains were being reported.

Agenda
Commission on Parasitic Diseases
Claypool Hotel, Indianapolis, Indiana
27 October 1959

GENERAL SESSION

0930	Introductory remarks Dr. Thomas Francis, Jr., President, AFEB Colonel John Rizzolo, USAF (MC), Executive Secretary, AFEB Dr. Gustave J. Dammin, Director, CPD	
1000	Reports of Preventive Medicine Officers of the Armed Forces	
1030	Coffee break	
1045	Current work on the treatment of malaria	Dr. Alf S. Alving
1145	Discussion: Commission Members and Guests	
1215	Lunch	
1330	Malaria and other research in parasitology at the Naval Medical Research Institute	Dr. Clay G. Huff
1400	Recent work of AFPCB on control of insect vectors	Colonel Ralph W. Bunn, MSC
1420	General discussion—Malaria	
1440	Informal reports and discussion of training, therapy, research and travel— Dr. Ernest Bueding Dr. Franz von Lichtenberg Dr. Donald McMullen Dr. Harry Most Dr. Henry van der Schalie Dr. Thomas H. Weller	
1540	Coffee break	
1600	Executive Session	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
7–8 April 1960

GENERAL SESSION—7 April

0930 Introductory Remarks
Dr. Gustave J. Dammin, Director
Colonel John Rizzolo, USAF, MC, Executive Secretary, AFEB
Major Thomas B. Dunne, MC, R&D Command

1000 Reports of Preventive Medicine Officers of the Army, Navy, and Air Force

1030 Intermission

1045 Requirements for personnel and training for work in tropical areas
Subject to be introduced by Dr. Sadun
Discussion by representatives of the Military, Public Health Servic,e and Commission Members

1130 Dr. Henry van der Schalie: Studies of American *Pomatiopsis* Snails

1200 Film describing work of the 406th Med. Gen. Lab., Zama, Japan

1230 Recess for lunch

1400 Dr. Harry Most and Dr. Meir Yoeli: Biological Studies in Malaria

1445 Dr. Lloyd Rozeboom and Dr. L. M. Howard: Factors Influencing the Susceptibility and Immunity of the Mosquito to Infection by the Malaria Parasite

1530 Work of the Military in Malaria Chemoprophylaxis
Malaria: General Discussion

1700 Adjournment

GENERAL SESSION—8 April

0900 Dr. Paul Beaver, Dr. John Schacher, and Dr. T. J. Danaraj: Visceral Larva Migrans in Relation to Tropical Eosinophilia

0945 Dr. Robert Lewert, Dr. S. Mandlowitz, and Dr. D. Dusanic: Studies on *Schistosome cercariae* with Special Reference to Inhibition of Penetration by Various Agents

1030 Intermission

1045 Dr. Ernest Bueding: Mechanisms of Anthelminthic Action
1130 Dr. Nathan Entner: Enzymatic Aspects of Carbohydrate Metabolism in *Ascaris lumbricoides*
1200 Informal reports on research and travel
1300 Recess for lunch

EXECUTIVE SESSION

1400 Meeting of full members of the Commission on Parasitic Diseases for consideration of contract proposals, financing, and membership

At the 1957 fall meeting of the Commission, a special session on the status of malaria research was held. Discussions were led by the country's most eminent malariologists, Dr. Paul Russell of the Rockefeller Foundation, Dr. Huff of the U.S. Naval Medical Research Center, and Dr. Coatney of the NIH Laboratory of Tropical Diseases. Dr. Russell pointed out gaps in knowledge about malaria organisms, mosquito vectors, insecticides, and antimalarials. Dr. Huff discussed the need for basic research on the plasmodium's morphology and behavior, genetics, and physiology. Dr. Rozeboom reviewed the research needs regarding vector taxonomy, transmission potential, and resistance to insecticides. Dr. Coatney discussed problems of chemotherapy and Dr. Willard Wright outlined research currently in progress in the United States and elsewhere.

At the 1958 spring meeting, the needs for research on malaria were again reviewed, and an ad hoc committee called the Committee on Malaria Research was appointed for the purpose of stimulating applications for support of research on malaria. At the 1958 fall meeting of the Commission, members of the committee reported that as a direct result of the committee's discussions in Bethesda earlier in the year, members of the Commission had submitted the following two project applications: Dr. Harry Most and Dr. Meir Yoeli had already begun their "Biological Studies in Malaria," initiated in July 1958 at New York University; Dr. Rozeboom and Dr. Lee M. Howard applied to do research on "Factors Influencing Susceptibility and Immunity in the Mosquito to Infection by the Malaria Parasite," to be initiated in January 1959 at The Johns Hopkins University.

Members of the Committee on Malaria Research included the Chairman, Dr. Most, and Drs. Coatney, Rozeboom, and Weller, who continued discussions at subsequent meetings. They reached no definite conclusions and made no recommendations until the 1962 fall meeting, when the ad hoc committee converted to a permanent, standing committee of the AFEB consisting of Drs. Most (Chairman), Coatney, Huff, Rozeboom, and Weller. Additional discussions about the committee's role and purpose took place at the spring 1963 meeting of the full Commission on Parasitic Diseases. Following discussions, and after reviewing recent malaria problems encountered by the military, the ad hoc committee was established by the AFEB as a permanent committee. The newly established committee presented the following recommendations: that immediate steps be taken to expand research and research training; that the AFEB encourage new studies and intensify studies on a new antimalarial drug; and that the AFEB consider the establishment of a joint governmental, military, and civilian committee on malaria.

Alaska Hydatid Field Investigation

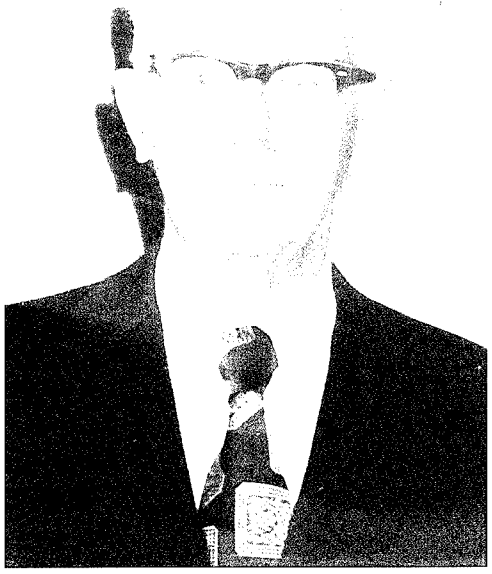
Because it posed a health hazard to military personnel on duty in Alaska, an ad hoc committee was formed to investigate hydatid disease. Ad hoc committee members included Drs. Gilbert Otto (Chairman), Most, and Wright. Dr. Robert Rausch of the Arctic Health Research Center (USPHS), whose research had called attention to the problem, attended the 1956 spring meeting of the Commission and met with the members of the ad hoc committee on hydatid disease. On the recommendation of the committee, a field party conducted a 2-week investigation in Alaska in July 1956. The field party consisted of Dr. Otto, Mr. John Bozicevich of the NIH, and Lieutenant Colonel H. E. Griffin, of the Preventive Medicine Division, Office of The Surgeon General. Based on the committee's epidemiological findings, extensive intradermal tests with controls and confirmation of results by two laboratories (CDC and First Army Laboratory), and based on further discussions at the 1956 fall and 1957 spring meetings of the Commission, it was concluded that hydatid infection in Alaska was not a medical hazard of more than minimal significance to military personnel.

Schistosomiasis Research Methodology

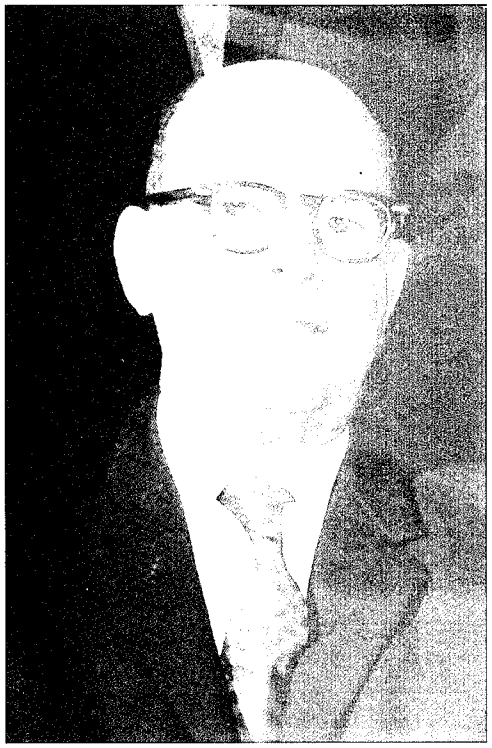
In view of the high importance of schistosomiasis in the Commission's program and the frequency of disappointing results due to oversight of essential experimental conditions, an ad hoc committee was asked to prepare an outline of essential conditions to be considered and included in the planning



G. ROBERT COATNEY, PH.D.



LLOYD E. ROZEBOOM, SC.D.



WILLARD H. WRIGHT, D.V.M., PH.D.



HENRY VAN DER SCHALIE , M.D.



ELVIO H. SADUN, SC.D.

Elvio H. Sadun received his early education in Italy and obtained graduate degrees from Harvard University (M.A.) and The Johns Hopkins University School of Hygiene (Sc.D.). He taught parasitology for a few years each at the University of Arkansas School of Medicine, Tulane University School of Medicine, and Thai University of Health in Bangkok, Thailand. For 3 years (1954–1957), he was in charge of the helminthological unit at the Communicable Disease Center in Atlanta. He then was parasitologist at the U.S. Army 406th Medical, General Laboratory in Japan, and in 1959 began an illustrious career as Chief of Medical Zoology at Walter Reed Army Institute of Research (WRAIR). At each location, his research contributed significantly to knowledge of immunological or nutritional aspects of parasitic infection.

Dr. Sadun was a member of the Commission on Parasitic Diseases from 1965 to 1972 and was Deputy Director from 1969 to 1972. He was a ready participant in discussions of a wide range of disease problems and was an outstanding leader in the areas of schistosomiasis and malaria. A notable achievement was the organization, direction, and editing of comprehensive malaria research symposiums in 1966, 1969, and 1972. In 1974 he was awarded posthumously the Distinguished Civilian Service Award of the Department of Defense.

and reporting of schistosomiasis research projects. The following members of the Commission served on the committee: Chairman Henry van der Schalie and members Dr. McMullen, Dr. Robert Kuntz, and Dr. Elmer Berry. Their report covered the sources of eggs, the storage of eggs, and their method of hatching. The report also discussed the background of the snails; the possible methods of exposure to the snails; the duration and conditions of development in snails; the number, behavior, and infectivity of cercariae; method of exposure of vertebrate hosts; and the methods of collecting and handling the adult worms. A bibliography of selected papers on the maintenance of schistosomes in the laboratory was appended to the report.

TB-Medications (TB-MEDS)

At the Commission's first meeting in October 1953, it was noted that a number of TB-Medications (TB-Meds) and other publications were awaiting revision; and that the assistance of the AFEB and commissions was expected. When the 1954-55 Director's Annual Report was released, the revision of the four TB-MEDS assigned to the Commission had been completed. Suggestions were then made at the fall 1964 meeting by Commission members concerning the revision of TB-MEDS on common intestinal helminths and on African trypanosomiasis. The status of the TB-MEDS was again discussed at the 1965 spring meeting. In 1965, the suggestion was offered that the TB-MEDS should be made more generally available through the Government Printing Office. There was no recorded follow-up of that suggestion. By November 1965, the TB-MEDS had been revised on African trypanosomiasis, common intestinal helminths, trematodes other than schistosomes, malaria, filariasis, amebiasis, and schistosomiasis. In October 1972, the need for further revisions of the TB-MEDS was again discussed at the last meeting of the Commission.

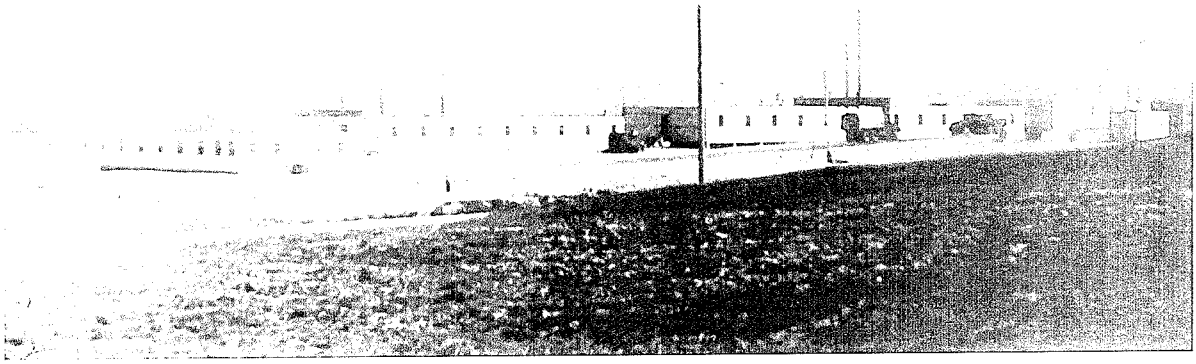
Procurement of Antiparasitic Drugs

In February 1961, and at subsequent spring meetings of the Commission, the attention of the AFEB was called to the serious lack of availability of drugs effective in the prophylactic, suppressive, and curative treatment of parasitic infections. Of the 32 listed drugs for prevention or treatment of parasitic infections, fewer than a third were recorded as available in the Federal Supply Catalogue. At the Commission meeting in October 1961, a resolution was prepared for use by the AFEB in an effort to remedy the situation. Later, the list was submitted to the appropriate offices to permit stockpiling the drugs.

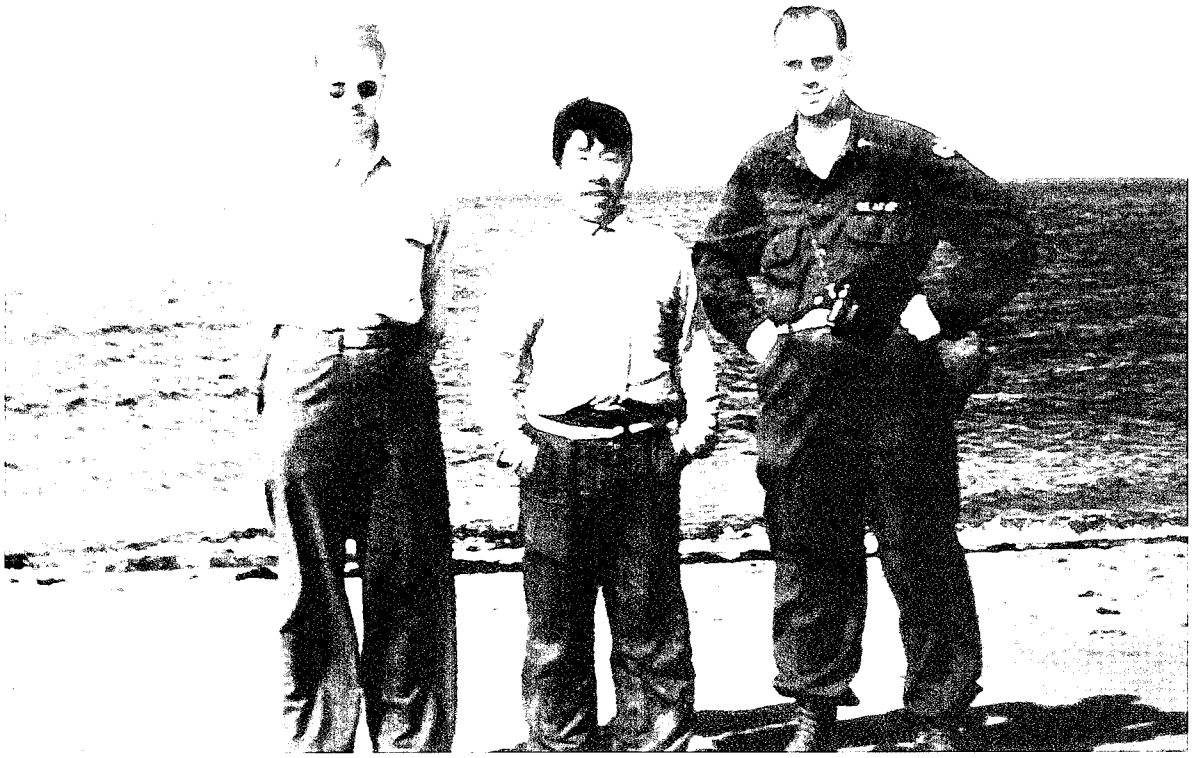
During the 1965 spring meeting, members reported that discussions were underway to encourage some pharmaceutical companies to establish a central institute, supported by the industry, to foster and support research on the synthesis, pharmacology, and chemotherapy of drugs needed in tropical medicine. Another key purpose of the institute would be to prepare and produce certain drugs that were currently unavailable because of low demand. Little progress was made toward that goal in 1966. So, the Commission on Parasitic Diseases established an ad hoc committee composed of Drs. Most, Neva, and Bueding to explore ways to resolve the problem. As a result of the work of the Commission, significant progress was reported at the 1967 spring meeting. The Communicable Disease Center (CDC) agreed to act as a sponsor for drugs not approved by the Food and Drug Administration for use in this country. To make such drugs more readily available to military and civilian physicians, members of the ad hoc committee recommended that repositories be established to serve various geographic areas. At the Commission's next meeting, the scarcity or nonavailability of needed antiparasitic drugs was still a matter of concern, but eventually a satisfactory service was established by the CDC in Atlanta, Georgia.

Special Reports and Symposia

The Commission attempted to integrate its program with that of other agencies by holding the following symposia on parasitology topics at leading institutions:



Air Force Base, Northeast Cape, St. Laurence Island, Alaska, July 1956.



Dr. Robert Rausch (Left), Lieutenant Colonel H.E. Griffen (Right), and an Unidentified Eskimo, St. Laurence Island, Alaska, July 1956.

- *Research Laboratories.* At the 1954 fall meeting, the parasitology research program of the 406th Medical General Laboratory in Japan was presented by Dr. L. S. Ritchie. Ongoing research at the Naval Medical Research Institute was described by Dr. Huff, and Dr. Wright described the parasitology research conducted at the NIH.
- *NIH Schistosomiasis.* At the 1955 spring meeting, Dr. Wright presented a summary of the research in progress on schistosomiasis at the NIH.
- *LSU Parasitology.* At the 1956 fall meeting of the Commission in New Orleans, the research program in parasitology at Louisiana State University School of Medicine was presented by Dr. Bueding and others (Drs. R. Reeves, H. J. Saz, B. E. Mansour).
- *Malaria Research.* The 1957 fall meeting of the Commission was held at Hotel Benjamin Franklin in Philadelphia. The afternoon session was devoted to reviews of current research on malaria by Drs. Russell, Huff, Rozeboom, and Coatney. Their presentations were followed by a discussion of the role of the Commission in relation to the status of research on malaria.
- *Vector Control.* At the 1959 spring meeting held at WRAIR, Colonel Ralph Bunn presented a report on current research to control of insect vectors at the Armed Forces Pest Control Branch laboratories in Florida.
- *Malaria Research.* At the 1960 spring meeting, Dr. Huff reported on the malaria research in progress at the Naval Medical Research Institute. At the same meeting, Dr. Alf S. Alving described the malaria research programs at University of Chicago and the Illinois State Penitentiary at Statesville.
- *CDC Program.* The 1962 fall meeting held at the CDC in Atlanta, the organization and programs of the CDC were described by Dr. Alan Donaldson, departmental chief. Individual programs were presented by four CDC laboratory chiefs.
- *Chicago Area Programs.* The 1963 fall meeting was held at University of Chicago. Dr. Lewert presented his own work and that of his colleagues at the university. He also outlined other research in progress in the Chicago area.
- *Malaria Research.* The 1964 fall meeting was held in New York on November 3rd at the New York University School of Medicine. Reports by representatives of the Preventive Medicine Services indicated that their principal concern was the occurrence of *Falciparum malaria*, a strain resistant to synthetic antimalarials. Dr. Sadun reviewed the current Walter Reed program on malaria research. Dr. Coatney presented a summary of the proceedings of the first meeting of the newly constituted Commission on Malaria. Although malaria had become the responsibility of a new commission, the Commission on Parasitic Diseases continued to be interested in the subject.
- *Tulane University Parasitology.* The 1965 fall meeting was held at Tulane University School of Medicine following the annual meeting of the American Society of Tropical Medicine and Hygiene. Dr. Beaver and several staff members presented reports on subjects under investigation at Tulane and at its overseas units in Singapore and in Colombia, South America.
- *Hemoflagellate Conference.* A conference on hemoflagellates was held at the 1967 spring meeting of the Commission on Parasitic Diseases of the AFEB. Dr. Stauber presided. A general introduction and review of fine structure and differentiation was given by Dr. Trager of Rockefeller University. Three speakers covered topics that included the current knowledge and problems of trypanosomiasis The three speakers also spoke on the *Leishmania* species. Dr. Neva of Harvard University spoke on Chagas' disease, Dr. Frans Goble of Ciba Pharmaceuticals spoke on chemotherapy, and Dr. Nathan Enter of New York University spoke on immunity. The speakers on leishmaniasis were Dr. Kevin Cahill from St. Clare's Hospital in New York City, who covered the clinical aspects and epidemiology in Africa; Dr. Bruce Walton of the U.S. Army Research Unit in Panama, who talked about American cutaneous leishmaniasis; and Dr. Stauber of Rutgers University, who spoke on the identification and evaluation of reservoir hosts. Drs. Howard Hopps, D. Price, and D. Weisberg of the Armed Forces Institute of Pathology; Drs. Sadun and E. Fife of the WRAIR; Dr. A. Pipkin of the Naval Medical Research Institute; Dr. T. von Brand of the NIH; and Dr. Young of the Gorgas Laboratory in Panama contributed to the discussions of leishmaniasis. In all of the discussions, the special needs for further research were stressed.

Agenda
Commission on Parasitic Diseases
Benjamin Franklin Hotel, Philadelphia
31 October 1967

0900 Introductory Remarks
Dr. Thomas Gill for Dr. Gustave J. Dammin, President
Dr. Paul C. Beaver, Director
Captain Sidney A. Britten, Executive Secretary

0915 Reports, Preventive Medicine Officers:
Department of the Army—Lieutenant Colonel John Einarson
Department of the Navy
Department of the Air Force—Major Amos Townsend
Representative, USA Medical R&D Command—Lieutenant Colonel Robert Cutting
Report on Niridazole Conference—Dr. Ernest Bueding and Dr. Elvio Sadun

0945 Recess—Coffee

SPECIAL REPORTS—Organized mostly by Elvio Sadun

1000 Lieutenant Colonel Norman E. Wilks, WRAIR: Parasitologic Investigations in Uganda
Major Duane G. Erickson, WRAIR, Problems in the Laboratory Diagnosis of Malaria and Amebiasis in Vietnam
Dr. Robert S. Desowitz, SEATO: Scope of Present Effort and Plans for Immediate Future of the SEATO Parasitological Program
Colonel Stefano Vivona, WRAIR: Overseas Components of WRAIR
Lieutenant Colonel James C. Burke, WRAIR: Parasitology as Presented in the WRAIR Global Medicine Course
Lieutenant Colonel L. J. Legters, WRAIR: Filariasis and Schistosomiasis in Vietnam
Dr. John Cross, NAMRU-2: Capillariasis in the Philippines

1130 Executive Session

1330 LEPTOSPIROSIS CONFERENCE
Introductory Remarks—Dr. Frank Neva, Program Chairman

I. Clinical and Epidemiological Features of Leptospirosis in S.E. Asia
Dr. Fred McCrumb, University of Maryland School of Medicine: Clinical Varieties of Leptospirosis in S.E. Asia
Dr. A. D. Alexander, WRAIR: Epidemiology of Leptospirosis with Particular Reference to S.E. Asia

II. Recent Experience with Leptospirosis in S.E. Asia
Lieutenant Colonel L. J. Legters, WRAIR: Known and Suspected Incidence of Leptospirosis in U.S. Military Personnel
Captain Andrew Whelton, WRAIR: Management of Renal Failure
Dr. A. D. Alexander: Criteria for Diagnosis of Leptospirosis

III. Approaches to Leptospirosis Control for the Military
Dr. Lyle E. Hanson, Univ. Ill. College of Veterinary Medicine: Experience with Leptospiral Vaccines in Veterinary Medicine, and Considerations for their Use in Man
Dr. Fred McCrumb: Treatment of Leptospirosis and Possibilities of Chemoprophylaxis

IV. Summing-Up and Open Discussion
1. Feasibility of Environmental Control of Leptospirosis
2. New Information Having Important Implications for Pathogenesis, Control, Treatment, and Diagnosis of Leptospirosis
Other Participants and Discussants: Dr. Charles D. Cox, Univ. Massachusetts, Dr. Victor M. Arean, Univ. Florida, and Dr. Russell C. Johnson, Univ. Minnesota

Leptospirosis Seminar

At the 1967 fall meeting in Philadelphia, leptospirosis was the subject of a half-day seminar organized and moderated by Dr. Neva. Although leptospirosis was known to be endemic in parts of Southeast Asia, it was not being dealt with by any other AFEB commission. Clinical and epidemiological features were presented by Dr. Fred McCrumb of the University of Maryland and by Dr. A. D. Alexander of the WRAIR. Recent experience with the disease in Southeast Asia was reported by Lieutenant Colonel L. J. Legters of WRAIR, Captain Andrew Whalton of WRAIR, and Dr. Alexander. Dr. Lyle Hanson of the University of Illinois College of Veterinary Medicine and Dr. McCrumb discussed approaches the military could take for leptospirosis control. Other discussants were Dr. Charles Cox of the University of Massachusetts, Dr. Victor Arean of the University of Florida, and Dr. Russell Johnson of the University of Minnesota.

Military Laboratory Programs. Also at the 1967 fall meeting of the Commission special

Reports on of research projects at military laboratories were also presented during the 1967 fall meeting of the Commission. Lieutenant Colonel Norman E. Wilks of WRAIR reported on parasitological investigations in Uganda. Major Duane G. Erickson of WRAIR reported on problems in the laboratory diagnoses of malaria and amebiasis in Vietnam. Dr. Robert S. Desowitz of SEATO reported on the scope of the SEATO parasitological program and on SEATO plans for the program in the near future. Colonel Stefano Vivano of WRAIR reported on the overseas components of WRAIR. Lieutenant Colonel James C. Burke of WRAIR outlined the WRAIR global medicine course in parasitology.

Lieutenant Colonel Legters of WRAIR reported on the military significance of filariasis and schistosomiasis in Vietnam and Dr. John Cross of the Naval Medical Research Unit-2 (NAMRU-2) reported on capillariasis in the Philippines.

Filariasis Program

At the 1968 fall meeting held at WRAIR, a half-day symposium on filariasis was held, consisting of a film on filariasis with introduction and comment by Colonel Lyman Frick and Dr. Donald Price;

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
25 March 1968

0900	Introductory Remarks Dr. Paul C. Beaver, Director Dr. Gustave J. Dammin, President Captain Sidney A. Britten, Executive Secretary
0915	Reports, Preventive Medicine Officers: Department of the Army—Lieutenant Colonel John Einarson Department of the Navy—Captain Charles Miller Department of the Air Force—Major A. Townsend Representative, USA Medical R&D Command—Lieutenant Colonel Robert Cutting
1030	Recess—Coffee
1045	Research at Overseas Military Installations—Dr. Elvio H. Sadun
1245	Recess—Lunch
1345	Executive Session Status of TB-MEDS, Drugs for Parasitic Diseases, Discussion of Grants, Contracts, Progress Reports, Personnel, Consideration of Short- and Long-Term Plans of Commission, Program of Fall Meeting

interpretation of microfilaremia by Dr. Guillermo Pacheco; immunological aspects and hypersensitivity by Dr. D. J. Stechschulte; serodiagnosis by Dr. Sadun and Dr. Ralph Duxbury; filariasis in Vietnam by Major Edward Colwell and Lt. Duane R. Armstrong; pulmonary filariasis by Dr. Beaver; pathogenesis of onchocercal dermatitis by Dr. Daniel Connor; and prophylaxis and treatment by Dr. Most.

Latin American Parasitic Diseases

At the 1969 spring meeting at WRAIR, reports on special problems of parasitic diseases in Latin America were presented. Dr. Hopps of the Armed Forces Institute of Pathology reported on the Amazon Basin, Dr. Alfred Buck of The Johns Hopkins University gave a summary of findings in a survey of parasitic infections in the Upper Amazon of the Andean Region, Dr. Bryce Walton reviewed the problem of leishmaniasis in South and Central America, and Dr. Young described the research program at the Gorgas Laboratory in Panama.

Immunology Symposium

On the 2nd day of the 1969 fall meeting, a 10-paper symposium was held on immunity in relation to parasitic diseases. Dr. H. N. Eisen spoke on immunization, Dr. K. F. Austen on allergy and hypersensitivity, G. B. Mackaness on mechanisms of resistance, J. S. Remington on immunoglobulins in toxoplasmosis, Dr. J. F. Barbaro on histamine release in schistosomiasis, Dr. E. J. L. Soulsby on cell-mediated immune response, Dr. C. W. Kim on delayed hypersensitivity and lymphocyte transformation, Dr. Kenneth S. Warren on granuloma formation in schistosomiasis, Dr. R. T. Damian on antigens common to host and parasite, and Dr. Sadun on immunization with irradiated parasites.

Special Reports

At the 1970 spring meeting, held at WRAIR, four special reports were presented. Major E. S. Colwell described a study at WRAIR on the in vitro leukocyte and passive cutaneous anaphylaxis reactions in experimental trichinosis and schistosomiasis. Current information on filariasis in Viet Nam was summarized by Captain T. J. Sullivan, concluding that Malayan filariasis had not been found in South Viet Nam and Bancroftian filariasis was uncommon in military personnel. Lieutenant Colonel Dale Wykoff reported that leishmaniasis had become endemic throughout much of East Africa and that both Gambian and Rhodesian trypanosomiasis had again become prevalent there. Dr. Louis Olivier of Pan American Health Organization reported on the prevalence and distribution of Chagas' disease and leishmaniasis in South America.

Schistosomiasis Symposium

At the 1970 fall meeting at WRAIR a symposium was held on schistosomiasis covering in-depth the results of current investigations in nine leading laboratories. The program , reported by Dr. Sadun, included pathogenesis in primates, immediate hypersensitivity, radioactive microprecipitin assay, and prophylactic and suppressive drugs in primates. Dr. George M. Davis of the 406th U.S. Army Medical Laboratory described programs in experimental treatment for schistosomiasis, and in medical malacology. Dr. Margaret Stirewalt, of the Naval Medical Research Institute, reported work on skin invasion

by cercariae and prevention of invasion. Captain D. C. Kent described the research on schistosomiasis at NAMRU-2. This included studies on treatment, pathogenesis, epidemiology, and immunology. The program at NIH, reported by Dr. A. W. Cheever, consisted of studies on pathogenesis in mammalian hosts and on genetics of vector snails. The work at Peter Bent Brigham Hospital in Boston, reported by Dr. von Lichtenberg, was mainly in the areas of pathogenesis and immunology, a large part of which was performed in collaboration with the group at WRAIR.

Work at the Harvard University School of Public Health, presented by Dr. Weller, was centered on factors in the invasion of host snails by miracidia in Dr. Eli Chernin's laboratory, pathogens of snails investigated by Dr. Edward Michelsen, and specific antigens in the urine of heavily infected animals and attempts to obtain cultures of cells from *Schistosoma mansoni* in progress by Dr. Weller and associates.

Research on the control of schistosomiasis in endemic areas of St. Lucia was reported by the team leader, Dr. P. Jordan. At The Johns Hopkins University, research on schistosomiasis, reported by Dr. Bueding, was directed toward describing the pharmacological characteristics of old and new antischistosomal drugs.

COMMISSION-SPONSORED SCIENTIFIC CONTRIBUTIONS

Among the parasitic diseases of military concern, schistosomiasis and filariasis were considered to be of greatest importance. With the advent of chloroquine resistance of falciparum malaria and mosquito resistance to insecticides, malaria assumed high priority status. A chief purpose of the Commission was to sponsor research investigations designed to solve problems in the prevention and management of these three diseases. Added later to the priority list were leishmaniasis, trypanosomiasis, amebiasis, and others.

Schistosomiasis

Several different aspects of the schistosomiasis problem were investigated. The biology of the snail intermediate host was investigated in a study by Dr. E. D. Wagner at Loma Linda and a long series of studies by Dr. Henry van der Schalie and his group of malacologists at University of Michigan. Possible prevention of infection by inhibition of skin penetration by the infective larvae (cercariae) was investigated by Drs. Hardy A. Kemp and George W. Hunter, III, the mechanisms of cercarial penetration of the skin and immune reactions to infection were studied by Dr. Robert Lewert, and the pathogenesis of the disease was the subject of investigations by Dr. Warren and by Dr. von Lichtenberg. Studies designed to isolate specific antigens from larval and adult schistosomes were undertaken by Dr. Niam Kent. Although early progress was satisfactory, because of a change in location, the project was discontinued without reported results.

Dr. Wagner's studies were performed on *Oncomelania quadrasi* from the Philippines, *Oncomelania nosophora* from Japan, and *Oncomelania hupensis* and *Oncomelania formosana* from Taiwan. Laboratory observations on methods of cultivation and conditions affecting reproduction and survival were followed by field observations by Dr. Wagner and his assistant, Dr. Lois Wong Chi, in the Philippines and Japan. Of special interest was the finding that when the four species were crossed, fertile hybrids were produced. Results of the 5-year study were published in the following reports.

- Chi, L. W., and Wagner, E. D. A rapid method of sexing snails, *Oncomelania nosophora*. *Trans. Am. Microsc. Soc.* 1954, 73, 66–67.
- Chi, L. W., and Wagner, E. D. Some effects of ultraviolet radiation on *Oncomelania nosophora* and *Oncomelania quadrasi*, snail intermediate hosts of *Schistosoma japonicum*. *Trans. Am. Microsc. Soc.* 1956, 75, 204–210.
- Chi, L. W., and Wagner, E. D. Studies on reproduction and growth of *Oncomelania quadrasi*, *O. nosophora*, and *O. formosana*, snail hosts of *Schistosoma japonicum*. *Am. J. Trop. Med. Hyg.* 1957, 6, 949–959.

- Wagner, E. D., and Chi, L. W. Some factors influencing egg laying in *Oncomelania nosophora* and *Oncomelania quadrasi*, intermediate hosts of *Schistosoma japonicum*. *Am. J. Trop. Med. Hyg.* 1956, 5, 544–552.
- Wagner, E. D., and Chi, L. W. Egg-laying inhibition in *Oncomelania nosophora* maintained on filter paper. *Am. J. Trop. Med. Hyg.* 1957, 6, 946–948.
- Wagner, E. D., and Chi, L. W. Methods on the rearing of the snail, *Oncomelania* species. *Trans. Am. Microsc. Soc.* 1959, 78, 421–423.
- Wagner, E. D., and Chi, L. W. Species crossing in *Oncomelania*. *Am. J. Trop. Med. Hyg.* 1959, 8, 195–198.
- Wagner, E. D., and Moore, B. Effects of water level fluctuation on egg laying in *Oncomelania nosophora* and *Oncomelania quadrasi*. *Am. J. Trop. Med. Hyg.* 1957, 5, 553–558.
- Wagner, E. D., and Moore, B. The development of *Schistosoma mansoni* in snails kept at certain constant temperatures. *Trans. Am. Microsc. Soc.* 1959, 78, 424–428.
- Winkler, L. R., and Wagner, E. D. Filter paper digestion by the crystalline style in *Oncomelania*. *Trans. Am. Microsc. Soc.* 1959, 78, 262–268.

Initially, Dr. van der Schalie's studies were mainly field observations on the environmental conditions at sites in Michigan where stable populations of *Pomatiopsis* snails were found. This snail, *Pomatiopsis cincinnatiensis* in Michigan, was noted to be "almost identical to *Oncomelania*, the vector of Oriental schistosomiasis," and therefore might have direct application to the control of *Schistosoma japonicum* in Asia. The project proved to be of greatest value in serving to train malacologists, and to provide infected snails and experimental animals for research by workers elsewhere in the United States. In the later years of this program, snail hosts of *Schistosoma mansoni* and *Schistosoma haematobium* were included and Dr. van der Schalie's laboratory provided research materials for numerous other workers, and emphasis was placed on describing methods of cultivation. Attempts to propagate *Lithoglyphopsis aperta*, the snail host of *Schistosoma mekongi*, were unsuccessful. The large number of collaborators and colleagues and the range of subjects studied are evident in published articles, as follows:

- Burch, J. B. A serological approach to molluscan systematics. *Papua New Guinea Sci. Soc. Annu. Rep. Proc.* 1967, 18, 29–36.
- Burch, J. B. Cytological relationships of some Pacific gastropods. *Venus Japan. J. Malacol.* 1967, 25 (3–4).
- Burch, J. B., and Lindsay, G. K. Some immunological relationships in the African genus *Bulinus*. *Annu. Rep. Am. Malacol. Union* 1966, 37–38.
- Burch, J. B., and Lindsay, G. K. Electrophoretic analysis of esterases in *Bulinus*. *Annu. Rep. Am. Malacol. Union* 1967, 39–40.
- Davis, G. M. Notes on *Hydrobiiae tottem*. *Venus Japan. J. Malacol.* 1966, 25, 27–42.
- Davis, G. M. The systematic relationship of *Pomatiopsis lapidaria* and *Oncomelania hypensis formosana* (Prosobranchia: Hydrobiidae). *Malacologia* 1967, 6, 1–143.
- Davis, G. M. A systematic study of *Oncomelania hypensis chiui* (Gastropoda: Hydrobiidae). *Malacologia* 1968, 7, 17–70.
- Davis, G. M., and Lindsay, G. K. Disc electrophoretic analysis of molluscan individuals and populations. *Malacologia* 1967, 5, 311–334.
- Davis, G. M., Moose, J. W., and Williams, J. E. Abnormal development in a hybrid *Oncomelania* (Gastropoda: Hydrobiidae). *Malacologia* 1965, 3, 81–102.
- Habe, T., and Burch, J. B. A new species of freshwater limpet, genus *Ferrissia*, from Japan. *Venus, Japan. J. Malacol.* 1965, 24, 1–7.
- Liang, Y. S. The effect of water quality on laboratory culturing of *Biomphalaria pfeifferi* and *Bulinus globosus*. *Malacol. Rev.* 1972, 5, 11.
- Lo, C. T. Survey for the molluscan hosts of *Schistosoma japonicum* in Laos. *WHO-WPRO Assignment Report*. 1969.
- Lo, C. T. Chromosomes of *Fasciolopsis buski* (Trematoda: Fasciolidae). *Bull. Inst. Zool. Acad. Sinica* 1969, 8, 1–5.

- Lo, C. T. Some abnormal tentacles and eyes of *Pachydrobia pellucida* Bavay, 1895 (Gastropoda: Hydrobiidae). *Venus, Japan. J. Malacol.* 1970, 28, 185–188.
- Lo, C. T. Compatibility and host–parasite relationship between species of the genus *Bulinus* (Basommatophora: Planorbidae) and an Egyptian strain of *Schistosoma* haematobium (Trematoda, Digenea). *Malacologia* 1972, 11, 225–280.
- Lo, C. T., Berry, E. G., and Iijima, T. Studies on schistosomiasis in the Mekong Basin. II. Malacological investigations on human *Schistosoma* from Laos. *Chinese J. Microbiol.* 1971, 4, 168–181.
- Lo, C. T., Burch, J. B., and Schutte, C. H. J. Infection of diploid *Bulinus* s.s. with *Schistosoma haematobium* (Tremaoda: Digenea). *Malacol. Rev.* 1970, 3, 121–126.
- Patterson, C. M. Chromosome numbers of some Japanese freshwater snails. *Venus, Jap. J. Malacol.* 1967, 25, 69–72.
- van der Schalie, H. The role of snail intermediate hosts in culturing *Schistosoma japonicum. Malacologia* 1967, 5, 17–20.
- van der Schalie, H. Snail control problems in Hawaii. *Annu. Rep. Am. Malacol. Union* 1969, 55–56.
- van der Schalie, H. Problems in culturing snail intermediate hosts. *Malacol. Rev.* 1972, 5, 10.
- van der Schalie, H., and Davis, G. M. Growth and stunting in *Oncomelania* (Gastropoda: Hydrobiidae). *Malacologia* 1965, 3, 81–102.
- van der Schalie, H., and Davis, G. M. Culturing *Oncomelania* snails (Prosobranchia: Hydrobiidae) for studies of Oriental schistosomiasis. *Malacologia* 1968, 6, 321–367.

Dr. Lewert's program began with a basic study of the mechanism of skin penetration by the schistosome cercaria. It was thought that with a fundamental knowledge of cercarial penetration, an effective protective ointment could be made for use in prophylaxis. When this approach failed to show promise, immune resistance of the snail host to penetration and development of miracidia was briefly studied. This was followed by an extended period of research on the immune reactions of humans and other mammalian hosts to schistosome infection. The immunological studies of Dr. Lewert were coordinated with those of Dr. Mariano Yogore. For their field studies in endemic areas in the Philippines, they developed and successfully applied a circumoval precipitin test that reliably showed characteristic differences in reactions at different stages of infection and before and after successful treatment. The significant findings were reported in the following published articles:

- Dusanic, D. G., and Lewert, R. M. Electrophoretic studies of the antigen-antibody complexes of *Trichinella spiralis* and *Schistosoma mansoni. J. Infect. Dis.* 1966, 116, 270–284.
- Kloetzel, K., and Lewert, R. M. Pigment formation in *Schistosoma mansoni* infections in the white mouse. *Am. J. Trop. Med. Hyg.* 1966, 15, 28–31.
- Lee, C. L., and Lewert, R. M. The maintenance of *Schistosoma mansoni* in the laboratory. *J. Infect. Dis.* 1956, 99, 15–20.
- Lee, C. L., and Lewert, R. M. Studies on the presence of mucopoly-saccharidase in penetrating helminth larvae. *J. Infect. Dis.* 1957, 101, 287–294.
- Lee, C. L., and Lewert, R. M. The distribution of various reactants in human anti-*Schistosoma mansoni* serums fractionated by starch electrophoresis. *J. Infect. Dis.* 1960, 106, 69–76.
- Lewert, R. M. Invasiveness of helminth larvae. Symposium on Resistance and Immunity in Parasitic Infections. *Rice Inst. Pamphlet* 1958, 45, 97–113.
- Lewert, R. M., and Dusanic, D. G. Effects of a symmetrical diaminodibenzylalkane on alkaline phosphatase of *Schistosoma mansoni. J. Infect. Dis.* 1961, 109, 85–89.
- Lewert, R. M., and Hopkins, D. R. Histochemical demonstration of calcium in preacetabular glands of cercariae and the role of calcium ions in invasiveness. *J. Parasitol.* 1964, 50, 30.
- Lewert, R. M., and Hopkins, D. R. Cholinesterase activity in *Schistosoma mansoni* cercariae. *J. Parasitol.* 1965, 51, 616.
- Lewert, R. M., Hopkins, D. R., and Mandlowitz, S. The role of calcium and magnesium ions in invasiveness of schistosome cercariae. *Am. J. Trop. Med. Hyg.* 1966, 15, 314–323.
- Lewert, R. M., and Lee, C. L. Quantitative studies of the collagenase-like enzymes of cercariae of *Schistosoma mansoni* and the larvae of *Strongyloides ratti. J. Infect. Dis.* 1956, 99, 1–14.

- Lewert, R. M., and Lee, C. L. The collagenase-like enzymes of skin-penetrating helminths. *Am. J. Trop Med. Hyg.* 1957, 6, 473–477.
- Lewert, R. M., Lee, C. L., Mandlowitz, S., and Dusanic, D. Inhibition of the collagenase-like enzymes of cercariae of *Schistosoma mansoni* by serums and serum fractions. *J. Infect. Dis.* 1959, 105, 180–187.
- Lewert, R. M., and Mandlowitz, S. Innate immunity to *Schistosoma mansoni* relative to the state of connective tissue. *Ann. N.Y. Acad. Sci.* 1963, 113, 54–62.
- Lewert, R. M., and Para, B. J. The physiological incorporation of carbon 14 in *Schistosoma mansoni* cercariae. *J. Infect. Dis.* 1966, 116, 171–182.
- Lewert, R. M., and Yogore, M. G., Jr. A field circumoval precipitin (FCOP) test for *Schistosomiasis japonica*. *Trans. R. Soc. Trop. Med. Hyg.* 1969, 63, 343–348.
- Mandlowitz, S., Dusanic, D., and Lewert, R. M. Peptidase and lipase activity of extracts of *Schistosoma mansoni* cercariae. *J. Parasitol.* 1960, 46, 89–90.
- Yogore, M. G., Jr., Lewert, R. M., Garcia, E. G., Madraso, E. D., and Ramos, E. R. Analysis of *Schistosoma japonicum* antigens by micro-Ouchterlony technic. In: *Proceedings of the First Regional Symposium on Scientific Knowledge of Tropical Parasites*, University of Singapore, 1962, 267.
- Yogore, M. G., Jr., Lewert, R. M., and Silan, R. B. The circumoval precipitin (COP) test in schistosomiasis japonica. *Am. J. Trop. Med. Hyg.* 1968, 17, 65–71.

In the period 1 September to 28 February 1956, Drs. Kemp and Dr. Hunter tested 247 ointment preparations for their inhibiting effect on the penetration of schistosome cercariae through the skin of the laboratory mouse. Forty-six of these ointments were effective. However, it was felt that before further screening, the most promising ones should be subjected to intensive toxicologic investigation. This apparently was not followed up.

In August 1964, Dr. Warren began a broad program of studies on the "Pathophysiology of Schistosomiasis." Using white mice exposed to precisely determined numbers of cercariae, he and associates Donald E. Moore and Donald Ostrow, conducted studies on a comparison of hepato-splenic disease caused by *Schistosoma mansoni* and *Schistosoma japonicum*, hepato-splenic disease caused by *Schistosoma mansoni* from different geographic regions (Puerto Rico, Brazil, Egypt, Tanzania), survival of *Schistosoma mansoni* in relation to hepatic fibrosis, character of pigment produced by *Schistosoma mansoni*, and suppressive effect of chloramphenicol on development of *Schistosoma mansoni* in the snail host. In subsequent years, and with additional associates (Drs. R. J. Stenger, E. O. Domingo, R. B. T. Cowan, A. S. Weisberger, P. A. Peters, and J. A. Jane), he expanded the program with experiments on clay-pipe-stem cirrhosis-like lesions in mice infected with *Schistosoma mansoni*; ultrastructure of liver in acute and chronic *Schistosoma mansoni* infection; hepatoma in *Schistosoma mansoni*-infected mice; effects of immunosuppression and neonatal thymectomy on granuloma formation in *Schistosoma mansoni*-infected mice; effects of *Schistosoma mansoni* on intestinal absorption; factors in virulence of *Schistosoma mansoni*; comparative susceptibility of squirrel monkey, slow loris, and tree shrew to *Schistosoma mansoni* infection; and effects of metabolic inhibitors, molluscicides, and schistosomicides on development of *Schistosoma mansoni* in its snail host. Most of these studies were completed with the results reported and published.

In the 2-year period beyond 1 August 1967, Dr. Warren and his several associates (Drs. Domingo, M. S. Rosenthal, L. B. Liu, Stenger, and L. Klein) directed their research on the mechanisms of immunity in schistosomiasis. Using the rat as the experimental mammalian host, they found that in the early stages of *Schistosoma mansoni* infection the response could not be enhanced or accelerated by the transfer of either serum or cells from histocompatible rats with late stages of infection at a time when the donor animals had largely eliminated their own infections. Results of these and earlier studies were reported in the publications listed below:

- Domingo, E. O., Cowan, R. B. T., and Warren, K. S. The inhibition of granuloma formation around *Schistosoma mansoni* eggs. I. Immunosuppressive drugs. *Am. J. Trop Med. Hyg.* 1967, 16, 284–292.
- Domingo, E. O., and Warren, K. S. The inhibition of granuloma formation around *Schistosoma mansoni* eggs. II. Thymectomy. *Am. J. Pathol.* 1967, 51, 757–767.
- Domingo, E. O., and Warren, K. S. The inhibition of granuloma formation around *Schistosoma*

mansoni eggs. III. Heterologous antilymphocyte serum. *Am. J. Pathol.* 1968, 52, 613–626.

- Domingo, E. O., and Warren, K. S. Endogenous desensitization: Changing host granulomatous response to schistosome eggs at different stages of infection with *Schistosoma mansoni*. *Am. J. Pathol.* 1968, 52, 369–377.
- Domingo, E. O., and Warren, K. S. Pathology and pathophysiology of the small intestine in murine schistosomiasis mansoni, including a review of the literature. *Gastroenterology* 1969, 56, 231–240.
- Domingo, E. O., Warren, K. S., and Stenger, R. J. Increased incidence of hepatoma in mice with chronic schistosomiasis mansoni treated with a carcinogen. *Am. J. Pathol.* 1967, 51, 307–321.
- Liu, L. B., Domingo, E. O., Stenger, R. J., Warren, K. S., Confer, D. B., and Johnson, E. A. An ultrastructural study of the toxic and carcinogenic effects of 2-amino-5-azotoluene on the livers of schistosome-infected and uninfected mice. *Cancer Res.* 1969, 29, 837–847.
- Moore, D. E., and Warren, K. S. Hepatosplenic schistosomiasis mansoni and japonica compared in mice each infected with one pair of worms. *Trans. R. Soc. Trop. Med. Hyg.* 1967, 61, 104-109.
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In 1961, Dr. von Lichtenberg began studies on schistosomiasis under the title "Host Parasite Relationships in Normal and Abnormal Hosts of Schistosomidae." On 1 March 1965 the title was changed



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to "Protective Mechanisms in Schistosome Infections." At that time, three studies performed in collaboration with Drs. Salvador Jaimes, Peter Peterson and Alfred Senft, respectively, had been completed: (1) Fluorescent antibody titers in mice infected with normal cercariae, radiated cercariae, and eggs of *Schistosoma mansoni*; (2) In vivo antigenicity of sequestered schistosome egg antigen in experimental pseudotubercles of *S. mansoni*; (3) Nonantigenicity of dialyzed culture medium after incubation of live, mating schistosome worms.

At this time, investigative emphasis shifted from immunology to pathogenesis, and a different group of collaborators became involved. With Dr. Sadun and others at WRAIR and Dr. Cheever and others at the NIH, a series of investigations compared schistosomiasis disease processes in several lower primates, including the chimpanzee. Examined also were differences in the pathological changes and pathogenesis produced by various geographic strains of the parasite in humans and experimental animals. Notable observations were made on the Hoeppli phenomenon. A major contribution was made with Dr. C. M. Edington and others on the pathological effects of urinary schistosomiasis in Nigeria, with Dr. J. H. Smith on the ultrastructure of the schistosome integument, urinary schistosomiasis in Egypt, and on tissue degradation of *Schistosoma haematobium* eggs. Other notable results were obtained from collaborative studies with Dr. D. H. Kelley on abnormal schistosome egg shell material in tissues, with Dr. P. Jordan and others on experimental schistosomiasis in primates in Tanzania, with Dr. T. M. Smith and others on phospholipids in the schistosome granuloma, and with Dr. H. A. Dunsford and others on granulomas caused by bentonite and latex carrier particles. Results of studies completed or in progress as of June 1972 were reported in the following published articles:

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Filariasis

In 1963 and 1964, Dr. Rozeboom, in collaboration with Dr. Benjamin D. Cabrera, conducted a study of the epidemiology of filariasis in the Philippine Islands. They showed that in addition to the widespread abaca growing areas in which filariasis was known to be endemic, the basic endemicity of the disease involved rural foci with *Anopheles minimus flavirostris* the chief vector. They also found a focus of subperiodic *Brugia malayi* infection in a swamp forest area on the west coast of Palawan, in which microfilaremia rates up to 64% were found in some communities. Infection rates in children under 5 years of age were as high as those in older age groups. The findings were reported in the following publications:

- Cabrera, B. D., and Rozeboom, L. E. Filariasis in Palawan, Philippine Islands. *Nature* 1964, 202, 725–726.
- Cabrera, B. D., and Rozeboom, L. E. The periodicity characteristics of the filaria parasites of man in the Republic of the Philippines. *Am. J. Epidemiol.* 1965, 81, 192–199.
- Cabrera, B. D., and Rozeboom, L. E. The occurrence of *Dirofilaria magnilarvatum* Price and *Brugia* specie in Philippine monkeys. *Acta Med. Philip.* 1965, 1, 119–123.
- Rozeboom, L. E., and Cabrera, B. D. Transmission of filariasis in the Philippine Islands by *Anopheles minimus flavirostris* Ludlow. *Nature* 1963, 200, 915.
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Filariasis and Tropical Eosinophilia

In 1955, under the title, "Visceral Larva Migrans in Relation to Tropical Eosinophilia," a collaborative study directed by Dr. Beaver of Tulane University was initiated at the University of Malaya Faculty of Medicine in Singapore. That site was selected because tropical eosinophilia, newly described in India in the early 1940s as a disease of unknown etiology, had recently been reported as commonly seen in Singapore. Singapore collaborators were Dr. T. J. Danaraj, Department of Medicine, and Dr. A. A. Sandosham, Department of Parasitology.

In the first 3 years of the project, the principal professional assistant was John Schacher, a Tulane graduate student, and the main objective was to examine the case histories, pathologic tissues, and related environmental conditions for clues to the causative parasite in cases of tropical eosinophilia. Examination of dogs, cats, and other animals commonly associated with people revealed no unusual parasites. Intradermal and serological tests, along with response to treatment, suggested filarial infection as a probable cause of tropical eosinophilia.

At this stage (1960), the project title was changed to "Filariasis in Relation to Tropical Eosinophilia." Schacher resumed graduate studies at Tulane, and Pacheco, a postdoctoral fellow, was sent to Singapore. At Tulane, Schacher did detailed studies on a candidate filaria, *Brugia pahangi*, in the cat and mosquito hosts. Another graduate student, Ming Ming Wong, performed experimental studies on *Dirofilaria immitis*, the heartworm of dogs, by examining the determining factors in levels of microfilaremia. In the Singapore studies, intensive examination of serially sectioned lung biopsies revealed the presence of microfilariae being destroyed in granulomas. This strongly suggested that tropical eosinophilia is an aberrant form of filariasis. Filariasis without microfilaremia, including cases of tropical eosinophilia, was a major problem in the Pacific area during World War II.

For a better understanding of the nature of the disease, Pacheco returned to Tulane, and postdoctoral fellows Wong and Hong Fang Lee were sent to The Institute for Medical Research (IMR) in Kuala Lumpur to resume collaboration with Dr. Danaraj. After 1 year, the Kuala Lumpur studies were discontinued for lack of suitable case material.

A final study involving a collaboration of Dr. T. C. Orihel and a graduate student, M. H. Johnson, turned attention again to the question of factors that determine the level of microfilaremia. With *Dipetalonema viteae* in birds, it was shown that below a critical level of infection with the adult worm, the level of microfilaremia is not determined by the number of microfilaria-producing worms.

Published results of the studies completed in Singapore and at Tulane follow:

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- Beaver, P. C., Orihel, T. C., and Johnson, M. H. *Dipetalonema viteae* in the experimentally infected bird, *Meriones unguiculatus*. II. Microfilaremia in relation to worm burden. *J. Parasitol.* 1974, 60, 310–315.
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- Danaraj, T. J. The treatment of eosinophilic lung (tropical eosinophilia) with hetrazan. A preliminary report. *Proc. Alumni Assoc. Malaya* 1956, 9, 172–187.
- Danaraj, T. J. The treatment of eosinophilic lung (tropical eosinophilia) with diethylcarbamazine. *Q. J. Med. NZ* 1958, 27, 243–263.
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- Pacheco, G. Serological studies on dogs experimentally infected with *Dirofilaria immitis*. *J. Parasitol.* 1961, 47(Suppl.), 24.
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- Pacheco, G., and Danaraj, T. J. Ethanol extracts of various helminths in a complement fixation test for eosinophilic lung (tropical eosinophilia). *Am. J. Trop. Med. Hyg.* 1963, 12, 745–747.
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Parasites of Oriental Primates

In a 4 -year period, 1962 to 1966, at the Institute for Medical Research in Malaya, numerous and diverse investigations were performed by collaborators of Dr. Ralph Audy. Essentially all of the observations were made by Dr. Fred L. Dunn, alone or with collaborators. The project was titled "Endoparasites of Oriental Primates" and included human aborigines (Orang Asli) and several species of monkeys. In addition, many parasitic protozoa and helminths were collected and identified from various forest mammals. Of special interest were the findings in extensive surveys of intestinal parasites of tribal hunter-gatherers and forest agriculturists. Dr. Dunn also described and evaluated a method of doing helminth egg counts by direct smear on merthiolate-iodine-formaldehyde (MIF)-preserved fecal specimens (MIF-DS). The findings of these studies were reported in numerous publications as follows:

- Dunn, F. L. A new trichostrongylid nematode from an Oriental primate. *Proc. Helm. Soc. Wash.* 1963, 30, 161–165.
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- Dunn, F. L. Erythrocyte sickling in the barking deer of Borneo. *J. Mammal.* 1964, 45, 492–493.
- Dunn, F. L. Blood parasites of Southeast Asian primitive primates. *J. Parasitol.* 1964, 50, 214–216.
- Dunn, F. L. Gua Anak Takun: Ecological observations. *Malayan Nature J.* 1965, 19, 75–87.
- Dunn, F. L. Observations on the fauna of Pulau Tioman and Pulau Tulai. II. Notes on the en-

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- Dunn, F. L. Patterns of parasitism in primates: Phylogenetic and ecological interpretations with particular reference to the Hominoidea. *Folia Primatol.* 1966, 4, 329–345.
- Dunn, F. L. The TIF direct smear as an epidemiological tool: With special reference to counting helminth eggs. *Bull. W.H.O.* 1968, 39, 439–449.
- Dunn, F. L. Epidemiological factors: Health and disease in hunter gatherers. In: Lee, R. B., and Devore, I., eds. *Man the Hunter.* Chicago: Aldine Publishing Co., 1968, 221–228.
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- Dunn, F. L., Eyles, D. E., and Yap, L. F. *Plasmodium sandoshami* specie nov., a new species of malaria parasite from the Malayan flying lemur. *Ann. Trop. Med. Parasitol.* 1963, 57, 75–81.
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- Dunn, F. L., and Ramachandran, C. P. Southeast Asian filariids, with special reference to those normally parasitic in vertebrates other than man. In: Sardosham, A. A., and Zaman, V., eds. *Proceedings of Seminar on Filariasis and Immunology of Parasitic Infections.* Singapore: SEAMEO, 1969, 194–209.
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- Eyles, D. E., Yap, L. F., Dunn, F. L., Guinn, E., Warren, M., and Sandosham, A. A. *Plasmodium youngi* species nova, a malaria parasite of the Malayan gibbon, *Hylobates lar lar. Am. J. Trop. Med. Hyg.* 1964, 13, 248–255.
- Inglis, W. G., and Dunn, F. L. The occurrence of *Lemuricola* (Nematoda: Oxyurinae) in Malaya: With the description of a new species. *Z. Parasitenk.* 1963, 23, 354–359.
- Inglis, W. G., and Dunn, F. L. Some oxyurids (Nematoda) from neotropical primates. *Z. Parasitenk.* 1964, 24, 83–87.
- Miyazaki, I., and Dunn, F. L. *Gnathostoma malaysiae* species nova from rats on Tioman Island, Malaysia (Nematoda: Gnathostomidae). *J. Parasitol.* 1965, 51, 382–384.
- Ramachandran, C. P., and Dunn, F. L. The development of *Breinlia sergenti* (Dipetalonematidae) in *Aedes* mosquitoes. *Ann. Trop. Med. Parasitol.* 1968, 62, 441–449.
- Ramachandran, C. P., Dunn, F. L., Sandosham, A. A., and Sivanandam, S. A *Dirofilaria* from the musang. *Singapore Med. J.* 1963, 4, 176–177.
- Ramachandran, C. P., Wharton, R. H., Dunn, F. L., and Kershaw, W. E. *Aedes* (*Finlava*) *togoi* Theobald. A useful laboratory vector in studies of filariasis. *Ann. Trop. Med. Parasitol.* 1964, 57, 443–445.

Malaria

A 1-year study (1958 to 1959) by Drs. Rozeboom and Howard included a histological survey of the sites of developmental failure of *Plasmodium gallinaceum* in five species of refractory mosquitoes. In

Culex fatigans and *Culex pipiens*, no midgut penetration was noted, whereas in *Aedes pseudoscutellaris*, *Anopheles albimanus*, and *Culex molestus* spherical intramural parasites occurred without evidence of growth. A technique was devised for in vivo study of the sporogonous cycle of the malaria parasite during the blood meal period. Direct observations failed to confirm that the malarial zygote develops into a motile organism at any time. The penetrating form was identical to the recently fertilized macrogamete, and was recoverable from the midgut wall between 24 and 40 hours following engorgement. Evidence indicated that the elongated parasites, formerly referred to as ookinetes and vermicules, were not intermediate between macrogamete and oocyst and that they were not infective. Passive forces were implicated as playing a major role in penetration. In a sequential study of the blood meal in the midgut of the adult female, *Aedes aegypti*, the principal areas of study were the natural dilution effects of fluids other than blood, weight loss in individual blood meals, coagulation time, the significance of the early clear rim about the meal clot, observations on peritrophic membrane formation, changes in meal volume and consistency, the function of midgut and hindgut musculature, morphological changes in midgut epithelium, and the behavior of inert particles within a blood meal. These studies suggested the nature of passive forces that largely account for the passage of zygotes through the stomach wall.

A series of studies by Drs. Most and Yoeli began in 1958 under the title "Biological Studies in Malaria (*Plasmodium berghei*)." In the fall of 1964, a separate Commission on Malaria was formed, and all sponsored projects in the area of malaria became the responsibility of the new Commission. In the intervening years, colonies of *Anopheles quadrimaculatus* and *Anopheles aztecus* were established in the laboratory, and strains of *Plasmodium berghei* were maintained by blood transfer in laboratory mice and hamsters. In January 1959, a gametocyte-producing strain of the parasite (Kasapa) was received from the Prince Leopold Institute of Tropical Medicine in Anvers, Belgium. Observations were made on morphology of the ookinete stage, the pigment pattern in the oocyst, and the relation between size of the inoculum and course of infection, and attempts were made to clarify the question regarding conditions causing the disappearance and reappearance of gametocytes in blood forms of the parasite.

In December 1963, the original type host of *Plasmodium berghei*, *Anopheles dureni*, was studied and collected in its native habitat (Congo) and successfully transported to New York. Transmission of *Plasmodium berghei* from naturally infected *Anopheles dureni* was accomplished both by bite and by inoculation of various animals with sporozoites derived from salivary glands and oocysts. New strains of *Plasmodium berghei* were isolated and preserved at low temperature for future study. *Anopheles quadrimaculatus* were successfully infected in the laboratory and cyclical transmission was carried out by sporozoites introduced in natural feeding as well as by infections from salivary glands and oocysts. Successful oviposition of *Anopheles dureni* was obtained in the laboratory, and limited success was achieved in rearing larval stages of the mosquito. A colony of Congo tree rats flourished, and the ability to infect *Anopheles quadrimaculatus* and achieve cyclic transmission made possible intensive searches of tissues to determine whether exoerythrocytic parasites exist. Published results obtained in the Most–Yoeli studies on *Plasmodium berghei* biology are reported in the history of the Commission on Malaria.

Ascariasis

In the period between March 1963 and June 1964, a study entitled "Biochemical Investigations of Host–Nematode Relationships in Ascariasis" was completed by Dr. John G. Adams. It had been started in September 1962 under the direction of Dr. P. W. Ragozzino, and some of the findings were reported in a doctoral dissertation by Luis E. Borello. Dr. Adams reported that the role of histamine and serotonin in the disease characteristics of acute experimental nematode infection was investigated in guinea pigs infected with *Ascaris lumbricoides* var. *suum*. The study included spectrophotofluorometric determination of blood and tissue levels of histamine and serotonin, determination of the toxicity of histamine and serotonin administered intracardially and as an aerosol, determination of monoamine and diamine oxidase activity of various tissues, and determination of lactic acid dehydrogenase and glutamic oxalacetic transaminase levels in serum and plasma steroid levels in infected and normal animals.

The effects of histamine and serotonin in the acute symptomatology of ascariasis appear to be overshadowed by other factors arising from mechanical tissue damage. Changes in respiratory patterns are probably associated with hypoventilation resulting from mechanical damage to lung tissue. Death, which appears to be due to respiratory causes, is concurrent with profound degenerative changes in liver and kidney tissues. Increased levels of plasma steroid and serum lactic acid dehydrogenase and glutamic oxalacetic transaminase are indicative of the presence of a stress reaction in response to the presence of the acute infection. Significant decreases occur in the histamine content of lung, brain, and kidney. A less significant but detectable increase occurs in the liver. A significant increase was noted in brain serotonin of infected animals and a less significant but detectable decrease in lung serotonin.

- Adams, J. G., D'Aquila, L., and Malone, M. H. Serotonin levels in acute experimental ascariasis. *J. Pharm. Sci.* 1969, 58, 279-280.

Beginning in January 1955, Dr. Nathan Entner completed a fundamental 4-year study entitled "Enzymatic Aspects of Carbohydrate Metabolism in *Ascaris lumbricoides*." The study was considered to be of potential value in the development of anthelmintic agents. In the first year, the experiments were focused on aspects of carbohydrate metabolism of mature *Ascaris* not previously studied in any helminth. In the final years, the study centered on synthetic processes in the reproductive tract beginning with RNA synthesis. Results were reported in three publications, the first of which described a demonstration of the enzymes of the pentose-phosphate pathway in the worm's smooth muscle. The second reported an analysis of the fate of sugar in *Ascaris* by the use of radioactive glucose labeled in different carbon atoms. In addition to showing the nature and extent of incorporation of the carbon atoms of glucose into the major parts of the worms, it was also shown that of the two pathways for carbohydrate metabolism, the glycolytic scheme is the major pathway of energy metabolism, whereas the pentose-phosphate pathway provides pentose for nucleic acid. The third reported that subcellular particles from the reproductive tract of *Ascaris* contain enzymes that synthesize RNA in two different ways, with nucleoside-diphosphate precursors, and with nucleoside-triphosphate precursors. These were the first such studies on the enzymatic synthesis of nucleic acid in any parasite. Publications are listed below.

- Entner, N. The occurrence of the pentose-phosphate pathway in *Ascaris lumbricoides*. *Arch. Biochem. Biophys.* 1957, 71, 52–61.
- Entner, N. Occurrence of polynucleotide phosphorylase in *Ascaris lumbricoides*. *Biochem. Biophys. Res. Commun.* 1959, 1, 333.
- Entner, N., and Gonzalez, C. Fate of glucose in *Ascaris lumbricoides*. *Exp. Parasitol.* 1959, 8, 471–479.

Leishmaniasis

The Commission sponsored studies on leishmaniasis by Dr. Donald W. Twohy at Michigan State University and Dr. John Janovy at University of Nebraska. Under the title, "The Nature of Immunity to Leishmaniasis," Dr. Twohy initiated in May 1967 studies on *Leishmania donovani*, in mice and in vitro macrophage cultures, designed to explain the basic characteristics of immune reactions to infection with *Leishmania* species and possibly other intracellular protozoa. Experiments designed to test the hypothesis that immunity to *Leishmania donovani* depends primarily on cellular factors, not on serum antibodies, showed that the organisms multiply in cultured macrophages from nonimmune but not from immune mice. Transfer of macrophages or macrophage RNA from immune to nonimmune mice and RNA of immune macrophages to cultures of nonimmune macrophages conferred a high degree of resistance. Serum from immune animals was ineffective. It was found that there was "cross-resistance" between different strains of *Leishmania donovani* and other intracellular parasites such as *Plasmodium* and *Eperythrozoon*. Thus, the cellular immunity to *Leishmania* resembles that to *Toxoplasma*, *Besnoitia*, and intracellular bacteria.

Later experiments showed that in vitro cultures of macrophages from mice that were superinfected with *Leishmania donovani* supported parasite growth as well as did macrophages from uninfected controls. Results obtained with these host–parasite models were too variable to point to specific factors in the development or expression of immunity. Further observations on the role of macrophages and lymphocytes in resistance to reinfection suggested that the ability of macrophages from immune mice to kill and digest the leishmania parasites was enhanced by in vivo stimulation with live parasites.

Some of the results of these studies were reported in the following publications:

- Miller, H. C., and Twohy, D. W. Infection of macrophages in culture by leptomonads of *Leishmania donovani*. *J. Protozool.* 1967, 14, 781–789.
- Miller, H. C., and Twohy, D. W. Cellular immunity to *Leishmania donovani* in macrophages, in culture. *J. Parasitol.* 1969, 55, 200–207.
- Skov, C. B., and Twohy, D. W. Cellular immunity to *Leishmania donovani*. I. The effect of T cell depletion on resistance to *Leishmania donovani* in mice. *J. Immunol.* 1974, 113, 2004–2011.
- Skov, C. B., and Twohy, D. W. Cellular immunity to *Leishmania donovani*. Evidence for synergy between thymocytes and lymph node cells in reconstitution of acquired resistance to *Leishmania donovani* in mice. *J. Immunol.* 1974, 113, 2012–2019.

Studies by Janovy and associates, active from May 1968 to October 1972, were designed to explain the localization of *Leishmania* parasites and lesions in particular anatomical sites in the hosts. A number of in vitro biochemical reactions of different strains and species were examined in relation to temperature. Marked differences were observed in the culture forms of the various strains, but the significance of the findings was not apparent. Experiments were designed to determine differences in anaerobic metabolism among species of *Leishmania* and to examine the possible correlations between the experimental findings and the disease features commonly associated with the infections. Temperature effects on total acid production, carbon dioxide fixation, and lactate production by *Leishmania donovani* in the presence or absence of glucose and in the presence of antileishmanial drugs (stibophen and sodium stibogluconate) revealed only that lactate production may be useful as an indicator of the site of drug action. However, the metabolic effects of the two compounds were not clearly delineated by the experiments. These findings were reported in the following publications:

- Bhattacharya, A., and Janovy, J., Jr. *Leishmania donovani*: Autoradiographic evidence for molecular exchanges between parasite and host cell. *Exp. Parasitol.* 1975, 37, 353–360.
- Daggett, P. M., Decker, J. E., and Janovy, J., Jr. Some physiological alterations accompanying infectivity to mammals by four genera of *Trypanosomatidae*. *Comp. Biochem. Physiol.* 1978, 59A, 363–366.
- Decker, J. E., and Janovy, J., Jr. *Leishmania donovani* and *Leishmania mexicana*: Production of the excretion factor. *Comp. Biochem. Physiol.* 1974, 49B, 513–523.
- Janovy, J., Jr. Temperature and metabolism in *Leishmania*. III. Some dehydrogenases of *Leishmania donovani*, *Leishmania mexicana*, and *Leishmania tarentolae*. *Exp. Parasitol.* 1972, 32, 196–205.
- Janovy, J., Jr., and Poorman, A. E. Temperature and metabolism in *Leishmania*. I. Respiration in *Leishmania donovani*, *Leishmania mexicana* and *Leishmania tarentolae*. *Exp. Parasitol.* 1969, 25, 276–282.
- Poorman, A. E., and Janovy, J., Jr. Temperature and metabolism in *Leishmania*. II. Aldolase in *Leishmania adleri*, *Leishmania donovani*, *Leishmania mexicana* and *Leishmania tarentolae*. *Exp. Parasitol.* 1969, 26, 329–335.

Trypanosomiasis

The possibility of obtaining protection against trypanosomiasis by vaccination was investigated in two studies in 1971 and 1972 on African trypanosomes, by Richard Seed and Gilbert Sanchez, and one 1970 to 1972 study on the American trypanosome, *Trypanosoma cruzi* by W. L. Hanson. The African

trypanosomiasis study by Seed and the *Trypanosoma cruzi* study by Hanson showed that vaccines derived from cultured organisms produced a discernible, although relatively slight, effect on the infections. Seed's studies also suggested that results of treatment with pentamidine isothionate were appreciably better when it was combined with the administration of hydrocortisone. Results obtained in the study by Sanchez were not significant. Hanson found that in passive transfer experiments, protective antibodies were demonstrated in sera taken at 6 weeks postinfection from neonatally thymectomized rats as well as controls. Also, mice immunized with either supernatant or sediment from sonicated mixtures of trypomastigotes and amastigotes of *Trypanosoma cruzi* grown in cell culture developed significantly lower mean parasitemia than controls after challenge with virulent *Trypanosoma cruzi*.

Results of some of Dr. Seed's experiments were reported in the following publications:

- Lumsden, R. D., Marciacq, Y., and Seed, J. R. *Trypanosoma gambiense*: Cytopathologic changes in guinea pig hepatocytes. *Exp. Parasitol.* 1972, 32, 369–389.
- Seed, J. R. *Trypanosoma gambiense* and *Trypanosoma equiperdum*: Characterization of variant specific antigens. *Exp. Parasitol.* 1972, 31, 98–108.
- Seed, J. R. Antigens and antigenic variability of the African trypanosomes. A review article. *J. Protozool.*, 1974, 21, 639–646.
- Seed, J. R., Marcus, H., and Risby, K. E. The effect of hydrocortisone on skin lesions, antibody titers, and parasitemia in *Trypanosoma gambiense*-infected rabbits. *Am. J. Trop. Med. Hyg.* 1972, 21, 150–156.
- Seed, J. R., and Varney, J. *Trypanosoma brucei gambiense*: Changes in body temperature rhythms of infected New Zealand albino rabbits. *Exp. Parasitol.* 1976, 40, 238–249.

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
26–27 October 1970

Monday, 26 October

0900 Introductory Remarks by Commission Director, President and Executive Secretary of the Board

0930 Reports, Preventive Medicine Officers
Department of the Army—Major J. W. Cutting
Department of the Navy—Commander R. D. Comer
Department of the Air Force—Colonel P. F. Nugent
Report, Representative of USA Medical R&D Command—Colonel R. F. Barquist

1030 Recess—Coffee

1045 PROGRESS REPORTS OF RESPONSIBLE INVESTIGATORS
Dr. William Hanson: Immunity to Chagas' Disease (Contract No. DADA 17-69-C-9167)
Dr. John Janovy, Jr.: Effects of Temperature on Leishmania Metabolism (Contract No. DADA 17-69-C-9122°
Dr. Iris Krupp: Immunodiagnosis and Molecular Components of *Entamoeba histolytica* (Contract No. DADA 17-69-C-9122)
Dr. Cornelius Kruse: Mode of Action of Halogens in Bacteria and Viruses and Protozoa in Water Systems (Contract No. DA-49-193-MD-2314)

1245 Lunch

1415 Dr. Donald Twohy: Nature of Immunity to Leishmaniasis (Contract No. DADA 17-69-C-9135)

	Dr. Henry van der Schalie: Biological Relationships of Pomatiopsis and Oncomelania (Contract No. DA-49-007-MD-604) Dr. Franz von Lichtenberg: Protective Mechanisms in Schistosomiasis (Contract No. DA-49-193-MD-2253) Dr. Nathan Zvaifler: Rabbit Anaphylactic Antibody in Schistosomiasis (Contract No. DA-49-193-MD-2911) (Dr. Zvaifler was unable to attend)
1615	Recess—Coffee
1630	Executive Session
Tuesday, 27 October	
0815	Introductory Remarks by Commission Director and President of the Board
0830	SYMPOSIUM ON SCHISTOSOMIASIS
0830	Second International Congress of Parasitology—Dr. E. H. Sadun
0845	Research at WRAIR—Dr. E. H. Sadun
0915	Research at 406th Medical Laboratory—Dr. G. M. Davis
1000	General Discussion
1030	Recess—Coffee
1045	Research at NAMRI—Commander M. H. Stirewalt
1115	Research at NAMRU-3—Captain D. C. Kent
1145	General Discussion
1215	Lunch
1345	Research at NIH—Dr. A. W. Cheever
1415	Research at Peter Bent Brigham Hospital—Dr. F. von Lichtenberg
1445	Research at Harvard University—Dr. T. H. Weller
1515	General Discussion
1545	Recess—Coffee
1600	Research at Santa Lucia, W.I.—Dr. P. Jordan
1640	Research at Johns Hopkins University—Dr. E. Bueding
1700	General Discussion

Amebiasis

In 1970 the problems related to amebiasis were transferred from the Commission on Enteric Infections to the Commission on Parasitic Diseases. Studies then in progress by Iris Krupp were continued for 1 year, but progress and final reports were submitted to the original Commission. Another study that dealt in part with amebiasis and was sponsored by the Commission on Environmental Health was brought to the attention of this Commission. Report of work concerned with transmission of the infection was presented at the 1970 f all meeting. Progress and final reports were submitted to the original Commission.



COMMISSION ON MALARIA

Fall Meeting 25 October 1972
Walter Reed Army Institute of Research
Washington, D.C.

Seated, left to right: Drs. Martin D. Young, Robert L. Kaiser (Deputy Director), Robin D. Powell (Commission Director), G. Robert Coatney, and Leslie A. Stauber.

Standing, left to right: Drs. Elvio H. Sadun, Carroll N. Smith, Lloyd E. Rozeboom, Geoffrey M. Jeffery, William D. Tigertt, John D. Arnold, Peter G. Contacos, Thomas H. Weller, Meir Yoeli, and William Trager.

Anaphylactic Antibody

A study entitled "Anaphylactic Antibody in Helminthic Infection" by Nathan J. Zvaifler was in progress from 1 August 1970 to 31 May 1972. The purpose of the experiments was to determine the possible role of anaphylactic reaction in the pathogenesis of schistosomiasis. The work confirmed the involvement of mast cells in the passive cutaneous anaphylaxis (PCA) reaction and suggested the involvement of neutrophils. Extensive tests comparing the immediate (4-hour) and delayed (72-hour) reactions supported the conclusion that in the rabbit, the PCA reaction with a short latent period cannot be used to define or distinguish immunoglobulin G homocytotropic antibody from immunoglobulin E. The study was terminated without having specifically related any of the findings to the pathogenesis of schistosomiasis or other helminthic infection.

At least one report was published:

- Bauer, H. Zvaifler, N. J., and Robinson, J. O. Immunoglobulin in the rabbit. *Lab. Invest.* 1972, 26, 448–458.

Anthelmintic Dithiazanine

In 1958, when Dr. Bueding initiated a study of dithiazanine, the drug was widely used as an anthelmintic, especially for trichuriasis and to a lesser extent for ascariasis. In a 3-year study. Dr. Bueding and his collaborator, Dr. Emil Kmetec, found that its action against *Ascaris lumbricoides* was a marked inhibitory effect on the utilization of carbohydrates, causing paralysis, and the effect was irreversible and caused by interference with either the uptake or metabolism of glucose. In experiments with *Trichuris vulpis*, the biochemical effects of the drug were found to interfere with the active transport of glucose into the worm, thus causing its death because of an inadequate supply of energy. While these studies were in progress, dithiazanine was reported to be toxic to humans and its use as an anthelmintic was discontinued.

Antigen Production and Testing

In 1962, Dr. Niam Kent began a program on the isolation of specific antigens from larval and adult schistosomes. Although he had made good progress toward the preparation and storage of such antigens, the work was interrupted by a move to a different location before any quality tests were completed.

In September 1966, under the direction of Dr. Paul Thompson at Parke Davis and Company, Ann Arbor, Michigan, a project was initiated to produce diagnostic antigens for amebiasis and schistosomiasis. Collaborators in the work were Dr. Curt Schneider and Dr. W. P. Stucki. After October 1968, the project was directed by Dr. Stucki. With lyophilized *Entamoeba histolytica* from Diamond's axenic cultures, a standard antigen was produced and shown to be suitable for use in indirect hemagglutination, complement fixation, and agar-gel tests. Sufficient antigen for 6,000 hemagglutination, 5,000 complement-fixation, and comparable numbers of agar-gel tests were delivered to the U.S. Army Medical Research and Development Command. Antigen of the Chaffee type was prepared from adult *Schistosoma mansoni* grown in experimental animals. Its usefulness in complement fixation and intradermal tests was demonstrated.

Later, antigens for the diagnosis of filariasis, leishmaniasis, American trypanosomiasis, and toxoplasmosis were produced and tested for stability and suitability for routine use. The program was completed in 1970. Some of the results were reported in published articles:

- Schneider, C. R. The effect of medium components on the specificity of axenic *Entamoeba histolytica* antigen. *J. Parasitol.* 1968, 54, 711–714.
- Stucki, W. P. Evaluation of *Schistosoma mansoni* intradermal test antigens in the rhesus monkey. *J. Parasitol.* 1968, 54, 174–175.
- Thompson, P. E., Graedel, S. K., Schneider, C. R., Stucki, W. P., and Gordon, R. M. Preparation and evaluation of standardized amoeba antigen from axenic cultures of *Entamoeba histolytica*. *Bull. W.H.O.* 1968, 39, 349–365.

TRAINING AND RECRUITMENT

One of the stated purposes of the AFEB Commission on Parasitic Diseases was to increase the number of professional workers in the field of parasitology and tropical medicine. It had been originally ruled inappropriate to use funds from the Defense Department budget for fellowship stipends, but investigators at all levels of skill and experience could be employed for contract research. In that way, it was possible to provide training and experience to many young workers who were employed as research assistants or associates. As shown by the number of coauthors on listed publications, notable examples of contracts providing such training opportunities are those of Drs. van der Schalie (malacology), Lewert (schistosomiasis, biochemistry, immunology), Warren (schistosomiasis pathology), von Lichtenberg (schistosomiasis pathology), Dunn (parasite survey), and Beaver (filariasis and tropical eosinophilia). Among the several predoctoral- and postdoctoral-level associates in the filariasis studies, four (Schacher, Pacheco, Wong, Lee) profited from overseas experience for 1, 2, or 3 years. Essentially, all contracts provided professional training experience to one or more trainee-level investigators.

SUMMARY AND CONCLUSIONS

Active during the period between 1953 and 1972, the Commission on Parasitic Diseases involved 21 members and 11 associate members. Members serving throughout the period were Beaver, Bueding, Most, Rozeboom, van der Schalie, and Weller. Drs. Weller, Most, and Beaver were directors of the Commission for periods of 5 or 6 years each.

The Commission's mission, outlined by Dr. Bayne-Jones, who was acting for AFEB President Dr. MacLeod, was to develop parasitic disease projects of concern to the Armed Forces by conducting field investigations or research projects in the laboratories of members of the Commission or others. It was not conceived as an agency for stimulating grant proposals, but rather one for recommending contracts for research consonant with the mission of the Armed Forces. As a part of its mission, the program of the Commission was expected to increase the number of professional workers in the field of parasitology and tropical medicine.

Early in the history of the Commission, malaria was recognized as the parasitic disease of greatest and most immediate concern to the military. An ad hoc Malaria Committee was appointed, and several symposia on malaria were held. Research projects on rodent malaria and on development of the malaria parasite in the mosquito were sponsored by the Commission. However, with the recognition of chloroquine-resistant strains of malaria, it became evident that the magnitude of the malaria problem justified the establishment of a separate Commission on Malaria.

A field investigation of hydatid disease in Alaska led to the conclusion that the probability of its significance as a health hazard to military personnel was minimal. Ad hoc committees dealt with the methodology of research on schistosomiasis, the revision of tuberculosis medications, and the procurement of antiparasitic drugs.

Special reports, seminars, or symposia were held as part of regular meetings on timely topics including the following:

- research programs at the 406th Medical General Laboratory, NIH, **and** Department of Parasitology at Louisiana State University in New Orleans;
- current research on malaria in 1957;
- insect vector control;
- research on malaria at the Naval Medical Research Institute;
- research at the CDC in Atlanta;
- parasitology programs in the Chicago area;



COMMISSION ON PARASITIC DISEASES, 1972

Seated, left to right: Drs. Elvio H. Sadun (deputy director), Willard H. Wright, Paul C. Beaver (Commission Director), and Thomas H. Weller.

Standing, left to right: Drs. Robert H. Lewert, Henry van der Schalie, John E. Scanlon, Martin D. Young, Ernest B. Bueding, Lloyd E. Rozeboom, William W. Frye, Leslie A. Stauber, and Rodney C. Jung.

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
26 October 1972

0900	Introductory Remarks by Commission Director, President and Executive Secretary of the Board
0915	Reports of Preventive Medicine Officers Department of the Army—Colonel Robert Cutting Department of the Navy—Captain C. E. Alexander Department of the Air Force—Lieutenant Colonel F. T. Corker Representative, USA Medical R&D Command—Colonel D. W. Sample
1000	Recess—Coffee
1015	PROGRESS REPORTS OF RESPONSIBLE INVESTIGATORS Dr. Henry van der Schalie: Studies of the Intermediate Snail Hosts of Oriental and African Schistosomiasis Infections (DA-49-193-MD-2651) Dr. Nathan Zvaifler: Anaphylactic Antibody in Helminthic Infections (DADA-17-71-C-1002) Dr. Donald Twohy: Nature of Immunity to Leishmaniasis (DADA 17-69-C-9135)
1215	Recess—Lunch
1330	Dr. John Janovy: Temperature Effects on Leishmania Metabolism (DADA 17-69-C-9122) Dr. William Hanson: Immunity to Chagas' Disease (DADA 17-69-C-9167) Dr. Franz von Lichtenberg and Jerome Smith: Protective Mechanisms in Schistosomiasis (DADA 17-72-C-2056) Dr. Gilbert Sanchez: Biochemical and Antigenic Changes in Trypanosomes (DADA 17-72-C-2020) Dr. John R. Seed: Immunization Against *Trypanosoma gambiense* (DADA 17-72-C-2058)
1600	Recess—Coffee
1615	Executive Session
1800	Adjournment

- current malaria research in 1964;
- parasitology research at Tulane University;
- current research on hemoflagellates;
- the problem of leptospirosis;
- research at military laboratories;
- filariasis research;
- problems of parasites in Latin America;
- immunology of parasitic diseases; and
- current schistosomiasis research in progress at leading laboratories.

The scientific contributions that were sponsored by the Commission were mostly in the general areas of schistosomiasis and filariasis. Significant observations were made in studies on parasites of Malaysian primates, leishmaniasis, and trypanosomiasis.

Studies by Dr. van der Schalie and associates showed that although the American snail *Pomatiopsis* species is biologically and ecologically similar to the natural intermediate host of *Schistosoma japonicum*, it is not a satisfactory substitute for *Oncomelania* in experimental studies. Methods for the laboratory propagation of snail intermediate hosts of common species of schistosomes of humans were useful in maintaining a supply source of material for studies in other laboratories. Biochemical studies by Dr. Lewert and associates on skin penetration by cercariae failed to reveal ways to bar their entry into the skin, but in immunological studies, they perfected a highly reliable circumoval precipitin test for diagnosis of infection in humans. The work of Dr. Warren and associates described factors in granuloma formation and the production of schistosomal disease in the mouse model. They also discovered that development of schistosomes in snails is suppressed by chloramphenicol. The various and numerous contributions on schistosomiasis by Dr. von Lichtenberg and associates included the basic nature and pathogenesis of schistosomiasis mansoni and haematobia in different species of primates including the chimpanzee. Of special interest also were granulomas produced by antigen-coated beads and latex particles in the lungs of experimental animals. Postmortem findings in Egyptian and Nigerian patients with urinary schistosomiasis were of great interest.

Filariasis studies by Drs. Rozeboom and Cabrera described the epidemiology of *Wuchereria bancrofti* infection in one area of the Philippines and confirmed the endemicity of *Brugia malayi* in the Philippines. Studies by Drs. Beaver, Danaraj, and Tulane associates in Singapore demonstrated that tropical eosinophilia is a form of filariasis in which the microfilariae that normally would circulate in the blood are screened out and destroyed in the lungs. In New Orleans, the Tulane workers found that in *Dipetalonema viteae*-infected birds and *Dirofilaria*-infected dogs, the levels of microfilaremia are determined by factors other than the number of adult worms present. Also, details of development of *Brugia pahangi* in the mosquito and cat hosts were described.

In a study of parasites of Oriental primates by Dr. Dunn, numerous helminths and some protozoa, including three new species of malaria, were reported. In a survey of intestinal parasites of primitive humans, a new method of quantitative diagnosis was developed.

Before the formation of the Commission on Malaria in 1964, two malaria projects were initiated in 1958 under the sponsorship of the Commission on Parasitic Diseases: One characterized in detail the early development of the parasite in the mosquito, the other described the full life cycle of *Plasmodium berghei*, the rodent malaria parasite. These studies were basic to understanding the later experimental studies on malaria.

Biochemical studies on acute ascariasis in guinea pigs and metabolic studies on adult *Ascaris lumbricoides* gave interesting new information, as did also studies on cellular immunity to *Leishmania donovani* in mice, the metabolic effects of temperature on *Leishmania* species in vitro, immunization against *Trypanosoma gambiense* and *T. cruzi* in experimental animals, and anaphylactic antibody. The anthelmintic action of dithiazanine was shown to be caused by a blocking effect of the transport of nutrients into the worms.

Antigens were produced, tested, and supplied for military, experimental, and diagnostic use in the diagnosis of amebiasis, schistosomiasis, filariasis, leishmaniasis, American trypanosomiasis, and toxoplasmosis.

Research investigations involving 20 active contracts were sponsored by the Commission on Parasitic Diseases. Listed as coauthors were approximately 100 workers who were not already recognized professional parasitologists. Programs offering the greatest number of opportunities for training experience in parasitology were those in the fields of schistosomiasis, malaria, filariasis, and leishmaniasis.

The last meeting of the Commission was held on 26 October 1972, and the last annual report of the Commission Director was submitted 12 December 1972. The decision to terminate the Commission and some other advisory groups had been taken earlier and announced in a letter addressed to the Director, dated 11 October 1970 and signed by Richard R. Taylor, M.D., Brigadier General, MC, Special Assistant for Research and Development. The letter noted that an appearance of conflict of interest had been created by the arrangement wherein the Commissions of the AFEB reviewed and recommended research proposals submitted by its own members. Roughly, a third of the principal investigators of proposals recommended by the Commission had been member submitted. In the beginning, it had been recognized that the persons best qualified to conduct research in some areas of military interest were members of the Commission. Therefore, support of investigations in laboratories of members was anticipated. The reversal of policy was made necessary by newly established governmentwide standards pertaining to conflict of interest in advisory groups (see Appendix 4).

SECTION 6— APPENDIX 1

INFORMATION ABOUT CONTRACTS

This table of information on contracts was prepared by Colonel Robert Wells, AFEB Executive Secretary, and Jean P. Ward, AFEB Staff Assistant. In some instances, the list includes both the responsible investigator and a coinvestigator (Audy and Dunn, Rozeboom and Cabrera, Kemp and Hunter, Thompson and Stucki) or an investigator whose project was not sponsored by the Commission (Burckhalter), not activated (Kessel), or support was for administrative costs only (Beaver, Weller). For numerous projects, information on funding was incomplete or unknown, and for some, the indicated level of funding may be that authorized, not the amount expended. One project was omitted (Zvaifler, NJ, University of California at San Diego, Anaphylactic Antibodies in Helminth Infection, DADA 17-71-C-1002, 1 August 1970–31 May 1972).

Investigator/Institute	Title of Project and Contract Number	Period	Amount
Adams, John G.	Biochemical Investigation of the Host–Nematode Relationships in Asacariasis. (TERMINATED)	1962–1964	
	Contract #DA-49-193-MD-2338		
Audy, Ralph	Endoparasites of Oriental Primates	1963–1966	
Hooper Foundation	Contract #DA-49-193-MD-2291		
Beaver, Paul C.	Visceral Larva Migrans in Relation to	1955–1956	$ 13,993
Tulane University	Tropical Eosinophilia	1956–1957	$ 12,974
	Contract #DA-49-007-MD-633	1957–1958	$ 13,116
	Filariasis in Relation to Tropical Eosinophilia	1958–1959	$ 6,130
	Contract #DA-49-193-MD-2677	1959–1960	$ 6,837
		1961–1963	$ 30,163
		1966–1967	$ 37,170
		1967–1968	$ 29,377
		1968–1969	$ 46,193
	Director's Office	1967–1968	$ 1,000
	Contract #DADA-70-C-0106	1970–1972	$ 8,972
Bueding, Ernest B.	Mechanism of Anthelminthic Action of	1958–1959	$ 5,628
Louisiana State	Dithiazanine	1959–1960	$ 5,628
	Contract #DA-49-007-MD-975	1960–1961	$ 6,000
Burkhalter, Joseph H.	New Agents for Parasitic Infections	No period	No amount
	No contract number		
Cabrera, Benjamin D.	Filariasis Studies in the Phillipines	No period	No amount
	No contract number	1963–1965	No amount
Dunn, Frederick L.	Endoparasites of Oriental Primates. Investi-		
San Francisco Med.	gations in Malaysia and San Fransisco		
	Contract #DA-49-193-MD-2291		
Entner, Nathan	Enzymatic aspects of Carbohydrate	1955–1956	$ 6,450
New York University	Metabolism in *Ascaris lumbricoides*	1958–1959	$ 6,011
	Contract #DA-49-007-MD-692	1959–1960	$ 1,667
Hanson, William L.	Immunity to Chagas' Disease	1970–1972	$ 25,403
University of Georgia	Contract #DADA17-69-C-9167		
Hunter, George W.	Screening Potential Protective Oint-	1954–1955	
	ments Against Schistosomiasis		
	Contract #DA-49-007-MD-468		

Investigator/Institute	Title of Project and Contract Number	Period	Amount
Janovy, John, Jr. University of Nebraska	Effects of Temperature on *Leshmania* Metabolism Contract #DADA17-69-C-9122	1969–1972	
Kemp, Hardy A. Baylor University	Screening Potential Protective Ointments Against Schistosomiasis Contract #DA-49-007-MD-468	1954–1955	
Kent, Niam H.	Isolation of Specific Antigens From Larval and Adult Stages of Schistosomes Contract #DA-49-193-MD-2276	1962–1964	
Kessel, John F.	The Correlation of Serologic Tests for Amebiasis with Clinical and Pathological Findings No contract number		
Lewert, Robert M. University of Chicago	Studies on *Schistosome Japonicum* in Man and *Schistosome Cercariae* with Special Reference to Inhibition of Penetration of Various Agents Contract #DA-49-007-MD-516 Immunity to *Schistosoma Japonicum* in Man Contract #DA-49-193-MD-2320	1954–1955 1955–1956 1958–1959 1959–1960 1960–1068 1962–1963 1962–1963	$ 8,000 $ 11,600 $ 13,850 $ 14,000
Most, Harry New York University	Biological Studies in Malaria (*P. berghei*) Contract #DA-49-007-MD-964	1958–1959 1959–1960 1960–1966	$ 22,000 $ 22,000 $ 22,000
Ragozzino, Patrick W. University of Connecticut	Serotonin and Histamine Productin in Ascariasis Contract #DA-49-007-MD-2338	1962–1963	
Rozeboom, Lloyd E. Johns Hopkins University	Epidemiology of Filariasis Among Mountain Tribes in Northern Luzon, Philippine Islands Contract #DA-49-007-MD-2370	1958–1959	$ 13,220
	Factors Influencing Susceptibility and Immunity of the Mosquito to Infection by the Malaria Parasite Contract #DA-49-007-MD-1023	1963–1964	
Sanchez, Gilbert New Mexico Institute of Mining and Technology	Mechanisms of Biochemical and Antigenic Changes in Parasitic Trypanosomes Contract #DADA17-72-C-2020	1971–1972	
Seed, John R. Tulane University	Active Immunization Against *Trypanosoma gambiense* with a Partially Purified Protective Antigen Contract #DADA17-72-C-2058	1971–1972	
Stucki, William P. Parke, Davis & Co.	Parasite Antigens Contract #DA-49-193-MD-2927	1966–1972	
Thompson, Paul E. Parke, Davis & Co.	Parasite Antigens Contract #DA-49-193-MD-2927	1966–1968	
Twohy, Donald W. Michigan State University	The Nature of Immunity to Leishmaniasis Contract #DADA17-67-7142 Contract #DADA17-69-C-9135	1968–1969 1969–1972	 $ 44,202

Investigator/Institute	Title of Project and Contract Number	Period	Amount
van der Schalie, Henry University of Michigan	Studies of American *Pomatiopsis* Snails with Biological Relationships Almost Identical to *Oncomelania*, the Vector of Oriental Schistosomiasis	1955–1956 1958–1959 1959–1960 1960–1961	$ 5,000 $ 15,480 $ 11,550 $ 14,000
	Contract #DA-49-007-MD-604 Contract #DA-49-007-MD-2651	1968–1972	
von Lichtenberg, Franz Harvard Medical School	Protective Mechanisms in Schistosome Infections (previous title: Host–parasite Relationship in Normal and Abnormal Hosts of Schistosomidae)	1966–1971	$ 11,846
	Contract #DA-49-007-MD-2253		
	Protective Mechanisms in Schistosome Infection	1971–1972	
	Contract #DADA17-72-C-2056		
Wagner, Edward D. College of Medical Evangelists	Study of the Biology of Oncomelania. A Study of the Biology, Feeding Habits, and Nutritional Requirements of the Snail Hosts of *Schistosoma japonicum*	1954–1955	
	Contract #DA-49-007-MD-307		
Warren, Kenneth S. Western Reserve University	Pathophysiology of Schistomsmiasis Contract #DA-49-193-MD-2639	1965–1967	
Weller, Thomas H. Harvard School of Public Health	Contract #DA-49-007-MD-530	1958–1959	$ 2,520

Summary of Reserach Funds for AFEB-Reviewed Research for the Periods 1 July 1958–30 June 1959, 1 July 1959–30 June 1960, and 1 July 1960–30 June 1961

1 July 1958–30 June 1959	1 July 1959–30 June 1960	1 July 1960–30 June 1961
$ 82,592	$ 61,532	$ 63,000

SECTION 6—APPENDIX 2

COMMISSION ON PARASITIC DISEASES—DATES AND LOCATIONS OF MEETINGS

2 October 1953	Walter Reed Army Medical Center, Washington, D.C.
2 November 1954	Hotel Peabody, Memphis, Tennessee
4 April 1955	Walter Reed Army Medical Center, Washington, D.C.
1 November 1955	Hotel Somerset, Boston, Massachusetts
5 April 1956	Walter Reed Army Institute of Research, Washington, D.C.
30 October 1956	Louisiana State University School of Medicine, New Orleans, Louisiana
15–16 March 1957	Walter Reed Army Institute of Research, Washington, D.C.
29 October 1957	Hotel Benjamin Franklin, Philadelphia, Pennsylvania
7–8 March 1958	Walter Reed Army Institute of Research, Washington, D.C.
4 November 1958	Hotel Deauville, Miami Beach, Florida
9–10 March 1959	Walter Reed Army Institute of Research, Washington, D.C.
27 October 1959	Claypool Hotel, Indianapolis, Indiana
7–8 April 1960	Walter Reed Army Institute of Research, Washington, D.C.
Fall 1960	Records not available
Spring 1961	Records not available
31 October 1961	Walter Reed Army Institute of Research, Washington, D.C.
6–7 March 1962	Walter Reed Army Institute of Research, Washington, D.C.
30 October 1962	Communicable Disease Center, Atlanta, Georgia
5–6 March 1963	Walter Reed Army Institute of Research, Washington, D.C.
5 November 1963	Center for Continuing Education, University of Chicago, Chicago, Illinois
12 March 1964	Walter Reed Army Institute of Research, Washington, D.C.
3 November 1964	New York University School of Medicine, New York City
1 March 1965	Walter Reed Army Institute of Research, Washington, D.C.
6 November 1965	Tulane University School of Medicine, New Orleans, Louisiana
14 March 1966	Walter Reed Army Institute of Research, Washington, D.C.
18 November 1966	Walter Reed Army Institute of Research, Washington, D.C.
13–14 March 1967	Walter Reed Army Institute of Research, Washington, D.C.
31 October 1967	Benjamin Franklin Hotel, Philadelphia, Pennsylvania
25 March 1968	Walter Reed Army Institute of Research, Washington, D.C.
2–3 December 1968	Walter Reed Army Institute of Research, Washington, D.C.
24 March 1969	Walter Reed Army Institute of Research, Washington, D.C.
16–17 October 1969	Walter Reed Army Institute of Research, Washington, D.C.
23 March 1970	Walter Reed Army Institute of Research, Washington, D.C.
26–27 October 1970	Walter Reed Army Institute of Research, Washington, D.C.
22 March 1971	Walter Reed Army Institute of Research, Washington, D.C.
27 October 1971	Walter Reed Army Institute of Research, Washington, D.C.
30 March 1972	Walter Reed Army Institute of Research, Washington, D.C.
26 October 1972	Walter Reed Army Institute of Research, Washington, D.C.

SECTION 6—APPENDIX 3

AGENDA OR OUTLINE OF MEETINGS

Outlines of meetings without available agenda are based on director's summaries in annual reports.

Outline of Meeting
Commission on Parasitic Diseases
Walter Reed Army Medical Center
4 April 1955

0930	Introductory Remarks by Commission Director	Thomas H. Weller
	Statement	Colonel Adam J. Rapalski, Executive Secretary, AFEB

Remarks by:
- Lieutenant J. F. Egan of the Navy
- Lieutenant Colonel H. G. Tousignant of the Air Force
- Colonel T. F. Whayne of the Army
- Colonel F. H. Mowrey of the Army

Progress report on work done under Contract DA-49-007-MD-307 — Dr. Edward D. Wagner

Summary of research activities on schistosomiasis at the National Microbiological Institute, NIH

Progress report on work done under Contract DA-49-007-MD-468 — Dr. Hardy A. Kemp

Progress report on parasitological studies on rhesus and cynomolgus monkeys — Dr. Gustave J. Dammin

Executive Session
- Review of status of action taken on previous recommendations
- Consideration of contract proposals
- Discussion of Contract DA-49-007-MD-468
- Recommendations regarding financing of contracts not subject to review at current meeting

Consideration of application by:
- Dr. R. S. Diaz-Rivera of the University of Puerto Rico Medical School

Meeting adjourned

Outline of Meeting
Commission on Parasitic Diseases
Hotel Somerset, Boston, MA
1 November 1955

0930	Introductory remarks by Commission Director	Thomas H. Weller
	Statement	Dr. Floyd Denny, speaking for Dr. John Dingle
	Statement	Captain R. W. Babione, Executive Secretary, AFEB

Comments by:
- Colonel Tousignant, Department of the Air Force
- Major H. L. Ley, Department of the Army

Progress report on contract DA-49-007-MD-516, "Studies on schistosome cercariae with special reference to inhibition of penetration of various agents" — Dr. Robert M. Lewert

Progress report on contract DA-49-007-MD-604 on "Studies of American *Pomatiopsis* snails with biological relationships almost identical to *Oncomelania*" — Dr. Henry van der Schalie

Review of hydatid situation in Alaska — Major Ley and Colonel Toussignant

Summary of activities of parasitological interest in the Philippines — Dr. L. E. Rozeboom

Report on trip under AFEB auspices to advise on and to observe research on *Oncomelania* in Japan and the Philippines — Dr. van der Schalie

Liaison report on recovery of viral agents from cases of *Shigella* infection — Dr. G. Dammin

Executive Session
- Consideration of nominations for associate membership
- Recommendations concerning contract renewals
- Consideration of application of Dr. Nathan Entner
- Follow-up on Kemp–Hunter project, "Screening protective ointments against schistosomiasis"

Outline of Meeting
Commission on Parasitic Diseases
Walter Reed Army Institute for Research
5 April 1956

0940	Introductory remarks by Commission Director	Thomas H. Weller

Comments by:
- Dr. John J. Dingle, AFEB
- Captain J. R. Seal, Department of the Navy
- Colonel H. G. Toussignant, Department of the Air Force
- Major A. M. Reeve, Department of the Army

Progress reports on:
- Contract DA-49-007-MD-307, "A study of the biology, feeding habits, and nutritional requirements of the snail hosts of *Schistosoma japonicum*" — Dr. E. D. Wagner

Contract DA-49-007-MD-633, "Visceral larva migrans in relation to tropical eosinophilia" — Dr. Paul C. Beaver
Interim report of Ad Hoc Committee on Hydatid Disease
General comments on the program of the Commission
Executive Session
Considerations of proposals for contract extension
Discussion of possible new applications
Consideration of the action of the Ad Hoc Committee on Hydatid Disease
Discussion of status of Kemp–Hunter report.

Outline of Meeting
Commission on Parasitic Diseases
Louisiana State University School of Medicine
30 October 1956

0910 Meeting called to order by Commission Director Thomas H. Weller
Introductory remarks by:
Dr. Floyd W. Denny
Captain R. W. Babione
Comments by:
Colonel H. E. Griffin, Department of the Army
Colonel G. A. Fair, Department of the Air Force
Dr. C. G. Huff, Department of the Navy
Progress reports:
Contract DA-49-007-MD-516, "Studies on schistosome cercariae with special reference to inhibition of penetration by various agents" — Dr. R. M. Lewert
Contract DA-49-007-MD-604, "Some comparative studies of American *Pomatiopsis* with species of *Oncomelania*, the vector of Oriental schistosomiasis" — Dr. H. van der Schalie
Contract DA-49-007-MD-692, "Enzymatic aspects of carbohydrate metabolism in *Ascaris lumbricoides*" — Dr. N. Entner
Report of Ad Hoc Committee on Hydatid Disease
Comment on 6th International Congress on Hydatid Disease — Dr. Weller
Presentation of current investigations in the field of parasitology at Louisiana State University School of Medicine
Tour of Louisiana State University Medical School
Executive Session
Consideration of proposals for contract extensions
Old business:
Kemp–Hunter contract
Conditions for infectivity experiments with snails
New business:
African Regional WHO Conference on schistosomiasis
Interest of the Air Force in studies on canine filariasis
Recommendations regarding Alaskan hydatid disease problem

Outline of Meeting
Commission on Parasitic Diseases
Walter Reed Army Institute for Research
15–16 March 1957

15 March
0940 Meeting called to order by Commission Director — Thomas H. Weller
Introductory remarks by:
Dr. Floyd W. Denny, AFEB, for Dr. Dingle
Captain R. W. Babione, Executive Secretary, AFEB
Comments by:
Major Benjamin Hammers, Department of the Air Force
Captain J. R. Seal, Department of the Navy
Captain J. R. Kingston, Department of the Navy
Lieutenant Colonel H. E. Griffin, Department of the Army
Discussion of reports by Armed Forces representatives
Progress reports and applications for contract support:
Final report on Contract DA-49-007-MD-307, "A study of the biology, feeding habits, and nutritional requirement of the snail host of *Schistosoma japonicum*" — Dr. E. D. Wagner
Application for contract entitled, "Basic biologic studies on *Oncomelania*"
Annual report and request for 12 months' extension of Contract DA-40-007-MD-633," Visceral larva migrans in relation to tropical eosinophilia" — Dr. Paul C. Beaver
Interim report and request for 12 months' extension of contract DA-49-007-MD-692, "Enzymatic aspects of carbohydrate metabolism in *Ascaris lumbricoides*" — Dr. N. Entner
Interim report and request for 7 months' extension of contract DA-49-MD-516, "Studies on schistosome cercariae with special reference to inhibition of penetration by various agents" — Dr. R. M. Lewert
Interim report and request for 7 months' extension of contract DA-49-007-MD-604, "Some comparative studies of American *Pomatiopsis* with species of *Oncomelania*, the vector of Oriental schistosomiasis" — Dr. H. van der Schalie
Report of the Ad Hoc Committee on Hydatid Disease
Report on the WHO schistosomiasis conference at Brazzaville
17:45 Session adjourned

March 16
0900 Executive Session
Discussion of activities and responsibilities of the Commission on Parasitic Diseases
Discussion of malaria and filariasis, possible new fields of interest
Consideration of report of the Ad Hoc Committee on Hydatid Disease
Action on requests for contract support
1255 Meeting adjourned

Outline of Meeting
Commission on Parasitic Diseases
Hotel Benjamin Franklin, Philadelphia
29 October 1957

1400	Introductory remarks by Commission Director	Thomas H. Weller
Status of research on malaria		Dr. Paul F. Russell
		Dr. Clay Huff
		Dr. Lloyd Roseboom
		Dr. Robert Coatney
		Dr. Willard Wright
		Dr. D. McMullen

Consideration of the role of the Commission on Parasitic Diseases in relation to the status of research on malaria

1715 Meeting adjourned

1910 Meeting reconvened

Remarks by:

Dr. Floyd W. Denny, AFEB, for Dr. Dingle
Lieutenant Colonel H. E. Griffin, Department of the Army
Lieutenant Colonel C. N. Moss, Department of the Air Force

Discussion of the problem of training in the Armed Forces

Report of Committee on Experimental Conditions to be Considered in Studies on Schistosomes

Report on the 8th Alaskan Science Conference	Dr. Gilbert Otto
Comment on experiences in Durban, South Africa	Dr. Paul C. Beaver

2055 Meeting adjourned

Outline of Meeting
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
7–8 March 1958

March 7

1005	Introductory remarks by Commission Director	Dr. Thomas Weller

Comments by:

Dr. Thomas Francis, President, AFEB
Captain R. W. Babione, Executive Secretary, AFEB

Reports on parasitological problems by:

Captain S. A. Britten, Department of the Navy
Colonel G. K. Fair, Department of the Air Force
Colonel H. E. Griffin, Department of the Army

Reports of contract research

Contract DA-49-007-MD-633, "Visceral larva migrans in relation to tropical eosinophilia"	Dr. Paul C. Beaver
Contract DA-49-007-MD-692, "Enzymatic aspects of carbohydrate metabolism in *Ascaris l umbricoides*"	Dr. Nathan Entner
Contract DA-49-007-MD-516, "Studies on schistosome cercariae with special reference to inhibition of penetration by various agents"	Dr. Robert Lewert

Contract DA-49-007-MD-604, "Some comparative studies of American *Pomatiopsis* with species of *Oncomelania*, the vector of Oriental schistosomiasis"	Dr. Henry van der Schalie
Summary prepared by the Ad Hoc Committee on Experimental Conditions to be Considered in Studies on Schistosomes and Their Hosts	Dr. H. van der Schalie
Report by Dr. G. J. Dammin concerning his visit to Guatemala City in connection with the activities of the Commission on Enteric Infections	
Presentation of data on origin of cases of schistosomiasis occurring in Navy personnel	Captain John R. Seal
Comments on investigations on eosinophilic bowel infiltrates	Drs. Beaver and Dammin
1745 Regular session adjourned	

March 8

0935 Executive Session	
Introductory remarks by Commission Director	Dr. T. H. Weller
Review of applications for extension of contracts:	
"Visceral larva migrans and its relation to tropical eosinophilia"	Dr. Paul Beaver
"Further studies on carbohydrate metabolism of *Ascaris lumbricoides*"	Dr. Nathan Entner
"Studies on schistosome cercariae with special reference to inhibition of penetration by various agents"	Dr. Robert M. Lewert
"Studies of American *Pomatiopsis* snails with biological relationship almost identical to *Oncomelania*, the vector of Oriental schistosomiasis"	Dr. Henry van der Schalie
Consideration of application for new contract	Dr. Ernest Bueding
Report on status of Alaskan hydatid problem	
Consideration of status of program of the Commission on Parasitic Diseases	
Old business	
New business	
1403 Meeting adjourned	

Outline of Meeting
Commission on Parasitic Diseases
Hotel Deauville, Miami Beach, Florida
4 November 1958

1000	Meeting called to order by Commission Director	Dr. Thomas Weller
	Introductory remarks	Dr. Thomas Francis, Jr., President of AFEB
		Captain R. W. Babione, Executive Secretary

Reports by:
- Colonel G. K. Fair, Department of the Air Force
- Lieutenant Colonel J. W. Cooch, Department of the Army
- Commander B. Gundelfinger, Department of the Navy

Comment by Dr. Weller on his visit to Lebanon
Report of Ad hoc Committee on Malaria Research
Review of status of research on vector repellents
Report on activity of alkyldibenzylamines on *Schistosoma mansoni* in vitro — Dr. Ernest Bueding
Executive session
- Consideration of contract applications by:
  - Dr. L. Rozeboom
  - Dr. F. B. Bang
  - Dr. Marion Brooke on behalf of Dr. Irving Kagan
- Action on membership of the Commission
- Reports on other activities of members
- Other business
- Memorandum concerning use of human volunteers

Meeting adjourned

Tentative Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
9–10 March 1959

March 9
GENERAL SESSION

1000		
1.	Introductory remarks	Dr. Thomas Francis, Jr., President, AFEB
1015		
2.	Comments on administrative matters	Captain R. W. Babione, MC, USN, Executive Secretary, AFEB
1030		

3. Presentation on status of parasitic diseases in the Armed Forces

1030	Department of the Air Force
1045	Department of the Army
1100	Department of the Navy
1115	Intermission

1130	
4. Report on work under contract DA-49-007-MD-633, "Visceral larva migrans in relation to tropical eosinophilia"	Dr. Paul Beaver, Tulane University School of Medicine
a. Clinical, therapeutic, and etiologic studies on tropical	Dr. T. J. Danaraj, Lecturer in Medicine, University of Malaya
b. Parasitological studies (15 min)	Mr. J. F. Schacher, Research Associate
c. Summary (15 min)	Dr. Paul Beaver
d. Discussion	
1230–1345	
RECESS FOR LUNCH	
1345	
5. Progress report on contract DA-49-007-MD-975 of Dr. Ernest Bueding, "Study on the mechanism of anthelminthic action of dithiazanine"	Dr. Emil Kmetec, Research Associate, Department of Pharmacology, School of Medicine, Louisiana State University
1405	
Discussion of Dr. Kmetec's Report	
1415	
6. Report and request for extension of contract DA-49-007-MD-692, "Enzymatic aspects of carbohydrate metabolism in *Ascaris lumbricoides*"	Dr. Nathan Entner, New York University
1445	
Discussion of Dr. Entner's Report	
1500	
7. Progress report on contract of Dr. Lloyd Rozeboom, DA-49-007-MD-1023, "Factors influencing susceptibility and immunity of the mosquito to infection by the malaria parasite"	Dr. Lee M. Howard, Research Associate, Johns Hopkins University
1520	
Discussion of Dr. Howard's Report	
1530	
Intermission	
1540	
8. Report on contract, DA-49-007-MD-516, "Studies on schistosome cercariae with special reference to inhibition of penetration by various agents"	Dr. Robert M. Lewert, University of Chicago
1615	
Discussion of Dr. Lewert's Report	
1625	
9. Progress report on Dr. Harry Most's contract, DA-49-007-MD-964, "Biological studies in malaria (*P. berghei*)"	Dr. Meir Yoeli, Department of Preventive Medicine, New York University College of Medicine
1645	
Discussion of Dr. Yoeli's report	
1655	
10. Report on contract DA-49-007-MD-604, "Some	Dr. Henry van der Schalie, Univer-

	comparative studies of American *Pomatiopsis* with species of *Oncomelania*, the vector of oriental schistosomiasis"	sity of Michigan

1725
Discussion of Dr. van der Schalie's Report
Adjournment

March 10
EXECUTIVE SESSION
0930

1. Remarks regarding membership
2. Consideration of proposals by contractors.
   a. Dr. Beaver
   b. Dr. Bueding
   c. Dr. Entner
   d. Dr. Rozeboom
   e. Dr. Lewert
   f. Dr. Most
   g. Dr. van der Schalie
3. Matter of priorities on research contracts and of "advance financing"
4. Discussion of AFEB policy on "consultantships"
5. Consideration of response from Department of Agriculture on easing of restrictions on strains of malaria
6. Statement from Department of Agriculture on support of research on repellents
7. Other business

Agenda
Commission on Parasitic Diseases
Claypool Hotel, Indianapolis, Indiana
27 October 1959

GENERAL SESSION

0930	Introductory remarks	Dr. Thomas Francis, Jr., President, AFEB Colonel John Rizzolo, USAF (MC), Executive Secretary, AFEB Dr. Gustave J. Dammin, Director, CPD
1000	Reports of Preventive Medicine Officers of the Armed Forces	
1030	Coffee Break	
1045	Current work on the treatment of malaria	Dr. Alf S. Alving
1145	Discussion: Commission Members and Guests	
1215	Lunch	
1330	Malaria and other research in parasitology at the Naval Medical Research Institute	Dr. Clay G. Huff
1400	Recent work of AFPCB on control of insect vectors	Colonel Ralph W. Bunn, MSC
1420	General discussion—Malaria	
1440	Informal reports and discussion of training, therapy, research and travel	Dr. Ernest Bueding Dr. Franz von Lichtenberg

		Dr. Donald McMullen Dr. Harry Most Dr. Henry van der Schalie Dr. Thomas H. Weller
1540	Coffee	
1600	Executive Session	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
7–8 April 1960

General Session—7 April		
0930	Introductory Remarks	Dr. Gustave J. Dammin, Director Colonel John Rizzolo, USAF, MC, Executive Secretary, AFEB Major Thomas B. Dunne, MC, R & D Command
1000	Reports of Preventive Medicine Officers of the Army, Navy and Air Force	
1030	Intermission	
1045	Requirements for personnel and training for work in tropical areas Subject to be introduced by Dr. Sadun Discussion by representatives of the Military, Public Health Service and Commission Members	
1130	Dr. Henry van der Schalie: "Studies of American *Pomatiopsis* snails"	
1200	Film describing work of the 406th Med. Gen. Lab., Zama, Japan	
1230	Recess for lunch	
1400	Dr. Harry Most and Dr. Meir Yoeli: "Biological Studies in Malaria"	
1445	Dr. Lloyd Rozeboom and Dr. L. M. Howard: "Factors Influencing the Susceptibility and Immunity of the Mosquito to Infection by the Malaria Parasite"	
1530	Work of the Military in Malaria Chemoprophylaxis	
MALARIA: GENERAL DISCUSSION		
1700	Adjournment	
General Session—8 April		
0900	"Visceral Larva Migrans in Relation to Tropical Eosinophilia"	Dr. Paul Beaver, Dr. John Schacher, and Dr. T. J. Danaraj
0945	"Studies on Schistosome Cercariae with Special Reference to Inhibition of Penetration by Various Agents"	Dr. Robert Lewert, Dr. S. Mandlowitz, and Dr. D. Dusanic
1030	Intermission	
1045	"Mechanisms of Anthelminthic Action"	Dr. Ernest Bueding
1130	"Enzymatic Aspects of Carbohydrate Metabolism in *Ascaris lumbricoides*"	Dr. Nathan Entner
1200	Informal Reports on Research and Travel	
1300	Recess for Lunch	
1400	EXECUTIVE SESSION Meeting of full members of the Commission on Parasitic Diseases for consideration of contract proposals, financing and membership	

Records of meetings were not available
for fall of 1960 and spring of 1961

Outline of Joint Meeting
AFEB Commission on Parasitic Diseases and
Commission on Enteric Diseases
Walter Reed Army Institute of Research
31 October 1961

0900	Meeting called to order by the Director	Dr. Harry Most
Comments of AFEB President		Dr. G. J. Dammin
Reports of military representatives:		
	Lieutenant Colonel J. W. Cooch, Army	
	Commander J. W. Miller, Navy	
	Lieutenant Colonel F. L. Bowling, Air Force	
	Lieutenant Colonel H. J. Donnelly, R & D Command	
	Brigadier General J. H. Forsee, R & D Command	
Comments by Commission on Enteric Disease's Director		Dr. F. S. Cheever
Review of WRAIR research program on parasitic diseases		Dr. Elvio Sadun
Lunch		
Laboratory demonstration, WRAIR Department of Medical Zoology		
Brief reviews of:		
	Schistosomiasis research program in Puerto Rico	Lieutenant Colonel L. P. Frick
	Research on schistosomiasis at 406th Laboratory in Japan	Mr. J. E. Williams
	Research on *T. cruzi* infection at 3rd Army Area Laboratory	Major B. Walton
	Research and other activities of U.S. Army in East Africa (Uganda)	Major D. Price
Executive Session		
1740	Meeting adjourned	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
6–7 March 1962

6 March 1962
Joint Meeting—Commission on Enteric Infections and Parasitic Diseases

0930–1000	Remarks	President, AFEB, Directors of Commissions and Executive Secretary, AFEB
1000–1045	Comments by Service Representatives Division of Army Division of Navy Division of Air Force	
1045–1115	Coffee and informal reports by Commission Members	
1115–1300	Presentations by Commission on Enteric Infections	Dr. Cheever presiding
1300–1400	Lunch	
1400–1700	Presentation of progress reports and consideration of proposal for extension of contracts and new contracts	
1700–1800	Executive Session	
1800	Adjournment	

7 March 1962

0930–1230	Meeting—Ad Hoc Committee on Malaria	

Agenda
Commission on Parasitic Diseases
Communicable Disease Center
30 October 1962
Dr. Harry Most—Presiding

0930–1000	Welcome Remarks	Dr. James Goddard, Chief, CDC President, AFEB, Executive Secretary, AFEB and Commission Director
1000–1100	Comments by Service Representatives covering: a. Disease problems in Vietnam and Thailand, etc. b. Current status of drugs for parasitic infections c. Status of revision of all TB-MEDS related to our Commission Division of Army Division of Navy Division of Air Force	
1100–1130	Coffee and informal reports by Commission Members and miscellaneous additional Commission business	Executive Secretary
1130–1200	Report on Malaria	Drs. G. Robert Coatney and Martin D. Young
Discussion		
1200–1230	Organization and Program of the CDC	Dr. Alan Donaldson, Deputy Chief, CDC
1230–1300	Lunch	

1300–1400	Conducted Tour of CDC Facilities (Meet in laboratory of auditorium, Building 2)	Mr. Wallace Richter, Information Office
1400–1430	Continuation of Report on Malaria	Drs. Coatney and Young
1430–1445	Coffee	
1445–1645	Parasitological Activities of CDC	
	a. Dr. Marion Brook, Chief, Laboratory Consultation & Development Section	
	b. Dr. Mae Melvin, Chief, Parasitology Training Unit	
	c. Dr. Harry Pratt, Chief, Vector Control Services Training Section	
	d. Dr. Irving Kagan, Chief, Parasitology Unit	

Agenda
Joint Meeting of Commissions on Environmental Hygiene
Enteric Infections
Parasitic Diseases
Walter Reed Army Institute of Research
Wednesday, 6 March 1963

0900–1000	Concluding Presentations	Dr. Geiman
	Commission on Enteric Infections	Dr. Reeves
1000–1015	Recess, Coffee	
	Commission on Parasitic Diseases, Dr. Most, Director	
1015	Opening Remarks	President, AFEB, Executive Secretary, Commission Director
Reports by Responsible Investigators		
1045	Visceral Larva Migrans in Relation to Tropical Eosinophilia	Dr. Beaver
1105	Isolation of Specific Antigens from Larval and Adult Stages of Schistosomes	Dr. Kent
1125	a) Studies on Schistosome Cercariae with Special Reference to Inhibition of Penetration by Various Agents	
	b) Immunity to *Schistosoma japonicum* in Man	Dr. Lewert
1200	Recess, Lunch	
1330	Serotonin and Histamine Production in Ascariasis	Dr. Rogozzino
1350	Studies of American *Pomatiopsis* Snails with Biological Relationships Almost Identical to *Oncomelania*, the Intermediate Host to Oriental Schistosomiasis	Dr. van der Schalie
1410	Host–parasite Relationship in Normal and Abnormal Hosts of Schistosomidae	Dr. von Lichtenberg
1430	Biological Studies in Malaria (*P. berghei*)	Dr. Harry Most
1450	Recess, Coffee	
1500	Executive Session	
	Commission on Parasitic Diseases	Dr. Most
	1. Personnel Recommendations	
	2. Contract Recommendations	
	3. General Recommendations	
	4. Future Meetings	

Agenda
Commission on Parasitic Diseases, AFEB
Center for Continuing Education
University of Chicago
5 November 1963

0930–1000	Remarks Executive Secretary, AFEB; Commission Director	President, AFEB;
1000–1100	Comments by Service Representatives Army Navy Air Force	
1100–1130	Coffee and miscellaneous additions relative to Commission business Research Program in Illinois Area	Executive Secretary Chairman—Dr. Lewert
1130–1200	Presentation "Detection of Soluble Antigen-Antibody Complexes in Helminth Infections"	Mr. Donald G. Dusanic
1200–1230	Film covering the endemic area of schistosomiasis on Leyte	Dr. Lewert
1230–1400	Lunch	
1400–1530	DISCUSSION RELATIVE TO MALARIA Dr. Alving's Program in Statesville Current Status of CI-501 General discussion	 Dr. Coatney
1530–1600	Consideration of grant applications and new business	
1600	Adjournment	

Tour of laboratories—optional

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
12–13 March 1964

12 March 1964

0900	Opening Remarks	President, AFEB—Dr. Dammin Executive Secretary—Captain Britten Commission Director—Dr. Most
0915	Reports by Service Representatives Army Navy Air Force	
1045	Coffee break and informal reports by Commission Members	

PRESENTATION OF PROGRESS REPORTS

1100	Dr. R. Audy
1130	Dr. P. Beaver
1200	Dr. N. Kent (by Dr. E. Bueding)
1230	Lunch

1400 Dr. R. Lewert
1430 Dr. H. Most
1500 Dr. van der Schalie
1530 Dr. von Lichtenberg
1600 Coffee Recess
1630 New Contracts:
Dr. J. Burckhalter
Dr. K. Warren
1730 Supper
1930 Executive Session
Personnel Recommendations
Contract Recommendations
General Recommendations
Future Meetings

13 March 1964
0930 Malaria
1100 Coffee Recess
1230 Lunch
1400 A possible meeting of Malaria Committee:
Recommendations

Agenda
Committee on Malaria
Parasitic Diseases Commission
Armed Forces Epidemiology Board
13 March 1964, WRAIR, Washington, D.C.

Dr. A. Alving
Dr. R. Coatney
Dr. R. Elderfield
Dr. C. Huff
Dr. L. Rozeboom
Dr. E. Sadun
Dr. L. Schmidt
Dr. L. Stauber
Dr. W. Trager
Dr. T. Weller
Dr. H. Most
Chairman

1. Current Malaria Research
A.
1. Biology
2. Physiology and Metabolism
3. Immunology
4. Chemotherapy
5. Entomology

Army
Dr. C. Huff
Dr. W. Trager
Dr. L. Stauber
Dr. R. Elderfield
Dr. L. Rozeboom
Lieutenant Colonel J. Geary
Colonel W. Tigertt

NIH
Dr. E. Sadun
Dr. A. Alving
Dr. J. Andrews
Dr. J. Jeffery

Navy
Dr. J. Millar

Air Force	General F. Duff
State Department	Dr. P. Lee
National Academy of Sciences	Dr. K. Cannon

Agenda
Commission on Parasitic Diseases
New York University Medical Center
3 November 1964

Opening remarks and welcome	Commission Director
Comments	President, Armed Forces Epidemiological Board, and report of travel abroad
Executive Secretary Report	
Coffee	
Reports of Preventive Medicine officers and discussion	
Report—Pest Control Board	
Luncheon	
Summary report of first meeting, Commission on Malaria	
Status of TB-MEDS	
New applications	
Personnel and membership	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
1 March 1965

0900–0920	Call to order and introductory remarks	Commission Director and President of AFEB
0920–0940	Report of Executive Secretary	
0940–1030	Reports from preventive medicine officers	Departments of the Army, Navy, Air Force, and R & D Command
1030–1100	Coffee Break	
1100–1200	Report on status of drugs for treatment of parasitic diseases	
	Report on status of TB-MEDS	
	Discussion of potential problems for research in the parasitic diseases area of military importance	
1200–1300	Lunch	
1300–1500	Presentation of progress reports of responsible investigators:	
	"Endoparasites of Oriental Primates" Contract No. DA-49-193-MD-2291	Dr. J. Ralph Audy
	"Visceral Larva Migrans in Relation to Tropical Eosinophilia" Contract No. DA-49-007-MD-633 and DA-49-193-MD-2677	Dr. Paul C. Beaver
	"Immunity to *Schistosoma japonicum* in man" Contract No. DA-49-193-MD-2320	Dr. Robert M. Lewert

	"Epidemiology of Filariasis in the Philippine Islands" Contract No. DA-49-193-MD-2370	Dr. Lloyd Rozeboom
1500–1515	Coffee Break	
1515–1630	Presentation of progress reports continued:	
	"Studies of American *Pomatiopsis* snails with Biological Relationships Almost Identical to *Oncomelania*, the Vector of Oriental Schistosomiasis" Contract No. DA-49-007-MD-604	Dr. Henry van der Schalie
	"Host–Parasite Relationship in Normal and Abnormal Hosts of Schistosomide" Contract No. DA-49-193-MD-2253	Dr. Franz von Lichtenberg
	"Pathophysiology of Schistosomiasis" Contract No. DA-49-193-MD-2639	Dr. Kenneth S. Warren
1700	Executive Session	

Consideration of renewal applications, personnel action, reappointments and appointments
Date of next meeting: November 6, 1965 in New Orleans

Agenda
Commission on Parasitic Diseases
Tulane University School of Medicine
6 November 1965

Opening remarks and welcome	Dr. Paul C. Beaver
Comments	President, AFEB; Director, Commission on Parasitic Diseases; and Executive Secretary

Reports by Preventive Medicine Officers, Armed Services; discussion by military and R&D representatives; report by Major Legters
Luncheon and after-luncheon scientific presentations: Research activities in parasitic and tropical diseases, Tulane University, Dr. Beaver presiding
Reports relative to drugs and TB-MEDS
Summary of attendance at foreign meetings and foreign travel
Business matters relative to contracts and funds
Adjournment

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* In compliance with directive of the President, AFEB, to permit review of current military situation and needs, priorities in the research program, etc.

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute for Research
14 March 1966

0900–0920	Call to order and introductory remarks	Commission Director and President of AFEB
0920–0940	Report of the Executive Secretary	
0940–1040	Reports from Preventive Medicine officers	Departments of the Army, Navy, and Air Force
1045	Coffee break	
1100–1130	*Reports*: Status of TB-MEDS: Status of drugs for treatment of parasitic diseases; discussion of potential problems for research in the parasitic disease area of military importance	
1300–1400	Lunch	
01400–1530	Presentation of progress reports of responsible investigators	
	"Filariasis in Relation to Tropical Eosinophilia" Contract No. DA-49-193-MD-2677	Dr. Paul C. Beaver
	"Immunity to *Schistosoma japonicum* in Man" Contract No. DA-49-193-MD-2320	Dr. Robert M. Lewert
	"Studies of American *Pomatiopsis* snails with Biological Relationships Almost Identical to *Oncomelania*, the Vector of Oriental Schistosomiasis" Contract No. DA-49-MD-604	Dr. Henry van der Schalie
1530	Coffee break	
1545–1645	Presentation of progress reports continued	
	"Protective Mechanisms in Schistosome Infections" Contract No. DA-49-193-MD-2253	Dr. Franz von Lichtenberg
	"Pathophysiology of Schistosomiasis" Contract No. DA-49-193-MD-2639	Dr. Kenneth S. Warren
1645–1700	Special report	Dr. Ernest Bueding
1700	Executive Session	
	Consideration of renewal applications	
	Personnel actions, reappointments, and appointments	
	Date of next meeting	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
18 November 1966

SCHISTOSOMIASIS CONFERENCE

I. Current Status of Schistosomiasis in Southeast Asia
   1. "Report on a Recent Visit to Thailand" — Dr. Donald McMullen, WRAIR, Washington, D.C.
   2. "Report on a Recent Visit to the Philippines, Thailand, Taiwan, and Japan" — Dr. Steve Pan, Harvard School of Public Health, Boston, Massachusetts
   3. "Report on Several Cases Apparently Contracted in Laos" — Dr. Harry Most, New York University School of Medicine

Discussion of Part I

II. Quantitative and Comparative Pathology of Human Schistosomiasis
   1. "Autopsy Studies in Bahia, Brazil" — Dr. Allen Cheever, National Institutes of Health, Bethesda, Maryland
   2. "*S. haematobium* Pathology in Ibadan, Nigeria—Impressions and Projected Studies" — Dr. Franz von Lichtenberg, Harvard School of Public Health

Discussion of Part II

III. Treatment of Schistosomiasis
   1. "Studies on Treatment of Schistosomiasis in Egypt and Puerto Rico" — Dr. William DeWitt, NIH
   2. "Preliminary Observations on the Biochemical Actions of CIBA 32, 644-Ba (Ambilhar)" — Dr. Ernest Bueding, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland
   3. Informal Reports on Ambilhar
      Dr. Thomas Weller
      Dr. Harry Most

Discussion of Part III

IV. Recent Immunological Developments Concerning Human Schistosomiasis
   1. "Anaphylactic (Reaginic) Antibodies in Schistosomiasis" — Dr. Elvio Sadun, WRAIR

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
13–14 March 1967

13 March 1967

Call to order and introductory remarks	Commission Director and President of AFEB
Report of Executive Secretary	
Reports from Preventive Medicine officers	Departments of the Army, Navy, and Air Force

Coffee Break
Presentation and discussion by R & D representatives
Reports
- Status of TB-MEDS
- Status of drugs for treatment of parasitic diseases
- Discussion of potential problems for research in the parasitic diseases area of military importance

Lunch
Presentation of progress reports of responsible investigators

"Filariasis in Relation to Tropical Eosinophilia" Contract No. DA-49-193-MD-2677	Dr. P. C. Beaver
"Immunity to *Schistosoma japonicum* in man" Contract No. DA-49-193-MD-2320	Dr. R. M. Lewert
"Studies of American *Pomatiopsis* Snails with Biological Relationships Almost Identical to *Oncomelania*, the Vector of Oriental Schistosomiasis" Contract No. DA-49-193-MD-2651	Dr. H. van der Schalie

Coffee Break
Presentation of progress reports continued

"Protective Mechanisms in Schistosome Infections" Contract No. DA-49-193-MD-2253	Dr. F. von Lichtenberg
"Pathophysiology of Schistosomiasis" Contract No. DA-49-193-MD-2639	Dr. K. S. Warren
"Parasitic Antigens"	Dr. P. E. Thompson

Executive Session
- Consideration of new and renewal applications
- Personnel actions, reappointments, and appointments
- Date of next meeting

14 March 1967

Conference on Hemoflagellates—Dr. Leslie Stauber, Presiding

General

Fine Structure and Differentiation	William Trager, Rockefeller University

Trypanosomes

Highlights of Current Status of Chagas' Disease	Frank Neva , Harvard Medical School
Chemotherapy	Frans Goble, Ciba Pharmaceutical
Immunology	Nathan Entner, New York University Medical Center

Leishmaniasis	
Clinical Aspects and Epidemiology in Africa	Kevin Cahill, St. Clare's Hospital
Chemotherapy of Cutaneous in the Americas	Bryce Walton, U.S. Army Research Unit, Panama
Reservoir Hosts—Identification and Evaluation	Leslie Stauber
Other participants and discussants	
Armed Forces Institute of Pathology	H. Hopps D. Price D. Winslow
Walter Reed Army Institute of Research	E. Sadun E. Fife
Naval Medical Research Institute	A. Pipkin
Laboratory of Parasitic Diseases, NIAID	T. von Brand
Gorgas Memorial Laboratory	Martin Young

Agenda
Commission on Parasitic Diseases
Benjamin Franklin Hotel, Philadelphia
31 October 1967

0900	Introductory Remarks	Dr. Thomas Gill for Dr. Gustave Dammin, President Dr. Paul C. Beaver, Director Captain Sidney Britten, Executive Secretary
0915	Reports, Preventive Medicine Officers:	
	Department of the Army	Lieutenant Colonel John Einarson
	Department of the Navy	
	Department of the Air Force	Major Amos Townsend
	Representative, USA Med R&D Command	Lieutenant Colonel Robert Cutting
	Report on Niridazole Conference	Dr. Ernest Bueding Dr. Elvio Sadun
0945	Recess—Coffee	
SPECIAL REPORTS—Organized mostly by Elvio Sadun		
1000	WRAIR: Parasitologic Investigations in Uganda	Lieutenant Colonel Norman E. Wilks
	WRAIR: Problems in the Laboratory Diagnosis of Malaria and Amebiasis in Vietnam	Major Duane G. Erickson
	SEATO: Scope of Present Effort and Plans for Immediate Future of the SEATO Parasitological Program	Dr. Robert S. Desowitz
	WRAIR: Overseas Components of WRAIR	Colonel Stefano Vivona
	WRAIR: Parasitology as Presented in the WRAIR Global Medicine Course	Lieutenant Colonel James C. Burke
	WRAIR: Filariasis and Schistosomiasis in Vietnam	Lieutenant Colonel L. J. Legters
	NAMRU-2: Capillariasis in the Philippines	Dr. John Cross

1130 Executive Session
1330 LEPTOSPIROSIS CONFERENCE

Introductory Remarks		Dr. Frank Neva, Program Chairman
I.	Clinical and Epidemiological Features of Leptospirosis in S.E. Asia	Dr. Fred McCrumb, University of Maryland School of Medicine
	Clinical Varieties of Leptospirosis in S.E. Asia WRAIR: Epidemiology of Leptospirosis with Particular Reference to S.E. Asia	Dr. A. D. Alexander
II.	Recent Experience with Leptospirosis in S.E. Asia	
	WRAIR: Known and Suspected Incidence of Leptospirosis in U.S. Military Personnel	Lieutenant Colonel L. J. Legters
	WRAIR: Management of Renal Failure	Captain Andrew Whelton
	Criteria for Diagnosis of Leptospirosis	Dr. A. D. Alexander
III.	Approaches to Leptospirosis Control for the Military Experience with Leptospiral Vaccines in Veterinary Medicine, and Considerations for their Use in Man	Dr. Lyle E. Hanson, University of Illinois, College of Veterinary Medicine
	Treatment of Leptospirosis and Possibilities of Chemoprophylaxis	Dr. Fred McCrumb
IV.	Summing-up and Open Discussion	
	1. Feasibility of Environmental Control of Leptospirosis	
	2. New Information Having Important Implications for Pathogenesis, Control, Treatment, and Diagnosis of Leptospirosis	
Other Participants and Discussants		Dr. Charles D. Cox, University of Massachusetts Dr. Victor M. Arean, University of Florida Dr. Russell C. Johnson, University of Minnesota

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
25 March 1968

0900	Introductory Remarks	Dr. Paul C. Beaver, Director Dr. Gustave Dammin, President Captain Sidney A. Britten, Executive Secretary
0915	Reports, Preventive Medicine Officers:	
	Department of the Army	Lieutenant Colonel John Einarson
	Department of the Navy	Captain Charles Miller
	Department of the Air Force	Major A. Townsend
	Representative, USA Med R&D Command	Lieutenant Colonel Robert Cutting
1030	Recess—Coffee	
1045	Research at Overseas Military Installations	Dr. Elvio Sadun
1245	Recess—Lunch	
1345	Executive Session	
	Status of TB-MEDS and Drugs for Parasitic Diseases	
	Discussion of Grants, Contracts, and Progress Reports	
	Personnel	
	Consideration of Short- and Long-Term Plans of Commission	
	Program of Fall Meeting	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
2–3 December 1968

Monday, 2 December

0930	Introductory Remarks	Dr. Paul C. Beaver, Director Dr. Gustave Dammin, President Colonel Bradley Prior, Executive Secretary
	SYMPOSIUM ON FILARIASIS	
0945	Film on Filariasis—Introduction and Comment	Colonel Lyman Frick Dr. Donald Price
1030	Recess—Coffee	
1045	Interpretation of Microfilaremia	Dr. Guillermo Pacheco
1115	Immunological Aspects and Hypersensitivity	Dr. D. J. Stechschulte
1145	Serodiagnosis	Dr. Elvio Sadun Dr. Ralph Duxbury
1215	Filariasis in Vietnam	Major Edward Colwell Lieutenant Duane R. Armstrong
1245	Recess—Lunch	
1400	Pulmonary Filariasis	Dr. Paul C. Beaver
1430	Pathogenesis of Onchocercal Dermatitis	Dr. Daniel Connor
1500	Recess—Coffee	
1515	Prophylaxis and Treatment	Dr. Harry Most

1545	General Discussion	
1630	Adjournment	

Tuesday, 3 December

0900	Introductory Remarks	Dr. Paul C. Beaver, Director Dr. Gustave Dammin, President
0910	Reports of Preventive Medicine Officers:	
	Department of the Army	Lieutenant Colonel John R. Gauld
	Department of the Navy	Commander Stephen J. Kendra
	Department of the Air Force	Major Amos Townsend
	Representative, USA Med R & D Command	Captain Robert Edelman
1030	Defense Research in Latin America	Colonel Hugh Keegan
1045	Recess—Coffee	

PROGRESS REPORTS OF RESPONSIBLE INVESTIGATORS

1100	Filariasis in Relation to Tropical Eosinophilia (Contract DA-49-193-MD-2677)	Dr. Paul Beaver
	Biological Relationships of *Pomatiopsis* and *Oncomelania* (Contract DA-49-007-MD-604)	Dr. Henry van der Schalie
	Protective Mechanisms in Schistosomiasis (Contract DA-49-193-MD-2253)	Dr. Franz von Lichtenberg
	Parasite Antigens (Contract DA-49-193-MD-2927)	Dr. William Stucki
1300	Recess—Lunch	
1400	Nature of Immunity to Leishmaniasis (Contract DADA-17-67-7142)	Dr. Donald Twohy
	Studies on *Schistosoma japonicum* in the Philippines (Contract DA-49-193-MF-2320)	Drs. Robert Lewert and M. Yogore
	Biological Properties of *Trypanosoma rhodesiense* and *Trypanosoma gambiense*	Dr. John Seed
1530	Recess—Coffee	
1545	Rabbit Anaphylactic Antibody	Dr. Nathan Zvaifler
	Geographic Pathology in Northeast Thailand	Dr. Sylvanus Nye
1645	Executive Session	
	Consideration of new and renewal applications	
	Programs and dates of future meetings	
	Short- and long-term plans of the Commission	
	Other business	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
24 March 1969

0900	Introductory Remarks	Dr. Paul C. Beaver, Director Dr. Gustave J. Dammin, President Colonel Bradley W. Prior, Executive Secretary
0920	Reports of Preventive Medicine Officers	
	Department of the Army	Lieutenant Colonel John R. Gauld
	Department of the Navy	Lieutenant J. M. Sachs
	Department of the Air Force	Lieutenant Colonel P. F. Nugent
	Report of Representative of USA Med R&D Command	Major Robert Edelman
1030	Recess—Coffee	
1045	Special Reports on LATIN AMERICAN PARASITIC DISEASE PROBLEMS	
	The Amazon Region (Lower Amazon)	Dr. Howard Hopps
	The Andean Region (Upper Amazon)	Dr. Alfred Buck
	Leishmaniasis	Lieutenant Colonel Bryce Walton
	Research Program at Gorgas Laboratory	Dr. Martin Young
1245	Recess—Lunch	
1345	Executive Session	
	Contracts	
	Commission Program	
	General Recommendations	
1700	Adjournment	

Agenda
Meeting of the Commission on Parasitic Diseases and the Commission on Immunization
Walter Reed Army Institute of Research
16–17 October 1969

Thursday, 16 October

0830	Introductory Remarks	Drs. Abram S. Benenson and Paul C. Beaver, Commission Directors Dr. Gustave Dammin, President Colonel Bradley W. Prior, Executive Secretary
0845	Reports, Preventive Medicine Officers	
	Department of the Army	Lieutenant Colonel Phillip Winter
	Department of the Navy	Commander Stephen J. Kendra
	Department of the Air Force	Lieutenant Colonel Otis W. Jones
	Report, Representative of USA Med R&D Command	Lieutenant Colonel Donald W. Sample
1000	Recess—Coffee	
1015	Progress Reports on Research Sponsored by Commission on Parasitic Diseases	
	Filariasis in Relation to Tropical Eosinophilia	Dr. Paul C. Beaver

	Intermediate Snail Hosts of Oriental and African Schistosomiasis	Dr. Henry van der Schalie
	Protective Mechanisms in Schistosome Infections	Dr. Franz von Lichtenberg
	Parasite Antigens	Dr. William P. Stucki
	Effects of Temperature on *Leishmania* Metabolism	Dr. John Janovy, Jr.
	The Nature of Immunity to Leishmaniasis	Dr. Donald W. Twohy
	Biological Properties of African Trypanosomes	Dr. Richard Seed
	Immunity to *Trypanosoma cruzi* Infection	Dr. William L. Hanson
1245	Recess—Lunch	
1400	Progress Reports on Research Sponsored by Commission on Immunization	
	Factors Influencing the Pattern of the Immune Response	Dr. Geoffrey Edsall
	Effect of Dosage Interval on Response to Re-immunization with Cholera Vaccine	Dr. Willard F. Verwey
	Studies on Immunization of Man Against Plague	Dr. Karl F. Meyer
	Isolation and Characterization of Lympho-granuloma Venereum Agents	Dr. Karl F. Meyer
1530	Recess—Coffee	
1545	Mechanisms of Hypersensitivity	Dr. Abraham G. Osler
	Antibody Formation and Immunity	Dr. Jonathan W. Uhr
	Antibody Structure and Function	Dr. Hernan N. Eisen
1700	Adjournment	

Friday, 17 October

SYMPOSIUM ON IMMUNITY AND PARASITIC DISEASES

0900	Structure and Functions of Immunoglobulins	H. N. Eisen
0920	Mechanisms of Allergy and Hypersensitivity	K. F. Austen
0940	Immune Mechanisms of Resistance	G. B. Mackaness
1000	General Discussion	
1030	Recess—Coffee	
1045	Immunoglobulins and Hypersensitivity in Toxo-plasmosis	J. S. Remington
1115	Mechanisms of Histamine Release in Rabbing Schisto-somiasis	J. F. Barbaro
1145	Cell Mediated Immune Response	E. J. L. Soulsby
1215	Recess—Lunch	
1330	Delayed Hypersensitivity and Lymphocyte Transfor-mation in *Trichinella spiralis*	C. W. Kim
1400	Delayed Hypersensitivity and Granuloma Formation in Schistosomiasis	K. S. Warren
1500	Immunization by the Use of Irradiated Parasites	E. H. Sadun
1535	Recess—Coffee	
1545	Commission on Parasitic Diseases, Executive Session	
1700	Adjournment	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
23 March 1970

0900	Introductory Remarks	Commission Director, President, and Executive Secretary of the Board
0915	Reports of Preventive Medicine Officers	
	Department of the Army	Lieutenant Colonel J. E. Ward
	Department of the Navy	Lieutenant J. M. Sachs
	Department of the Air Force	Colonel G. W. Powell
	Report from the Representative of USA Med R&D Command	Colonel G. Rapmund
1015	Recess—Coffee	
1030	Special Reports	
	In vitro leukocytic and passive cutaneous anaphylaxis reactions in trichinosis and schistosomiasis	Major E. J. Colwell
	Filariasis in South Vietnam	Captain T. J. Sullivan
	Leishmaniasis and trypanosomiasis in E. Africa	Lieutenant Colonel Dale Wykoff
	American leishmaniasis and trypanosomiasis	Dr. Louis Olivier
1245	Recess—Lunch	
1345	Executive Session	
1700	Adjournment	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
26–27 October 1970

Monday, 26 October

0900	Introductory Remarks	Commission Director, President, and Executive Secretary of the Board
0930	Reports, Preventive Medicine Officers	
	Department of the Army	Major J. W. Cutting
	Department of the Navy	Commander R. D. Comer
	Department of the Air Force	Colonel P. F. Nugent
	Report, Representative of USA Med R&D Command	Colonel R. F. Barquist
1030	Recess—Coffee	
1045	PROGRESS REPORTS OF RESPONSIBLE INVESTIGATORS	
	Immunity to Chagas' Disease (Contract No. DADA 17-69-C-9167)	Dr. William Hanson
	Effects of Temperature on *Leishmania* Metabolism (Contract No. DADA 17-69-C-9122)	Dr. John Janovy, Jr.
	Immunodiagnosis and Molecular Components of *Entamoeba histolytica* (Contract No. DADA 17-69-C-9122)	Dr. Iris Krupp
	Mode of Action of Halogens in Bacteria and Viruses and Protozoa in Water Systems (Contract No. DA-49-193-MD-2314)	Dr. Cornelius Kruse

1245	Lunch	
1415	Nature of Immunity to Leishmaniasis (Contract No. DADA 17-69-C-9135)	Dr. Donald Twohy
	Biological Relationships of *Pomatiopsis* and *Oncomelania* (Contract No. DA-49-007-MD-604)	Dr. Henry van der Schalie
	Protective Mechanisms in Schistosomiasis (Contract No. DA-49-193-MD-2253)	Dr. Franz von Lichtenberg
	Rabbit Anaphylactic Antibody in Schistosomiasis (Contract No. DA-49-193-MD-2911)	Dr. Nathan Zvaifler (Dr. Zvaifler was unable to attend)
1615	Recess—Coffee	
1630	Executive Session	

Tuesday, 27 October

0815	Introductory Remarks	Commission Director and President of the Board

SYMPOSIUM ON SCHISTOSOMIASIS

0830	Second International Congress of Parasitology	Dr. E. H. Sadun
0845	Research at WRAIR	Dr. E. H. Sadun
0915	Research at 406th Medical Laboratory	Dr. G. M. Davis
1000	General Discussion	
1030	Recess—Coffee	
1045	Research at NAMRI	Commander M. H. Stirewalt
1115	Research at NAMRU-3	Captain D. C. Kent
1145	General Discussion	
1215	Lunch	
1345	Research at NIH	Dr. A. W. Cheever
1415	Research at Peter Bent Brigham Hospital	Dr. F. von Lichtenberg
1445	Research at Harvard University	Dr. T. H. Weller
1515	General Discussion	
1545	Recess—Coffee	
1600	Research at Santa Lucia, W.I.	Dr. P. Jordan
1640	Research at Johns Hopkins University	Dr. E. Bueding
1700	General Discussion	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
22 March 1971

0900	Introductory Remarks	Commission Director, President, and Executive Secretary of the Board
0915	Reports of Preventive Medicine Officers	
	Department of the Army	Major John Cutting
	Department of the Navy	None
	Department of the Air Force	Colonel P. F. Nugent
	Representative, USA Med R&D Command	Colonel Donald W. Sample
1030	Recess—Coffee	
1045	Discussion of Commission Objectives	
1200	Recess—Lunch	
1330	Executive Session	
1700	Adjournment	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
27 October 1971

0900	Introductory Remarks	Commission Director, President, and Executive Secretary of the Board
0915	Reports of Preventive Medicine Officers	
	Department of the Army	Major C. T. Kaelber
	Department of the Navy	Lieutenant Commander J. W. Poundstone
	Department of the Air Force	Lieutenant Colonel O. W. Jones
	Representatives, USA Med R&D Command	Colonel D. E. Wykoff, Colonel R. F. Barquist, and Colonel D. W. Sample
1000	Recess—Coffee	
1015	Progress Reports of Responsible Investigators	
	Biological Relationships of *Pomatiopsis* and *Oncomelania* (DA-49-193-MD-2651)	Dr. Henry van der Schalie
	Anaphylactic Antibody in Schistosomiasis (DA-49-193-MD-2911)	Dr. Nathan Zvaifler
	Nature of Immunity to Leishmaniasis (DADA 17-69-C-9135)	Dr. Donald Twohy
	Temperature Effects on *Leishmania* Metabolism (DADA 17-69-C-9122)	Dr. John Janovy
1215	Lunch	
1330	Immunity to Chagas' Disease (DADA 17-69-C-9167)	Dr. William Hanson
	Transmission of *Entamoeba histolytica*	Dr. Richard Stringer for Dr. Cornelius Kruse

	Protective Mechanisms in Schistosomiasis (DA-49-193-MD-2253)	Dr. Franz von Lichtenberg
	Biochemical and Antigenic Changes in Trypanosomes	Dr. Gilbert Sanchez
	Immunization Against *Trypanosoma gambiense*	Dr. John R. Seed
1630	Recess—Coffee	
1645	Executive Session	
1745	Adjournment	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
20 March 1972

0900	Introductory Remarks	Commission Director, President and Executive Secretary of the Board
0915	Reports of Preventive Medicine Officers	
	Department of the Army	Lieutenant Colonel P. E. Winter
	Department of the Navy	Lieutenant Commander J. W. Poundstone
	Department of the Air Force	Lieutenant Colonel F. T. Corker
	Representative, USA Med R&D Command	Colonel D. W. Sample
1000	Recess—Coffee	
1015	Executive Session	
1230	Recess—Lunch	
1330	Executive Session	
1700	Adjournment	

Agenda
Commission on Parasitic Diseases
Walter Reed Army Institute of Research
26 October 1972

0900	Introductory Remarks	Commission Director, President, and Executive Secretary of the Board
0915	Reports of Preventive Medicine Officers	
	Department of the Army	Colonel Robert Cutting
	Department of the Navy	Captain C. E. Alexander
	Department of the Air Force	Lieutenant Colonel F. T. Corker
	Representative, USA Med R&D Command	Colonel D. W. Sample
1000	Recess—Coffee	
1015	Progress Reports of Responsible Investigators	
	Studies of the Intermediate Snail Hosts of Oriental African Schistosomiasis Infections (DA-49-193-MD-2651)	Dr. Henry van der Schalie
	Anaphylactic Antibody in Helminthic Infections (DADA-17-71-C-1002)	Dr. Nathan Zvaifler

	Nature of Immunity to Leishmaniasis (DADA 17-69-C-9135)	Dr. Donald Twohy
1215	Recess—Lunch	
1330	Temperature Effects on *Leishmania* Metabolism (DADA 17-69-C-9122)	Dr. John Janovy
	Immunity to Chagas' Disease (DADA 17-69-C-9167)	Dr. William Hanson
	Protective Mechanisms in Schistosomiasis (DADA 17-72-C-2056)	Drs. Franz von Lichtenberg and Jerome Smith
	Biochemical and Antigenic Changes in Trypanosomes (DADA 17-72-C-2020)	Dr. Gilbert Sanchez
	Immunization Against *Trypanosoma gambiense* (DADA 17-72-C-2058)	Dr. John R. Seed
1600	Recess—Coffee	
1615	Executive Session	
1800	Adjournment	

SECTION 6—APPENDIX 4

ANNOUNCEMENT OF GOVERNMENTWIDE CHANGE OF POLICY REGARDING ADVISORY GROUP

MEDDH-RP 11 DEC 1970

Paul C. Beaver, Ph.D.
Director
Commission on Parasitic Diseases
Department of Tropical Medicine & Public Health
Tulane University School of Medicine
1430 Tulane Avenue
New Orleans, Louisiana 70112

Dear Dr. Beaver:

I am writing to inform you, along with the directors or chairmen of other advisory groups to The Surgeon General, of a change in policy that has been made regarding the review of research proposals submitted to the US Army Medical Research and Development Command.

Many members of our civilian advisory groups making recommendations concerning the direction and funding of Army-sponsored medical research also conduct investigations supported by Army contracts. The dual role of these individuals has been necessary because the relatively small number of investigators engaged in studies in certain areas of military interest includes those persons best qualified to provide advice. It has been of concern that an appearance of conflict of interest has been created by this arrangement wherein advisory groups review and recommend research proposals which have been submitted by their own members.

Current government standards regarding conflict of interest demand not only that there be no bias or exercise of improper influence but that there be no appearance that such practices might arise. To satisfy these standards, the function of civilian scientists as contractors must be clearly separated from their function as scientific advisors.

To ensure this clear differentiation, research proposals, including renewal proposals, from members of advisory groups will no longer be submitted to the same advisory groups for review. For example, research proposals submitted by members of the Armed Forces Epidemiological Board or its Commissions will not be reviewed by that Board or its Commissions. Appropriate representatives of the U.S. Army Medical Research and Development Command will review such proposals. Research proposals from individuals who are not members of advisory groups to The Surgeon General will continue to be referred to the appropriate commission or committee. The technical portion of all research proposals pertinent to a committee's area of interest and advisory responsibility will be made available for information, even though the committee will not be asked to make recommendations regarding funding of those proposals submitted by its own members.

MEDDH-RP
Paul C. Beaver, Ph.D.

11 DEC 1970

The revision of procedure is made to comply with present governmentwide standards pertaining to advisory groups. This change is not intended to discourage anyone from continuing to be a member of an advisory group, a contractor or both. The Army Medical Department continues to have a great need for the services of outstanding civilian scientists as investigators and as advisors. We solicit your continued help and understanding.

Sincerely,

/s/ Richard R. Taylor

RICHARD R. TAYLOR, M.D.
Brigadier General, MC
Special Assistant for
Research and Development

SECTION 7

Commissions on Immunization and Rickettsial Diseases

History of the Commissions on Immunization and Rickettsial Diseases

Theodore E. Woodward, M.D.

INTRODUCTION

Limitations of space do not allow inclusion of other commission historical accounts in this edition, which chronicles the activities of the Armed Forces Epidemiological Board (AFEB). Rather close identification with the Commissions on Immunization and Rickettsial Diseases prompted me to prepare short accounts of their important contributions. These two Commissions made significant contributions to the AFEB and its research system that were most relevant for control of infectious diseases in the military services. No attempt has been made to discuss administrative and procedural details involving each of these commissions; rather, a few of their important activities, including the persons involved, are briefly considered.

COMMISSION ON IMMUNIZATION

My first exposure to AFEB activities was via its Commission on Immunization, which was first chaired by Drs. Joseph Smadel and then by Geoffrey Edsall and Bud Benenson. Because of past experience with Rickettsial infections, human vaccine efficacy trials, and work on scrub typhus and typhoid vaccines, I was asked to serve as a consulting member. The first meeting I attended was in Philadelphia at the Jefferson Medical College, when Dr. Ken Goodner served as host for a two-day meeting. At the time, I could not understand why two full days were needed. As it turned out, there were many scientific and strategic details that needed to be thoroughly evaluated, discussed, and agreed on before further studies on any specific problem could be approved.

During the meeting, the results of many ongoing projects were heard, evaluated, and ultimately put into action. There was close collaboration and complete understanding and trust between military and civilian scientific investigators; this was absolutely essential if an extensive program of this type could be successful. This collaboration and understanding was, and continues to be, a basic tenet or modus operandi of the AFEB, its commission members, and its military representatives.

So many scientific pioneers contributed to the commissions of the AFEB. Indeed, a 2-day meeting of any commission group represented the latest and best scientific review of a specific topic that could be heard anywhere.

Plague was an important topic at the time, and who among us could ever forget Dr. K. P. Meyer's discussion of this ancient disease? Not only was plague then an infection of worldwide importance, but the plague bacillus ranked highly as an effective weapon for biologic warfare. This was a very hot topic in the early 1950s. Our Russian adversaries were highly sophisticated and very active in this general field.

In a discussion of the various means of transmission of the plague germ between humans, Dr. Meyer spoke of the "traffic of saliva at a Mexican funeral." He was describing a practice in Mexico and certain other ethnic settings in endemic areas of plague, including the Greek culture, where it was common practice to kiss the dead. There could be no better way to transmit plague than by this route.



ABRAM S. BENENSON, M.D.

After he graduated from Cornell University Medical College in 1937, Bud Benenson trained at Bellevue Hospital, New York, and entered the U.S. Army Medical Corps in 1940. From then until 1962, he progressed through the ranks to colonel and served at Tripler General Hospital; the Medical Field Service School at Carlisle, Pennsylvania; the Fourteenth Field Hospital, Korea; the Army Medical Service Graduate School; the Second Army Area Medical Laboratory at Fort George G. Meade; the Tropical Research Medical Laboratory at San Juan, Puerto Rico; USAMRIID at Fort Detrick, Maryland; and the Walter Reed Army Institute of Research. His medical service embraced the fields of microbiology, virology, immunology, epidemiology, and tropical medicine. He made important contributions to cholera research in Dacca, Pakistan. The Jefferson Medical College of Thomas Jefferson University, the University of Kentucky College of Medicine, and the Gorgas Memorial Laboratory and the School of Public Health in San Diego have all had the advantage of his academic contributions.

Bud Benenson has served the AFEB and many of its commissions, and he directed the AFEB's Commission on Immunization for a number of years. He is an infectious-disease authority whose fundamental background is excellent, whose memory of historical findings is uncanny, and whose ability to correlate the old with the new is impressive. Bud now heads the AFEB's Subcommittee on Infections, a public service that merely highlights his long list of contributions to the AFEB.



CHARLES L. WISSEMAN, JR., M.D.

At the University of Texas Southwestern Medical School at Dallas, Charlie Wisseman was a top student, and throughout his life he was a scholarly and productive scientist. He was Chairman of the Department of Microbiology at the University of Maryland for 38 years.

Following World War II, he worked with Joe Smadel at Walter Reed Army Institute of Research. He pursued the mysteries of typhus, encephalitis, leptospirosis, and other diseases of military importance both at the bench and in the fields of Malaya, Borneo, Pakistan, and Africa. He was Director of the Commission on Rickettsial Diseases from 1959 to 1973, when the commission system of the AFEB ceased. Since then, he has been a consultant to many governmental and international agencies, including the World Health Organization.



GEOFFREY EDSALL, M.D.

Geoff Edsall graduated from Harvard Medical School in 1934 and served his house officership at the Massachusetts General Hospital from 1934 to 1936. Research fellowships at Harvard and instructorships in bacteriology and immunology at the Harvard Schools of Medicine and Public Health followed. From 1940 until 1942, he was Assistant Director of the Division of the Biologic Laboratories of the Massachusetts Department of Public Health, and was its Director until 1949. For several years, he was Professor and Chairman of the Department of Microbiology at Boston University School of Medicine, which was followed by his appointment as Director of the Division of Immunology at Walter Reed Army Institute of Research in 1951.

Geoff served the AFEB in many ways, particularly as the Director of its Commission on Immunization from 1952 to 1963. This Commission was graced by the membership of some of the leaders in American medicine in the fields of biology and immunology, and it accomplished, under Geoff's direction and in collaboration with other commissions, a vast amount of work. The three-day meetings that this Commission held at WRAIR were actually reviews of the contemporary work in immunology and vaccine development. Geoff also served as a member of the Commission on Epidemiological Survey, where his advice was put to good use. His research interests were broadly distributed throughout immunology, and his special contributions were in the purification of toxoids, particularly those of tetanus and diphtheria.



JOSEPH E. SMADEL, M.D.

For 32 years, Joe Smadel was a physician and investigator whose contributions to medical science either saved or prolonged the lives of thousands of people. At the time of his death in 1963, Joe was recognized as one of the outstanding scientists of the mid-20th century. Expecting no reward, he performed research because he liked it, and his labors provided the essential bridge between the laboratory and the physician who cares for infected patients. One of his most satisfying experiences was the therapeutic triumph with chloramphenicol in the treatment of typhus and typhoid fevers, and the successful field trials that showed that this antibiotic effectively suppressed scrub typhus infection.

A major contributor to the AFEB, he organized and directed three of its Commissions: those on Immunization, Rickettsial Diseases, and Epidemic Hemorrhagic Fever; each of these Commissions bears the indelible Smadel mark. He was also a member of the Commissions on Epidemiological Survey, Virus Diseases, and Influenza, and his stabilizing influence during the developmental phases of the poliomyelitis vaccine trials contributed significantly to that success.

Joe had little patience for armchair philosophy, and he crusaded against shallow thinking. He demanded unswerving performance from his associates, who were expected to exercise good judgment and to adhere to his work, and his enthusiasm sparked the enthusiasm of his associates. He worked intently and set an example for others.

Just a year or two later I learned of another method of the spread of plague in Madagascar. It was a local custom there to remove a body from a family burial site each year, redrape the corpse, hold a family celebration, and return the body to the ground. This was another efficient way to transmit the germ of plague, which is hardy and resists drying. This practice led to governmental intervention that stipulated that patients dying of La Peste (plague) must be buried in a government burial site without chance for reburial.

During the meetings of the Commission on Immunization, Dr. Albert Sabin always had his say and argued effectively with anyone. Drs. John Paul and John Enders, the top gentlemen of the group, always made their points carefully, authoritatively, and painstakingly. Drs. Thomas Francis, Colin MacLeod, Gustave J. Dammin, John Dingle, and Charles Rammelkamp never failed to make important points, clarify the issues, and effectively summarize the known data of a problem. Dr. Smadel was not known for mincing words. Capable persons, such as these and many others, served the AFEB for many years and really represented a national resource of public health knowledge.

Out of the many commission meetings, came a much better understanding of immunological principles and the methods for developing new vaccines for such diseases as influenza, poliomyelitis, measles, mumps, adenovirus infections, rickettsial diseases, typhoid fever, tularemia, plague, and others. To evaluate efficacy, all such work was group supervised and carried through from its planning to implementation of field studies, and finally to testing in humans. The work of this Commission, which was performed in close collaboration with other commissions and the AFEB itself, represented some of the best work available on immunization for infectious diseases.

During these active and productive years of the Board and its commissions, Betty Gilbert was remarkably efficient in ensuring that the administrative affairs of the program ran well.



CAPTAIN WILLIAM M. PARSONS, USN, MSC

Executive Secretary of the Board 1990 to 1992



COLONEL MICHAEL P. PETERSON, USAF, BSC, DVM

Executive Secretary of the Board 1992 to present



BETTY L. GILBERT

Administrative Assistant



JEAN WARD

Administrative Assistant



COMMISSION ON IMMUNIZATION
Fall Meeting 18–20 October 1972
Walter Reed Army Institute of Research, Washington, DC

Standing, left to right: Drs. C. Harry Kempe; Robert O. Oseasohn; Bernard B. Levine; Willard F. Verwey; Thomas J. Gill III; Richard B. Hornick; Arthur M. Silverstein; Bruce Dull; and John C. Wagner.

Seated, left to right: Drs. Jonathon W. Uhr, Deputy Director; Abram S. Benenson, Commission Director; Margaret Pittman, and Elmer L. Becker.

COMMISSION ON RICKETTSIAL DISEASES

In 1954, the AFEB determined that Rickettsial diseases were of sufficient importance for a separate commission and, accordingly, transferred the older Rickettsial disease component of the viral and Rickettsial Disease Commission to a newly established commission on Rickettsial diseases with Dr. Joseph E. Smadel as director. Membership of the newly created commission drew heavily from the ranks of the World War II United States of America Typhus Fever Commission for initial membership. Dr. Charles L. Wisseman, Jr., became director beginning at the annual meeting of the Commission held at Walter Reed Army Institute of Research on 4 and 5 March, 1960.

This Commission of the AFEB has a proud heritage, and it was comprised of the leading rickettsiologists in the country. It was privileged to have the consultative advice of world leaders in this field such as Drs. Raymond Lewthwaite (United Kingdom), Marcel Baltazard (France), James Gear (South Africa), and Ralph Audi (United Kingdom). Drs. Smadel and Charles Wisseman were its directors for many years, with heavy and steady input from Jack Snyder, Bob Traub, John Fox, Charley Shepard, Buz Wheeler, Andy Yeomans, Ed Murray, Paul Fiset, Neil Philip, Willy Burgdorfer, Dick Ormsbee, Henry Fuller, and Lew Barker. I was privileged to serve as a full member of this Commission.

Epidemic typhus fever was not really a threat to our military forces during World War II because of better health standards, an effective vaccine, and the use of dichlorodiphenyltrichloroethane (DDT), which prevented louse infestation. Indeed, there were no deaths during the war from louse-borne typhus except those few suffered by our British allies. In North Africa alone, there were 33 cases in British Military Forces and 3 deaths that could have been avoided. During the war, louse typhus was quite prevalent in civilians in North Africa and in Southern Italy, particularly in Naples. When the British adopted use of the American typhus fever vaccine, this problem ceased.

Q fever was another concern in the Mediterranean area, particularly in Italy. Our forces experienced many cases of this illness, which was then known as the "Balkan grippe." The illness was manifested by headache, fever, muscle pains, and an atypical pneumonia-like syndrome. Fortunately, there were no deaths. Nevertheless, it was temporarily harassing and disabling for those infected. Dr. Fred Robbins worked with patients in Italy, and Dr. Chris Zarafonetis was responsible for obtaining a Q fever strain (carried in a blood specimen), which he obtained from Greek authorities at the Pasteur Institute in Athens.

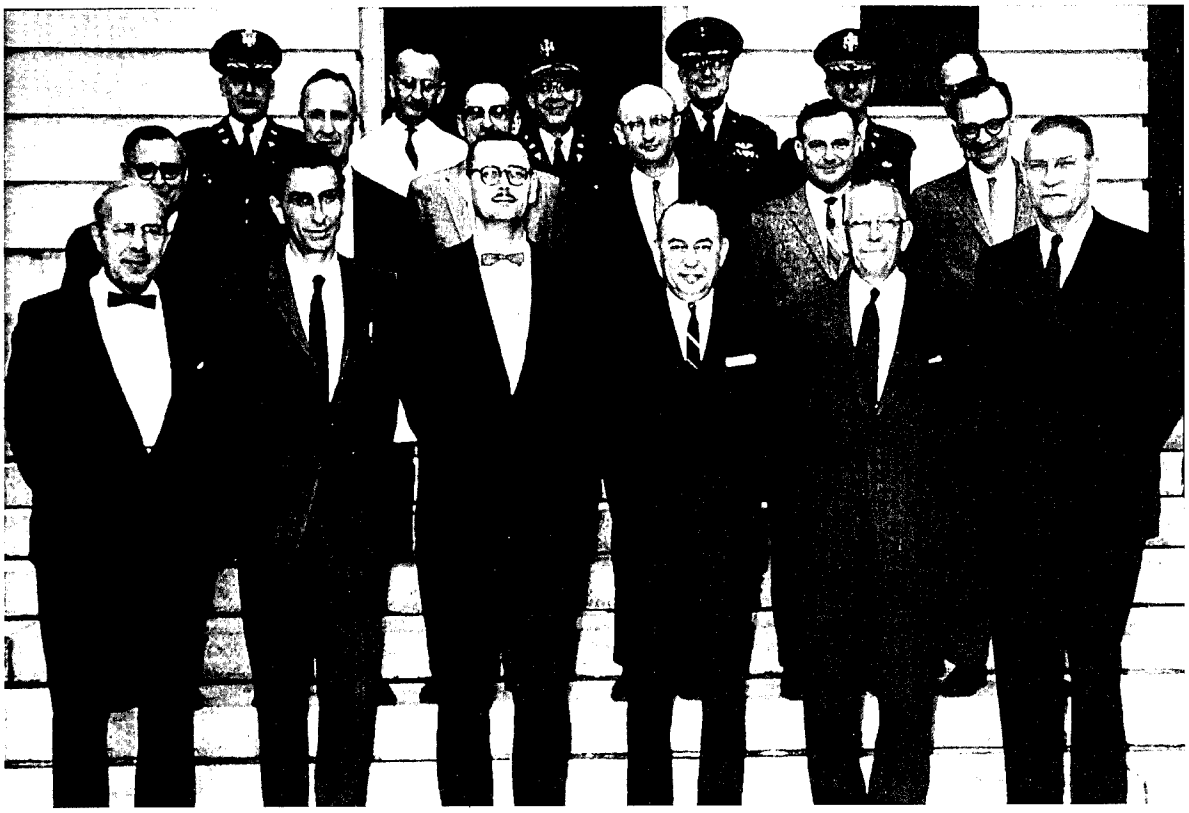
Rocky Mountain spotted fever was never an epidemic threat nor was murine typhus, which involved a rat–flea–human cycle. However, scrub typhus, which is transmitted by mites, was another matter. During World War II, it was responsible for disabling and killing a number of American military personnel in the southwest Pacific area.

The Commission on Rickettsial Diseases helped solve many of these riddles. Actually, the typhus project mission in Malaya in 1948 was conducted under the umbrella of the Commission on Immunization of the AFEB. The important contributions that resulted from this work included

- the first known specific treatments of scrub typhus, murine typhus, and Rocky Mountain spotted fever,
- the first known specific treatment of typhoid fever, and
- the first known demonstration that an antibiotic given prophylactically and intermittently to persons exposed to scrub typhus fever in the field could prevent them from developing the illness.

The third item was a contribution of significant military importance. The total expenditure for the project was less than $50,000. Thus, potent weapons were now available that practically guaranteed protection against death from any rickettsial infection, particularly scrub typhus. Also, patients promptly responded to specific antibiotic treatment with full recovery. Better understanding of the pathologic and physiologic changes in patients even led to recovery in advanced cases.

Effective vaccines for the rickettsial diseases, particularly epidemic typhus, Rocky Mountain spotted fever, and Q fever, were developed under the auspices of the Commission.



COMMISSION ON RICKETTSIAL DISEASES
Walter Reed Army Institute of Research, Washington, DC
March 1963

First row, left to right: John P. Fox; Charles C. Shepard; Charles L. Wisseman, Jr.; Edwin H. Lennette; Joseph E. Smadel; and Gustave J. Dammin.

Second row, left to right: Unidentified; Edward S. Murray; Richard A. Ormsbee; Emilio Weiss; Unidentified; and Herbert L. Ley.

Third row, left to right: Unidentified; Henry S. Fuller; Colonel Adam Rapalski; Unidentified; Unidentified; and Colonel Stefano Vivona.



COMMISSION ON RICKETTSIAL DISEASES
Fall Meeting 30 November–1 December 1972
Walter Reed Army Institute of Research, Washington, DC

Seated, left to right: Drs. John P. Fox; Bennett L. Elisberg, Deputy Director; Charles L. Wisseman, Commission Director; Edwin H. Lennette; and Richard A. Ormsbee.

Standing, left to right: Mrs. Hope E. Hopps; Miss F. Marilyn Bozeman; Lewellys F. Barker; Robert Traub; Emilio Weiss; Richard A. Mason; Edward S. Murray; Sanford L. Berman; Joseph P. Lowenthal; Paul Fiset; Willy Burgdorfer; and Irene B. Fabrikant.

Strain E type epidemic typhus, an attenuated strain of *Rickettsia prowazekii* first identified and studied by Dr. Snyder, was developed further by Drs. Fox and Wisseman. This vaccine caused some reactions in humans, which limited its use.

A scrub typhus vaccine was never successfully developed because of difficulties in identifying specific antigens and problems related to producing pure vaccine material. Yet the Commission helped sponsor studies that were conducted by investigators at Walter Reed Army Institute of Research (WRAIR) and the University of Maryland. These studies showed that either chloramphenicol or tetracycline, given in single doses at an interval of once weekly for 5 weeks, prevented illness from developing in an infected person. This work involved classic human field trials conducted during several years in Malaya.

Under the Commission, the Maryland group tested older type vaccines for Rocky Mountain spotted fever, including the original tick tissue strain first used by Ricketts in Montana. It was shown not to be significantly protective when tested in volunteers in Baltimore, Maryland. Even the newer, whole rickettsial cell vaccines lacked full protective properties. Dr. Richard Hornick and his team conducted these studies under Commission sponsorship and encouragement.

The Commission's work on Q fever ranks very highly. A new and inactivated protective vaccine was developed at WRAIR and Ft. Detrick. Much good work that involved extensive studies in primates and in humans was initiated on attenuated vaccines. The work on humans first involved exposure of volunteers at Ft. Detrick in a large sphere called the "8-ball" that could measure the exact number of *Rickettsiae* delivered to a single person. Such resultant infections could be quickly stopped with prompt antibiotic treatment. Later trials in the field, first with sheep and then with volunteers, were conducted in the salt flats in Utah just outside Salt Lake City. These studies conducted in the 1950s showed that a cloud laden with living *Coxsiella burnetti* (Q fever) could infect sheep and humans a number of miles downwind. Drs. William Tigertt and Bud Benenson spearheaded these studies along with Commission members Drs. Richard Shope, Smadel, MacLeod, Wisseman, and Woodward.

In addition, important and better understanding of Q fever resulted from the work of Dr. Paul Fiset, who showed that Q fever *Rickettsiae* could wear several faces, called Phase I and Phase II, a change that was important for vaccine development and accurate diagnosis.

These studies and those of others have pushed rickettsial diseases "backstage," but their potential threat remains. Even now, scrub typhus fever is a considerable problem in North Thailand, where it is endemic and accounts for about 25% of the cases of Fever of Unknown Origin (FUO).

In April 1970, on request, the Commission developed a revised mission statement.

> To provide, through the AFEB, to the military department scientific and research assistance and to advise on all pertinent aspects of prevention, control, diagnosis and treatment of diseases caused by Rickettsia agents, Chlamydia and such other non-viral bacteria-like intracellular parasites which require similar methods of study, for example Ehrlichia.

Some of the first and significant contributions to better public health made by members of the Commissions on Immunization and Rickettsial Diseases (based on publication in leading medical journals)

- Reported a series of studies that showed that very small doses of diphtheria toxoid were effective in recalling established immunity and that adverse reactions were minimized by use of a purified toxoid.
- Developed tetanus and diphtheria toxoids and introduced their use in the military. These became the standard in the United States until an alum-adjuvanted tetanus and diphtheria toxoid later permitted significant extension of the booster intervals.
- Sponsored and assisted in the development of jet injectors with intradermal capability, a technique for vaccine administration that was instrumental in helping control smallpox and other microbial diseases.
- Demonstrated the first known specific cures of scrub typhus, murine typhus, and Rocky Mountain spotted fever with chloramphenicol in 1948.



Major General Edward J. Huycke, MC, (left) presents the
Commander's Civilian Service Award to Abram S. Benenson, M.D.
1 September 1983



Dr. Theodore Woodward presents the Smadel Award to
Abram S. Benenson, M.D.
1 February 1981

- Reported the chemoprophylactic field studies that showed that the intermittent administration of chloramphenicol (later tetracycline) prevented scrub typhus in volunteers.
- Reported the first known effective cure of typhoid fever with chloramphenicol in 1948.
- Reported the infectious dose of *Salmonella typhosa* in a series of studies using volunteer subjects and demonstrated that inactivated typhoid vaccine (acetone-killed) resulted in short-term but limited immunity. (Because paratyphoid A- and B-type vaccines were of limited efficacy, newer vaccines used a monovalent, acetone-killed, dried product.)
- Developed the first specific chemoprophylaxis for leptospirosis.
- Reported that field surveillance studies magnified the importance of leptospirosis as a common cause of FUO in various geographic areas and that available antibiotics were ineffective as therapeutic agents.
- Reported the first therapeutic efficacy of chloramphenicol and tetracycline in bubonic, septicemic, and pulmonic plague using the oral route, which simplified the therapeutic regimen in the event of a sizable outbreak because streptomycin, a very effective antibiotic, must be injected.
- Demonstrated the importance of cellular immunity (as differentiated from humoral immunity) and the transferability of this cellular immunity by the subcellular "transfer factor." (These studies sparked the whole field of immunology.)
- Developed the entirely new immunological technique of fluorescent labeling of antibodies, which enhanced the confirmed diagnoses of many microbial diseases and clarified their pathogenesis.
- Sponsored the original studies of properdin, which was the basis for the greatly extended interest in complement pathways.
- Greatly clarified the differing strains of dengue virus and elucidated the concept of dengue-shock syndrome, an important cause of death among children in Asian countries.
- Developed new immunizing agents or vaccines for infectious diseases, including the following:
  (a) vector-borne virus diseases such as dengue, yellow fever, St. Louis encephalitis, Western equine encephalitis, Eastern equine encephalitis, Venezuelan equine encephalitis, Japanese encephalitis, and others;
  (b) the hemorrhagic fevers;
  (c) the rickettsial diseases, such as epidemic typhus, Rocky Mountain spotted fever, Q fever;
  (d) malaria;
  (e) measles;
  (f) mumps;
  (g) diphtheria and tetanus toxoids;
  (h) enteric infections such as bacillary dysentery, Shigella, *Salmonella typhosa, Vibrio cholerae, Endamoeba histolytica;*
  (i) plague and *Francisella tularensis;*
  (j) enteroviral diseases including poliomyelitis and others;
  (k) meningococcal gonococcal diseases; and
  (l) adenovirus infections.