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**MEDICAL DEPARTMENT
UNITED STATES ARMY
IN VIETNAM**

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MEDICAL DEPARTMENT, UNITED STATES ARMY

INTERNAL MEDICINE IN VIETNAM

Volume II

GENERAL MEDICINE AND INFECTIOUS
DISEASES

Editors for Internal Medicine

Brigadier General ANDRE J. OGNIBENE, MC, USA, and

Colonel O'NEILL BARRETT, Jr., MC, USA (Ret.)

OFFICE OF THE SURGEON GENERAL

AND

CENTER OF MILITARY HISTORY

UNITED STATES ARMY

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It should be the duty of every soldier to reflect on the experiences of the past, in the endeavor to discover improvements, in his particular sphere of action, which are practicable in the immediate future.

—B. H. Liddell Hart (*Thoughts on War*, 1944)

Authors

O'NEILL BARRETT, Jr., M.D.

Colonel, MC, USA (Ret.). Professor of Medicine and Assistant Dean for Academic Affairs, University of South Carolina School of Medicine, Columbia. Chief, Medical Service, and Chief, Professional Services, 8th Field Hospital, Nha Trang, Vietnam, 1962-63; Chief, Department of Medicine, Tripler General Hospital, and USARPAC Medical Consultant, 1968-71; Chief, Department of Medicine, Walter Reed Army Medical Center, 1971-73.

RAYMOND W. BLOHM, Jr., M.D. (Deceased)

Colonel, MC, USA. Formerly Chief, Professional Services, Fitzsimons General Hospital. USARV Medical Consultant, Vietnam, 1966-67; Assistant Chief, Department of Medicine, Walter Reed General Hospital, 1967-69; Chief, Department of Medicine, Walter Reed General Hospital, 1969-71; Clinical Associate Professor of Medicine, Georgetown and Howard Universities, 1969-77.

FRANCIS C. CADIGAN, Jr., M.D.

Colonel, MC, USA. U.S. Army Medical Liaison Officer to British Military Medical Services, London; Lecturer in Military Medicine, Uniformed Services University of the Health Sciences. Deputy Director, SEATO Medical Research Laboratory, Bangkok, Thailand, 1964-67; Director, U.S. Army Medical Research Unit, Kuala Lumpur, Malaysia, 1969-72; Director of Medical Research, U.S. Army Medical Research and Development Command, Washington, D.C., 1972-76; Director, Biomedical Laboratory, Edgewood, Md., 1976-79.

DONALD CATINO, M.D.

Adjunct Assistant Professor of Clinical Medicine and Community Medicine, Dartmouth Medical School, Hanover, N.H.; Chief of Internal Medicine, New London Hospital, New London, N.H. Formerly Captain, MC, USAR. Member, U.S. Army Medical Research Team, WRAIR, Vietnam, 1967-68.

DAN C. CAVANAUGH, Ph.D.

Colonel, MSC, USA (Ret.). Member, Expert Panel, Bacterial Diseases (Plague), World Health Organization. Chief, Plague Section, Medical Research Team, WRAIR, Vietnam, 1964-65; Chief, Department of Hazardous Microorganisms, Walter Reed Army Institute of Research, 1973-81.

EDWARD J. COLWELL, M.D.

Attending physician, Internal Medicine, Peninsula General Hospital, Salisbury, Md. Formerly Lieutenant Colonel, MC, USA. Member, U.S. Army Medical Research Team, WRAIR, Vietnam, 1967-68; Deputy Director, SEATO Medical Research Laboratory, Bangkok, Thailand, 1970-72; Member, Departments of Immunochemistry and Virology, Walter Reed Army Institute of Research, 1969 and 1973.

NICHOLAS F. CONTE, M.D.

Colonel, MC, USA (Ret.). Consultant in Internal Medicine to the Surgeon, USARV, 1967-68; Army Liaison Representative, Endocrinology Study Group, National Institutes of Health, 1969-72; Chief Medical Consultant to The Surgeon General, 1972-75; Governor (Army), American College of Physicians, 1972-75.

JOE A. DEAN, M.D.

Gastroenterologist, Medical and Surgical Clinic, Wichita Falls, Tex. Formerly Lieutenant Colonel, MC, USAR. Formerly Chief, Gastroenterology Service, Brooke Army Medical Center; Chief, Army Medical Re-evaluation Program for Prisoners of War, Vietnam.

JOHN J. DELLER, Jr., M.D.

Colonel, MC, USA (Ret.). Director of Education and Research, Eisenhower Medical Center, Rancho Mirage, Calif. Chief, Department of Medicine, Letterman Army Medical Center, Presidio of San Francisco, 1969-76.

JAMES V. DONADIO, Jr., M.D.

Professor of Medicine, Mayo Medical School, and Chairman, Division of Nephrology, Department of Internal Medicine, Mayo Clinic, Rochester, Minn. Formerly Captain, MC, USAR. Co-director, 629th Medical Detachment (Renal), Saigon, Vietnam, 1966-67; Member, Department of Medicine, Walter Reed General Hospital, 1967-68.

DAVID T. ENGLISH, M.D.

Associate Clinical Professor of Medicine, Department of Dermatology, University of Washington School of Medicine, Seattle. Formerly Major, MC, USAR.

RONALD P. FISHER, M.D.

Chairman, Departments of Surgery and Emergency Medicine and Trauma, Kino Community Hospital, Tucson, Ariz.; Adjunct Professor, University of Arizona Health Sciences Center, Tucson. Formerly Lieutenant Colonel, MC, AUS. Surgeon, 3d Field Hospital, and Surgeon, U.S. Army Dialysis Center, Vietnam, 1969; Chief, Department of Human Studies, Division of Surgery, Walter Reed Army Institute of Research, 1969-71.

LAYNE O. GENTRY, M.D.

Associate Professor of Internal Medicine, Microbiology, and Immunology, Baylor College of Medicine, Houston, Tex. Formerly Lieutenant Colonel, MC, USAR. Assistant Chief, Infectious Disease Service, Brooke Army Medical Center, 1971-74.

CARL R. GUITON, M.D.

Assistant Professor of Medicine, University of Minnesota Medical School, Minneapolis. Formerly Lieutenant Colonel, MC, AUS. Assistant Chief, Pulmonary Disease Service, Fitzsimons Army Medical Center, 1970-72; Chief, Professional Services, USAH, Saigon, Vietnam, 1972-73.

JAMES E. HANCHETT, M.D.

Assistant Professor of Clinical Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Director, ESRD Unit, Veterans Administration Medical Center, Pittsburgh. Formerly Captain, MC, USAFR. Member, Medical and Hemodialysis Service, U.S. Air Force Hospital, Tachikawa, Japan, 1965-68.

KENNETH W. HEDLUND, M.D.

Colonel, MC, USA. Chief, Division of Bacteriology, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Md.

JAMES H. KNEPSHIELD, M.D.

Associate Clinical Professor of Medicine, Georgetown University School of Medicine; Co-director, Hemodialysis, Hemoperfusion, and Transplantation Service, Georgetown University Hospital; Co-director, Metropolitan Washington Renal Dialysis Centers, Washington, D.C. Formerly Lieutenant Colonel, MC, USA. Chief, Medical Service, 3d Field Hospital, and Com-

mander, 629th Medical Detachment (Renal), Saigon, Vietnam, 1968-69; Chief, Renal Dialysis Service, Walter Reed General Hospital, 1969-72; Chief, Nephrology Service, Walter Reed General Hospital, 1971-72; Consultant in Renal Disease to The Surgeon General, 1971-72.

LLEWELLYN J. LEGTERS, M.D., M.P.H.

Colonel, MC, USA (Ret.). Professor and Chairman, Department of Preventive Medicine and Biometrics, School of Medicine, Uniformed Services University of the Health Sciences. Chief, U.S. Army Special Forces-WRAIR Field Epidemiologic Survey Team (Airborne), 1966-68; Preventive Medicine Officer and Deputy Post Surgeon, U.S. Army Training Center, Fort Ord, 1968-70; Chief, Training Evaluation Group, Directorate of Plans and Training, Fort Ord, 1971-72; Chief, Ambulatory Health Services, Silas B. Hays Army Hospital, Fort Ord, 1972-74.

DANIEL L. MACKEN, M.D.

Assistant Clinical Professor of Medicine, Colombia University College of Physicians and Surgeons, New York, N.Y. Formerly Lieutenant Colonel, MC, USAR.

JOHN D. MARSHALL, Jr.

Colonel, MSC, USA. Commander/Director, Letterman Army Institute of Research, Presidio of San Francisco, Calif.

WILLIAM E. MILLER, M.D.

Chief, Nephrology Section, Wilmington Medical Center, Wilmington, Del. Formerly Clinical Professor of Medicine, Thomas Jefferson University, Philadelphia, Pa.; Consultant in Nephrology, St. Francis Hospital, Wilmington; Kent General Hospital, Dover, Del.

WILLIAM L. MOORE, Jr., M.D.

Colonel, MC, USA. Chief, Department of Medicine, Eisenhower Army Medical Center, Fort Gordon, Ga.; Clinical Professor of Medicine, Medical College of Georgia. Commander, 156th Medical Detachment, Southeast Asia Action Force, 1965; Assistant Chief, Department of Medicine, Brooke Army Medical Center, 1970-74.

ANDRE J. OGNIBENE, M.D.

Brigadier General, MC, USA. Commander, Brooke Army Medical Center, Fort Sam Houston, Tex.; Clinical Professor of Medicine, The University of Texas Health Science Center, San Antonio, Tex. USARV Medical Consultant, Vietnam, 1969; Assistant Chief, Department of Medicine, Walter Reed General Hospital, 1969-72; Chief, Department of Medicine, Brooke Army Medical Center, 1972-76.

ROBERT F. PROCTOR, M.D.

Formerly Lieutenant Colonel, MC, AUS. Chief, Medical Section, U.S. Army Medical Research Team, WRAIR, Vietnam, 1966-67; Chief, General Medicine Service, Martin Army Hospital, 1968.

ADOLF E. RAHM, Jr., M.D., M.P.H.

Colonel, MC, USA. Chief, Department of Medicine, Darnall Army Community Hospital, and Director, Brooke Army Medical Center Affiliated Internal Medicine Residency and Intern Training Program, Fort Hood, Tex. Commander, 20th Preventive Medicine Unit, and Assistant USARV Preventive Medicine Consultant, Vietnam, 1969-70.

PHILIP K. RUSSELL, M.D.

Colonel, MC, USA. Director, Walter Reed Army Institute of Research. Chief, Virology Department, U.S. Army Medical Component, SEATO, Bangkok, Thailand, 1965-68; Chief, Department of Virus Diseases, Walter Reed Army Institute of Research, 1968-73.

JAY P. SANFORD, M.D.

Professor of Medicine and Dean, School of Medicine, Uniformed Services University of the Health Sciences. Civilian Consultant in Medicine to The Surgeon General, U.S. Air Force, 1963-75; Civilian Consultant in Medicine, Brooke Army Medical Center, 1964-75.

DALLAS E. SMITH, M.D.

Assistant Professor of Medicine, Eastern Virginia Medical School, Norfolk; Consultant in Rheumatology, Kecoughtan Veterans Hospital, Virginia; Lecturer in Rheumatology, Portsmouth Naval Hospital, Virginia. Formerly Major, MC, USAR.

EDWARD G. SOUTHWICK, M.D.

Clinical Instructor, Division of Dermatology, University of Utah School of Medicine, Salt Lake City. Formerly Lieutenant Colonel, MC, USAR.

FRED R. STARK, M.D.

Colonel, MC, USA. Chief, Department of Medicine, Letterman Army Medical Center, San Francisco, Calif.; Associate Clinical Professor of Medicine, University of California, San Francisco.

WILLIAM J. STONE, M.D.

Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn. Formerly Major, MC, AUS. Member, 629th Medical Detachment (Renal), Saigon, Vietnam, 1968-69.

RALPH F. WELLS, M.D.

Colonel, MC, USA (Ret.). Clinical Professor of Medicine, University of Texas Health Sciences Center, San Antonio, Tex. Commander, 61st Medical Battalion, 1967; Commander, 17th Field Hospital, 1968; Consultant in Internal Medicine to the Surgeon, USARV, 1968; Chief, Gastroenterology Service, Brooke Army Medical Center, 1968-76.

JAMES E. WILLIAMS, Ph.D.

Major, MSC, USA. Chief, Plague Section, Department of Hazardous Microorganisms, Walter Reed Army Institute of Research.

ANDREW WHELTON, M.D.

Associate Professor of Medicine, The Johns Hopkins University School of Medicine. Formerly Major, MC, USAR. Co-director, 629th Medical Detachment (Renal), Saigon, Vietnam, 1966-67; Civilian Consultant in Renal Disease to The Surgeon General, U.S. Air Force, 1971-76.

Foreword

For the Army, U.S. involvement in the Vietnam war occurred at a time when the Medical Department was best prepared to accept the challenge of increasing numbers of patients with complex medical diseases. The physician draft had infused the Medical Corps with young, eager, and talented physicians; Army medical education programs had generated mature staff officers, capable of knowledgeable decisions on the wards, in the clinics, and in management and command positions. Year after year throughout the conflict, a steady stream of these physicians moved back and forth across the Pacific. As I see it, the demands on these medical officers in Vietnam were different and more difficult than those required during the prolonged but continuous service experienced in World War II, or by the involvement in the Korean war. A continuity of medical care had to be maintained despite the yearly turnover of the medical staffs. Effective care depended upon the perpetuation of knowledge gained each year. The USARV Medical Bulletin, the consultant system utilizing conferences and reports, the ultimate standardization of therapy for such diseases as malaria and hepatitis all provided some basis for maintaining a continuing proficiency in the delivery of health care.

Internal Medicine in Vietnam, Volume II, chronicles the efforts of the Army Medical Department in the management of those diseases encountered by troops obliged to fight in a tropical environment. There was a determined effort to meet the challenge of this new environment and the large numbers of patients with febrile illness or other infrequently encountered diseases, some of which were previously chronicled only in the aging textbooks of a past era. The amalgamated efforts of the Regular Army staff and the drafted physician and the constant contributions of Army research activities achieved a remarkable success which was translated into a decrease of mortality and morbidity in the U.S. soldier stationed in Vietnam. For the maneuver battalions, it meant a reduction in combat man-days lost, unparalleled in previous conflicts. The achievements in medical care, especially the enhanced knowledge of tropical diseases presented in this comprehensive review, will provide the historical perspective so necessary to an appreciation of the requirements for a strong medical department capable of response on a worldwide basis when the health and welfare of the U.S. soldier are threatened.

I believe the reader will find these chapters replete with the essentials of a military medical history with emphasis on the intimate association of war and medicine. The text provides a lasting contribution to global health care in any tropical setting and serves as a sourcebook for medical and military planners

who wish to broaden their experience by study of these lessons of history. In addition, it provides insight into the medical care required to maintain the health of the Army while fighting abroad.

The volume represents a consolidation of a remarkable amount of information garnered from the yearly experience of thousands of medical officers who served during the Vietnam era. As one of those participants, I can appreciate the magnitude of the effort required to produce it and its value as a contribution to the medical literature.

CHARLES C. PIXLEY, M.D.,
Lieutenant General,
The Surgeon General.

Preface

This volume, the second of three in the Internal Medicine in Vietnam series, encompasses those disorders generally recognized as belonging to the broad field of internal medicine, with special emphasis on infectious and tropical diseases. Its purpose is to serve as both a historical document and a text providing present concepts of the diagnosis and treatment of those conditions which were of special importance in Vietnam. By comparison with classical textbooks of internal medicine, disproportionate emphasis on certain topics is apparent. Some diseases, like melioidosis, are highlighted because they were previously unheralded disorders which suddenly became serious and because they present unresolved therapeutic problems. Others, such as plague and cholera, are treated in detail not because their potential as serious threats actually developed but because U.S. experience with them in Vietnam reflects the response of Army research capability to unusual challenges and demonstrates how investigations in one area may lead to progress in others. Scrub typhus, amebiasis, and tropical sprue are given generous attention, not because they were difficult to diagnose or treat but because they were common problems relatively, or absolutely, unique to Southeast Asia and particularly uncommon to the experience of most American physicians. Diseases commonly recognized in the United States, such as tuberculosis, receive but brief mention since they did not become a serious problem among U.S. troops in Vietnam, either in terms of incidence or in the development of drug resistance.

This volume follows "Skin Diseases in Vietnam, 1965-72," written by Lt. Col. (later Col.) Alfred M. Allen, MC, and published separately (1977) because of the magnitude of the problem with skin disorders and the highly specialized material which was developed. Volume III, "Drug Abuse in Vietnam," currently in preparation, deals with a topic which is serious and unique as a medical as well as a command problem.

Some background information concerning the planning for the series may assist the reader. The first meeting of the Advisory Editorial Board for the History of the U.S. Army Medical Department in Vietnam and Southeast Asia was held at The Historical Unit, Forest Glen, Md., on 7 May 1970. The purpose of the meeting, chaired by Maj. Gen. James A. Wier, MC, was to establish a clinical and administrative historical series to chronicle the medical events of the war. The editors chosen for the Internal Medicine series were Col. Thomas W. Sheehy, USA (Ret.), and Lt. Col. (later Brig. Gen.) Andre J. Ognibene, MC. In the months that followed, the editors selected an Advisory Editorial Committee for the Internal Medicine series; on 1 May 1972, that group gathered at The Historical Unit for the initial working meeting. Lieutenant Colonel Allen was given the responsibility for "Skin Diseases in Vietnam." Col. O'Neill Barrett, Jr.,

USA (Ret.), was to develop material on the early years and on rickettsial diseases, while Col. John J. Deller, Jr., MC, was to provide material for all other infectious diseases. Because of the scope of the malaria story, both Col. Raymond W. Blohm, Jr., MC, and Col. Nicholas F. Conte, MC, agreed to write that part. Sections on evacuation and support were to be written by Lt. Col. Thomas A. Verdon, Jr., MC, and the section on gastrointestinal disorders, by Colonel Sheehy and Col. Ralph F. Wells, MC. Unfortunately, personal commitments did not permit Colonel Sheehy's continued participation in the series, and the burden fell to Colonel Wells. Because the 629th Medical Detachment (Renal) obviously contributed significantly to troop care, Maj. (later Lt. Col.) James H. Kneppshield, MC, was appointed to assemble data on renal diseases. In 1975, Col. John Castellot, MC, and Lt. Col. (later Col.) Norman W. Ream, MC, were asked to develop Volume III, "Drug Abuse in Vietnam," to complete the series. When Colonel Verdon left the Army and Colonel Wells resigned from the committee in 1976, Colonel Barrett and Colonel Ognibene assumed broader responsibility for direct input to Volume II and concurrently served as cochairmen and principal authors from that time forward.

When medical care of American troops in Vietnam is finally assessed, several aspects will deserve special emphasis. The immediate helicopter evacuation of seriously wounded troops to definitive treatment centers is cited in this volume. No less important is the establishment, for the first time in U.S. Army Medical Department history, of a renal unit in a combat area capable of providing immediate and appropriate treatment of acute renal insufficiency; the success of that effort is documented in the section on renal care.

Finally, there is the story of malaria and its ultimate control in the combat zone. This disease, known from antiquity, has affected many military campaigns as dramatically as has combat itself. In the late fifties and early sixties, malaria was looked upon condescendingly as a condition for which there was adequate epidemiological control and individual treatment and thus no longer a threat to world health. Then, almost predictably, history began to repeat itself. First came isolated case reports of drug-resistant falciparum malaria from several areas around the world; next, the unheeded warnings from visionaries like Brig. Gen. William D. Tigertt. This was followed by the first case of drug resistance in falciparum disease in an American officer in Vietnam and, finally, the complete unfolding of the seriousness of drug-resistant disease and the remarkable effort required to control it in Vietnam. A postscript to the story in Vietnam was the problem of imported and induced malaria in the United States, mostly the consequences of poor prophylaxis compliance by returning troops. The task of telling the malaria story was assigned first to Colonel Conte and Colonel Blohm. Recognition of the vastness of the project led to the addition of Colonel Ognibene to the group. Finally, Colonel Barrett also became a member after the death in September 1977 of our colleague and friend, Colonel Blohm, to whom the section on malaria is respectfully dedicated. This section, therefore, represents the collaborative efforts of four members of the Advisory Editorial Committee, all of whom served in Vietnam and all of whom had extensive experience with the disease, both in Vietnam and in the United States.

Obviously the efforts of many people were required to bring this volume to successful fruition. Those of the personnel of the former Medical History Division, U.S. Army Center of Military History (previously The Historical Unit, U.S. Army Medical Department), were continuously superb despite interruptions caused by moves of the activity first from Forest Glen to Fort Detrick (Frederick), Md., then to the Forrestal Building in Washington, D.C., and then to its present location in the Pulaski Building in Washington, D.C. The driving force in that continuing effort was Mr. Charles J. Simpson, Director of the Clinical History Program, who provided the perspective, organization, and encouragement necessary to develop a valuable historical treatise. The editors are personally indebted for his counsel, memory, and gracious support. We would also like to thank Mrs. Martha R. Stephens for her editorial suggestions, Miss Mary C. Efdimis for her administrative support, and the archivists at Fort Detrick and the Center of Military History for their assistance in obtaining documents and records. Special thanks are due Mrs. Linda A. Kincaid, the first prepublications editor, Ms. Ann Rhodes Conley, who completed the prepublications editing, and Mrs. Mary Nelson, who shepherded galley and page proof through the publication stages. They painstakingly reviewed the manuscript, plagued the editors with questions, and assured publication quality. We also appreciate the assistance of secretarial personnel at the many institutions who typed textual material and that of Mr. Howell C. Brewer and Mr. Roger D. Clinton, who prepared the charts and the maps, respectively.

The manuscript could not have been completed without the statistical data which were supplied by the Office of Patient Administration, Office of the Surgeon General, and by the biostatistical agency of the U.S. Army Health Services Command; Mr. H. F. Ewert fulfilled the many requests which we placed upon these two agencies.

Finally, we must recognize all those who generously contributed material to the authors of this work. To them and all physicians who participated in the care of the U.S. soldier in Vietnam, this text is dedicated; it stands as a tribute to their efforts. They provided an abundance of data, both published and unpublished, which enriched the treatise and broadened our understanding of the medical activities of the period.

ANDRE J. OGNIBENE,
Brigadier General, MC, USA.

O'NEILL BARRETT, Jr.,
Colonel, MC, USA (Ret.).

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Volume II

GENERAL MEDICINE AND INFECTIOUS DISEASES

Part I

BACKGROUND

Setting

Colonel O'Neill Barrett, Jr., MC, USA (Ret.)

Vietnam, one of the smaller nations of Asia, has for 2,000 years enjoyed a prominence in history far out of proportion to its size or economic resources. American military assistance there began in 1950 when the United States decided to give military and economic aid to the French and Vietnamese to assist in the fight against the Vietminh. The defeat of the French forces at Dien Bien Phu in May 1954 and the subsequent Geneva agreement of July 1954 marked the end of colonialism and the establishment of independence and nationalism for the countries of Laos, Cambodia, and Vietnam. Vietnam was divided into areas, North and South, with the 17th parallel as the provisional Demarcation Line. General elections were to be held in July 1956 throughout the country to decide its future. However, such elections were never held.

In South Vietnam in July 1954, Emperor Bao Dai directed the formation of a new government under the leadership of Ngo Dinh Diem. In 1955, Prime Minister Diem called a national referendum to decide if the country should become a republic under his leadership. Diem, with 98 percent of the votes, replaced Bao Dai and proclaimed South Vietnam a republic and himself its first president. In support of the Republic of Vietnam, and especially because of increasing pressure of the Vietcong (Vietnamese Communists), the United States government established several military missions in South Vietnam, the largest and most permanent of which was the MAAGV (Military Assistance Advisory Group, Vietnam). Subsequent buildup of American forces resulted in a total of more than 2½ million U.S. troops having served there by March 1973.* Medical support was established and grew with this effort. This volume tells the story of internal medicine in the United States Army as it evolved and describes the lessons learned and relearned and the advances made in the recognition and treatment of disease.

GEOGRAPHY AND PEOPLE

Despite its small size and its location completely within the Tropics, South Vietnam has three well-defined geographic areas, each of which presents dif-

*Department of Defense Statistics Service. Inquiry, 20 Feb. 1975.

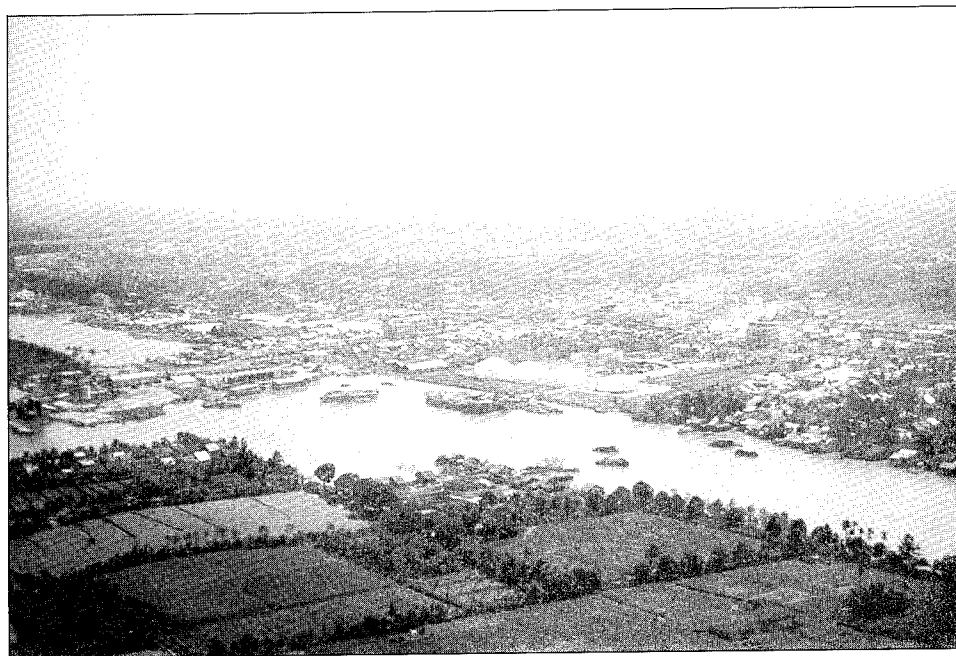


FIGURE 1.—Can Tho, a principal city of the Vietnam Delta, astride the Hau Giang River. Note the fields in cultivation in the outlying part of the city.

ferent environmental, military, and medical problems. The Mekong Delta occupies the southern two-fifths of the country, has heavy rainfall, and is an excellent rice-producing area. The delta, approximately 26,000 square miles, was built up by five branches of the Mekong River, one of the 12 great rivers in the world. Deposition of sediment advances the coastline to the south at a rate of 250 feet per year. Of the total area, 9,000 square miles are under rice cultivation. An extensive series of levees and dikes has been developed for flood control, but during the flood periods, the only dry land is that which forms the banks of canals and rivers (figs. 1 and 2). The high humidity in this area and the necessity for long periods of exposure in rice paddies contributed to the development of the serious dermatologic conditions in American troops described in the volume on skin diseases in the Internal Medicine in Vietnam series (MD-IM1).

The Chaîne Annamitique, with several high plateaus, dominates the area extending from the delta north to and beyond the Demarcation Line. One of these plateau areas, known as the Central Highlands, covers an area of 20,000 square miles. This area is composed primarily of bamboo and tropical broadleaf forests interspersed with rubber plantations and farms (fig. 3). In this area, troops developed malaria and scrub typhus.

The Central Lowlands consists of a fertile but quite narrow coastal strip lying to the east of the Chaîne Annamitique. Rice and sugarcane are the major



FIGURE 2.—Aerial view of flooded rice paddies in the Mekong Delta.

crops. Fishing is an important industry along the coast, and small fishing villages are scattered throughout the coastal plain (fig. 4). Several of the large cities of Vietnam—Cam Ranh, Nha Trang (fig. 5), Da Nang, and Hue—are located along the coast.

The population of South Vietnam in the mid-1960's was estimated at 16 million. The majority, perhaps as many as 10 million, lived in the delta area where Saigon is located, 5 million lived in the Central Lowlands, and approximately 600,000 lived in the Central Highlands. At least 2 million people were refugees, half of whom arrived in South Vietnam soon after the end of the Indochina War. Another million had fled from areas controlled by the Vietcong. Because of the striking differences in geography, the population was unevenly distributed. Involuntary mobility because of the war compounded this problem. The majority of the population either was rural or lived in small urban centers; only 10 percent of the population lived in the major cities (fig. 6).

At least 85 percent of the population in the mid-1960's were ethnic Vietnamese who had settled in the Mekong Delta or the river valleys and coastal portions of the Central Lowlands (fig. 7). Culturally and ethnically they are related closely to the Chinese, the largest minority group. The Chinese numbered approximately 1 million, living primarily in the Cho Lon area of Saigon (fig. 8). They retained a cultural distinctness and had a tremendous economic impact on the country, despite an attempt at government-directed assimilation. The next largest minority group, the Montagnards (mountain people), lives in the highlands. This group included more than 30 tribes, probably numbering 700,000 to 1 million people (fig. 9). Referred to as *Moi*—a derogatory term meaning



FIGURE 3.—Grazing cattle on the open plains near Pleiku in the Central Highlands, an ideal farming area.

“savage”—by the Vietnamese, they suffered most from racial discrimination in Vietnam. In the late 1960’s, at least the official attitude toward the Montagnards began to change in order to counter the efforts of the Vietcong to infiltrate and win over rural populations. Despite some attempts at improved economic standards and living conditions, this group represented a serious political, economic, and medical problem to the central government. Other prominent minorities included the Khmers and the Chams.

VIETNAMESE AND FRENCH MEDICAL EXPERIENCE

Had they been actively sought, some data, although admittedly sketchy, were available to American physicians which could have served as background information for the medical experience which was to develop. In fact, however, almost no information was presented to those first medical units to arrive in Vietnam. The advance party of the 8th Field Hospital, the first medical unit assigned to Vietnam, was briefed by the office of the USARPAC (U.S. Army, Pacific) surgeon and by the commander of the U.S. Army Hospital, USARYIS (U.S. Army, Ryukyu Islands). Available information was vague and consisted of an awareness of malaria, some concern about the high incidence of tuberculosis in the civilian population, and a knowledge that there were large numbers of poisonous snakes in the country. On the other hand, the potential scope of the

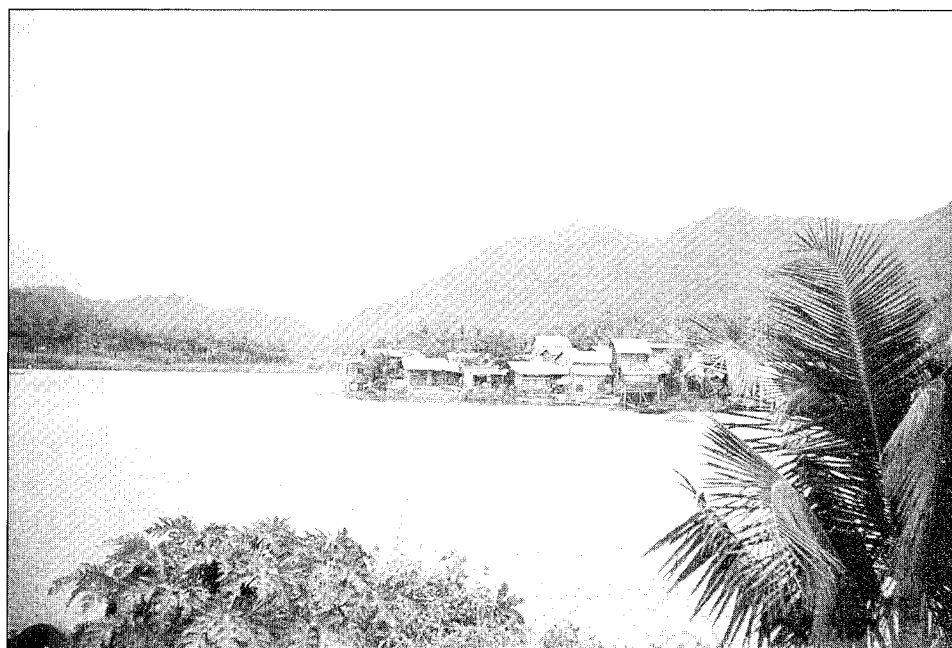


FIGURE 4.—Small fishing village near Nha Trang, nestled to the east of the Chaîne Annamitique.

malaria problem was not anticipated, and although both scrub typhus and leptospirosis were under active study at the U.S. Army Research Unit, Kuala Lumpur, Malaya, the presence of these diseases in Vietnam was not reported. Cholera, though anticipated, never became a problem in American troops. Bubonic plague, endemic and epidemic in the civilian population, also did not seriously affect U.S. personnel.

In this review, the more important diseases, by comparison and contrast, are discussed together from the Vietnamese and French points of view. The data gathered on diseases in the Vietnamese population and French forces reflect experience remarkably similar to that later recorded by American medical personnel and would have been useful background information. The preciseness and validity of the Vietnamese data are admittedly questionable because of the difficulty in gathering data in that country, unavailability of data from ARVN (Army, Republic of Vietnam) sources, and lack of trained personnel and diagnostic facilities to confirm suspected diagnoses. The problem was compounded by the negative Vietnamese attitude toward autopsy based on both custom and religious belief. In the Buddhist faith, with its concept of reincarnation, corporal mutilation is forbidden. Therefore, except in rare legal cases, autopsy was not performed.

Civilian medical services in Vietnam were poor, even though support was provided by official and unofficial groups from outside the country. This support

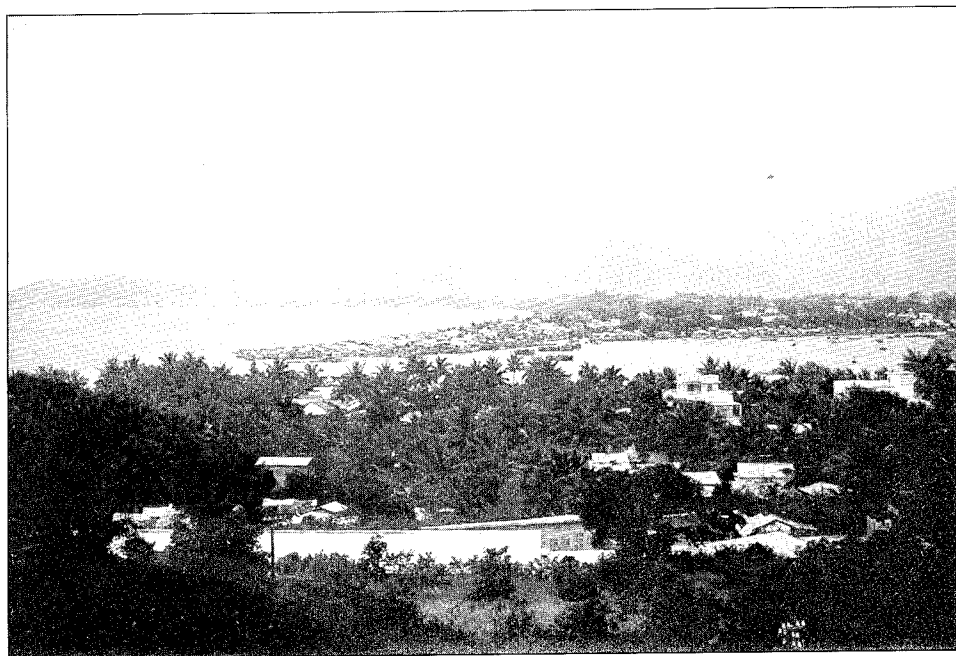


FIGURE 5.—Nha Trang, situated along the east coast of the fertile lowlands, commands an ideal harbor.

included Project Vietnam, sponsored by the American Medical Association; Project HOPE (Health Opportunity for People Everywhere); MEDICO (Medical International Cooperation Organization); the MILPHAP Program (Military Provincial Health Assistance Program); and the MEDCAP (Medical Civic Action Program) teams of the U.S. Army Medical Corps. A department of public health had been in existence since independence, ostensibly operating through provincial medical officers, responsible for all governmental health facilities and programs in each province. In many instances, however, facilities and personnel existed only on paper; in others, facilities were so understaffed and personnel so poorly trained that their impact was negligible. Although Western-style medicine first was introduced into Vietnam before 1800 by medical missionaries, and despite French activities in establishing hospitals and clinics, the majority of Vietnamese received care via traditional oriental medicine.

In 1965, there were approximately 800 Western-trained physicians in the country, 500 serving in ARVN and 150 civilian physicians in private practice in Saigon, with the remainder of the country having a total of 150 doctors, or one for each 100,000 persons. Inadequate supplies, facilities, and training further limited the effectiveness of this potential reservoir for sound medical care. Two medical schools, one in Saigon and one in Hue, were the only continuous source of physicians. The school in Saigon, however, graduated only 50 students per year, nowhere near the number needed to meet the requirements of the country.



FIGURE 6. — Aerial views of Saigon. Top: Natural access to the sea along the Saigon River. Bottom: An example of congestion in major cities.

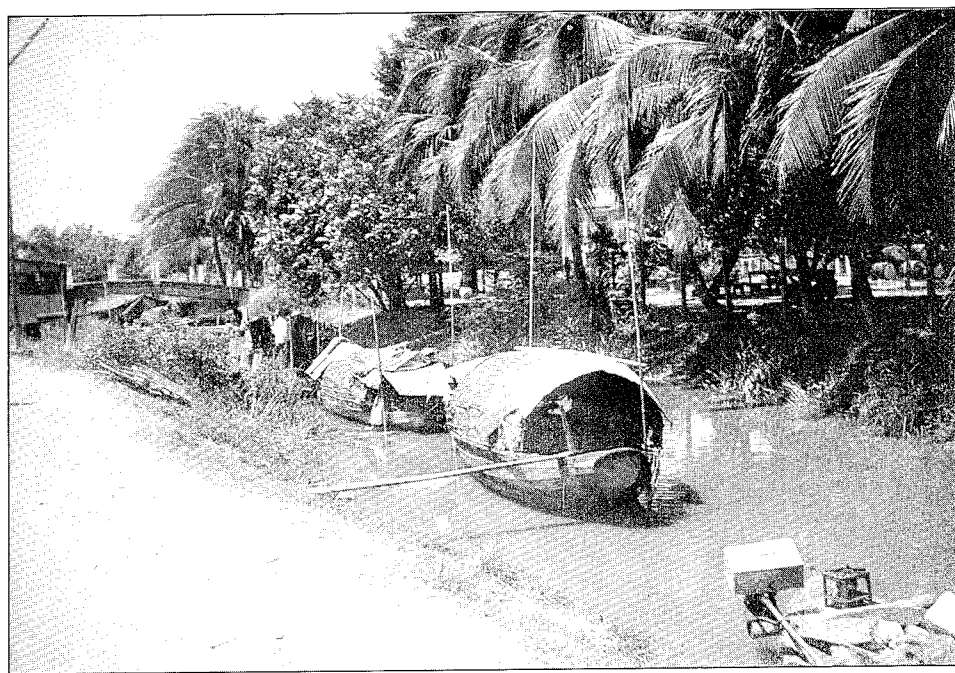
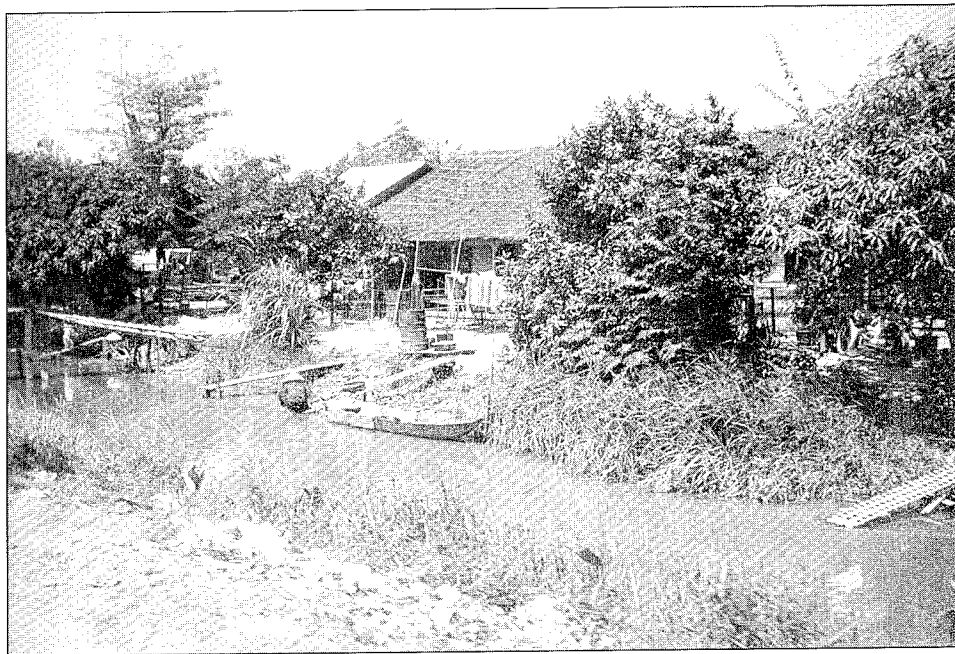


FIGURE 7.—Canals were used for commercial and public transportation, as well as a source of water for the people. Top: Typical dwelling on a levee in the Mekong Delta. Bottom: Sampans.

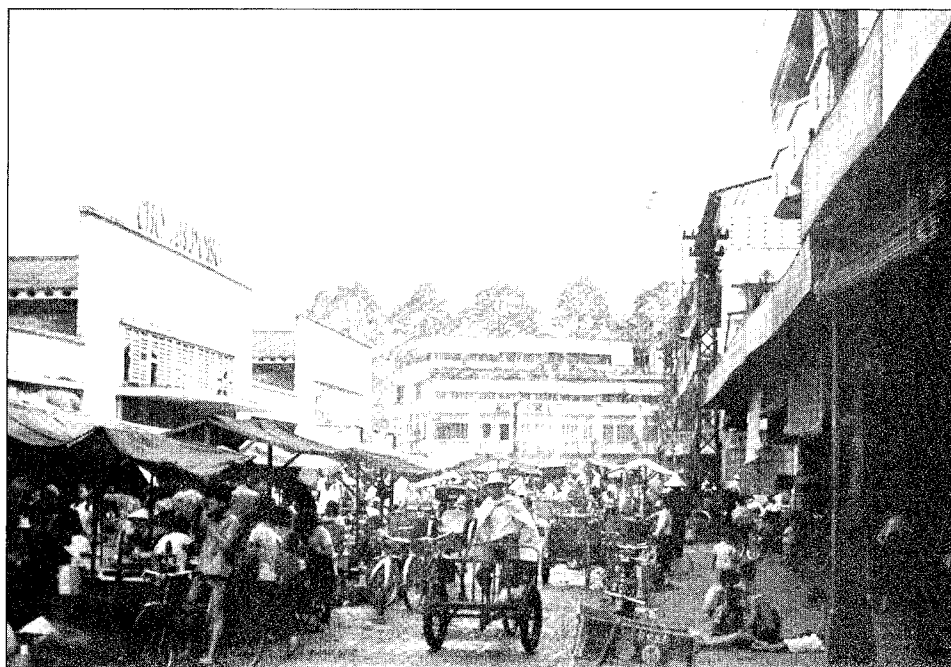


FIGURE 8.—Commercial activity on crowded Cho Lon street.

The three branches of l'Institut Pasteur, located in Saigon, Da Lat, and Nha Trang, offered some degree of medical sophistication, especially in microbiology and the production of vaccines and serums. In addition to the meager supply of physicians, there were 3,100 nurses, 1,213 midwives, and 5,000 other paramedical workers, including health workers, sanitary agents, and dispensary personnel (Smith et al. 1967, p. 131). Despite the French and later the American influence in the country, the prestige and acceptance of Western medicine had developed slowly throughout most of the country.

By contrast, the country had at least 4,600 practitioners of traditional oriental medicine (*ong lang*) (Smith et al. 1967, p. 133). These doctors retained great prestige, especially since they represented deep-rooted cultural values and social traditions. Their techniques included acupuncture, cupping, moxibustion, and the use of a large pharmacopoeia of herbs, many of which have therapeutic value.

For the French forces in Vietnam, the incidence* of the 10 most common causes for hospital admissions from 1945 to 1954 was as follows (MI-OTSG, p. 3):

Skin diseases	42	Venereal diseases	21
Digestive disorders (except amebiasis).....	36	Diseases of the sense organs	21
Respiratory disorders (except tuberculosis).....	28	Malaria	19

*The incidence is expressed as a 9-year average of the number of cases per 1,000 troops and corresponds to the ratio between the average monthly number of troops and the average monthly number of patients.

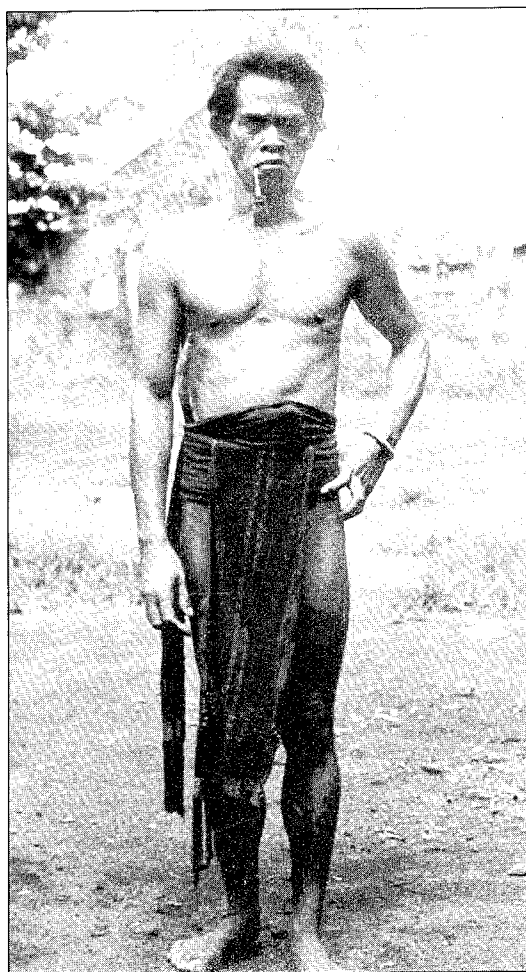


FIGURE 9.—Typical Montagnard tribesman seen in Central Highlands village.

Amebiasis	11	Neuropsychiatric disorders	2
Contagious diseases	3	Beriberi	1

Skin diseases, gastrointestinal problems, and respiratory infections (excluding tuberculosis) were the most frequent problems, a pattern similar to that seen in American troops in later years.

As was true for Americans, most of the skin disorders among French troops resulted from inadequate personal hygiene and especially the inability to obtain clean and dry underclothes and socks. The official French files (MI-OTSG, p. 22) stated that mechanical washing installations, though not attaining the perfection of washing equipment in the American Army, would have made it possible to boil linen and thus kill germs which would otherwise not be destroyed through washing.

The most common digestive disorders affecting French troops, aside from amebiasis, were salmonellosis and shigellosis. Shigellosis was never a serious problem; only a few minor epidemics were reported and only two deaths occurred in a 9-year period. On the other hand, salmonellosis was an important infectious disease among the expeditionary forces. Epidemiologically, *Salmonella typhosa* was the predominant organism, isolated in 89 percent of all positive cultures. Its seriousness was emphasized by an 11-percent mortality rate. The disease was generally sporadic in nature and not seasonal in occurrence. One major epidemic of typhoid fever occurred in 1954 during resettlement of a tribe of Nungs. This group of natives had not been vaccinated, and the mortality rate was approximately 25 percent (MI-OTSG, pp. 12-13). In the Vietnamese, the incidence of typhoid fever and of salmonellosis was considered high, but reliable figures are lacking. When culture data were available, *S. typhosa* again was the prevalent organism isolated. Possible sources of infection were pigs and the gecko (*Gecko verticillatus*), a reptile whose meat is eaten and in whom the carrier rate is as high as 50 percent. On the other hand, poultry sources, including duck eggs, played an insignificant role in the dissemination of salmonellosis in Vietnam.

In contrast to the American experience, amebiasis was considered the most serious endemic disease encountered in Indochina. During the 1945-54 period, 193,308 cases were diagnosed, resulting in 192 deaths (mostly among prisoners captured at Dien Bien Phu) and 4,953 medical discharges (MI-OTSG, p. 9).

Two striking statistical observations were made concerning the occurrence of amebiasis. The first was that the rate of occurrence was as high among medical corps units as among combat troops. Further, the incidence was quite high (8 to 10 percent) in European and North African troops, lower (5 percent) in African troops, and quite low (4 percent) among Indochinese troops of the "French Union." These data are shown in table 1. There is no information to suggest whether or not this difference represented partial immunity to the disease in native troops in the French forces. Hepatic amebic abscess was a serious complication, and in 1954 alone, 50 such abscesses were surgically drained (MI-OTSG, p. 11). Epidemiologically, the disease was noted to be seasonal, most cases occurring during the hot season. In contrast to the French experience, amebiasis was a serious cause of morbidity in the Vietnamese population, was listed as the third most common communicable disease in the country, and

TABLE 1.—Incidence of amebiasis by race and combat status, French forces, 1945-54

Origin	Combat units (percent)	Medical units (percent)
European	10.6	9.9
North African	8.2	8.3
African	5.5	3.1
Indochinese	3.8	1.7
Other	1.2	0.5

Source: Medical Intelligence Office, Office of the Surgeon General. *Health conditions among the French forces in Indochina (1950-1954)*. Unclassified report, undated.

occured four times as often as bacillary dysentery. The seasonal variation noted in the French statistics is not reflected in the Vietnamese data.

Venereal disease was one of the principal problems encountered by the French Army Health Service during the Indochina War. A total of 207,893 cases were reported from 1946 to 1954, including gonorrhea, syphilis, granuloma inguinale, and lymphogranuloma venereum (MI-OTSG, pp. 21-22). Numbers of cases and incidence rates are shown in table 2. These data differ from the American experience in at least two ways. The relative number of cases of syphilis was high in the French experience and extremely low in the American data. On the other hand, chancroid was relatively common in American troops and is not even listed as a cause of disease in the French data. Definitive data on the occurrence of venereal disease in the Vietnamese population were lacking.

TABLE 2.—*Venereal diseases in French troops in Vietnam, 1946-54*

Disease	Cases	Incidence per 1,000 troops
Gonorrhea	117,943	6.79
Granuloma inguinale	58,185	3.83
Syphilis	26,486	1.69
Lymphogranuloma venereum	5,279	0.30
Total	207,893	12.01

Source: Medical Intelligence Office, Office of the Surgeon General. *Health conditions among the French forces in Indochina (1950-1954)*. Unclassified report, undated.

In the Tropics, malaria is ever present. In combat, it often has produced more ineffectiveness than all battle and nonbattle injuries. Col. C. H. Melville (1910) wrote: "The history of malaria in war might almost be taken to be the history of war itself, certainly the history of war in the Christian era." In German East Africa in 1918, there were 72,000 hospitalizations among 50,000 troops, or an occurrence rate of 1,440 cases per 1,000 troops per year. For the 1946-54 period, a total of 293,814 cases of malaria were recorded among the French forces. During 1946, the incidence was 40 per 1,000 troops per year; it decreased dramatically by 1954 to 8.6 per 1,000. The death total for the entire period was 620. In contrast to that of amebiasis, the incidence of malaria among medical troops was far lower than in combat units (MI-OTSG, pp. 6-7).

The striking reduction in incidence of malaria by 1954 was attributed to two factors, chemoprophylaxis and preventive measures. During the 1946-48 period, chemoprophylaxis was provided through use of quinine and quinacrine. The incidence during this period was quite high. By 1949, paludrine was the prophylactic agent used, and the decline in incidence began at that point. Of equal importance, however, was the institution of stringent preventive measures including the use of mosquito nets, long sleeves and pants, and insect repellent. At all cantonments, DDT was regularly sprayed, either in suspension or dissolved in petroleum. Although it was a serious problem, malaria did not play the tragic role in the Indochina War that it had in earlier campaigns in the Tropics.

Malaria has always been one of the most important causes of morbidity and mortality among the Vietnamese. The government, through the Malaria Eradication General Administration and the World Health Organization teams, had made significant strides toward the control of malaria in Vietnam during the late 1950's. Increasing hostilities after 1960 made the task of malaria eradication impossible.

In South Vietnam, malaria is primarily a disease of the mountain areas. A hyperendemic area exists in the southern Central Highlands, a region extending broadly in the north and east toward the mountainous part of the provinces of Binh Tuy, Long Khanh, Phuoc Long, Binh Long and the northern parts of the provinces of Bien Hoa, Binh Duong, and Tay Ninh. There is no good evidence for endemic malaria in the coastal plains, and cases seen in urban areas are believed to have been imported by persons migrating or traveling extensively in endemic areas (Smith et al. 1967, p. 126).

In the American malaria experience discussed later (Part III), the species difference, especially after the recognition of chloroquine-resistant falciparum malaria, was an important consideration in the evaluation of the malaria problem. Available data, including French and Vietnamese records, contained no comments about the species encountered, and certainly no evidence suggested that the falciparum species would present the problem it did in terms of drug resistance.

Three other common infectious diseases in the Vietnamese population—tuberculosis, leprosy, and trachoma—deserve comment, although they were of no significance in either French or American troops. Tuberculosis has always been a serious problem in Vietnam. Following independence, the central government established an antituberculosis program. Best available data suggest that as many as 500,000 cases of active disease existed in 1960. Of the almost 23,000 new cases reported in 1955, approximately 9 percent had involvement of bones or joints. If all extrapulmonary forms are considered, 32 percent of all new cases were nonpulmonary forms of the disease (Zeville 1961, pp. 75-77).

Leprosy was another serious infectious disease common in the Vietnamese civilian population (fig. 10) but not reported in either French or American troops. An assessment of the disease in Vietnam by "The Anti Leprosy Struggle National Plan" indicated approximately 50,000 cases in the country, with 9,000 cases in Saigon. The disease occurred predominantly in inhabitants of the highlands; endemic rates here were among the highest in the world. Some statistical evidence suggests that the frequency of new cases was declining during the 1948-59 period (Zeville 1961, pp. 37-39).

Trachoma was one of the great social and medical problems in Vietnam, ranking second only to malaria in the list of the most common infectious diseases in the country (excluding acute respiratory infections). While most of the cases were mild and chronic in nature, an estimated 30 percent of those affected suffered partial loss of vision. There was a striking geographic difference in incidence of the disease within the country. It was common in the coastal districts of central Vietnam, especially in the provinces of Quang Ngai and Quang Tri, and

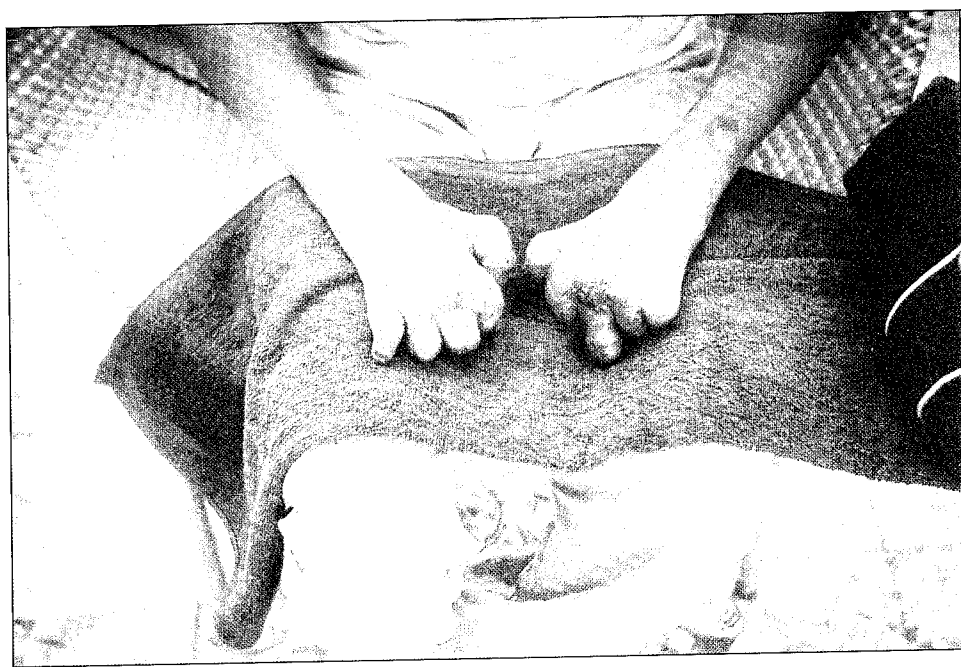
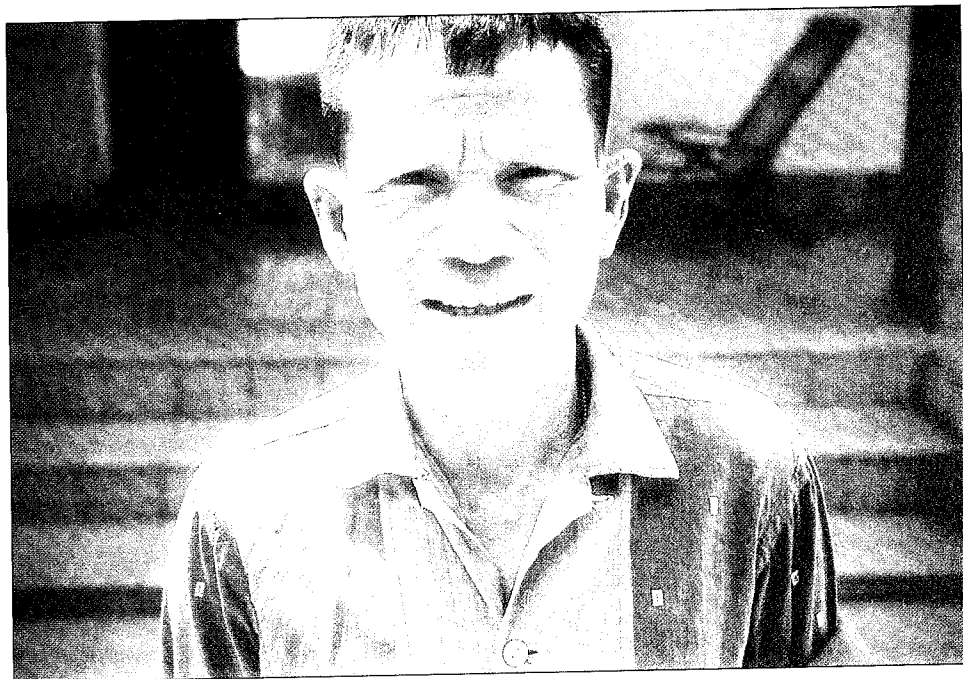


FIGURE 10.—Leprosy patients were treated in the hospital in Qui Nhon. Top: Characteristic leonine facies. Bottom: Deformed hands of lepromatous leprosy.

the areas of Phan Thiet and Phan Rang. Rates were significantly lower in the highlands and the delta areas. The disease apparently is contracted early in childhood; in some endemic areas, 60 percent of children tested were found to have the disease. Vigorous efforts by the central government and USOM (U.S. Operations Mission), using trachoma-prevention teams and aureomycin ophthalmic ointment, seemed to have had some effect in decreasing the incidence of the disease (Zeville 1961, pp. 93-95).

Scrub typhus was first suspected in Vietnam in 1935 and was confirmed by l'Institut Pasteur in 1937. Scant data are available from Vietnamese sources since it was not a reportable disease in the country. Occasional cases were known to occur, and at least two minor epidemics have been described. In 1942, 22 cases occurred in North Vietnam; in 1950 an "epidemic" was reported among troops in Chau Doc, but details are not available. No information is available concerning the species or vector of the disease (Zeville 1961, p. 63).

Despite knowledge of scrub typhus in Vietnam, the disease was not considered important at the beginning of the Indochina campaign. Only 4 cases were reported in 1949, and 19 more in 1950. As French troops entered the Chaîne Annamitique, the endemic area for scrub typhus, they experienced violent outbreaks. By the end of the campaign, a total of 5,708 cases and 158 deaths had been recorded (MI-OTSG, pp. 19-20).

An uncommon disease, which has nevertheless generated much interest, is melioidosis. It was first identified in Vietnam in 1925, both in human cases and in epizootic form. Vietnamese epidemiological data suggested that human infection developed by exposure to contaminated mud or water by way of the skin or respiratory tract. Evidence also suggested that arthropods might be involved in transmission of the disease. Among French troops sporadic cases were noted, although the incidence was probably higher than recognized since the pulmonary form resembles tuberculosis. Again, epidemiological data suggested that soil from rice fields and irrigation canals was the primary source, explaining why accident victims and troops with open wounds who fell in rice fields developed the disease. During the 1953-54 period, 21 cases among French troops were reported (MI-OTSG, p. 15).

Intestinal parasitism is widespread in Vietnam and is especially common among children. Infection rates are unknown, but one Vietnamese physician commented (Zeville 1961, p. 45): "Everybody is infected." In fact, surveys of schoolchildren in some areas showed a 100-percent infection rate. The parasites most commonly seen included *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Trichuris trichiura*, *Giardia lamblia*, and *Strongyloides stercoralis*. Multiple organisms in the same patient were not uncommon.

Cholera has occurred in epidemic proportions in Indochina since the second half of the nineteenth century. In 1850, an epidemic involving 2 million people was reported. In 1908, an attack occurred in Hue affecting half the population of the city, with a mortality rate of 70 percent. The highest incidence of disease was noted in the south, especially in the delta region where control of coastal traffic was difficult. Cholera, however, was not a problem for the French expeditionary

forces during the 9 years of the Indochina War. A total of only 110 cases, leading to 55 deaths, was seen (MI-OTSG, p. 5). Although two minor epidemics occurred in the civilian population in 1946-47, the spread of disease was prevented, in large part, by the use of repeated vaccination, enforcement of hygienic measures, and the use of fresh water supplies. In the spring of 1964, a cholera epidemic occurred throughout South Vietnam. More than 15,000 cases but only 700 deaths were recorded. This relatively low death rate was the result of massive United States aid. More than \$1.8 million worth of intravenous fluids were provided and administered by United States and Vietnamese personnel. Immunization activities were undertaken in several provinces, but effectiveness was hampered by Vietcong propaganda which convinced the local population that "the needle" would kill them (Smith et al. 1967, pp. 127-28).

Plague has been a persistent problem for the Vietnamese. The first reported epidemic in South Vietnam occurred in 1906. Rats transported to Saigon in material brought from Canton and Hong Kong were apparently responsible. The epidemic spread to Cho Lon, Gia Dinh, and Soc Trang. Serotherapy was attempted at this time but was unsuccessful. Mortality in untreated patients was 86 percent; in those treated, it was 72 percent. In 1914, during an outbreak at Can Tho which spread to Vinh Long, a 100-percent mortality rate was observed in cases of pneumonic plague. Before the onset of the Indochina War, some sporadic cases were noted, although none were reported from 1937 to 1941. As judged by more recent experience, this information probably does not represent a true decline in the disease but rather imprecise reporting, as was seen in 1962 when the central government refused to acknowledge proven cases in Nha Trang. In 1948, 355 cases were reported from Indochina, although only 80 were recorded in South Vietnam. Between 1952 and 1960, sporadic cases were reported, especially from coastal areas in South Vietnam (Zeville 1961, pp. 54-55). Like cholera, plague was not a problem for French troops in Indochina. Of a total of 17 cases recorded throughout the entire war, 14 were among Indochinese troops. Two of these patients died. Because of the presence of murine agents in camp areas, French authorities always enforced vigorous control measures, including control of the rat population and close supervision of food and garbage disposal (MI-OTSG, p. 5).

A final comment concerning alcohol and drug abuse is appropriate, especially in view of the drug problem which developed in American troops. Alcoholism was a serious problem throughout the Indochina War, almost exclusively involving troops of the "French Union," primarily European troops. A contributing factor, in addition to whisky, was the availability of beers with a high alcoholic content. In 1953, there were 1,438 admissions for alcoholism, or 0.05 percent of all hospital admissions. Of all medical discharges in 1953, 10 percent were for chronic alcoholism. The true impact of alcoholism is underemphasized by these figures since they reflect only the direct effects of alcohol. The consulting physician for the Armed Forces of the Far East estimated that alcoholism was the indirect cause of 50 percent of medical deaths in 1947 (MI-OTSG, p. 24).

Regarding the use of drugs by French forces during the Indochina War, the experience is tersely summarized by the statement, "Health problems caused by drug abuse were practically non-existent during the Indochinese campaign" (MI-OTSG, p. 27). This is in dramatic contrast to the tragic story concerning American troops told in the forthcoming volume on drug abuse in the Internal Medicine in Vietnam series (MD-IM3).

The final medical results of the Indochina War, 1945-54, as listed below, were tabulated by Surgeon-General Blanc and Surgeon-Captain Armengaud of France and graphically relate the problems of the medical service of the Expeditionary Corps (Black):

Men serving tours in Indochina, 1945-54.....	1,609,989
Hospitalized for medical reasons.....	694,123
Died of disease.....	5,154
Evacuated for medical reasons.....	33,913

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U.S. Medicine in Vietnam: The Early Years

Colonel O'Neill Barrett, Jr., MC, USA (Ret.)

Our God and the soldier we alike adore
 Ev'n at the brink of danger, not before:
 After deliverance, both alike requited,
 God is forgotten, and the soldier slighted.
 —Quarles, 1635

Francis Quarles might also have commented upon the diseases which soldiers encounter in time of war and which are likewise all too quickly slighted or forgotten. As Lt. Col. (later Col.) Robert H. Moser (1965) noted: "Disease is woven intricately into the fabric of war. The story of one cannot be told without the other. Yet each succeeding generation, soldier and scholar alike, seems reticent to concede to the microbe its historical role as an awesome factor in the wars of man." So it was in Vietnam, where the involvement of the U.S. Army exposed an unprepared generation of physicians to diseases which for them were but vague recollections from a dreary course in tropical medicine, mercifully brief, in an already overcrowded medical school curriculum. This despite the prophecies of such military medical visionaries as Col. (later Brig. Gen.) William D. Tigertt, MC (1966), who predicted the problem of drug-resistant malaria in early 1962.

Before 1962, the total American troop strength in Vietnam was small and composed primarily of MAAGV (Military Assistance Advisory Group, Vietnam) personnel. American medical care in Saigon was available through a small State Department dispensary; hospitalization, when required, was provided at the local Seventh Day Adventist Hospital or the Swedish Hospital. In late 1961, as a consequence of the decision by President John F. Kennedy to increase support to RVNAF (Republic of Vietnam Armed Forces), a significant buildup of U.S. Army combat advisory support took place. Overall support of this activity was provided by the USARYIS (U.S. Army, Ryukyu Islands) Support Group (Provisional), under the command of Col. Marvin H. Merchant; the medical section consisted of one Medical Service Corps officer, Maj. (later Lt. Col.) Frank Filtsch, and an enlisted clerk.

The information in this chapter, unless otherwise noted, is from the personal observations and records of the author or from Neel, S. 1973. *Medical support of the U.S. Army in Vietnam, 1965-1970*. Vietnam Studies. Washington: Government Printing Office.

In March 1962, the USARYIS activity was redesignated USASGV (U.S. Army Support Group, Vietnam) and placed under the command of Brig. Gen. Joseph W. Stilwell, Jr. The USASGV and MAAGV units were, in turn, placed under control of MACV (Military Assistance Command, Vietnam), commanded by Lt. Gen. Paul D. Harkins. The first MACV surgeon was Cmdr. (later Capt.) Paul G. Bamberg, MC, USN, who served in this capacity for several months and was replaced by Col. (later Maj. Gen.) William Moncrief, Jr., MC. Medical support for this 1961-62 troop buildup was provided by three OA* medical detachments, located respectively at Tan Son Nhut (Saigon), Qui Nhon, and Nha Trang. These detachments were able to provide minor surgical and outpatient medical services. The detachment in Nha Trang was inactivated following the arrival of the 8th Field Hospital in that city.

Based on the anticipated increase in troop strength, the need for greater medical support was recognized. As a consequence, the 8th Field Hospital, part of the 43d Medical Group stationed at Fort Lewis, Wash., was alerted for movement. This hospital was in a training status, minus professional complement, under the competent command of Maj. Jack D. A. Dickey, MSC, who served as the executive officer of the unit in Vietnam. Command of the hospital was given to Lt. Col. (later Col.) Carl A. Fischer, MC, who had served as a corps surgeon during the Korean conflict. Other key staff members included Maj. (later Col.) O'Neill Barrett, Jr., MC, Chief of Medical Service and coordinator for professional activities; Maj. (later Col.) Ariel Rodriguez, MC, Chief of Surgical Service; Maj. (later Col.) Louise F. Bitter, ANC, Chief Nurse; and M. Sgt. Chester Spain, sergeant major.

Several weeks before the anticipated deployment of the unit, an advance party, consisting of Major Barrett, Maj. Paul E. Hartenstein, MC, Major Dickey, and Maj. (later Lt. Col.) Murray Lieberman, DC, departed for Saigon. En route this team was briefed by the USARPAC (U.S. Army, Pacific) surgeon and his staff in Hawaii and by the USARYIS surgeon in Okinawa. Following discussions with the USARYIS Support Group commander in Saigon, the group flew to Nha Trang, the designated location for the hospital. It is perhaps symbolic that this city was chosen as the site for the first United States hospital in Vietnam, for there Alexander Yersin, the discoverer of plague who died while studying the disease, is buried. Preparation for the receipt and installation of the hospital was made there. The remaining hospital personnel soon arrived by air, but all equipment and supplies were delayed several weeks by a shipping error which caused the equipment to be delivered to the Philippine Islands rather than Vietnam. By 18 April 1962, however, the 8th Field Hospital, consisting of a headquarters and one hospitalization unit (100 beds), became operational and was to be the major treatment center in the country until the establishment of a U.S. Navy dispensary in Saigon in October 1963. The next U.S. Army hospital was not to arrive in-country until 26 April 1965, when the 3d Field Hospital was opened in Saigon.

*TOE (table of organization and equipment) designation for medical detachments with one Medical Corps officer and eight enlisted personnel.

Area medical support during this time was provided by medical detachment (OA) teams whose locations included:

Vung Tau.....	91st Medical Detachment
Bien Hoa.....	93d Medical Detachment
Pleiku.....	94th Medical Detachment
Tan Son Nhut.....	129th Medical Detachment
Tan Son Nhut.....	45th Transportation Battalion (Medical Section)
Qui Nhon.....	130th Medical Detachment
Soc Trang.....	134th Medical Detachment

During the period of March 1962 to November 1965, no medical consultant was assigned formally under the USARV (U.S. Army, Vietnam) surgeon. Informal medical consultation for both American and Vietnamese medical units was provided by the internist serving as chief of the Medical Service, 8th Field Hospital. Subsequently, medical consultants were assigned formally to the USARV surgeon. The following individuals served as medical consultants, 1962-71:

Maj. (later Col.) O'Neill Barrett, Jr.*.....	March 1962-February 1963
Maj. (later Lt. Col.) Walter Dawson Durden, Jr.*.....	February 1963-March 1964
(Consultant unknown)*.....	March 1964-February 1965
(Consultant unknown)*.....	March 1965-October 1965
Lt. Col. Thomas W. Sheehy**.....	November 1965-May 1966
Lt. Col. (later Col.) Raymond W. Blohm, Jr.	April 1966-June 1967
Lt. Col. (later Col.) Nicholas F. Conte.....	June 1967-June 1968
Lt. Col. (later Col.) Ralph F. Wells.....	June 1968-July 1968
Lt. Col. (later Col.) Samuel C. Jefferson.....	July 1968-January 1969
Lt. Col. (later Brig. Gen.) Andre J. Ognibene.....	January 1969-November 1969
Lt. Col. Thomas A. Verdon.....	November 1969-July 1970
Lt. Col. Joseph W. Edgett, Jr.	July 1970-March 1971
Col. Joseph E. Kmiecik.....	March 1971-June 1971
Col. John J. Castellet, Sr.....	July 1971-December 1971

*Primary duty as chief, Medical Service, 8th Field Hospital.

**First fulltime medical consultant, USARV.

The 8th Field Hospital commander and the hospital staff served in multiple roles during this early period, carrying the responsibility of daily care and supply for all Army medical units and future planning for the Vietnam medical mission.

8TH FIELD HOSPITAL

In 1962, in addition to the basic medical and general surgical capability of the field hospital, several medical detachments were attached for command but not operational control. These included the 44th Medical Detachment (KB), an orthopedic team, commanded by Maj. (later Col.) Spencer Walton, MC; the 66th Medical Detachment (KF), a thoracic surgery team, commanded by Maj. (later Lt. Col.) Paul Thomas, MC; and the 41st Medical Detachment (KE), a neurosurgical unit, commanded by Capt. Michael Mason, MC. A large efficient dental unit, the 36th Medical Detachment (KJ), commanded by Lt. Col. John Rudisill, DC, and the 57th Medical Detachment (RA), a helicopter ambulance

unit, commanded by Capt. (later Lt. Col.) John Temperilli, MSC, were also originally included in this medical center. Later in the year, the 7th Medical Laboratory, a general laboratory unit, and the 20th Medical Laboratory, a preventive medicine unit, were added. Much of the early history of Army medicine in Vietnam is, therefore, the story of the 8th Field Hospital and its attached units.

Unfortunately, the potential of this organization far exceeded the professional demands placed upon it, especially during the first year. The lack of challenge, primarily to the highly skilled surgical teams, had a negative effect on morale. Therefore, with the recommendations of both USASGV and MACV surgeons, two specialty teams were moved from Nha Trang. The thoracic surgery team was relocated to the ARVN (Army, Republic of Vietnam) General Hospital, Cong Hoa, in Saigon. Here it provided outstanding care to Vietnamese soldiers with thoracic injuries and also offered continuing thoracic surgery training to members of the local hospital surgical staff. The neurosurgical team was moved out of country and assigned to the U.S. Air Force hospital at Clark Air Force Base, Philippine Islands. This unit was thus able to provide a previously lacking neurosurgical capability for this hospital and also served as a regional neurosurgical referral center for all of Southeast Asia until its return to Walter Reed Army Medical Center the following year.

An important and unique medical contribution during this early period was made by the orthopedic surgical team. Its commander, Major Walton, was an energetic and aggressive surgeon not content with the prospect of an idle year. The remainder of the group, who shared this attitude, included an anesthesiologist, a surgical nurse, and several enlisted technicians. This unit became, in fact, a traveling medicine show reminiscent of the patent medicine shows of the 19th century U.S. frontier. With the approval of USASGV Headquarters, and through arrangements with Air Force and Army flight detachments, Major Walton managed to travel extensively through the II Corps area visiting American military and Vietnamese military and civilian hospitals. Orthopedic surgical procedures were performed at the ARVN Hospital and Province Hospital in Nha Trang and at the ARVN Hospital, Province Hospital, and Holy Family Hospital at Qui Nhon. The team made two trips to the Province Hospital at Quang Ngai. On each occasion, they remained for a week and performed a large number of major and minor operations. In addition, the team made at least a weekly visit to the Christian Mission Alliance Hospital in Nha Trang (fig. 11). This remarkable little hospital received special interest and support from the entire professional staff of the 8th Field Hospital.

While the care of patients was an important contribution in its own right, the team also furthered the education of the Vietnamese physicians, teaching them basic orthopedic principles and procedures. Introduction of the "hanging cast" technique for treatment of humeral fractures was a simple but extremely important contribution, for example. While handling the usual problems of orthopedic trauma, congenital lesions, and residual deformity from poliomyelitis, the team also encountered several serious problems common in Vietnam but unusual in American surgical experience. Pott's disease (tuberculosis of the

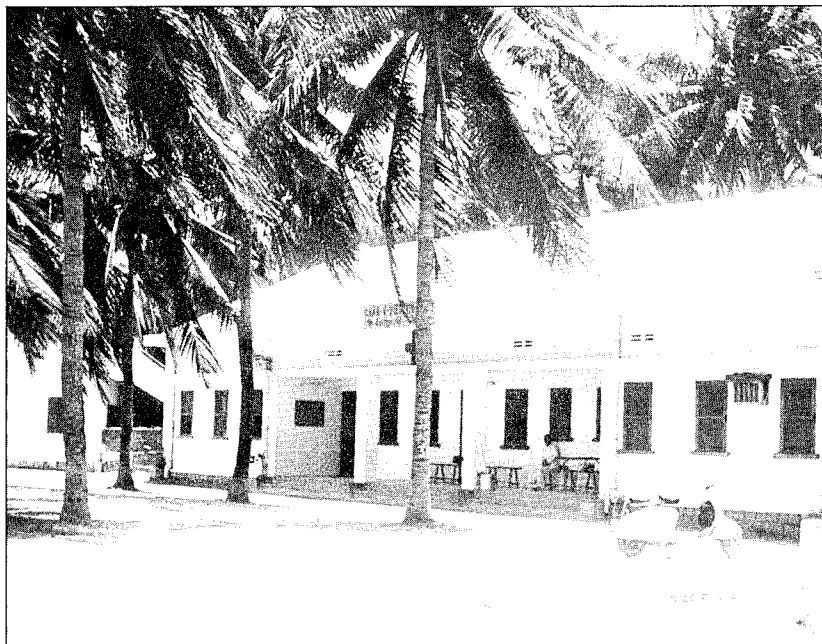


FIGURE 11.—Christian Mission Alliance Hospital, Nha Trang, 1963.

spine) was especially tragic because patients were seen late in the course of the disease when spinal cord compression and paraplegia had developed. Acute osteomyelitis, especially of the lower extremities, was also frequent, as was extensive joint destruction caused by leprosy.

In addition to providing orthopedic care to Vietnamese military and civilian hospitalized patients, the team made a series of field trips to refugee camps in the II Corps area. Here they were able to treat a wide variety of minor illnesses and in some instances provided immunization, especially for plague, which had become a serious problem in some areas. In one such camp, 40 kilometers west of Tuy Hoa, they saw 250 patients during a 14-hour period. On another occasion, they visited a camp in the "ambush alley" sector just outside Qui Nhon and treated 400 patients. This camp was attacked and completely destroyed by Vietcong troops 2 months later. Although modest in its overall impact on disease in Vietnam, the orthopedic surgical team nonetheless established an informal program of medical care, a pioneer effort antedating the formal programs later provided through the Agency for International Development and the Military Provincial Health Assistance Program.

ADMINISTRATION AND PATIENT EVACUATION

While the professional requirements of the 8th Field Hospital were easily handled, the administrative and logistical burdens were too great to be managed



FIGURE 12.—HU-1A aeromedical helicopter of the 57th Medical Detachment, Nha Trang, 1963.

adequately by the small hospital administrative staff. Few of the attached medical detachments had intrinsic administrative support, so their requirements were added to those of the hospital. Also, because of the distance from Nha Trang to Saigon and the difficulty of travel between these two areas, much of the administrative work of the USASGV surgeon's office had to be performed by the 8th Field Hospital staff, further compounding the administrative burden. In addition, the hospital was designated as the central medical supply point for all Army medical units in Vietnam. At this time, the supply section of the hospital consisted of one MSC (Medical Service Corps) lieutenant, the supply officer, and one supply sergeant. With insufficient manpower, no clerical support, and an erratic supply line from USARYIS, this activity was and remained a serious weakness in the medical support system in Vietnam for several years. Medical supply support improved somewhat with deployment of the 32d Medical Depot to Vietnam in October 1965.

Although the 8th Field Hospital was placed in Nha Trang because of its strategic central location in the country, movement of patients to this area was difficult at best and frequently impossible. No formal air evacuation system was established in-country until 1967.

The 57th Medical Detachment, based in Nha Trang, provided excellent air ambulance support, especially in moving nearby emergency cases to the hospital. The effectiveness of this unit was impaired, however, by the relatively short range of the HU-1A helicopters (fig. 12), recurrent maintenance problems, lack of repair parts, problems associated with dispersing JP-4 fuel, and lack of

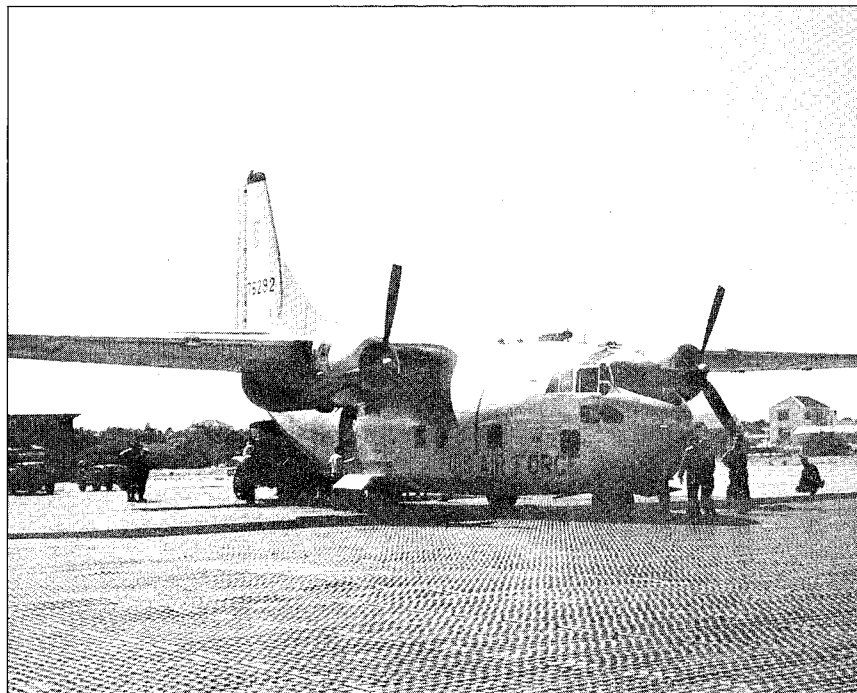


FIGURE 13.—U.S. Air Force C-123 cargo plane used for aeromedical evacuation in-country.

an adequate communications system. The unit was also required to transfer two of its helicopters to Saigon for tactical use, further restricting its effectiveness.

In general, patients who required attention at the 8th Field Hospital arrived as "hitchhikers" on aircraft flying tactical missions into Nha Trang. This resulted in frequent delays of patients getting to the hospital. Return of patients to duty from Nha Trang was an even greater problem as a low priority was given to these individuals. An entirely new unit was finally established within the hospital area to house discharged patients until transportation could be arranged. Transportation was most often accomplished via Air Force C-123 aircraft (fig. 13) or by U-1 Otter aircraft of air transportation companies located throughout Vietnam (fig. 14). In Nha Trang, the 18th Aviation Company, commanded by Capt. (later Maj.) Robert Felix, was especially helpful in this regard. When emergency evacuation of patients from Nha Trang to Clark Air Force Base was required, the Air Force responded in splendid fashion and was always able to provide a C-130 for such missions. Only the most severe weather prevented individual movement of such patients. In 1967, a formal in-country aeromedical evacuation system was established and operated by the 903d Aeromedical Evacuation Squadron. By early 1968, C-118 cargo aircraft, specifically modified for medical evacuation, were in use.

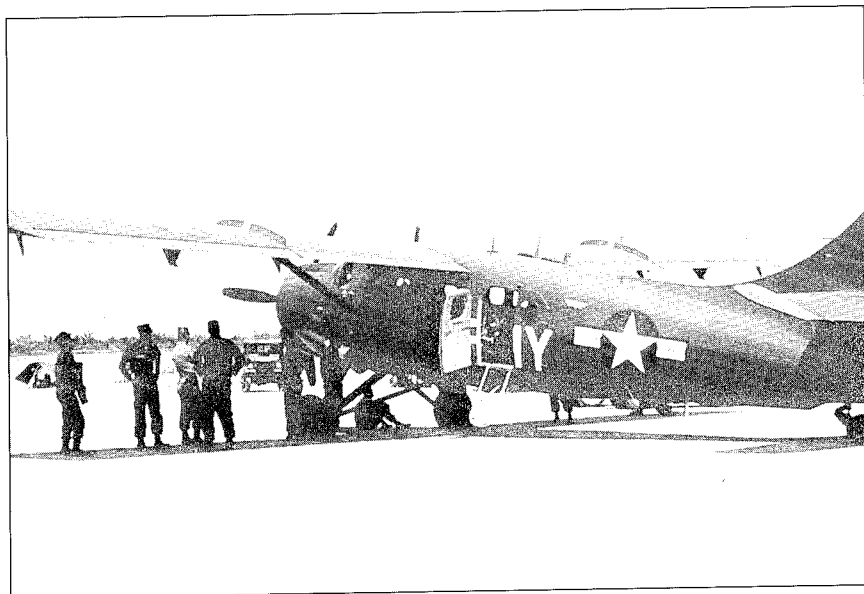


FIGURE 14.—U-1 Otter of the 20th Aviation Company, Nha Trang, 1963.

HOSPITAL CONSTRUCTION

The original 8th Field Hospital was established under canvas on a large, soft, sandy area immediately adjacent to the Nha Trang airport (fig. 15). Fortunately, the USARYIS Support Group engineers anticipated the requirement for solid floors and poured concrete slabs over which the tents were placed. On the other hand, original wiring for the compound was done through a local contractor using Vietnamese electrical wire which malfunctioned when attached to the American generators. Subsequent rewiring was accomplished with American material; two 100-kW and two 60-kW generators were installed and there was never a shortage of power thereafter.

The unsuitability of the canvas-covered hospital for the local geographic conditions became immediately apparent (fig. 16). Tents could not be adequately ventilated, and the intense heat made the patients extremely uncomfortable. In the operating suite, temperatures under the operating room drapes frequently exceeded 110° F. The USASGV supply section immediately provided two large air conditioning units for the operating room area. This area was specially constructed with a wood frame for the canvas cover and an asbestos cement roof. However, the tents, despite reinforcement liners, could not withstand the high winds which accompanied local tropical storms. On one occasion, patients were moved into temporary quarters in two nearby villas in anticipation of one such storm. Although damage to the hospital was slight, two patient care areas and the supply tent were blown down. Later in 1963, construction of a semipermanent wood and screen facility for the patient care areas was begun; it was completed in November 1963 (fig. 17).



FIGURE 15.—Headquarters area of the 8th Field Hospital “under canvas” in 1962.

Support areas, including pharmacy, X-ray, and laboratory, as well as some of the administrative buildings, also were constructed in this manner. This type of construction was used until 1965 when a permanent, completely air-conditioned cement block hospital was completed (figs. 18 and 19). This structure was subsequently turned over to RVNAF in 1970, and the 8th Field Hospital was inactivated except for a small detachment which remained in Tuy Hoa.

LABORATORY AND RADIOLOGY SUPPORT

Intrinsic laboratory and radiology support for the field hospital in 1962 was spartan at best. Laboratory capability included one laboratory technician with enough equipment to perform routine blood counts and urinalyses, and radiologic equipment consisted originally of a single 30-kV field X-ray unit. One radiologist, Capt. (later Maj.) Bert Sosnow, MC, and one radiology technician were assigned to the hospital. Completion of a small but completely air-conditioned building and acquisition of a 100-kV unit subsequently provided more radiologic support. With the arrival of the 7th Medical Laboratory in May 1962, extensive support was available, including blood chemistry, electrolyte, bacteriologic, and parasitic studies, as well as histologic tissue processing. One serious drawback, which persisted until late 1966, was the lack of serologic diagnostic capability in-country. All serums were processed by the 406th

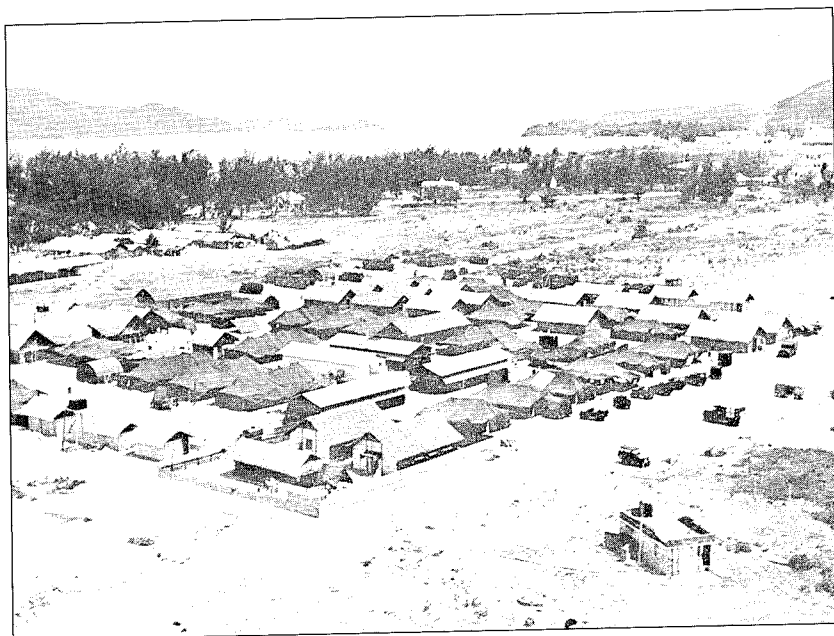


FIGURE 16.—Aerial photograph, 8th Field Hospital, 1963. (Courtesy, Spencer Walton, M.D.)

Medical Laboratory in Japan. Service was frequently slow and erratic and, in several instances, there was apparent disparity between clinical experience and reported laboratory results. Much of this difficulty was eliminated by the arrival of the 9th Medical Laboratory in-country in 1966.

In September 1963, a mobile laboratory unit of the 406th Medical Laboratory, Japan, was attached to USASGV. This unit replaced and absorbed the personnel and equipment of the 7th Medical Laboratory. Throughout the Vietnam conflict, this unit remained under command of USARJ (U.S. Army, Japan) but was attached to, and generally controlled by, various in-country medical headquarters. On 1 August 1966, the 9th Medical Laboratory became operational and acted as the control element for all medical laboratories in Vietnam, including the mobile unit of the 406th Medical Laboratory.

Despite its own intrinsic surgical capability and the addition of the three surgical specialty teams, the hospital had no blood bank capability, in terms of either equipment or a trained blood bank technician. Fortunately the internist, Major Barrett, had had training in clinical hematology, and both he and the assigned laboratory technician had received training in blood bank techniques at Madigan General Hospital before going to Southeast Asia. Typing serums and plastic containers for storing blood were obtained from the Madigan Army Hospital supply section and added to the 8th Field Hospital supply stock.*

*The value of this preparation was to be shortly demonstrated. Less than 3 weeks after becoming operational, the 8th Field Hospital received its first American combat casualty, a helicopter pilot who sustained serious gunshot wounds of the left hip, bladder,

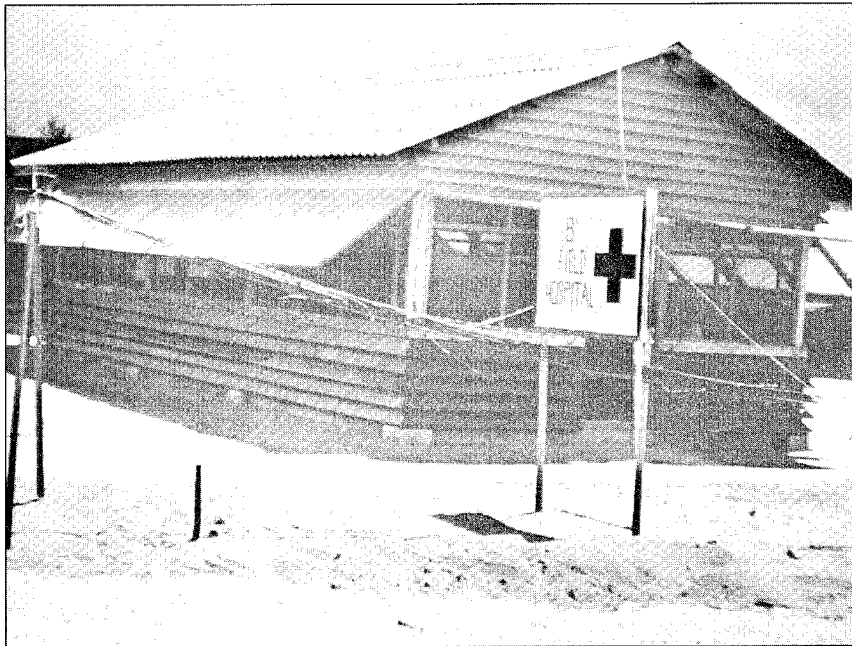


FIGURE 17.— Wood and screen facility near Headquarters, 8th Field Hospital, 1963.

It became immediately obvious that hospital personnel could not be used as a primary source of blood donations. Therefore, the 8th Field Hospital commander contacted all unit commanders of organizations in Nha Trang, requesting volunteers to have themselves blood-typed and registered in a “walking blood bank.” The response was gratifying, and several hundred donors were available whenever blood was required. In late 1962, arrangements were made with the 406th Medical Laboratory in Japan, and five units of fresh, type O, low-titer blood were flown to Nha Trang from Tokyo on a weekly basis. This supplement assured that a small reserve was always immediately available. Outdated blood was given to either the Vietnamese military or the Province Hospital in Nha Trang and was always used to good advantage for Vietnamese patients. This was an especially important contribution to these hospitals since the Vietnamese had a remarkable reluctance to serve as blood donors even for seriously injured Vietnamese casualties. Several cases are recorded in which American military personnel served as donors for Vietnamese patients because their own troops refused to donate. The dramatic story of the blood program in Vietnam which developed in subsequent years will be told in another volume.

and left ureter. During surgery, he required 19 units of whole blood, all of which was drawn from hospital personnel. Because of his extensive injuries, he was evacuated to Walter Reed General Hospital. Here an ironically fortuitous complication, a ureterocutaneous fistula, was found. During preoperative evaluation for fistula repair, an asymptomatic carcinoma of the left kidney was discovered and removed without difficulty.

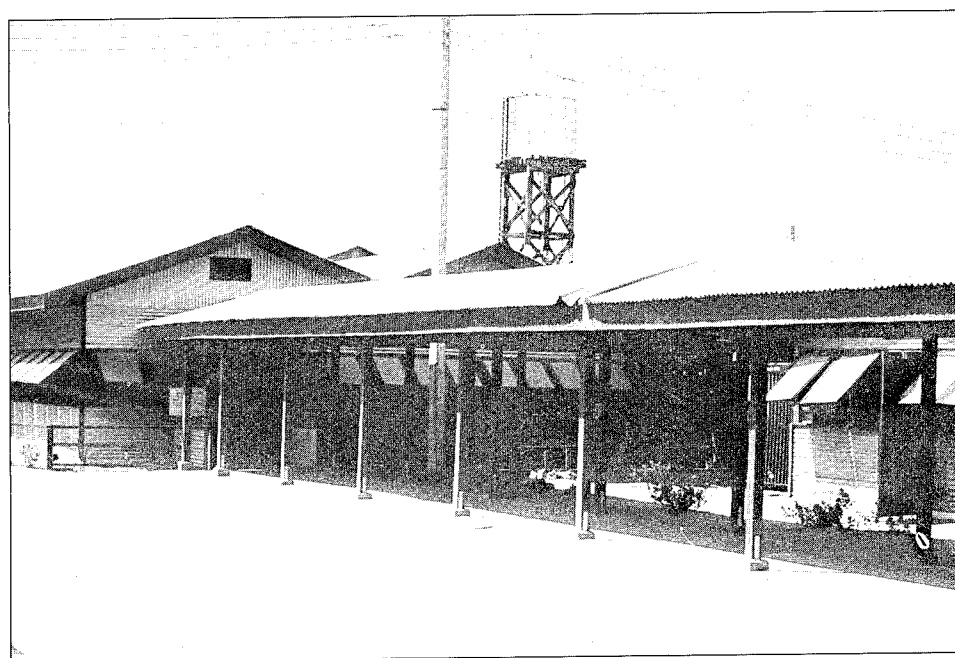
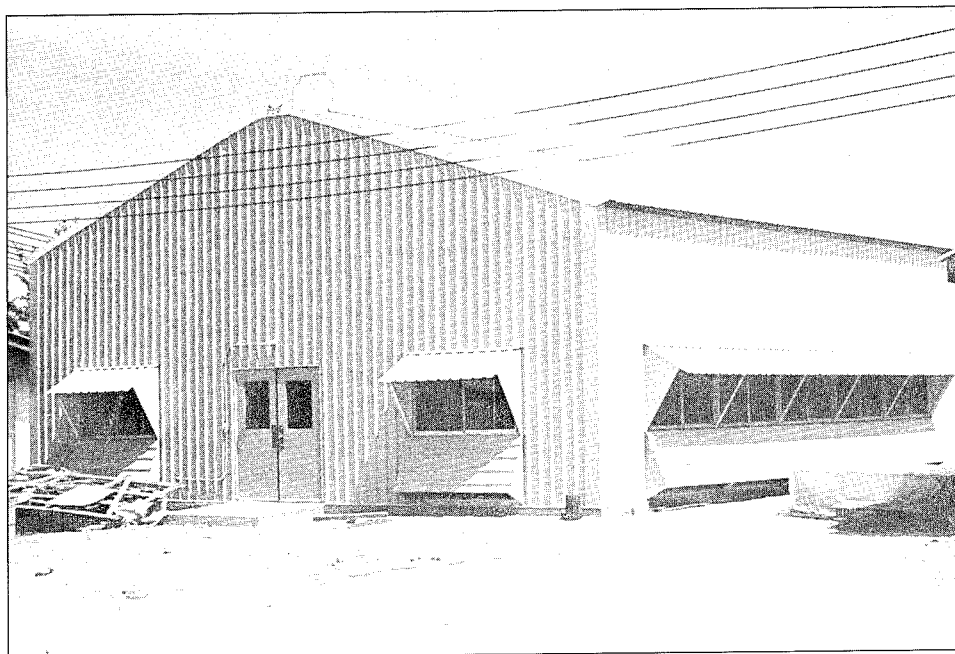


FIGURE 18.— The 8th Field Hospital, 1965. Top: Typical ward unit. Bottom: Messhall and walkway.



FIGURE 19.—The 8th Field Hospital, 1965. Aerial view of the permanent construction of the hospital.

MEDICAL PROBLEMS

American Troops

During 1962, the general health of the troops assigned to Vietnam was quite good. Most of the hospital admissions were for combat and noncombat trauma, upper respiratory infections, and nonspecific gastroenteritis. Stool cultures were obtained in most cases of diarrhea and reports generally revealed no pathogenic organism; the clinical disorders were mild to moderate in severity and required only supportive therapy. One outbreak of shigellosis which occurred in Qui Nhon affected 30 individuals, all of whom had uncomplicated disease. No other epidemic occurrences were recorded that year.

The most serious gastrointestinal disorder seen was amebic colitis. The occurrence was sporadic and noted primarily in troops who served as advisers to

Vietnamese units and who usually ate local food. While most cases had a typical clinical course, less severe manifestations were noted. Frequently, these patients complained of persistent diarrhea, some weight loss, and fatigue, but not of hematochezia, severe abdominal cramping, or temperature elevation. As there was concern about serious diarrhea for which no obvious cause could be found despite appropriate direct stool examination and culture, a program of routine sigmoidoscopy for such cases was instituted with rewarding results. Since diagnosis of acute amebic dysentery depended on the demonstration of motile trophozoites in the stool, freshly collected specimens were examined promptly for parasite identification. The frequency of diagnosis increased when smears were obtained directly from the base of ulcerated bowel lesions through the sigmoidoscope with the stool examination being done immediately.

All cases of amebic colitis, approximately 25 in that first year, responded to standard Diodoquin-tetracycline therapy. Despite awareness of liver abscess as a potential complication, no classic cases were observed. One patient, a 22-year-old white male, was admitted to the 8th Field Hospital with high fever, weight loss, marked jaundice, hepatomegaly, and a large abdominal mass with signs of intestinal obstruction. He was operated upon shortly after admission and the large mass in the transverse colon was resected and found to be an ameboma. Despite intensive therapy, he died shortly thereafter. At autopsy, the liver was diffusely involved with amebiasis, but no discrete abscess was found.

Perhaps the most ominous medical warning which was sounded in 1962 dealt with malaria. In 1922, Santayana admonished that "Those who cannot remember the past are condemned to repeat it." Unfortunately, he did not specifically mention malaria in his discourse. The discovery of the aminoquinolines, which were proven effective as early as 1943, produced a false sense of security concerning drug control of malaria despite isolated case reports of chloroquine-resistant falciparum malaria from New Guinea, Colombia, and Thailand (Young et al. 1963).

From March 1962 until February 1963, 20 cases of malaria were diagnosed and treated at the 8th Field Hospital. Nineteen of these were caused by *Plasmodium falciparum*, and all but one responded to the standard chloroquine regimen. Captain Sn., a 34-year-old Marine Corps officer, had served as an adviser for almost 1 year with Vietnamese troops in an endemic malaria area. He had routinely taken the weekly chloroquine prophylaxis tablet. On 27 August 1962, he was admitted to the hospital and found to have falciparum malaria; he was treated with chloroquine and responded well. He remained asymptomatic until 20 September when he was rehospitalized with typical symptoms and was found to have falciparum parasitemia and evidence of moderate hemolysis. He again responded to chloroquine therapy, given for a total of 6 days. Hematocrit rose to normal and he remained afebrile and asymptomatic for 14 days, but then developed recurrent chills, fever, and falciparum parasitemia. Since the problem of drug-resistant falciparum disease had been anticipated, arrangements were quickly made through the efforts of Colonel Tigertt, and the patient was evacuated by air to the Army Medical Research Project at the University of Chicago. Here, under the direction of Dr. Alf S. Alving, the first malaria case

caused by a chloroquine-resistant falciparum strain from Vietnam, the Sn. strain was described as was the strain's response to pyrimethamine (Powell et al. 1964).

Despite mounting evidence of the existence of this new strain of malaria, Colonel Tigertt (1972) reflected: "I was in Southeast Asia during this period and yet it is beyond my capabilities to describe the incredulity with which such reports were received by public health workers. It was equally difficult to gain acceptance of these facts elsewhere in the world." The tremendous impact which this new strain of malaria was to have upon the military effort in Vietnam, as well as its occurrence in Vietnam returnees in the United States (Barrett et al. 1969), is chronicled in Part III of this volume.

The story of the venereal diseases during the early years is an interesting one and reflects the impact of social "reform" upon their occurrence. Before mid-1963, only an occasional case of gonorrhea was treated at the 8th Field Hospital. Following the abrupt passage of the "morality law" sponsored by Madam Nhu, literally thousands of previously gainfully employed young Vietnamese women were suddenly without jobs. Legitimate dancehalls were closed, and the employees either became bar girls or turned openly to prostitution. There was a corresponding and striking rise in the incidence of gonorrhea, far out of proportion to the increase in troop strength within the country. Fortunately, most cases responded well to penicillin therapy. Almost at once, however, an occasional case of apparently penicillin-resistant gonorrhea (a real problem in later years) was observed (Pedersen 1972). Later, with the bacteriologic support of the 7th Medical Laboratory, these cases were shown to be examples of *Mima polymorpha* urethritis, sensitive to tetracycline. Striking by its absence was syphilis. Despite careful surveillance, examination of all ulcerated penile lesions, and appropriate VDRL (Venereal Disease Research Laboratory) serologic studies, no case of primary syphilis was diagnosed during that first year.

The second most commonly encountered venereal disease was chancroid. Diagnosis was made on the basis of penile ulceration, multiple ulcers often being present, and the demonstration of typical organisms of *Haemophilus ducreyi* on smear. Response to tetracycline was generally good and most buboes, when present, regressed spontaneously. Occasionally, however, because of a large, painful inflammatory mass in the groin, needle aspiration and even incision and drainage, with predictable slow healing, were required. No cases of lymphogranuloma venereum were diagnosed during this period.

"Exotic" infectious diseases, seen in significant numbers in later years, were encountered only occasionally in this early period. Two cases of typical scrub typhus were treated, but no murine typhus was diagnosed. Ten cases of febrile disease clinically compatible with dengue fever were observed, but no serologic diagnosis was available at that time. Subsequently, however, dengue fever was a recognized cause of FUO (fever of undetermined origin) in Vietnam. No cases of encephalitis were observed, although Japanese B encephalitis was also to become a serious problem in later years. Melioidosis was not recognized during this early period.

Vietnamese Patients

Physicians of the 8th Field Hospital had the remarkable opportunity to observe and treat a wide variety of diseases in the Vietnamese population. Admission of selected Vietnamese patients to the 8th Field Hospital was authorized by the MACV commander. The internist, Major Barrett, and the general surgeons, Major Rodriguez and Major Hartenstein, served as consultants both to the military hospital in Nha Trang and to the Cong Hoa Military Hospital in Saigon. They also visited the Province Hospital in Nha Trang and the Christian Mission Alliance Hospital just outside that city. In addition, each general surgeon spent a month at the Province Hospital at Quang Ngai.

While many of the cases seen were those ordinarily encountered by American physicians, others occurred only in the Vietnamese population and posed unusual and challenging problems. Tuberculosis was both a clinical and a public health problem. Extrapulmonary forms of the disease were common, especially bone and joint involvement, as was tuberculous meningitis in infants. Lepromatous leprosy was frequently seen, and while there were several leprosariums in the areas, most patients either were seen as outpatients or received no treatment at all. Trachoma was the cause of blindness in a large number of patients, and although a few corneal transplants were performed by local physicians, most patients suffered permanent visual impairment.

Bubonic plague has been endemic in Vietnam for centuries, and epidemic outbreaks are not uncommon. In 1962, several outbreaks were reported from surrounding provinces, although this was denied both at the province level and by the central government in Saigon. Late that year, 10 cases of plague occurred in civilians who were hospitalized and treated in the Province Hospital in Nha Trang (fig. 20). All cases were typical clinically, had characteristic gram-negative pleomorphic rod-shaped organisms on smear of aspirates from buboes, and responded well to streptomycin therapy. Although reported to the province government officials, the occurrence of the disease in Nha Trang was never officially recognized. Rats trapped within Army compounds, including the 8th Field Hospital, were found to carry plague, but no cases were reported in United States personnel. Vaccination for plague was required for all American troops in Vietnam.

Typhoid fever was another serious problem in the civilian population, and the mortality rate was high because of bowel perforation. During their visits to Quang Ngai, 8th Field Hospital surgeons operated upon 12 patients with this complication. Early recognition of peritonitis, use of chloramphenicol, and prompt externalization of the perforation, with or without subsequent bowel resection, were highly effective and this approach was subsequently adopted by Vietnamese physicians. No cases of typhoid fever were seen in American military personnel during this early period.

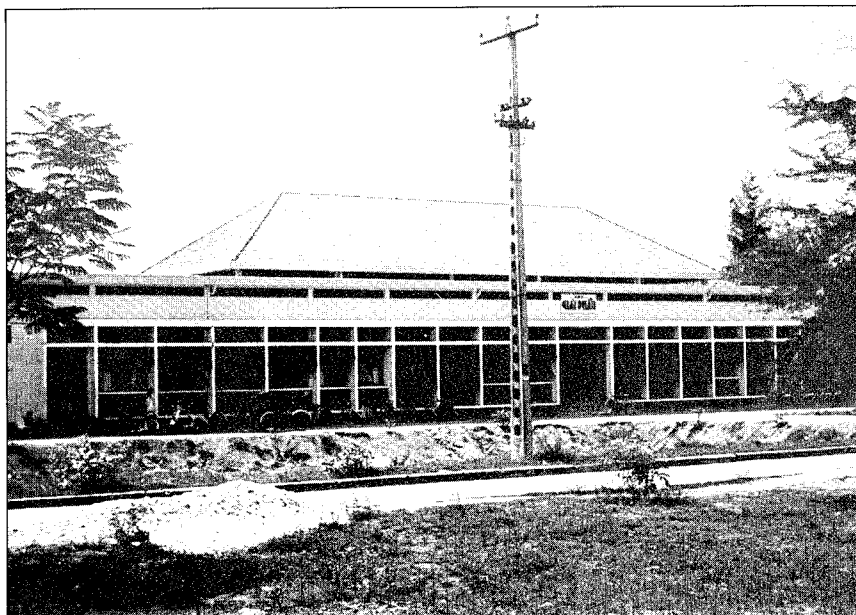


FIGURE 20.—Province Hospital, Nha Trang.

SUMMARY

The early years of medicine in Vietnam were a combination of frustration and great professional satisfaction. The challenge of establishing medical support for widely scattered American forces throughout Vietnam was met by the dedicated effort of both medical and nonmedical support troops. Shortages of supplies, inadequate communication, and a poor patient evacuation system coupled with an administrative and logistic burden too great for 8th Field Hospital facilities caused many problems. Innovation, improvisation, and total dedication to care of the sick soldier resulted in outstanding patient care despite these difficulties and set the stage for the unfolding drama of combat medicine in Vietnam which is subsequently described.

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Full-Scale Operations

Brigadier General Andre J. Ognibene, MC, USA

COMMAND STRUCTURE

As the medical commitment in Vietnam increased, the facilities of the 8th Field Hospital in Nha Trang were strained. On 1 April 1965, the 1st Logistical Command arrived in Vietnam and the 8th Field Hospital was subordinated to it. The requirement for providing the commander of the 1st Logistical Command with advice on all aspects of nondivisional medical support was clearly too large a task for the commander of the 8th Field Hospital. Therefore, the 58th Medical Battalion was assigned to the 1st Logistical Command to perform that mission.

The medical advisory effort at field level increased dramatically with the establishment of USARV (U.S. Army, Vietnam) Headquarters on 20 July 1965. The USARV medical section assumed staff responsibility for the health service of the U.S. Army medical structure in Vietnam. The USARV surgeon was given the task of planning medical service, which would be correlated at USARV Headquarters with troop concentrations and tactical operations. In November 1965, the 43d Medical Group arrived and assumed the medical service mission for the II CTZ (Corps Tactical Zone) while the 58th Medical Battalion continued its mission in III and IV CTZ's. I CTZ was predominantly under Marine Corps control.

With the continued medical buildup in Vietnam, The Surgeon General activated the 44th Medical Brigade for assignment to Southeast Asia. He had concluded that the medical brigade should be a major subordinate command of USARV Headquarters as were the aviation and military police brigades and the engineer command. However, despite efforts by the USARV surgeon, the brigade was assigned to the 1st Logistical Command and became responsible for medical units not organic to divisions or separate brigades. This involved coordinating activities of incoming units and supervising medical plans, operations, supply, and maintenance and professional medical and dental activities.

The 44th Medical Brigade expanded in proportion to the expansion of the military effort in Vietnam. By early 1967, more than 7,830 medical personnel operated under the unit (Neel 1973, p. 17). In the ensuing years, a clearly predictable confusion of command and control, support, and operations occurred between the 44th Medical Brigade and the Professional Services Division of USARV Headquarters. The senior professional consultants were assigned to the Office of the USARV Surgeon. Therefore, their recommendations often were

made directly to the USARV surgeon but involved units under the control of the 44th Medical Brigade. Medical officers were assigned and transferred by the USARV surgeon's office, often without the knowledge of the 44th Medical Brigade commander. Had medical and command control activity been placed in an integrated command structure initially, duplication and confusion could have been avoided.

The functions of the Professional Services Division of the Office of the USARV Surgeon expanded rapidly as tactical operations and troop strength increased. By June 1967, the USARV surgeon was the senior medical officer and also controlled the highest level of professional talent in the Professional Services and Plans and Operations Divisions. On 10 August 1967, the 44th Medical Brigade was released from the 1st Logistical Command and assigned directly to USARV Headquarters. This unified the medical service in Vietnam, with the USARV surgeon now also becoming the commanding general of 44th Medical Brigade. He was able, therefore, to exercise full command and control responsibility as the brigade commander while retaining staff responsibilities as USARV surgeon.

The shift of the 44th Medical Brigade to USARV Headquarters did not solve all problems, however. The duplicate functions of the 44th Medical Brigade and the USARV surgeon's office remained a major deficiency until early in 1970. With the creation of the U.S. Army Medical Command, Vietnam, more efficient medical service, including field-level medical service, could be provided throughout the country, and duplication of effort at all functional areas of command was eliminated (Neel 1973, p. 28-31). It was indeed ironic that only as the war phased down did the medical service achieve a structural organization that was functional, organized vertically, and without duplication. The consultant staff finally had been placed directly in contact with administrative and operations units.

THE CONSULTANT SYSTEM

The consultant staff grew out of a requirement to provide high quality professional advice to the USARV surgeon on all aspects of health-care delivery to the U.S. soldier in Vietnam. Dental, veterinary, preventive medicine, nursing, food service, optometry, and pharmacy consultants were among those assigned to assist in the development of plans and operations. The major professional consultant efforts were in internal medicine, neuropsychiatry, and surgery. The role of the medical consultant expanded rapidly as the number of medical units increased.

To standardize medical care of the soldier, the medical consultant visited all units providing that care. Following visits to treatment facilities, he made policy recommendations to the USARV surgeon. By 1969, medical consultants had taken direct charge of assignment and placement of internists in USARV hospitals and also provided consultant services to all organic medical units of combat organizations. The consultant channel of communications overlapped traditional administrative chains of command and extended from an area

medical service concept into the traditional field and divisional medical service systems. Because of artificial command boundaries early in the war, the relationship of the medical consultant to internists in Vietnam was sometimes loose and informal and often unofficial. It was always a strong professional relationship, however. Thus, the consultant was able to guide medical practice, establish policy, improve effectiveness in medical care, develop communications channels, and provide information to both divisional and nondivisional units.

The Professional Services Division was headed by the deputy USARV surgeon, who served essentially as the chief of professional services for the Vietnam medical effort. This organizational structure followed traditional hospital or other civilian medical organizational arrangements. Although throughout 1967 and 1968 most consultants were assigned to both the 44th Medical Brigade and the USARV surgeon's office, permitting command and control authority over medical activities in both jurisdictions, those in the fields of medicine, neuropsychiatry, and surgery were not dually assigned. Despite this command and control deficiency, medical consultants could still exercise a powerful influence over standards in internal medicine. Not until 1970 did the internal medicine consultant carry the weight of the U.S. Army Medical Command into his visits and recommendations. By this time, the war had begun to wind down.

A critical aspect of personnel assignment was the proper placement and utilization of specialists in internal medicine. Early planners did not realize that the requirement for care in internal medicine in USARV hospitals was equivalent to that in any hospital medical service in the United States. By 1969, control of personnel assignments allowed the medical consultant to place only fully trained B3139 (board certified) or C3139 (board qualified) internists in USARV hospitals. Before this time, D3139 (partially trained) physicians were not distinguished clearly from those fully trained, and assignments to hospitals rather than field units occasionally made a partially trained individual a consultant to one fully certified. The medical consultants maintained this assignment control until the American withdrawal. With frequent visits to hospitals and medical groups, the necessary coordination was continuous, allowing for an effective use of available internists.

The need to attach a fully trained internist to surgical hospitals and MUST (medical unit, self-contained, transportable) units was carefully assessed as the war progressed. While some surgical hospitals, such as the 27th Surgical Hospital, did accept other than wounded patients, most operated strictly in a surgical combat support role. These hospitals did not have the laboratory support to allow much more than a blood count, urinalysis, and necessary X-rays. Consequently, following initial surgery, patients were moved to an evacuation hospital or directly to Japan. Since the internist had been serving as a triage officer or surgical assistant, a position which could be filled adequately by a D3139, removal of fully trained internists from these hospitals began in 1968 and was complete by 1969. This allowed concentration of 52 internists in 13 hospitals with improvement in the quality of care as well as the development of subspecialty expertise in designated centers. These refinements dictated even finer control of assignments by the medical consultant to maintain the center

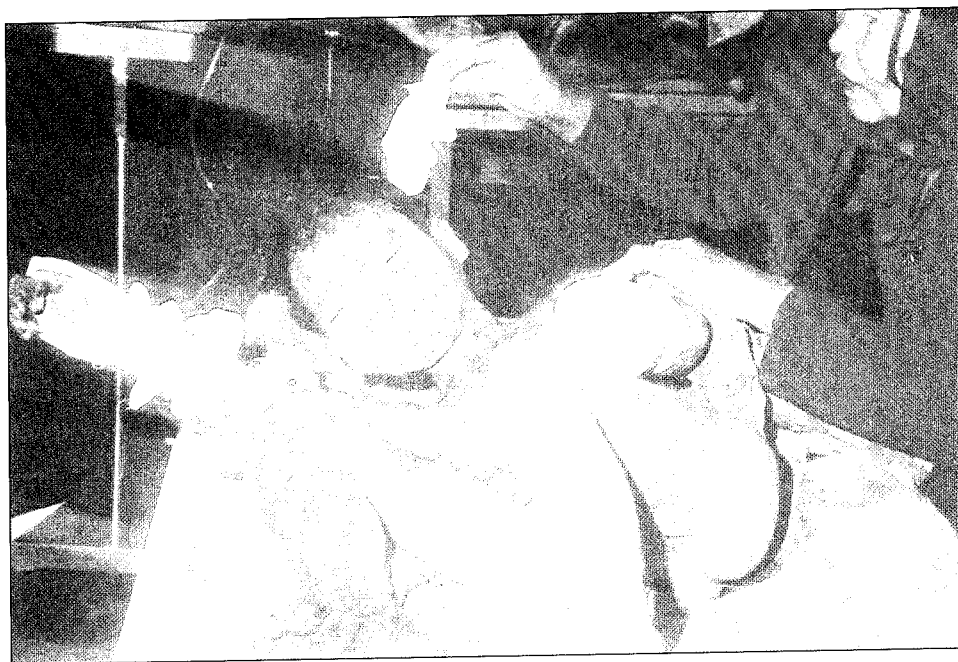


FIGURE 21.—Severely injured child being attended in a U.S. medical facility under the provision of the Civilian War Casualty Program.

designations. The subspecialty designations of internists in 1970, by hospital, were as follows:*

3d Field (Saigon)—hemodialysis; coronary care unit; gastrointestinal endoscopy; hematology; pulmonary function laboratory; dermatology
 93d Evacuation (Long Binh)—neurology (EEG); snake bite center; endocrinology
 24th Evacuation (Long Binh)—peritoneal dialysis; dermatology
 95th Evacuation (Da Nang)—angiography; cardiology; dermatology; snake bite center
 8th Field (Nha Trang)—neurology (EEG); gastroenterology

The subspecialty assignments placed expert personnel in a position to use their medical skills for those patients who required them. Unfortunately, despite an obvious need, no one assigned to Vietnam in a patient-care capacity had any background in the subspecialty of infectious disease. It was in this area that the greatest need, and the most serious deficiency in assignment, existed. By 1969, an internist was attached to the 9th Medical Laboratory as a liaison in infectious disease, and a specific effort was made to improve the capability of diagnosing FUO (fever of undetermined origin). While significant research continued, the actual clinical education of the internist in infectious disease was accomplished by self-instruction and the timeless methods of trial and error and experience.

*Lt. Col. T. A. Verdon, Jr., MC, USARV Medical Consultant, Nov. 1969-July 1970: Personal communication.

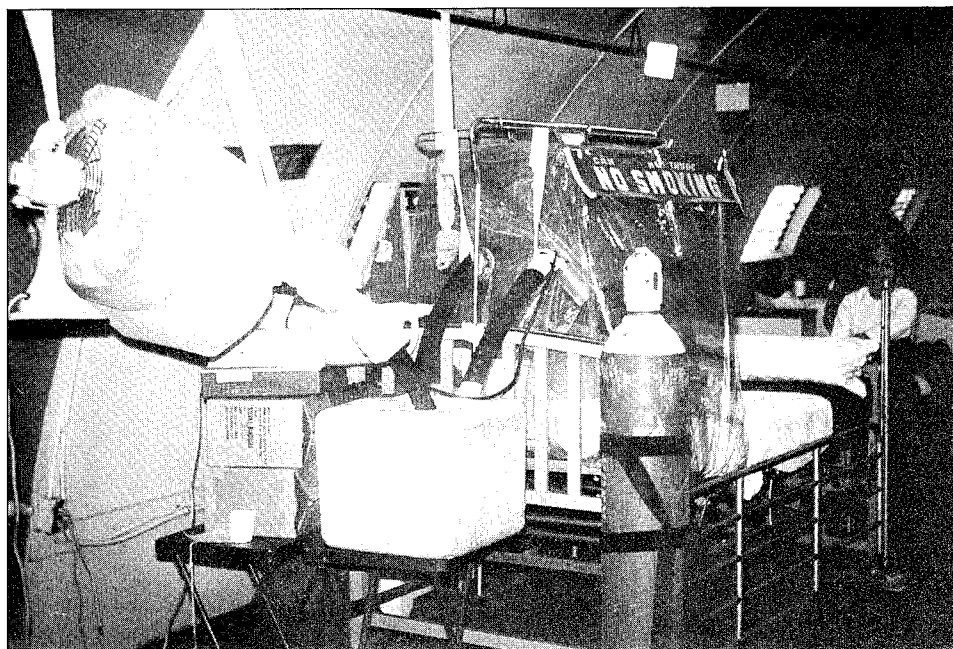


FIGURE 22.—Treatment of infants in combat hospitals taxed the ingenuity of the medical staff. A makeshift croupette at the 24th Evacuation Hospital used a fan, plastic bags, hoses, Styrofoam ice chest, oxygen tank, and portable oxygen tent.

The assignment of pediatricians to Vietnam was prompted by the establishment of the CWCP (Civilian War Casualty Program). MACV (Military Assistance Command, Vietnam) Directive Number 40-14 (MACV-66, sec. 3a) stated: "Vietnamese civilians injured by an instrumentality of the Armed Forces of the United States are authorized complete emergency care, including hospitalization when necessary. Care is authorized to be continued until the patient's condition is stabilized sufficiently to permit discharge or transfer to a civilian hospital, or to a civilian facility for convalescence." The U.S. Army was thus directed to develop a program of care for civilian casualties, estimated at 50,000 yearly (fig. 21) (Neel 1973, p. 166). In 1967, a temporary allocation of 300 beds in USARV hospitals was made for this purpose. Three Army hospitals, with a bed capacity of 1,100, were then designated for the care of Vietnamese civilians.

By 1968, all USARV hospitals accepted Vietnamese civilians on a space-available basis. Pediatricians initially were assigned to these facilities, but pediatric care never developed beyond a small effort for a limited number of patients (fig. 22). Before the assignment of pediatricians to hospitals, care had been provided by an internist-surgeon team and, when available, a general medical officer with some pediatric training. At the peak of assignment in 1969, six pediatricians were assigned to USARV hospitals, as large a complement as the



FIGURE 23.—Vietnamese child with advanced cirrhosis of unknown cause brought to a U.S. military medical facility although the parent was reluctant to release the child for inpatient care.

dermatology commitment. Their caseload was small and their time was best spent assisting the internist in adult care. Most pediatric care was provided by MEDCAP (Medical Civic Action Program) or through self-help and MACV programs. Most important, Vietnamese families were reluctant to release their children for care in USARV hospitals (fig. 23). After 1969, medical consultants urged that pediatricians not be assigned to USARV hospitals. By the end of 1971, the abortive pediatric program in USARV hospitals had ended.

PROBLEMS OF AREA MEDICAL SERVICE

While the development of the practice of internal medicine proceeded rapidly in USARV hospitals, there could be no parallel development in the forward area or in unit-level medical service. The absence of significant laboratory support and the exigencies of missions made the development of that expertise in field units impractical; more important, the ready availability of consultation at fixed-hospital installations made it unnecessary. Some individual physicians were able to establish investigative and therapeutic protocols in some areas of medicine but, for the most part, the advent of the helicopter and rapid air evacuation removed any requirement for sophistication in medical practice in the forward area (fig. 24). A decision as to whether the patient was suffering



FIGURE 24.—Dustoff arriving at the 24th Evacuation Hospital helipad.

from a self-limited or a progressive disease or required more than symptomatic therapy was sufficient at the unit level. The battalion surgeon's role thus changed considerably, and in the transition, many difficulties were encountered.

In general, the medical education of the unit surgeon did not prepare him for the myriad skin diseases, diarrheal syndromes, fevers, and other problems. He was hampered by the lack of meaningful publications. No written systematized approach to common problems was available or being developed. He was unable to rely totally on his enlisted support since, although well trained, they too lacked Vietnam experience. If any major lesson is learned from this conflict, it should be that therapeutic methods must be designed for common problems to prevent the disorganization and mismanagement which invariably occur when proper medical background is lacking.

Despite the excellent efforts in the field units, many difficulties arose in diagnosis and triage of patients whose illnesses were severe or prolonged. Often patients were held for an inordinate time in outlying units before transfer. Statistics will never reveal the number of days lost when officers and enlisted personnel were first held out of duty for a few days for skin disease, fever, or other causes, and then hospitalized at units or clearing companies for further therapy. Heavily staffed division-level medical services had the space and physicians to hold patients for many days and to institute therapeutic intervention of a very significant nature (fig. 25). The condition of patients evacuated to USARV

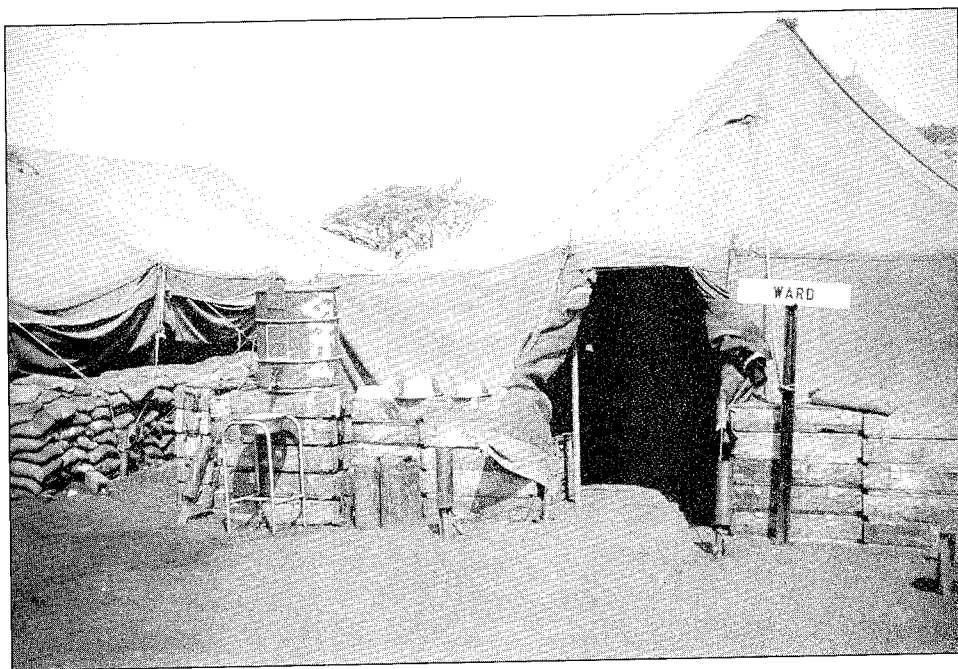


FIGURE 25.—Top: Typical aid station supporting a fire base. Tent structures were heavily sand-bagged for protection. Bottom: Aid station in an advanced area, well dug in and appropriately marked. Note the chaplain's proximity to the aid station.

hospitals had often been complicated iatrogenically, and diagnosis was very difficult when antibiotics had been given in the absence of cultures.

Such problems made it clear that in addition to USARV-wide conferences, newsletters, reports, and educational and training programs, a professional channel of communication from hospital to local unit level was urgently needed. The development of the MEDCON (Operation Medical Consultant) concept improved triage capabilities in field units and helped prevent unnecessary therapeutic maneuvers at a unit incapable of proper followup and treatment of serious disease. Physicians needed to communicate with other physicians directly when patient welfare was concerned.

Field medical service was, in reality, an extension of hospital service in the Vietnam evacuation concept, and the physician caring for the patient along the route of evacuation had to perform at the required level for the job at hand. He was encouraged to seek advice of those qualified to give it, who in turn were directed to extend themselves to provide it. In the absence of this cooperation, medical service deteriorates to isolated enclaves trying to outperform each other, often for unit aggrandizement rather than in the best interest of the patient. The unique superimposition of area medical service upon field medical service in Vietnam offered the opportunity to exploit the best of both systems. Resolution of conflicts or problems had to be decided in favor of the patient, the U.S. soldier. In the spirit of this philosophy, the USARV surgeon in 1969, Brig. Gen. Hal B. Jennings, issued a directive to the commander of the 44th Medical Brigade regarding internal medicine services, from which the following is excerpted.

1. * * * The Chief, Department of Medicine in the 44th Medical Brigade hospitals will develop in conjunction with supported division, group, and separate brigade surgeons a system of liaison visits on a recurring basis, the aid station or unit surgeon visiting the hospital medical service on a monthly basis, and the chief of medicine and his representative visiting the unit surgeon on a quarterly basis; for certain subspecialties such as dermatology, this would be necessary more frequently.

2. It is suggested that standard operating procedures be introduced in the following areas and that these areas be continually under active discussion: (a) selection of patients for evacuation; (b) types of patients requiring consultation; (c) efficiency of consultation systems; (d) methods of patient evacuation; (e) handling of culture materials; (f) improvement of laboratory capability; (g) methods of treatment of medical disease; (h) increasing familiarity with current medical practice; (i) review of specific hospital routines as they affect the unit.

3. This program will require full support by the 44th Medical Brigade in the area of transportation and billeting when necessary. Hospital commanders should give their full measure of support to the chiefs of medicine in this effort.

4. Monitoring will be accomplished through remarks by the chiefs of medicine in the monthly medical reports: aid station/dispensary commanders visiting the hospitals, units visited, personnel contacted, areas of discussion and unresolved problems. The requirement for these remarks in the report will be announced in the Medical Consultant's Newsletter.

5. The MEDCON concept was presented at the USARV Surgeon's Conference on 28 March 1969 and was accepted with great enthusiasm by the division surgeons, and the group and separate brigade surgeons. The group was told that this letter would be dispatched to the 44th Medical Brigade and to have their physicians initiate liaison visits to USARV hospitals rendering them support on or about 1 May 1969.

The unified, total-care concept allowed unit surgeons to participate in the

complete care of their patients. Faced with the exigencies of the situation, these competent physicians had often embarked on therapy in the absence of available diagnostic facilities. For the patient with self-limited disease, this was not a problem, but difficulties clearly arose in the complex case since therapy often clouded diagnosis even further. MEDCON allowed the unit surgeon and the hospital-based internist to view each other's practice firsthand, recognize individual problems, raise their mutual esteem, coordinate the delivery of health care, and bridge an artificial organizational gap. It brought forward-area medical service into the professional channel of evacuation and control and unified professional care policies in internal medicine throughout the U.S. Army in Vietnam.

EDUCATION AND TRAINING

With the appearance of problem cases of considerable interest at each hospital, medical consultants recognized that individual visits to USARV hospitals could not bring together all the internal medicine activities in Vietnam. Conferences for all chiefs of medical services began in 1968. At these meetings, difficult cases were discussed and policies were reviewed. Under the guidance of the medical consultant, new policies were formulated. One of these was the requirement to enforce 2 days of afebrile status before transfer of falciparum malaria patients to the 6th Convalescent Center. Two patients had died en route in the previous months, one from cerebral malaria and one with splenic rupture. Neither patient had been completely stable or become afebrile before transfer (Ognibene 1969a).

The medical and surgical consultants initiated a combined 2-day conference at the 93d Evacuation Hospital in Long Binh in 1968, and the following list of the subjects discussed on 16 May attests to the breadth of medical interest and expertise represented:

Introduction—Lt. Col. Gene V. Aaby, MC
The American in Asia—Col. Matthew D. Parrish, MC
Fevers of Undetermined Origin—Maj. Fred R. Stark, MC
Clinical Manifestations of Melioidosis—Maj. Neal W. Culp, MC
Malaria—Lt. Col. Nicholas F. Conte, MC
Hepatitis—Col. Robert E. Nitz, MC
Diarrheal Diseases—Lt. Col. Joseph D. Bartley, MC
Rabies—Maj. Lawrence H. Gottlieb, MC
Liver Function Tests—Capt. Ralph G. Oriscello, MC
Renal Failure—629th Medical Detachment (Renal) physician
Army Psychiatry—Capt. Herbert Block, MC

The first USARV-wide internal medicine conference was held on 31 January 1969 at the 3d Field Hospital in Saigon. Maj. James H. Kneppshield, MC, of the 3d Field Hospital, was morning session moderator and Lt. Col. (later Brig. Gen.) Andre J. Ognibene, MC, USARV Medical Consultant, was moderator in the afternoon. Thirty-eight internists from USARV hospitals and 65 unit surgeons attended the intensive 1-day program, which had the following agenda:

Opening remarks—Col. Merle D. Thomas, MC, 3d Field Hospital

Problems in Diagnosis and Treatment of Amebiasis—Capt. Henry B. Head, MC, 3d Field Hospital
Diagnosis and Management of Renal Insufficiency—Capt. William J. Stone, MC, 3d Field Hospital
Management of Cardiac Arrhythmias—Capt. Theodore L. Paletta, MC, 3d Field Hospital
Diabetes and Mucormycosis—Capt. Lawrence W. Koch, MC, 93d Evacuation Hospital
Solitary Hyperfunctioning Thyroid Nodules—Maj. Clyde W. Wagner, Jr., MC, 24th Evacuation Hospital
Exercise in Hepatitis—Capt. Lawrence H. Repscher, MC, 6th Convalescent Center

With the conference came the opportunity to discuss standardizing approaches to diseases in Vietnam. Physicians in internal medicine services of the 44th Medical Brigade hospitals and field-unit surgeons from supported units exchanged information which proved fruitful in the ensuing year.

In July 1969, a second internal medicine conference, a 1-day program at the 8th Field Hospital in Nha Trang, was attended by more than 80 Medical Corps officers. The third annual internal medicine conference, held in 1970 at Cam Ranh Bay, was the last USARV-wide conference because of the decline of medical activity in Vietnam.

The feasibility of holding a large-scale medical conference during hostilities was demonstrated by the number of persons able to attend. Because of the difficulty in communication in widely scattered areas and the need for direct dissemination of information and discussion of mutual problems related to improvement in patient care, the requirement to bring physicians together outweighed the risk. The medical consultants hosting these conferences agreed that there was no better way of disseminating valuable information.

The medical consultants issued a monthly medical report and a professional newsletter which, under the MEDCON concept of 1969, were distributed to all field units. These, and the USARV Medical Bulletin which began publication in 1966, were of great value. The bulletin contained many administrative and professional articles and provided an opportunity for expression from both field unit and hospital service. With the talented assemblage of Regular Army and drafted internists in Vietnam, a compendium of guidelines and principles was readily developed for the newly arrived internist. The data collected were assembled in January 1969 and published in the USARV Medical Bulletin in an internal medicine issue. The bulletin was designed to be a means of rapid publication of professional material of consequence emanating from the Vietnam experience. The introduction to the first compendium (USARV-MB 1969) stated its aims as follows:

A number of questions regarding disease trends and basic medical policies have been raised by physicians newly arrived in-country. The purpose of this publication is to provide a concise, up-to-date background on those diseases which are of military importance or of particular medical interest. Secondly, it is designed to provide a ready reference to pertinent USARV Regulations and policy letters, TB Meds and selected articles in the current medical literature. Thirdly, it is designed as a guide book for those entering the practice of internal medicine in Vietnam. Knowledge of these standard operating procedures is necessitated by the need for maintaining continuity of care as the patient progresses through evacuation channels. Familiarity with the variety of illness seen here will also facilitate therapy at a local level and obviate the need, in many cases, for multiple consultations and subsequent loss of duty time.

In January of 1970 and 1971, a revised edition was formulated and

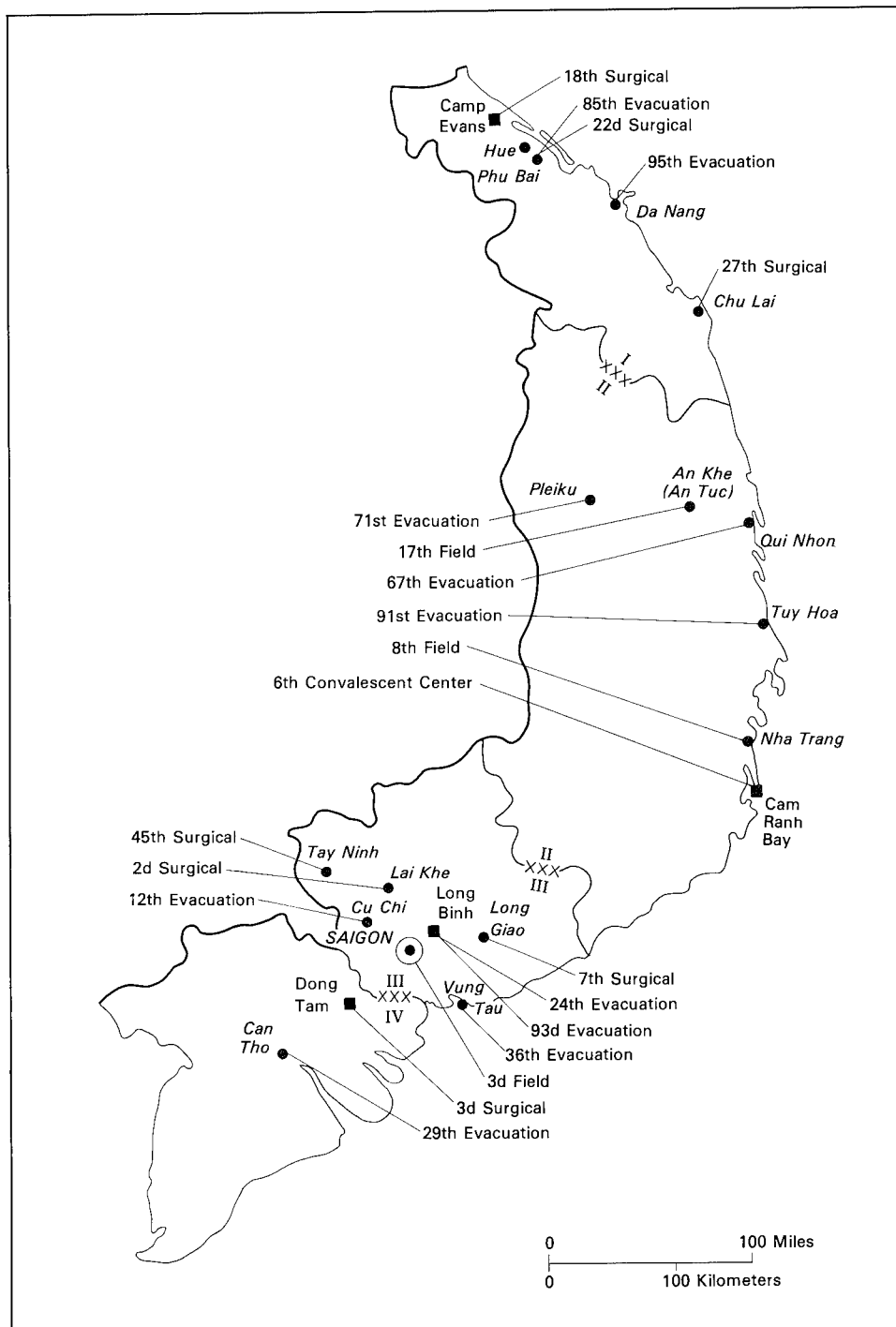
distributed to each physician arriving in Vietnam. As a medical source book, the compendium was an invaluable aid to the physician unfamiliar with the practice of medicine in Vietnam. For many, it was the only medical guidebook during their first months in the country. The table of contents of the 1971 edition (USARV-MB 1971) indicates the breadth of subject matter covered, which included the following: malaria, hepatitis, shigellosis, amebiasis, nonspecific gastroenteritis, tropical sprue, cholera, parasitic infestations, typhoid fever, plague, melioidosis, tuberculosis, tetanus, gas gangrene, leptospirosis, dengue fever, chikungunya, Japanese encephalitis, scrub typhus, murine typhus, rabies, snake bites, dermatologic problems, venereal diseases, immunization, toxins, allergies and asthma, heat injury, duodenal ulcer, cardiac disease, trauma (early treatment of wounds and injuries), diagnosis and management of acute renal failure, and use of blood and blood products in Vietnam.

In addition to the medical education effort in Vietnam, the medical consultants were responsible for administering the American Board of Internal Medicine examination each year. Despite difficulties in transportation, site selection, air conditioning, security, and communications, each of the examinations was given without loss of records or absence of an assigned participant. The innumerable problems surmounted to achieve this end are recorded only in many anecdotes of frustration, panic, and tears. It remains a tribute to the proctors that management errors were less common in a combat theater than in some centers in the United States. To the internist, the effort meant no loss of time between his eligibility for examination and the time he was able to take it. This had a positive impact on his morale, renewing his faith that the system was responsive and his efforts in patient care were recognized and appreciated.

HOSPITALIZATION AND EVACUATION

In 1965, the incomplete 8th Field Hospital at Nha Trang, with a 100-bed capacity, was the only U.S. Army hospital in-country, and the 100-bed Navy facility in Saigon was the only other U.S. military hospital. With the buildup of U.S. combat forces in 1965, a large number of hospital units were deployed to Vietnam. Initially, because of limited beds, patients had to be evacuated from the country within 15 days. A small number of special cases were retained for 30 days. By mid-1966, a 30-day holding policy was finally invoked for Vietnam. Those patients who could be treated within this period and returned to duty were held in-country (Neel 1973, p. 60).

In early 1966, 1,627 beds were available in Vietnam (Neel 1973, p. 60). With the deployment of additional hospitals to the country throughout 1966 and 1967, the number of Army hospital beds rose, by 31 December 1968, to more than 5,000 (AMEDD-AR). At the peak of deployment, hospitals were located in accordance with the division of Vietnam into four Corps Tactical Zones (map 1). As Army strength fell from 331,100 in January 1970 to 119,700 by the end of 1971, the number of available hospital beds in Army facilities decreased proportionately from 3,513 to fewer than 1,000 (MACV-73). By the end of 1972, the medical operations of the U.S. Army in Vietnam had ended.



MAP 1.—U.S. Army hospitals in South Vietnam, 31 December 1968.



FIGURE 26.—The 45th Surgical Hospital, Tay Ninh.

Not all USARV hospitals were equipped to handle medical patients. Evacuees at surgical hospitals generally required no internal medicine service. Fully trained internists were not assigned to the 2d Surgical Hospital in Lai Khe, the 45th Surgical Hospital at Tay Ninh (fig. 26), the 3d Surgical Hospital in Dong Tam, the 7th Surgical Hospital at Blackhorse Firebase at Long Giao south of Xuan Loc, the 18th Surgical Hospital at Camp Evans, or the 22d Surgical Hospital at Phu Bai. However, medical services were functional at the 12th, 24th, 29th, 36th, 67th, 71st, 85th, 91st, 93d, and 95th Evacuation Hospitals (fig. 27), the 3d, 8th, and 17th Field Hospitals, and the 6th Convalescent Center. During 1969, the year of peak troop strength, 52 internists were assigned to hospitals and functioned in teams of three and four. As hospital units were deactivated or redeployed, the need for specialists in internal medicine was reduced proportionately.

In general, most internal medicine services in Vietnam had 100 to 200 beds. Since hospitals were built in a wide variety of configurations, a number of unusual wards existed. Throughout the war patients at the 93d Evacuation Hospital were treated in bunk beds. The nurses' station was located at the center of a large cross, and hundreds of patients could be seen from the single nursing station. The initial lack of air conditioning in these wards made it difficult to treat serious problems of fever and fluid and electrolyte balance; air conditioning was at times the only requirement to treat severe miliaria rubra (prickly heat). During 1966 and 1967 the physical plant improved. Through concerted

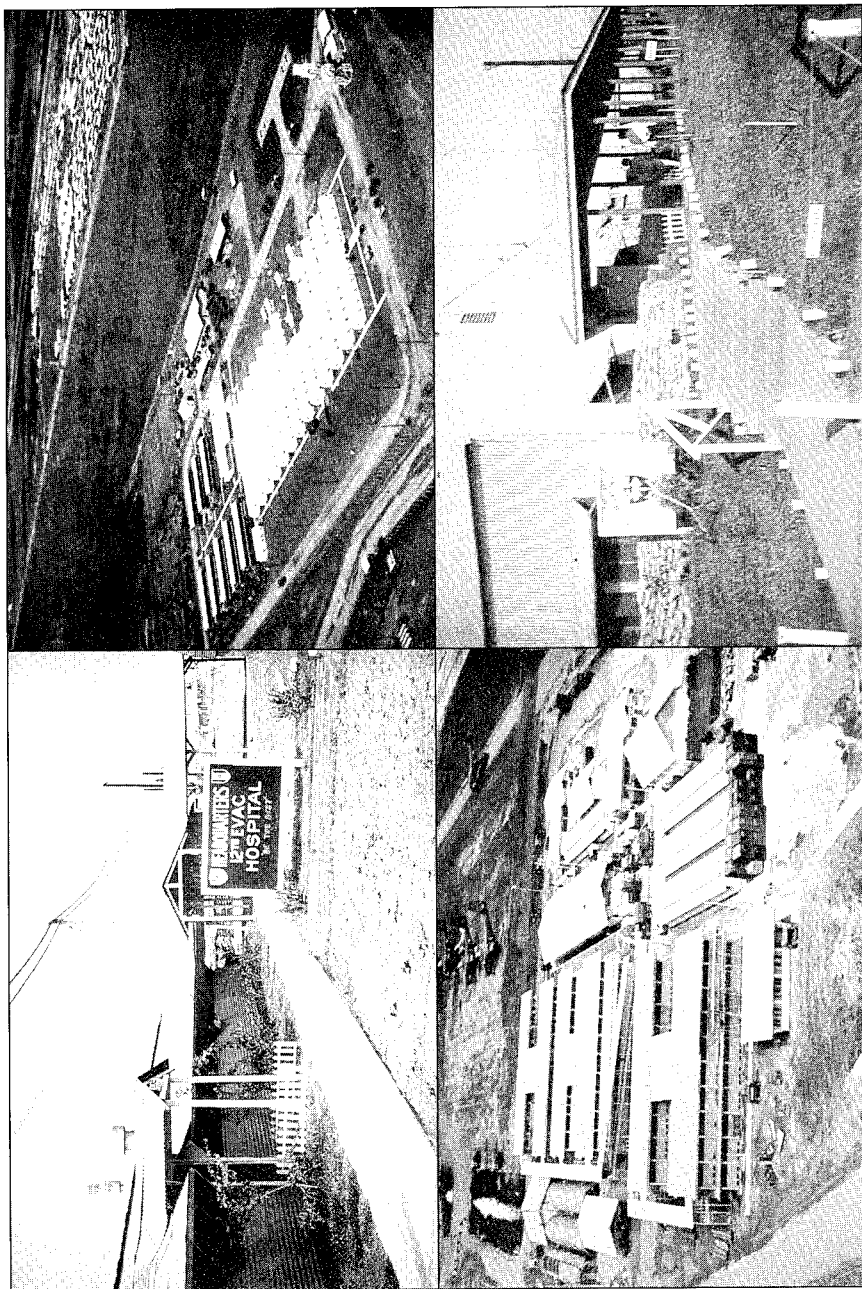


FIGURE 27.—Evacuation hospitals in South Vietnam. Top left: The 12th, at Cu Chi. Top right: The 29th, at Can Tho. Bottom left: The 67th, at Qui Nhon. Bottom right: The 71st, at Pleiku.



FIGURE 28.—Aerial view of the 3d Field Hospital complex.

efforts of contractors, the Corps of Engineers, and self-help medical personnel, most hospitals by the end of 1968 were comparable to many modern hospitals in the United States. In particular, the 3d Field Hospital was considered by many to be the “Walter Reed of the East” (fig. 28).

In addition to the internal medicine activities in evacuation and field hospitals, a major medical effort was centered in the convalescent center at Cam Ranh Bay (fig. 29). Since malaria and hepatitis were significant medical problems, the number of patients who would be evacuated out of country was high. These patients could not be held in evacuation or field hospitals because of lack of bed space. Under the recommendations of Lt. Gen. Leonard D. Heaton, the development of a convalescent center began. On 29 November 1965, the 6th Convalescent Center opened with 1,300 operating beds (Hall and Shafer 1970, p. 1) (fig. 30). A number of excellent studies on falciparum malaria and infectious hepatitis were performed there and are alluded to in the chapters related to these diseases.

The 6th Convalescent Center provided a controlled physical activity program and integrated this program with special physical therapy classes. Supervised calisthenics were performed in a graduated program of physical reconditioning (fig. 31). This allowed patients in the recovery stages of acute infectious diseases to return to duty in top physical condition. Any relapses or physical difficulties occurred at the center under the direct supervision and observation of the medical staff and the physicians in charge. The convalescent center in-



FIGURE 29.—Aerial view of the 6th Convalescent Center established on the beach of the South China Sea at Cam Ranh Bay.

egrated physical activity with the early medical and surgical care of patients. Patients evacuated from the country with malaria were reduced from 27 percent of medical evacuees in 1966 to about 10 percent by 1968. Specific figures are not available for hepatitis patients, but most medical consultants believed that hepatitis evacuations had been similarly reduced. In addition, after 1966, evacuation for medical causes never exceeded 20 percent of the total patient evacuation (AMEDD-AR, J).

The convalescent center concept was not new, having been initiated in 1943 and further refined in the Korean war. Patients with hepatitis, for example, had been returned to duty within 20 days during the Korean conflict. Early return to duty was also achieved at the convalescent center during the Vietnam war with a significant savings in combat manpower. The early physical activity concept brought the average theater length of stay to 7 days in forward hospitals and 18 days at the convalescent center, well within the limits of the 30-day evacuation policy (Repsher and Freeburn 1969; Hall and Shafer 1970, p. 6). Thus almost all patients with falciparum malaria, hepatitis, and scrub typhus returned to duty in Vietnam (Hall and Shafer 1970) (tables 3 and 4).

Out-of-country evacuation in the early years was generally by plane to Clark Air Force Base in the Philippines and subsequently to CONUS (continental United States). Not until the summer of 1966 did jet aircraft take patients from Vietnam directly to CONUS with one stop in Japan. Following this change in



FIGURE 30.—Patients arriving for rehabilitation at the 6th Convalescent Center.

evacuation routes, a fixed-bed capability was developed in Japan to care for patients who could be expected to return to duty within 60 days. This significantly reduced the requirements on medical services within the United States and actually maintained at the same level or reduced direct evacuation to CONUS despite the increasing troop strength. Army patient arrivals in CONUS from the Pacific were as follows:

1966	4,973	1970	7,364
1967	10,671	1971	7,473
1968	10,800	1972	16,033
1969	11,415		

A change in policy on drug abuse patients, on 25 June 1971, increased the total number of patients being channeled from Vietnam to the United States. In addition, facilities in Japan were reduced (AEROMED-2) (fig. 32).

On 30 October 1971, the 6th Convalescent Center at Cam Ranh Bay ceased to operate as a convalescent center. Drug treatment centers were established in this facility as well as at Long Binh (MD-IM3). By 20 April 1972, the medical installation at Cam Ranh Bay had closed permanently.

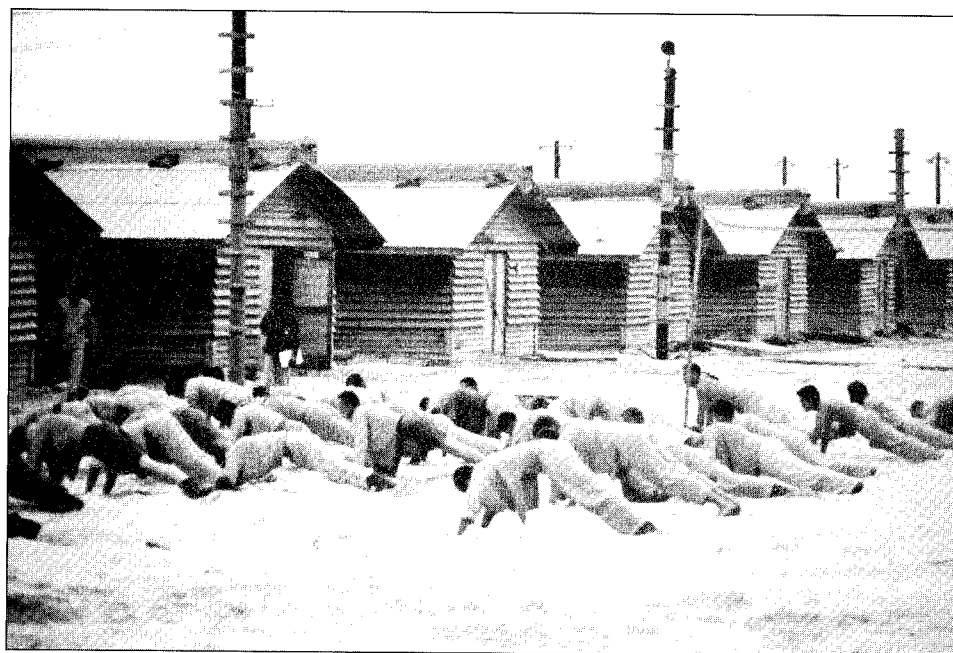
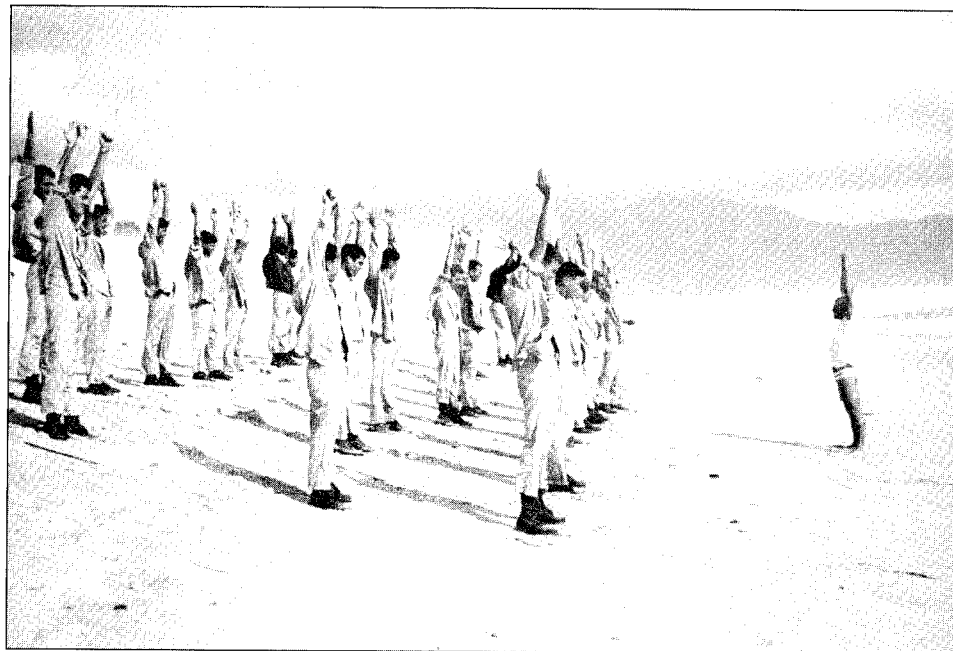


FIGURE 31.—Patients exercising at the 6th Convalescent Center. Top: Calisthenics on the beach. Bottom: Pushups in front of ward buildings.

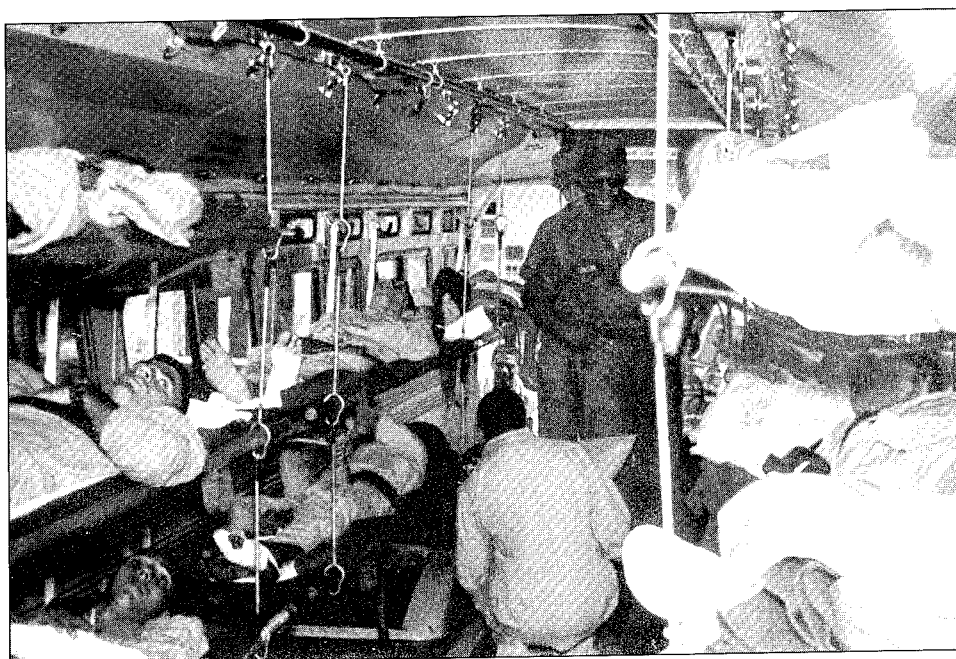


FIGURE 32.—The evacuation process. Top: Patients in staging area of 3d Field Hospital await loading on buses for transport to MAC (Military Airlift Command) aircraft. Bottom: Interior of ambulance bus after loading patients.



FIGURE 32. — Continued. Left: Ambulance bus unloading patients at Tan Son Nhut airport directly into MAC aircraft. Right: Interior of aircraft demonstrating four-deep loading technique.

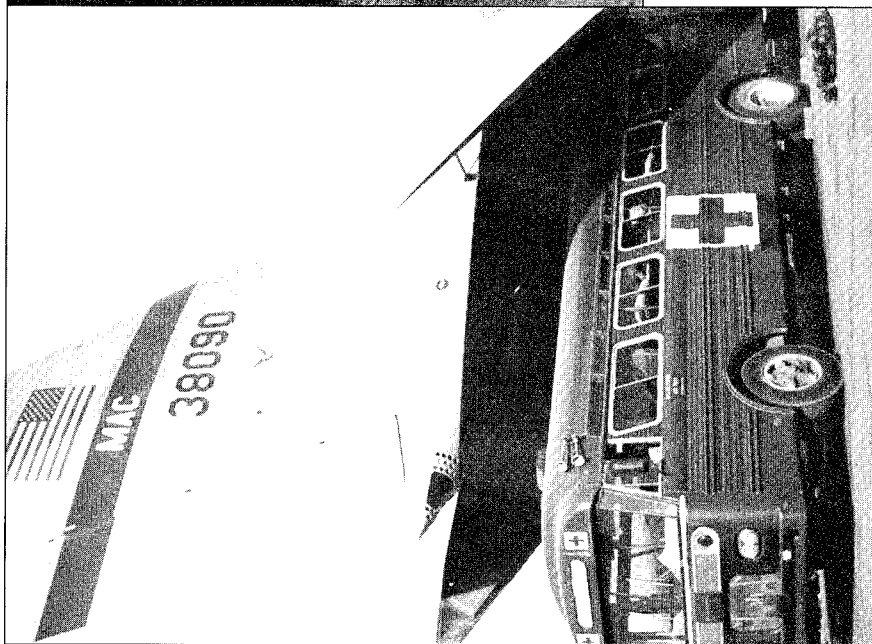


TABLE 3.—Data pertaining to U.S. Army medical and surgical patients in the 6th Convalescent Center, fiscal year 1969¹

Period	Admissions total	Dispositions			Days on census	Average daily census	Average length of stay (days)
		To duty	Evacuated out-of-country	Other dispositions			
1968							
July -----	1,593	1,568	71	43	30,729	991	18.3
August -----	1,832	1,617	78	30	30,603	987	17.8
September -----	1,426	1,460	162	25	26,440	881	13.4
October -----	1,389	1,281	141	23	24,231	781	17.0
November -----	1,300	1,239	79	19	24,334	811	19.0
December -----	1,104	1,189	63	12	24,830	800	20.0
1969							
January -----	760	783	60	21	14,873	479	17.2
February -----	842	722	121	12	13,255	473	16.1
March -----	1,040	726	74	29	17,182	554	21.2
April -----	1,000	906	122	17	20,587	686	19.7
May -----	1,578	1,218	127	21	24,239	781	17.5
June -----	1,433	1,284	84	38	26,444	881	19.0
Total or average -----	15,297	13,993	1,182	290	277,747	759	18.0

¹Data taken from records of the 6th Convalescent Center during the period of peak troop strength reflecting 1 year of operation.

Source: Hall A. P., and Shafer, J. A. 1970. The mission of the 6th Convalescent Center. Paper, dated 9 Apr. 70, unpublished.

TABLE 4.—Data pertaining to Army medical and surgical patients in U.S. Army hospitals in South Vietnam, fiscal year 1969¹

Period	Admissions		Dispositions			Days on census	Average daily census	Average length of stay (days)
	Direct or from nonhospital	Traffic from hospital	To duty	Traffic to 6th Convalescent Center	Other dispositions			
1968								
July	7,591	1,833	3,945	1,553	3,887	57,877	1,867	7.1
August	8,515	1,958	4,380	1,775	4,268	60,275	1,944	6.6
September	8,037	1,987	4,235	1,333	4,605	57,196	1,906	9.4
October	8,089	1,671	4,233	1,343	4,083	57,523	1,855	7.4
November	7,741	1,384	4,083	1,280	3,818	55,032	1,834	7.5
December	7,801	1,585	4,217	1,063	4,246	55,322	1,784	7.5
1969								
January	7,809	1,575	4,318	691	4,342	54,333	1,752	7.6
February	7,042	1,437	3,641	805	4,122	45,704	1,632	7.0
March	8,930	1,682	3,974	1,006	5,520	54,106	1,745	6.9
April	8,078	1,521	4,269	967	4,372	49,471	1,649	7.1
May	9,764	2,189	4,566	1,538	5,988	55,511	1,790	6.9
June	8,729	1,539	3,980	1,396	5,126	48,128	1,604	6.0
Total or average	98,126	20,361	49,841	14,750	54,377	650,478	1,780	7.2

¹Data taken from records of USARV hospitals, excluding the 6th Convalescent Center, during the period of peak troop strength reflecting 1 year of operation.

Source: Hall, A. P., and Shafer, J. A. 1970. The mission of the 6th Convalescent Center. Paper, dated 9 Apr. 70, unpublished.

The relationship of the internal medicine effort in Vietnam to hospitalization and evacuation can best be seen from the data collected by medical consultants during their service in Vietnam. At peak troop strength in 1969, there were generally more than 5,000 monthly medical admissions to USARV hospitals with internal medicine services, or 3 to 4 medical admissions per internist per day (Ognibene 1969b). Approximately 350 required out-of-country evacuation. In the later years of the war, only 10 to 15 percent of evacuees had malaria. Table 5 gives a breakdown of medical and surgical patients evacuated from Vietnam to Japan between 1966 and 1970.

TABLE 5.—*U.S. Army medical and surgical patient evacuations from Vietnam to Japan, 1966-70*

Type	1966	1967	1968	1969	1970
Medical	3,065	2,744	4,458	4,494	2,897
Malaria	822	434	444	478	307
Surgical ¹	8,138	20,272	33,000	31,054	15,089

¹Only general and orthopedic surgical patient data are included for 1966 and 1967.

Source: Commander, U.S. Army Medical Command, Japan. Army Medical Department Activities Reports to The Surgeon General, 1966-70.

Figures for 1971 and 1972 include many patients evacuated under the drug abuse program and are reviewed in Volume III of the Internal Medicine in Vietnam series (forthcoming). It is apparent from table 5 that the percentage of medical evacuations from Vietnam fell significantly in relation to the changes in evacuation policy, troop strength, and the opening of the 6th Convalescent Center. The reduction of the percentage of evacuations for malaria from 27 percent of medical evacuations to a stable figure of approximately 10 percent was a significant accomplishment in the maintenance of combat strength. Unfortunately, overall figures are not available for the percentage of hepatitis patients evacuated from country. However, these patients generally constituted, from medical consultants' figures, a consistently larger proportion than those with malaria. The records of the medical consultant in 1969 (Ognibene 1969b) indicate the following breakdown of the 338 average monthly evacuations to Japan:

Hepatitis (over 30 days).....	106	Peptic ulcer (with complication).....	10
Chest disease (asthma, bronchitis, etc.).....	37	Diabetes.....	8
Falciparum malaria (complicated).....	27	Anemia (unclassified).....	3
Skin diseases (unresponsive to treatment).....	26	Infectious mononucleosis (persistent fatigue).....	3
Heart disease.....	20	Tuberculosis.....	3
G6PD deficiency (with hemolysis).....	15	Melioidosis.....	3
Various arthritides (mainly Reiter's syndrome).....	13	Vivax malaria.....	1
Amebiasis (for liver scan).....	12	Venereal disease.....	0
Hypertension.....	11	Miscellaneous disorders.....	40

In the absence of a specific administrative evacuation requirement or drug abuse program, hepatitis was apparently the major cause for evacuating medical patients from Vietnam to Japan. Most of these patients were able to return to duty in Vietnam because of the 60-day evacuation policy in Japan. With con-

tinued interest at the 6th Convalescent Center in the early rehabilitation of hepatitis patients, the number requiring out-of-country evacuation was held to a minimum. The average time lost from duty because of infectious hepatitis early in the war was greater than 50 days; by 1969 this had been reduced to approximately 20 days. In addition, the aggressive development of treatment programs and new skills in the management of infectious diseases in Vietnam reduced hospitalization for *Plasmodium falciparum* malaria from 35 days in 1966 to 18 days in 1969 and for *Plasmodium vivax* infection from 21 days in 1966 to 5 days in 1969. This eliminated any need for transporting patients with vivax malaria to a convalescent center (Ognibene 1969a). With continued physician education and a reasonably flexible evacuation policy, the number of out-of-country evacuations for medical reasons remained significantly below the surgical evacuation figure despite the fact that medical admissions outnumbered surgical casualty admissions by 5 to 1 as is seen in chart 1.

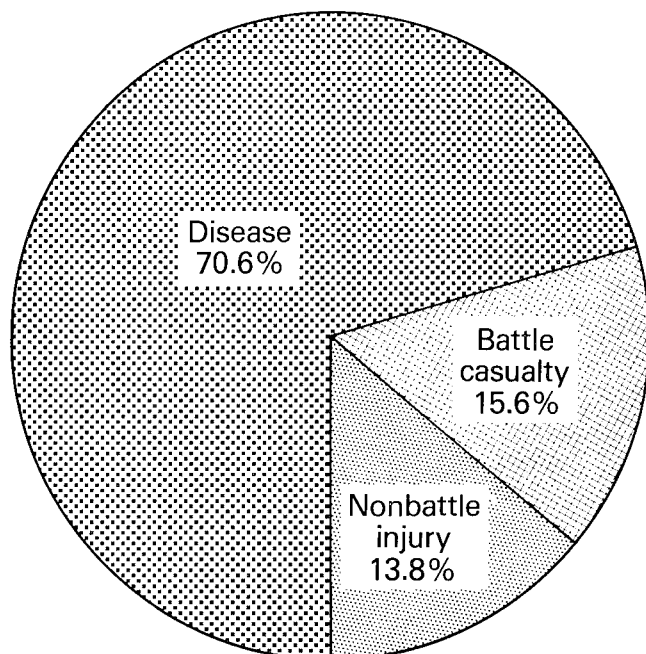
In addition to out-of-country evacuation, a flexible in-country medical evacuation system was required. Helicopters capable of transporting six to nine patients at a time were the backbone of the aeromedical evacuation system (fig. 33). With the development of this type of in-country transportation, significant traffic in outpatient consultation began in 1968, reaching its peak in the later years of the war. Unfortunately, neither evacuation hospitals nor field hospitals were constructed or staffed to render significant care to outpatients.

During the height of the buildup, in January 1969, the 24th Evacuation Hospital in Long Binh reported more than 1,300 internal medicine outpatient consultations by the three internists staffing the large ward service of the hospital. Outpatient services, with limited enlisted support, were made available in a small Quonset hut (EH-24) (fig. 34). As outpatient consultations increased, the pressure on internists to maintain an active inpatient service was overwhelming in view of the limited staffing. Severe stress was also placed on the air evacuation system since helicopters ferried patients back and forth from field units to hospitals for their consultations.

Many consultations could have been handled by doctor-to-doctor communication between hospital units and the field medical units they supported had it been available. Such communication must be established early to prevent an excessive consultation load and the loss of combat man-days which it entails. Lieutenant Colonel Ognibene (1969b), the medical consultant, wrote in his monthly report of July 1969:

A month-to-month increase in consultation requests is reaching a point where the patient load cannot be adequately handled by the medical staff at fixed hospitals. Unit surgeons are asked to review their consultation practices critically with a view toward handling everything possible at the unit or dispensary level. A patient referred to a hospital should mean that admission is being considered. As a general rule, young men with abdominal distress, nausea, or complaints of "gas" do not need barium studies of their intestinal tract. X-ray services of fixed hospitals are primarily engaged in casualty care and in-hospital X-ray and are not designed for outpatient loads. Outpatient care must of necessity be minimized. Action by unit surgeons at all levels to minimize requests on hospital facilities is immediately necessary [fig. 35].

CHART 1.—Comparison of causes of admission of active-duty Army patients at U.S. Army medical facilities in Vietnam, 1967



Source: Patient Administration Division, Health Services Command, Department of the Army. Individual Medical Records, 1965-70.

Patients must have access to specialized care through their unit medical service; however, policies and guidelines must be established early to insure proper use of available facilities so as to conserve the fighting strength. Proper triage technique is critical for effective care. The initiation of medical consultant visits under the MEDCON program reduced outpatient consultations at hospitals through education and actual onsite consultations. These visits were most successful in the area of dermatology, where they reduced the need for rear-echelon consultation and evacuation of patients with skin diseases.

SCOPE OF DISEASE

Maj. W. S. King, U.S. Army surgeon and medical director, commented after the first Battle of Bull Run that "diseases destroy more soldiers than do powder and the sword" (Woodward and Otis 1870, p. 1). During conflict, attention is focused on combat casualties, surgical requirements, evacuation, and combat support. When the glamor fades and the mists of war have cleared, the keen eye of history again affirms the huge impact of disease on the success or failure of military campaigns. The Vietnam conflict was no exception to this rule. Disease was listed as the cause of 56 to 74 percent of admissions to hospitals in Vietnam, 1965-70 (PAD) (table 6).



FIGURE 33.—Aeromedical evacuation is accomplished with onramp loading in a Sikorsky helicopter HH-53.

TABLE 6.—*Final dispositions of active-duty Army patients initially admitted to hospital in Vietnam, 1965-70*

Year	All causes	Nonbattle injury	Battle injury	Disease	Disease as percent of all causes
1965	7,682	1,141	844	5,697	74
1966	48,035	6,936	8,733	32,366	67
1967	75,677	10,027	16,473	49,177	65
1968	91,284	11,709	28,493	51,082	56
1969	93,417	13,142	24,778	55,497	59
1970	75,784	11,291	13,955	50,538	67

Source: Patient Administration Division, Health Services Command, Department of the Army. Individual Medical Records (IMR), 1965-70.

Fortunately, the Vietnam conflict was characterized by an intensive effort to return patients with medical illness to duty rapidly and to hold at a minimum those patients evacuated from the country. Because of this effort, days lost from duty were reduced and the potentially disastrous impact of disease on combat effectiveness was diminished. The total days lost from disease after 1967 never exceeded those lost from battle injury (PAD) (table 7).

It is essential to understand that internal medicine in Vietnam involved not only such "hallmarks" as tropical illnesses, esoteric disorders, and unusual infections but also the usual comprehensive lists of diseases afflicting military populations of the size found in South Vietnam. The continuous presence of common



FIGURE 34.—The 24th Evacuation Hospital dedicated a Quonset hut to ambulatory outpatient care. Most USARV hospitals reserved separate areas for this service.

medical diseases in large troop populations is often forgotten but, nonetheless, is a constant challenge to hospital medical services and the evacuation system. The ensuing chapters detail the effort in specific areas of importance and provide the basis for understanding the magnitude of the medical effort.

TABLE 7.—*Total noneffective days of active-duty Army patients initially admitted to hospital, dispensary, or quarters in Vietnam, 1965-70*

Cause	1965	1966	1967	1968	1969	1970
Malaria	21,001	324,253	277,770	187,609	180,262	169,043
Amebiasis	1,843	10,652	12,849	11,706	14,737	7,479
Diarrheal disease ¹	7,321	36,833	56,158	48,311	53,235	32,372
Pyrexia	42	482	202	272	428	108
Other medical	79,415	503,337	828,842	963,432	1,159,781	867,869
Nonbattle injury	27,522	201,694	343,979	527,940	668,744	571,104
All diseases	137,144	1,077,251	1,519,800	1,739,270	2,077,187	1,647,975
Battle injury	42,107	503,850	1,161,839	2,334,296	2,636,446	1,656,697
Grand total	179,251	1,581,101	2,681,639	4,073,566	4,713,633	3,304,672

¹Data for this time period were originally coded under the provisions of DDDIC (Department of Defense Disease and Injury Code). This particular classification was coded 5711 which included those conditions of both infectious and noninfectious origin. These counts are considered to be roughly equivalent to International Classification of Diseases, Adapted (8th revision) codes 0092, 0099, and 561.

Source: Patient Administration Division, Health Services Command, Department of the Army. Individual Medical Records (IMR), 1965-70.

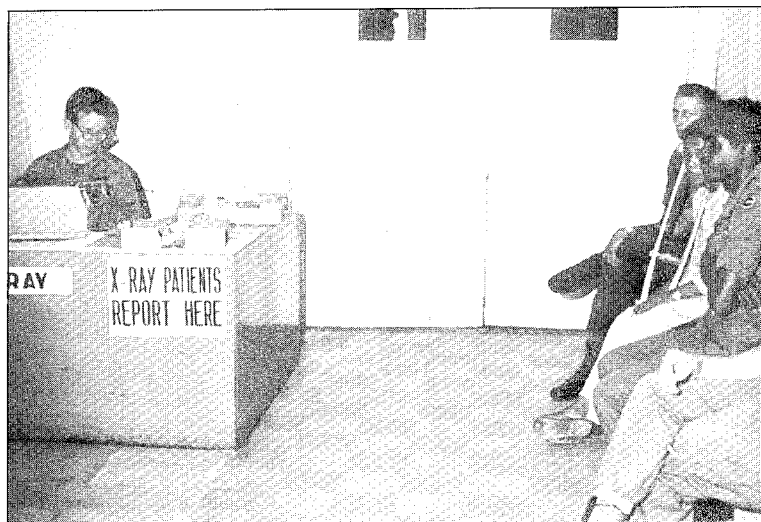


FIGURE 35.—X-ray reception center at the 24th Evacuation Hospital. Most individuals awaiting services are outpatients.

A conclusive statistical picture of the scope and character of patients admitted to internal medicine services in Vietnam is difficult to obtain. Most reporting forms did not specify types of internal medicine admissions. Registrar reports carried only gross figures in broad categories. However, some statistics were kept by chiefs of departments of medicine in relation to their own services. These generally reflect the broad variety of diseases facing the internist supporting a combat operation.

A statistical breakdown kept at the busy 85th Evacuation Hospital in 1967* supports the observation that medical admissions exceeded surgical admissions and combat casualties in almost every month of the year. However, the staffing of the internal medicine services was significantly less than that of any of the surgical departments. The breakdown of the 1,631 medical admissions and other selected cases for May, June, and July 1967 was as follows:

Malaria:		Cardiovascular:	
Falciparum.....	276	Hypertension.....	24
Vivax.....	211	Myocardial infarction.....	2
Mixed.....	18	Cardiac arrhythmia.....	3
Malariae.....	2	Rheumatic heart disease.....	2
Fever of undetermined origin.....	318	Acute pericarditis.....	1
Central nervous system:		Myocarditis.....	1
Syncope.....	19	Acute thrombophlebitis.....	6
Headache.....	20	Chronic venous insufficiency.....	5
Convulsive disorder.....	16	Respiratory:	
Viral meningoencephalitis.....	13	Upper respiratory infection.....	120
Cerebrovascular accident.....	1	Tuberculosis.....	8
Brain tumor.....	1	Chronic obstructive lung disease.....	5
Bell's palsy.....	1	Renal:	
Peripheral neuropathy.....	1	Renal calculus.....	4

*Maj. Robert E. Blount, MC, Chief of Medicine, 85th Evacuation Hospital, 1966-67: Personal communication.

Acute glomerulonephritis.....	1	Dermatologic:	
Chronic nephritis.....	2	Pyodermas, cellulitis.....	74
Prostatitis.....	13	Stevens-Johnson syndrome.....	1
Lymphogranuloma.....	3	Erythema multiforme.....	2
Chancroid.....	1	Herpes zoster.....	2
"Penicillin-resistant" gonococcal urethritis.....	2	Rheumatologic:	
Gastrointestinal:		Gout.....	5
Gastroenteritis (unclassified).....	175	Reiter's syndrome.....	2
Infectious hepatitis.....	99	Posttraumatic arthritis.....	3
Peptic ulcer disease.....	29	Osteoarthritis.....	2
Shigellosis.....	1	Other.....	5
<i>Salmonella typhosa</i>	1	Hematologic:	
Amebiasis.....	16	Infectious mononucleosis.....	19
Hookworm.....	6	Hemolytic anemia and G6PD deficiency.....	9
Strongyloidiasis.....	5	Idiopathic thrombocytopenia purpura.....	1
Giardiasis.....	1	Endocrinologic:	
Ascariasis.....	1	Thyrotoxicosis.....	1
Schistosomiasis (mansoni).....	1	Diabetes.....	8
Hiatus hernia.....	1	Hypoglycemia.....	1
Cholecystitis.....	1	Miscellaneous:	
Pancreatitis.....	1	Dubin-Johnson syndrome.....	1
Ulcerative colitis.....	1	Mumps orchitis.....	1
Hemorrhoids.....	8	Renal glycosuria.....	1
Acute diverticulitis.....	1	Clotting abnormality (unclassified).....	1
Allergic:		Carcinoma of the bowel.....	1
Asthma.....	22	Snake bite.....	1
Serum sickness.....	3	Scorpion bite.....	1
Urticaria.....	8	Drug overdose.....	2
Penicillin allergy.....	2	Ethanolism, acute.....	4

The average of 18 daily admissions at the 85th Evacuation Hospital, imposed on three or four physicians devoting an extended working day to direct patient care, was above the USARV hospital average of four admissions per internist per day (Ognibene 1969b). Little time was left for outpatient care. However, because the workday was prolonged, one physician could often accomplish the work of two. Unlike surgical admissions, medical admissions were constant and did not parallel combat activity. Breaks in the patient flow were rare and coverage could be planned with some certainty. The mass casualty situations which all too often faced the surgical staff were not characteristic of internal medicine practice in Vietnam.

At the peak of troop strength, 13 medical services, each with three to five internists, provided care to the 5,000 patients admitted per month (Ognibene 1969b). The diagnostic and therapeutic efforts directed at these patients in USARV hospitals were responsible for preventing a disastrous repeat of the French experience. A major requirement for diagnosis and treatment of such a challenging array of patients was laboratory support of medical facilities. Because certain conditions, especially those seen by the internist, must be diagnosed before any decision to treat or evacuate the patient can be made, a fully staffed and equipped laboratory must be functional with the opening of any

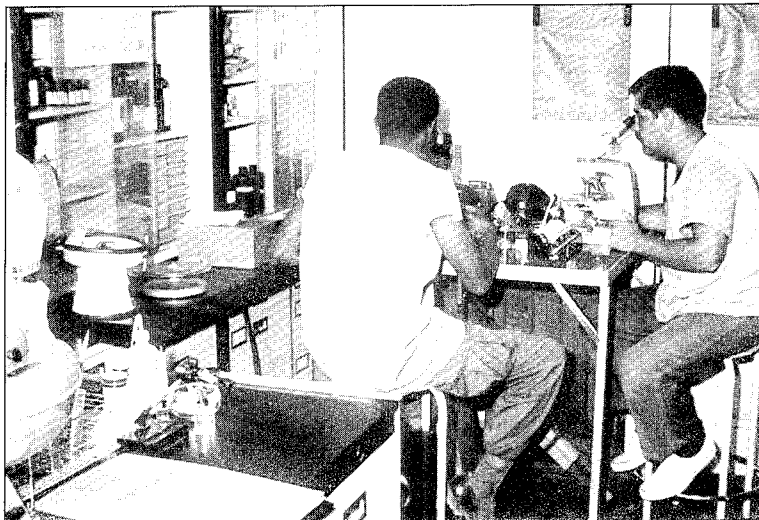


FIGURE 36.—Typical hospital-support laboratory. Laboratory services were the functional backbone of practice for hospitalized medical patients.

hospital in a combat-support activity (fig. 36). The importance of the availability of blood chemistries and bacteriologic and hematologic support cannot be overemphasized, as it relates directly to reduction in combat-days lost.

In addition to effective laboratory support, a formulary must be available to assist in the provision of efficient drug support for the treatment of complex medical diseases. In 1969, such a formulary (USARV-TF) was developed for Vietnam by the consultant staff in conjunction with the Medical Materiel Division. The number of drugs available and the unlimited and uncontrolled distribution to all units, however, hampered an efficient delivery system (fig. 37). Unsupervised procedures resulted in significant overordering. The USARV pharmacy consultant, the director of logistics, and the USARV medical consultant combined efforts to reduce both the number of line items and the distribution of drugs so that only the necessary medications would be delivered to each location, in consonance with the level of patient care. In addition to the improvement in health care that resulted, the cost savings of this program were significant. Curtailing requests for unlimited drugs provided the resources to streamline delivery of authorized drugs to physicians and patients who required them.

Designed to correspond with up-to-date formularies in CONUS, the formulary retained for use in large hospital centers those drugs which were required for patient care in medical centers and did not release these drugs for field use. This also facilitated delivery of drugs to physicians in the field as well as in fixed hospitals.

The formulary was produced in pocket size and issued to all physicians in September 1969. A representative page demonstrates the characteristic breakdown by drug class and issue restrictions as follows (stock number is also included):

PART B

Penicillins

Oral Dosage Forms

<i>NOMENCLATURE</i>	<i>FSN</i>	<i>ISSUE RESTRICTIONS</i>
Ampicillin, Cap, 250mg, 24s (Polycillin, Penbritin)	6505-783-0233	None
Ampicillin, Cap, 250mg, 100s, (Polycillin, Penbritin) Authorized Substitution 6505-935-1148 1 for 5	6505-770-8343	Hospital use only
Ampicillin, Cap, 250mg, 500s, (Polycillin, Penbritin) Authorized Substitution 6505-770-8343 5 for 1	6505-935-1148	Hospital use only
Ampicillin, Oral Susp, 125mg per 5 cc, 5 oz, (Polycillin, Penbritin)	6505-926-8924	None
Potassium Phenoxymethyl Penicillin, Tab, 400,000 units, 100s	6505-656-1612	None
Potassium Phenoxymethyl Penicillin, Tab, 800,000 units, 100s	6505-935-5856	None
Potassium Phenoxymethyl Penicillin, Oral Susp, 200,000 units per 5 cc, 5 oz	6505-226-1367	None
Sodium Oxacillin, Cap, 250mg, 48s (Prostaphlin)	6505-226-1202	Hospital use only
Sodium Oxacillin, Oral Susp, 250mg per 5cc, 100cc (Prostaphlin)	6505-C99-0866	Hospital use only

With established laboratory support and a maturing drug delivery system, medical care in Vietnam for the U.S. soldier was rapidly achieving the therapeutic sophistication of Army hospitals in the United States by 1970. The chapters which follow attest to this accomplishment and provide the basis for future reference in combat situations in a tropical setting.



FIGURE 37.—Typical aid station or clearing company pharmacy cabinet. Note the large volume and diversity of stocked items.

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Part II

**CLINICAL DISORDERS: INFECTIOUS
DISEASES AND GENERAL MEDICINE**

Fever of Undetermined Origin

Colonel John J. Deller, Jr., MC, USA (Ret.)

HISTORY AND MILITARY SIGNIFICANCE

In 50 years, the United States has engaged in four major wars. Despite the trend of history, people tend to forget the knowledge gained from wars past—perhaps that is why wars continue to happen. Likewise, we tend to forget from one war to the next the knowledge gained in military medicine, for each war has called upon a new generation of physicians to solve the medical problems of American soldiers. Tropical disease was not a popular subject in American medicine at the time of the Vietnam conflict; its scholars were few and, for the most part, belonged to an earlier generation. Within the military services, however, a few scholars of this field remained. Their foresight and well-laid plans for a “Vietnam contingency” allowed the new generation of physicians a quick start when it was needed.

The problem of FUO (fever of undetermined origin) was perhaps one of the greatest diagnostic dilemmas for military physicians in Vietnam. Historically, it was not very different from the FUO problem in World War II. At one time during the Pacific campaign there had been so many FUO diagnoses that Col. Henry M. Thomas, Jr., MC, Senior Consultant in Medicine, Southwest Pacific Area, 1943, was instructed to investigate the matter (MD-IM1, pp. 534-36). In every case he observed, he agreed that the etiology was indeed uncertain; in response, he compiled a list of the differential diagnoses of acute fevers (USASOS-TM). Despite the magnitude of the problem, however, no comprehensive FUO studies are recorded in the medical history of World War II. Several studies attempting to clarify the FUO problem were conducted when it emerged in Vietnam. This review is based primarily upon these studies and related published reports.

INCIDENCE AND EPIDEMIOLOGY

The first available statistics on the magnitude of the FUO problem in Vietnam stem from the USARV (U.S. Army, Vietnam) medical consultants' monthly reports beginning in October 1965 (USARV-MC). During the last 3 months of that year, disposition diagnoses from three major hospitals in Vietnam—the 3d

This chapter is a revised version of an article by the author entitled “History of fevers of undetermined origin in American soldiers in Vietnam,” originally published in *Present Concepts Int. Med.* 5 (supp. 1): 1-17, 1972.

Field Hospital, the 8th Field Hospital, and the 85th Evacuation Hospital—revealed 479 FUO cases. The average duration of hospitalization for this group was 7 days (AMEDS-AR65, p. 18). The monthly reports continued to show FUO as a major cause of hospitalization among American troops in the Republic of Vietnam through 1970. Between 1966 and 1969, monthly morbidity reports reflected an average incidence rate of 58 cases per 1,000 average strength per year (ranging from 35 to 100 per 1,000) (AMEDS/AMEDD-AR). These figures include nonhospitalized patients receiving division-level medical care and patients treated in field and evacuation hospitals.

In comparison with other common diseases, the diagnosis of FUO ranked second only to venereal disease; common respiratory disease, diarrheal diseases, skin diseases, and malaria all ranked lower. The average duty time lost because of FUO between 1965 and 1970 was 4.5 days (USARV-MC). Monthly incidence rates, as reflected in morbidity reports, are markedly inflated because a number of ill-defined conditions were reported as FUO from admission reports but were not reclassified after a more definitive diagnosis was established (Bartley 1968). Nevertheless, FUO probably constituted a major cause of man-days lost.

Combat troops had significantly more cases of FUO than did support troops and rear support troops (Bartley 1968). This distribution correlates with expected exposure to arthropod vectors and other environmental conditions conducive to development of tropical febrile diseases. In the first analysis of FUO in American soldiers in Vietnam, Deller and Russell (1967) found that a history of the soldier's activity—whether he had been in combat and exposed to the jungle or in a support unit at a large encampment—provided key information in separating the various causes of FUO. For example, the arbovirus diseases and murine typhus occurred most frequently in areas of heavy population density because such areas were the natural habitat of the vectors, whereas malaria and scrub typhus were contracted in heavily forested or jungle areas, the natural habitats of their vectors.

HINDRANCES TO EARLY SPECIFIC DIAGNOSES

A major hindrance to defining the spectrum of tropical febrile diseases in the early years of the war was the lag in obtaining adequate laboratory support. Although most hospitals arrived in South Vietnam with a full complement of personnel, the pathologists, bacteriologists, and laboratory technicians were as unfamiliar with tropical diseases as were the clinical personnel. More importantly, they did not have the equipment to accomplish the sophisticated laboratory procedures necessary to support tropical disease hospitals. It was only through USAMRTV (U.S. Army Medical Research Team, Vietnam) in Saigon and their close working relationship with the SEATO (Southeast Asia Treaty Organization) Laboratory in Bangkok that early studies were at all possible. Not until 1968 was full laboratory capability to investigate infectious disease established in Vietnam. The 9th Medical Laboratory established a separate department of infectious disease and made available multiple screening procedures for the serodiagnosis of FUO.

Although world health surveys of major disease prevalences had been conducted in Vietnam in the early 1950's (HD-5; HD-25), the data were incomplete for the needs of the U.S. Army physician. Nevertheless, they provided a beginning. By analyzing the surveys and reports from the French Indochina experience and from the archives of l'Institut Pasteur in Saigon, one could predict potential tropical disease problems. Table 8 lists some of the acute febrile diseases which one might have expected to encounter in Southeast Asia; such a probability table can serve as a useful guide.

The FUO story was written by physicians of various disciplines, few of whom had been in the field of tropical medicine. Thrown together on a common ground of frustration by the exigencies of war, they were faced with a new chapter in their medical careers. At first all febrile diseases seemed to be "FUO"; the triad of fever, chills, and headache was so common that everyone appeared to suffer from the same malady. It became obvious, however, that there was a spectrum of diseases within this massive group which could and should be separated.

The first step was to design a study which would survey the possible etiologies, prove in the laboratory what each patient actually had, and then attempt to correlate differentiating clinical features with specific disease entities. It would thus be possible to separate the various diseases on clinical grounds and reduce the number of FUO diagnoses to the minimum.

This approach was conceived at the 93d Evacuation Hospital in the spring of 1966. The hospital had just been converted from tents in a recently cut forest to crossed Quonset huts in an area which subsequently developed into the massive Long Binh military complex. It had a basic laboratory, but the study required

TABLE 8. — *Probability of acute febrile disease acquisition by American soldiers in Vietnam*

Type of disease	Probability of presence of disease		
	Not present	Present but immunization given or available	Present and likely to be acquired
Viral -----	Yellow fever Small pox	} Hepatitis (gamma globulin) ---	{ Dengue. Japanese B encephalitis. Adenovirus and acute respiratory disease.
Rickettsial -	Epidemic typhus Relapsing fever Spotted fever	} -----	{ Scrub typhus. Murine typhus.
Bacterial ---	-----	{ Plague Cholera Typhoid	{ Leptospirosis. Melioidosis. Tuberculosis. Shigellosis. Salmonellosis.
Parasitic, systemic -	Schistosomiasis -----	-----	{ Malaria. Amebic liver disease. Filariasis.

Source: Deller, J. J., Jr. 1972. History of fevers of undetermined origin in American soldiers in Vietnam. *Present Concepts Int. Med.* 5 (supp. 1): 1-17.

more sophisticated laboratory support. The idea of an FUO study was presented to Lt. Col. (later Col.) Robert J. T. Joy, MC, commander of USAMRTV. He was encouraging and arranged for Maj. (later Col.) Philip K. Russell, MC, at the SEATO Laboratory in Bangkok, to perform the appropriate diagnostic work on the specimens. Despite generator-run freezers, makeshift portable dry ice chests, 110° F weather, unsure jeep transportation to Saigon and courier airlifts to Bangkok, specimens were collected, stored, and delivered to their destination. Results were returned in record time. Not long after the first results were returned, it was possible to separate many of the FUO's into a limited number of specific diagnoses.

This initial study (Deller and Russell 1967) was conducted from April through August 1966. Two subsequent studies (Reiley and Russell 1969; Colwell et al. 1969) were done with the support of USAMRTV and the SEATO Laboratory. In addition, a study was conducted by the Navy in 1967 (Berman, Irving, and Kundin 1968), and another by the Air Force in 1967-68 (Deaton 1969). The combined results of these studies, which were done over a period of 2 years during various seasons and in different geographical zones, provide a good sample of the total spectrum of FUO among American servicemen in Vietnam.

THE SPECTRUM OF FUO

An FUO in the context of this chapter is defined as a febrile illness which required admission of the patient to a field or evacuation hospital and which could not be more specifically diagnosed during the initial 3 days of hospitalization. Among the five major FUO studies, the definition varied from "cases not diagnosed within the first 24 hours" to "cases remaining febrile during their hospital stay," but in general an undiagnosed fever for 3 days is applicable to all the data.

The Army studies of Deller and Russell (1967), Reiley and Russell (1969), and Colwell and associates (1969) were prospective and comparable in design. The study by Berman and associates (1968) specifically excluded all cases of malaria, whereas Deaton's retrospective study (1969) included all hospitalized malaria cases. Thus, there are some numerical differences between the non-Army studies and the Army studies. However, the data are similar enough to permit an appraisal of those illnesses which can initially masquerade as FUO as well as those which remain truly undiagnosable fevers.

The results of the studies are presented in table 9. The data indicate that it is possible to distinguish the specific diagnostic category for nearly three-fourths of all patients initially considered to have an FUO. The five major groups are: group A and B arboviruses—chikungunya, dengue, Japanese B encephalitis; rickettsial diseases—scrub and murine typhus; leptospirosis; malaria; and miscellaneous.

Table 10 divides the miscellaneous group into categories. Only two major categories represent significant contribution to the total FUO problem: enteric diseases, constituting 28 cases of the combined series, and respiratory tract

TABLE 9.—Results of five FUO studies¹ in Vietnam, 1966-68

Factor	Study 1 ²	Study 2 ²	Study 3 ²	Study 4 ³	Study 5 ⁴
Location	93d Evac. Hospital, Long Binh	8th Field Hospital, Nha Trang	Dong Tam, Mekong Delta	I Corps	12th USAF
Date	Apr.-Aug. 1966	Oct. 1966-Feb. 1967	June-Dec. 1967	Feb.-Sep. 1967	July 1967-June 1968
Number of cases	110	94	87	295	306
Percent specifically diagnosed:					
Malaria	7.0	6.4	12.6	(⁵)	70.0
Dengue	28.0	10.6	11.0	3.4	5.0
Japanese B encephalitis	1.0	0	1.0	8.1	0
Chikungunya	9.0	< 1.0	0	0	0
Leptospirosis	1.0	11.6	3.4	17.0	2.0
Scrub typhus	8.0	13.8	2.3	14.0	1.0
Murine typhus	0	0	0	0	8.0
Other diagnoses	17.0	18.0	16.0	10.0	3.0
Undetermined	26.0	38.0	54.0	51.0	12.0

¹Studies represented by numerals are as follows: (1) Deller, J. J., Jr., and Russell, P. K. 1967. *Ann. Int. Med.* 66: 1129-43. (2) Reiley, C. G., and Russell, P. K. 1969. *Mil. Med.* 134: 36-42. (3) Colwell, E. J. et al. 1969. *Mil. Med.* 134: 1409-14. (4) Berman, S. J.; Irving, G.; and Kundin, W. D. 1968. U.S. Naval Medical Research Unit No. 2, Taipei, Taiwan, Mar. 68, pp. 1-16. (5) Deaton, J. G. 1969. *Mil. Med.* 134: 1403-8.

²Army personnel.

³Navy personnel.

⁴Air Force (retrospective).

⁵Excluded by design.

⁶Includes all cases admitted as FUO.

Source: Deller, J. J., Jr. 1972. History of fevers of undetermined origin in American soldiers in Vietnam. *Present Concepts Int. Med.* 5 (supp. 1): 1-17.

diseases, of which there were 13 cases, including acute respiratory disease, bacterial pneumonia, and viral pneumonia.

The remaining truly undiagnosable fevers made up from one-fourth to one-half of the cases depending on the completeness of laboratory screening. These cases can be separated into two major groups on the basis of the clinical picture: approximately half of the cases had clinical features (fever patterns, rash, leukopenia) suggesting an arbovirus or typhus fever;* the remaining cases were a heterogeneous group usually with fevers of less than 72 hours' duration and often with upper respiratory or gastrointestinal symptoms. Perhaps more significant in an analysis of the total group is that all truly undiagnosable fevers were self-limited. Thus, even if a specific viral or rickettsial etiology was responsible, the outcome was favorable and no major life-threatening illnesses were unrecognized.

*In the Army studies of Deller and Russell (1967), Reiley and Russell (1969), and Colwell and associates (1969), the Weil-Felix test was not used to screen for rickettsial disease nor was the specific complement fixation test for murine typhus. Thus, a number of the "truly undiagnosable fevers" included in these reports may actually have been murine typhus.

TABLE 10.—*Miscellaneous diagnoses recorded in FUO studies¹ in Vietnam, 1966-68*

Diagnosis	Cases					
	Total	Study 1	Study 2	Study 3	Study 4	Study 5
Melioidosis	3	2				1
Amebiasis	14	1	3		7	3
Drug sensitivity	4	1		3		
Gonococcal and lower urinary tract infection	4	3		1		
Pericarditis	2	1	1			
Pneumonia, acute respiratory distress	13	1	6	6		
Shigellosis	4	4				
Other diarrheas	10	6				4
Encephalitis (nonspecific)	2		2			
Infectious mononucleosis	6		1	1	4	
Plague	1		1			
Hepatitis	3			3		
Others (nonspecific)	18					18

¹Studies represented by numerals are as follows: (1) Deller, J. J., Jr., and Russell, P. K. 1967. *Ann. Int. Med.* 66: 1129-43. (2) Reiley, C. G., and Russell, P. K. 1969. *Mil. Med.* 134: 36-42. (3) Colwell, E. J. et al. 1969. *Mil. Med.* 134: 1409-14. (4) Berman, S. J.; Irving, G.; and Kundin, W. D. 1968. U.S. Naval Medical Research Unit No. 2, Taipei, Taiwan, Mar. 68, pp. 1-16. (5) Deaton, J. G. 1969. *Mil. Med.* 134: 1403-8.

Source: Deller, J. J., Jr. 1972. History of fevers of undetermined origin in American soldiers in Vietnam. *Present Concepts Int. Med.* 5 (supp. 1): 1-17.

CLINICAL CONDITIONS PRESENTING AS FUO

Studies of FUO in South Vietnam served two major purposes: they established the spectrum of tropical febrile disease affecting American soldiers in different seasons and locations in the country; and they clarified important differential diagnostic features of specific illnesses which masquerade as fevers of undetermined origin.

The diagnostic features of the major diseases uncovered in these studies will be reviewed in subsequent pages. Relative incidences are shown in table 9. It is of both historical and practical significance that throughout the period of our highest troop concentration in Vietnam (1965 through 1970) the same diseases were encountered and only the relative frequencies varied.

Malaria

Malaria was the tropical disease of greatest concern in South Vietnam because it produced the most medical casualties (as well as the most cases of acute febrile disease imported into the United States from South Vietnam). Thus, in any patient with an FUO malaria received prime consideration. Four types of malaria were acquired by Americans in Southeast Asia, but 99 percent of the cases were caused by *Plasmodium falciparum* and *Plasmodium vivax* (Sheehy 1967).

Malaria is generally easy to diagnose if a peripheral blood smear can be examined and interpreted. Smears, however, do not always reveal parasites at the initial presentation, and thus a diagnosis of FUO may be recorded for conditions which are subsequently proven to be malaria. Since the *Anopheles* mosquito (the primary vector of malaria) is a jungle breeder, this disease was most often suspected in a soldier who had been in combat.

The majority of patients with malaria have a fever within the first 72 hours of illness. Frequently, the temperature rises to 105° or 106° F; when temperatures of this elevation are found, the diagnosis is usually malaria. The fever becomes even more distinctive when, following a spike, the temperature returns to 99° F or lower before the next paroxysmal elevation. Such a pattern is distinctly unusual in other tropical infections. The shaking chill, the hallmark of malaria, is generally present and is accompanied by headache, moderately severe myalgias, and a variety of gastrointestinal complaints in the majority of patients. The most remarkable feature about the physical examination is the absence of specific findings; except for percussion tenderness over the liver or spleen, or both, the examination is frequently negative unless the patient has one of the major complications of falciparum malaria. Splenomegaly is variable and probably depends on the duration of the subclinical illness before the onset of recognizable disease. When malaria is suspected, a series of blood smears, both thick and thin, must be done to confirm the diagnosis. A Wright-stained thin smear, carefully examined, may be the best diagnostic method for the physician. Thick smears, although reliable, are better left for the specialist or parasitologist to interpret.

Malaria is perhaps the most important tropical disease to rapidly distinguish from other FUO's because its treatment must be timely and specific. The treatment of malaria underwent several changes following the recognition of chloroquine-resistant strains of *P. falciparum*, by 1965, in South Vietnam. Despite increasing numbers of multidrug-resistant strains of *P. falciparum* after that time, the available drugs effected a primary cure in over 90 percent of the cases. Since over 90 percent of *P. falciparum* infections acquired in Vietnam were resistant to chloroquine, quinine was substituted for that drug. When used alone quinine was effective in only about 50 percent of *P. falciparum* cases, but it was curative in 90 to 98 percent when combined with an antifolate acid compound, such as pyrimethamine, and a sulfonamide (Modell 1968). Thus, a triple therapy program for falciparum malaria eventually evolved. The treatment schedule which emerged as standard is presented in Part III of this volume. The treatment of vivax malaria did not change as *P. vivax* did not demonstrate any significant resistance to the standard drugs.

Mixed infections may occur; in these cases treatment for falciparum malaria plus additional therapy, such as chloroquine, for the erythrocytic phase of vivax malaria should be administered. Patients with malaria of either type may also have another tropical disease simultaneously. In several FUO studies, scrub typhus was the disease most commonly associated with malaria, probably because both are acquired in the same jungle environment.

Dengue

Dengue was the most common of the three significant arthropodborne viruses presenting initially as FUO. It is usually acquired by a soldier residing in a large base encampment or urban area rather than in the jungle because the vector, the *Aedes* mosquito, is basically an urban dweller. The symptoms of dengue are not distinctive; three-fourths of the patients have a flu-like illness with malaise, backache, anorexia, fever, chills, and frequently severe frontal headache. They may present with lymphadenopathy, an important physical finding because patients with malaria do not have adenopathy and patients with scrub typhus generally develop adenopathy several days after the onset of the illness. A fleeting macular rash is present in at least one-third of the patients, and spontaneous petechiae occurring within this setting, especially on the lower extremities, provide good clinical evidence of an arbovirus disease. On occasion, the tourniquet test may be positive and unassociated with a reduction in platelet count. The course of dengue is usually short. Fever is rarely over 104° F, symptoms subside within 5 to 7 days, and few patients have a prolonged convalescence. Occasionally a patient will show a slight fever on the fifth day before a return to normal temperature by the seventh day. No specific therapy is indicated.

Chikungunya

Chikungunya was first recognized in Tanganyika in 1952 when an epidemic characterized by high fever and severe polyarthritis occurred among the natives. Specimens collected from patients and pools of *Aedes* mosquitoes during this epidemic were subsequently analyzed, and a new virus was reported in 1956. It was given the name "chikungunya," the natives' term for the disease, which means "that which bends up the joints."

Since the original epidemic, chikungunya has been identified throughout Southeast Asia and the southern parts of Africa and India. The clinical disease was not recognized in Americans in South Vietnam before the study of Deller and Russell (1968). Chikungunya has covered a wide clinical spectrum from severe polyarthritis to a dengue-like illness with mild arthritis to frank hemorrhagic fever. The same virus has been cultured from all these varieties.

One feature that distinguishes this disease from dengue is polyarthritis. Even though dengue has been referred to as "break-bone fever," it is not associated with true arthritis but rather with severe myalgias and arthralgias. Chikungunya is a known viral disease that can mimic rheumatoid arthritis or acute rheumatic fever and from which an organism can also be readily cultured. The arthritis of chikungunya may linger for several weeks following the return of the temperature to normal and the disappearance of all other clinical manifestations. Except for the arthritis, chikungunya among American troops was a mild dengue-like illness; it did not produce the severe crippling arthritis of the type reported in the initial epidemic, nor did it cause hemorrhagic fever. Like dengue, it requires no specific therapy.

Japanese B Encephalitis

Japanese B encephalitis is a more recently recognized arbovirus disease, first appearing in epidemic form in the summer of 1969 in South Vietnam (Ketel and Ognibene 1971). The virus is transmitted primarily by the *Culex* mosquito. Although an epidemic of encephalitis was recognized as a clinical entity in Japan as early as 1871, virus isolation and characterization did not occur until 1935. Japanese B encephalitis first became a military problem among American troops in Guam and Okinawa in World War II. It appeared in Korea during the summer of 1947, and in 1948 and 1950. The classical presentation of Japanese B encephalitis among American troops has been a persistent headache followed by chills, fever, anorexia, general weakness, and nuchal stiffness. Within a few days following the onset of these symptoms, somnolence occurs. In most instances, the disease is self-limited, with fever lasting 7 to 8 days and rapid recovery thereafter. However, in the Korean epidemic in the summer of 1950, of approximately 200 patients with Japanese B encephalitis, 8.5 percent died (Lincoln and Sivertson 1952).

In the more recent Vietnam experience, several fatalities were attributable to Japanese B encephalitis. An occasional case had subacute onset, while a few cases had hyperacute onset with dramatic presentation of psychosis, seizures, and early death. In contrast to the other arbovirus diseases seen in Vietnam, leukocytosis was present in most of these cases (average peripheral white blood cell count of 13,000/mm³). Spinal fluid in all cases showed a pleocytosis with a cell count of 10 to 2,000/mm³ and an average spinal fluid white cell count of 200/mm³ of which greater than 70 percent were lymphocytes (Ketel and Ognibene 1971). The disease can be positively diagnosed by isolation of the virus from the blood or from tissues in autopsy cases. Specific serologic tests using neutralizing antibodies, complement fixation, and hemagglutination techniques can confirm the diagnosis.

Rickettsial Diseases

Scrub typhus is caused by a miteborne rickettsia (*Rickettsia tsutsugamushi*) and is classically manifested by the triad of rash, eschar, and positive therapeutic response to tetracycline. With these features present, it is usually easy to diagnose. Unfortunately, not all cases present so clearly. Sometimes the eschars are hidden and may be overlooked on physical examination, or they may not be present at all, especially in dark-skinned races. Like malaria, scrub typhus was usually acquired by the combat soldier since the mites that carry the rickettsial organism breed in the scrub jungle areas of Vietnam. Hence, the history of exposure to the jungle environment is important for diagnosis.

The fever, chills, headache, malaise, adenopathy, and backache common to the other tropical diseases are also characteristic of scrub typhus. Severe retro-orbital headache is generally the most prominent complaint. Patients frequently have marked conjunctival suffusion, which increases the difficulty of differentiating this disease from leptospirosis. Cough and dyspnea are also common

symptoms. The most important feature on physical examination is the eschar, which typically resembles a cigarette burn. It is usually painless and has a black, necrotic center with a narrow rim of erythema. A macular rash, which is not so fleeting as the rashes of the arbovirus diseases and does not become confluent, is also a diagnostic sign. Lymphadenopathy and splenomegaly are occasionally found. Early recognition of this disease is important because, when treated promptly, it responds dramatically to tetracycline therapy (1 g every hour for four doses followed by 1 g every 6 hours for 5 to 7 days). Within 48 hours, and often within 12 hours, there is a dramatic lysis in fever. Patients not treated early may have a typical "saddleback" fever curve, and if the disease goes untreated for more than 10 days to 2 weeks, there is some morbidity and occasional mortality. Definitive diagnosis requires specific serological testing. A trial of therapy with tetracycline is warranted when there is a strong clinical suspicion of scrub typhus.

In Southeast Asia, human cases of murine typhus have been reported from Malaysia, the Philippines, and Thailand (Sankasuwan et al. 1969). Murine typhus, caused by *Rickettsia typhi* (mooseri), is probably the rickettsial disease most apt to be confused clinically with scrub typhus. Epidemiologically, however, these two conditions are quite different in that murine typhus is generally "urban-acquired," from the infected rat flea, while scrub typhus is generally "jungle-acquired." The diagnostic hallmark of scrub typhus, the eschar, is absent in murine typhus. Since this is not an invariable feature, its absence alone cannot be relied upon to make a differential diagnosis, and clinically there is little else to distinguish the two illnesses; thus, the final diagnosis must rest with the laboratory. Agglutinins against the OX-K strain of *Proteus vulgaris* occur in the serum of patients with scrub typhus while agglutinins against the OX-19 strain occur in murine typhus. The most definitive finding, however, is either a fourfold rise in titer against specific complement-fixing antibodies during convalescence, or the isolation of the specific rickettsial agents. However, the results of these laboratory tests may not be immediately available to help diagnose the condition in the patient. Although in most cases murine typhus disease is uncomplicated and self-limited, tetracycline therapy will speed recovery when initiated early.

It is difficult to state with certainty whether or not murine typhus was present to any degree early in the conflict in South Vietnam. It may have been present and missed because the Weil-Felix reaction was not part of the screening procedures, and specific complement fixation tests for murine typhus were not performed (Elisberg 1972). The disease did appear later and was uncovered in the FUO study of Deaton (1969) seen in table 9. Probably a number of cases which were recorded as self-limited, truly undiagnosable fevers in the earlier studies were caused by *R. typhi*.

Leptospirosis

Leptospirosis was most commonly acquired in Vietnam by combat troops who came in contact with the organism in mudbanks and rice paddies. Lep-

tospirosis closely mimics dengue and scrub typhus and has few distinguishing characteristics of its own; profound myalgias constitute the most distinctive symptom. Patients generally have a spiking temperature and often a "saddleback" fever curve similar to that which occurs in scrub typhus. Conjunctival suffusion is an important sign and is frequently associated with blurred vision. Gastrointestinal complaints and hepatic tenderness are common and make differentiation from malaria difficult. A laboratory finding of leukocytosis is occasionally helpful since most of the other tropical diseases (except Japanese B encephalitis) are characterized by normal leukocyte counts or by leukopenia. Although a normal count may be present in approximately half the cases, a neutrophilia is usually evident. Leptospirosis actually encompasses a spectrum of disease from a benign, self-limited form, such as our troops experienced in Vietnam, to a more severe hemorrhagic disease with deep jaundice and renal failure. Since U.S. troops generally manifested a benign form, there were few serious complications (Allen and Weber 1967). Because the benign form of leptospirosis is self-limited, it requires no specific therapy.

Overview

Some of the major differential features of the five most important illnesses which present as tropical FUO's are given in table 11. Data for 1969, the year of

TABLE 11.—*Differential features of patients having dengue, chikungunya, scrub typhus, leptospirosis, and malaria in five FUO studies¹ in Vietnam*

Feature	Percent of patients with feature				
	Dengue	Chikungunya	Scrub typhus	Leptospirosis	Malaria
Exposure history:					
Camp, urban	75-100	75-100	< 25	< 25	< 25
Jungle	< 25	< 25	75-100	75-100	75-100
Signs or symptoms:					
Fever, Fahrenheit:					
< 104°	75-100	75-100	25-49	75-100	< 25
> 104°	< 25	< 25	50-74	< 25	75-100
Arthralgias	< 25	75-100	< 25	< 25	< 25
Tender adenopathy	² 50-74	75-100	³ 75-100	25-49	< 25
Tender liver or spleen	< 25	< 25	50-74	50-74	75-100
Rash	25-49	50-74	50-74	< 25	< 25
Petechiae or positive tourniquet test	25-49	< 25	< 25	< 25	< 25
Leukocyte count, per mm ³ :					
< 5,000	50-74	50-74	< 25	< 25	< 25
> 5,000, < 10,000	25-49	25-49	75-100	75-100	75-100

¹Studies are as follows: (1) Deller, J. J., Jr., and Russell, P. K. 1967. *Ann. Int. Med.* 66: 1129-43. (2) Reiley, C. G., and Russell, P. K. 1969. *Mil. Med.* 134: 36-42. (3) Colwell, E. J. et al. 1969. *Mil. Med.* 134: 1409-14. (4) Berman, S. J.; Irving, G.; and Kundin, W. D. 1968. U.S. Naval Medical Research Unit No. 2, Taipei, Taiwan, Mar. 68, pp. 1-16. (5) Deaton, J. G. 1969. *Mil. Med.* 134: 1403-8.

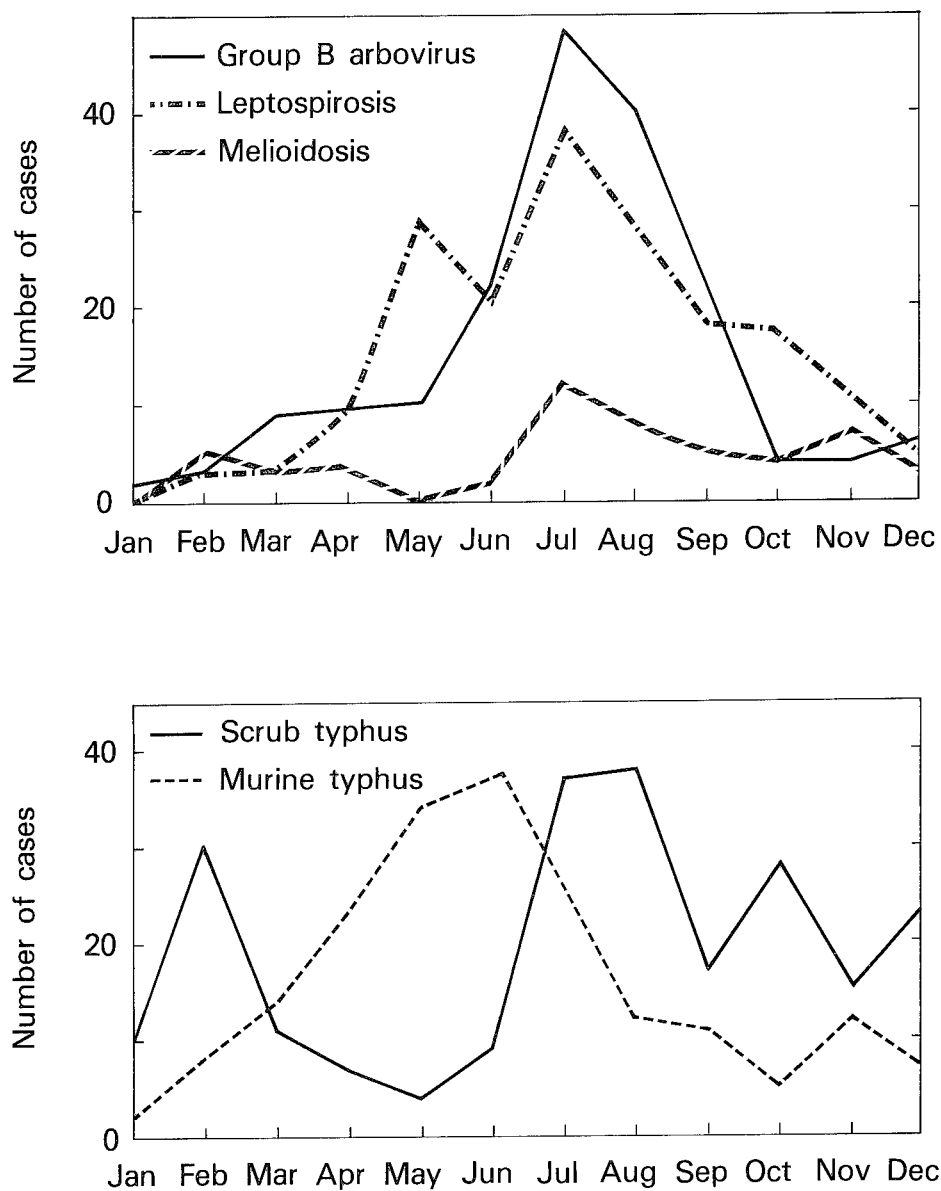
²Early.

³Later.

Source: Deller, J. J., Jr. 1972. History of fevers of undetermined origin in American soldiers in Vietnam. *Present Concepts Int. Med.* 5 (supp. 1): 1-17.

the greatest troop concentration, extracted from the files of the 9th Medical Laboratory, allow an overview of the distribution of confirmed serological cases of infectious disease in Vietnam (chart 2 and tables 12, 13, and 14).

CHART 2.—Number of cases of group B arbovirus, leptospirosis, melioidosis, scrub typhus, and murine typhus in Vietnam, January-December 1969



Source: Records of Lt. Col. Andre J. Ognibene, USARV Medical Consultant, 1969, from data collected at the 9th Medical Laboratory, Long Binh, Vietnam.

TABLE 12.—*Serological diagnoses (probable and confirmed) of FUO cases in Vietnam, by month, 1969*

Disease	Total	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Dengue	130	0	3	6	9	8	18	29	27	20	3	3	4
Japanese B encephalitis	49	2	0	3	1	2	5	19	12	2	1	1	1
Group A arbovirus	2	0	0	0	0	0	0	0	1	0	0	0	1
Murine typhus	195	2	9	15	23	34	37	27	13	11	5	12	7
Scrub typhus	228	10	30	11	7	4	9	37	38	17	27	15	23
Tick typhus	16	0	3	2	4	1	4	2	0	0	0	0	0
Leptospirosis	179	0	3	3	12	23	20	38	28	18	17	12	5
Melioidosis	45	0	4	3	3	0	1	11	7	4	4	6	2
Amebiasis	212	24	24	26	18	14	18	12	19	22	17	10	8
Lymphogranuloma venereum	59	4	10	6	4	4	1	1	8	8	3	1	9
Infectious mononucleosis	96	0	0	7	16	16	7	9	8	7	9	9	8
Typhoid	5	0	0	2	0	1	1	0	1	0	0	0	0
Paratyphoid	18	0	2	4	3	1	6	2	0	0	0	0	0
Primary atypical pneumonia	22	0	0	0	2	2	5	2	1	0	3	2	5
Total	1,256	42	88	88	102	110	132	189	163	109	89	71	73

Source: Records of Lt. Col. Andre J. Ognibene, USARV Medical Consultant, 1969, from data collected at the 9th Medical Laboratory, Long Binh, Vietnam.

TABLE 13.—*History and symptoms of serologically confirmed FUO cases in Vietnam, 1969*

History and symptoms	Reported percentage of cases						
	Scrub typhus (183 cases)	Murine typhus (189 cases)	Dengue (82 cases)	Japanese B encephalitis (26 cases)	Melioidosis (14 cases)	Lepto- spiro- sis (97 cases)	Amebiasis (73 cases)
Field duty	91	49	71	74	67	77	64
Sudden onset	44	46	57	62	43	40	38
Maximum fever:							
103° F	92	90	90	88	59	72	78
104° F or greater	63	51	44	55	16	53	36
Fever duration:							
7+ days	37	45	11	11	50	15	35
Shaking chill	58	62	59	50	21	63	40
Anorexia	60	65	73	69	57	66	69
Nausea	34	37	62	23	29	41	37
Vomiting	25	22	48	35	14	42	32
Diarrhea	16	16	27	4		19	43
Headache:							
Frontal	71	69	70	58	14	66	33
Other	14	15	21	31	29	19	12
Retrobulbar pain	17	21	33	23		20	4
Cough	23	12	20	12	71	29	23

TABLE 13.—*History and symptoms of serologically confirmed FUO cases in Vietnam, 1969—Continued*

History and symptoms	Reported percentage of cases						
	Scrub typhus (183 cases)	Murine typhus (189 cases)	Dengue (82 cases)	Japanese B encephalitis (26 cases)	Melioidosis (14 cases)	Leptospirosis (97 cases)	Amebiasis (73 cases)
Abdominal pain	11	10	10	11	7	26	51
Backache	33	36	45	31		44	25
Joint pain	12	15	39	12	7	26	12
Muscle pain	24	47	39	12	14	38	23
Conjunctival suffusion	20	14	33	23	7	34	15
Rash: macular	44	34	21	12		9	4
Lymphadenopathy	46	22	29	37		29	11
Pulmonary signs	6	1	1	4	21	5	10
Hepatic tenderness	7	6	1	4	7	21	27
Abdominal tenderness	10	10	8	4		13	47
Eschar	19	1	1	4		3	3
White blood count:							
> 15,000	1	2	4	15		4	17
10,000-15,000	23	13	19	35	54	27	22
4,000-10,000	72	77	54	50	46	67	50
< 4,000	4	8	22			3	11
Abnormal chest X-ray	3	1	2		36	8	10
Splenomegaly	33	31	10	4		11	19
Nuchal rigidity	2	2	15	46	7		1
Mental change	1		9	31			
Abnormal cerebrospinal fluid		1	13	46	7	4	1

Source: Records of Lt. Col. A. J. Ognibene, USARV Medical Consultant, 1969, from data collected at the 9th Medical Laboratory, Long Binh, Vietnam.

The distribution (probable and confirmed) of FUO cases serologically diagnosed in 1969 was as follows: *

Scrub typhus	228	Melioidosis	45
Amebiasis	212	Primary atypical pneumonia	22
Murine typhus	195	Paratyphoid	18
Group B arbovirus	179	Tick typhus	16
Leptospirosis	179	Typhoid	5
Infectious mononucleosis	96	Group A arbovirus	2
Lymphogranuloma venereum	59		

*Records of Lt. Col. Andre J. Ognibene, USARV Medical Consultant, 1969, from data collected at the 9th Medical Laboratory, Long Binh, Vietnam.

TABLE 14.—*FUO cases, by medical facility and diagnosis, Vietnam, 1969*

Submitting medical facility	Total FUO cases	Diagnosis ¹					
		Leptospirosis	Melioidosis	Group arbovirus	Scrub typhus	Murine typhus	Amebiasis
Hospitals:							
1st Australian Field ----	20	1		2	6		5
3d Field -----	115	12	5	11	11	18	19
6th Convalescent Center -----	35	6	2	1	4	3	8
3d Surgical -----	88	11		34	4	11	15
8th Field -----	18			2	5	6	5
12th Evacuation -----	72	5	7	12	39		6
12th U.S. Air Force -----	56	4	2	2	1	18	21
24th Evacuation -----	81	7	1	16	12	12	13
36th Evacuation -----	25	1	1	6	2	2	
67th Evacuation -----	56	3	3	9	20	5	10
71st Evacuation -----	148	25	1	8	18	58	21
85th Evacuation -----	65	15	4	22	9	6	6
91st Evacuation -----	51	4	3	11	11	6	18
93d Evacuation -----	200	29	10	28	38	22	38
95th Evacuation -----	39	3	1	3	17	4	2
Mobile laboratories:							
1st, Phu Bai -----	9	3				1	1
9th, Qui Nhon -----	15	2			3		2
74th, Nha Trang -----	35	5	2		6	5	14
Others -----	146	43	3	23	22	18	9

¹Infectious diseases most frequently diagnosed serologically, probable and confirmed.

Source: Records of Lt. Col. A. J. Ognibene, USARV Medical Consultant, 1969, from data collected at the 9th Medical Laboratory, Long Binh, Vietnam.

LESSONS LEARNED

Several lessons are to be learned from the FUO experience in Vietnam. First, a nucleus of tropical disease experts should be maintained from one generation to the next, as should an awareness of the major tropical diseases that might be encountered on future ventures into tropical countries. Second, worldwide tropical disease problems should be monitored so that one can accurately predict which diseases might be encountered in various areas of the world. Third, ongoing medical research studies in the less developed countries should be supported. These can contribute to eradication of such diseases in those countries. Finally, properly equipped laboratories for the study of tropical disease should accompany initial military units into all tropical environments so that unfamiliar medical problems can be recognized early and preventive measures instituted.

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Group B Arboviruses

Colonel Philip K. Russell, MC, USA, and Brigadier General Andre J. Ognibene, MC, USA

Section I. Dengue and Dengue Shock Syndrome

Colonel Philip K. Russell, MC, USA

HISTORY

Epidemics of an illness clinically resembling dengue fever have been recognized in tropical and subtropical areas of the world since the 17th century. A disease now thought by many to have been dengue was reported from the West Indies in 1635. In the latter part of the 18th century, epidemics were described in Java, Egypt, India, Spain, and the United States. In the 19th century, four widespread epidemics occurred in the Americas, mainly in the Caribbean region. Dengue epidemics of major proportion were also reported in Southeast Asia in the 19th century; however, in Indochina and the Philippines the disease was more frequently noted among foreigners than among the local populations. In this century, very large epidemics have occurred in the United States, Greece, Australia, Japan, and the Caribbean region.

Dengue has long been recognized as a major threat to nonindigenous troops operating in endemic areas. Before World War II, it frequently occurred among U.S. military personnel in the Philippines and was the subject of intensive research there under the auspices of the Army Medical Research Board. Early in the century, the viral etiology of dengue was proven and the presence of infectious virus in the blood was demonstrated in volunteers by Ashburn and Craig (1907). Siler and coworkers (1926) conclusively demonstrated that *Aedes aegypti* is a vector of dengue, confirming earlier work done by Cleland and associates (1919) in Australia. Simmons and associates (1931) proved that *Aedes albopictus* is also capable of biological transmission.

During World War II, epidemics of dengue assumed considerable military importance. For example, 24,079 cases were reported among U.S. troops in New Guinea in 1944, and more than 20,000 cases were reported among Army, Navy, and Marine Corps personnel on Saipan in June through October of the same year (MD-PM7, pp. 29-62). Epidemics during World War II often were related to combat operations, which complicated mosquito control measures. The continuous transportation of men and materiel associated with military operations may

have been related to the outbreaks of dengue which occurred in Japan, Hawaii, and Australia, as well as on many of the Pacific islands. The disease was also a problem for U.S. troops in China, Burma, and India. Extensive research on dengue was carried on by the U.S. Army during the war; of particular importance was the work of Sabin (1952), which resulted in the isolation of dengue viruses by intracerebral inoculation of mice and the demonstration of the existence of separate serotypes, dengue-1 and dengue-2, by experiments in volunteers.

DHF (dengue hemorrhagic fever) and DSS (dengue shock syndrome) were first recognized among children in the Philippines in 1954 and subsequently assumed importance throughout Southeast Asia. From 1960 to 1973, major DHF epidemics occurred in Bangkok, Manila, Singapore, Calcutta, Phnom Penh, Rangoon, Saigon, Hanoi, and Djakarta, as well as in many smaller cities; in several large cities, such as Bangkok, epidemics occurred annually during the rainy season. The dengue virus etiology of DHF was established by Hammon in 1958, and the existence of the dengue-3 and dengue-4 serotypes was discovered (Hammon, Rudnick, and Sather 1960).

EPIDEMIOLOGY

The transmission of dengue viruses is dependent on mosquitoes of the subgenus *Stegomyia*. The domestic mosquito, *Aedes aegypti*, is the principal vector throughout the world; other species, such as *A. albopictus*, *A. scutellaris*, and *A. polynesiensis*, have also been incriminated, usually as secondary vectors. Mosquitoes become infected by feeding on a viremic man and transmit the virus by bite after a short (5 to 7 days) extrinsic incubation period. No vertebrate hosts other than man are of major epidemiological importance. Monkeys can become infected, however, and a jungle cycle involving wild monkeys and forest-breeding *Aedes* mosquitoes may exist in Southeast Asia.

Four serotypes of dengue virus are now recognized, each of which has been associated with both dengue fever and DHF. These serotypes, although antigenically related, do not cross protect; infection with one confers homologous but not heterologous immunity. This fact accounts for closely spaced epidemics and the sequential reinfection of children in some endemic areas.

The three basic epidemiological patterns of dengue virus transmission are intermittent epidemic, endemic, and hyperendemic. The intermittent epidemic pattern usually involves a single serotype and occurs in areas where transmission is interrupted, often for long periods, by climate, vector control, or high levels of acquired immunity in a small population. Recurrence of disease requires reintroduction of a dengue virus when conditions are suitable for transmission. The classical epidemic is manifested by high clinical attack rates in nonimmune populations with all age groups being affected. Examples of this pattern are the epidemics which have occurred recently in island populations in Puerto Rico, Tahiti, New Caledonia, and Samoa.

The endemic pattern occurs when at least one dengue serotype is continuously present in a population and transmission continues uninterrupted over

a period of years. Clinical attack rates usually appear low since infections occur mainly in children and dengue infections in children most commonly result in mild undifferentiated febrile illnesses which are difficult to diagnose. A high level of acquired immunity protects the adult population from clinical illness. In endemic areas, dengue is frequently unrecognized. Nigeria, where dengue-1 and dengue-2 viruses are endemic, is a good example of the endemic pattern, as was most of Southeast Asia before the 1950's.

The hyperendemic pattern is manifested by the continued presence of multiple serotypes of dengue virus. In several hyperendemic areas of Southeast Asia, all four serotypes are present and continuous transmission occurs throughout the year with peaks during the rainy season. The most important clinical manifestations are DHF and DSS, which occur mainly in indigenous children. Hemorrhagic fever in hyperendemic areas is associated with second dengue infections. It is the hyperendemic pattern which allows multiple exposure and successive infection with heterologous serotypes among children. Clinical attack rates may be high, and case fatality rates for DHF may reach 5 to 15 percent. During U.S. Army involvement in Vietnam, hyperendemic dengue existed in Burma, Thailand, Cambodia, Vietnam, the Philippines, Indonesia, and India.

ETIOLOGY

Dengue viruses form a subgroup of the group B arboviruses (flaviviruses). These small (50 nm) RNA viruses are composed of a nucleocapsid with cubical symmetry surrounded by a lipoprotein envelope. The virion contains three virus-specific proteins, a large (mw 52,000) envelope glycoprotein, a very small (mw 8,000) envelope protein, and a single internal protein (mw 14,000). The envelope glycoprotein is associated with viral hemagglutinin activity and constitutes the major surface antigen. At least two nonvirion proteins specified by the viral genome and synthesized during infection are also known to evoke an antibody response during infection.

The four serotypes are designated dengue-1, -2, -3, and -4; in addition, a distinct subtype of dengue-3 exists. Serotypes are differentiated on the basis of neutralization tests and cross protection. Shared or cross-reactive antigenic determinants are located on the surface of the virion and on the nonstructural antigens and can be demonstrated by HI (hemagglutination inhibition) and CF (complement fixation) tests, which are commonly used for diagnosis. Dengue viruses also exhibit serologic cross-reaction with other group B arboviruses such as yellow fever and Japanese B encephalitis. Dengue viruses are infectious for man, several species of primates, and mosquitoes. In the laboratory, they can be adapted to grow in intracerebrally infected mice, and they replicate in several types of mammalian and insect cells in culture.

PATHOGENESIS

The deposition of virus by the bite of an infected mosquito is followed by an

incubation period of 3 to 15 days. In an experimentally infected monkey, the virus replicates in the skin at the site of infection and in local lymphatic tissues. Virus replication is thought to occur in lymphocytes. After the onset of symptoms a viremia occurs, which in man lasts 3 to 5 days. In plasma the virus may reach a concentration of 10^5 infectious units per ml. Since dengue fever very rarely is fatal, histopathologic observations in proven cases have been based solely on skin biopsies taken at the site of maculopapular and petechial eruptions. Nonspecific changes consist of endothelial swelling, perivascular edema, and, in petechiae, extravasation of blood. Mononuclear cell infiltration was observed by Sabin (1952, p. 36) in biopsies taken at the site of injection of virus in volunteers.

DHF and DSS result from an immunopathologic process in which complement activation and the formation of C3a and C5a anaphylatoxins play a major role (WHO). An anamnestic antibody response results when second heterologous dengue infections occur; this causes rapid formation of IgG antibody while virus and viral antigens are present in the blood. Complement is activated through C1 and by the alternate pathway through C3 activator. Plasma C3 levels fall abruptly, concomitant with a marked increase in vascular permeability which in turn results in hypovolemia and shock. Thrombocytopenia and varying degrees of diffuse intravascular coagulation occur, which contribute to a hemorrhagic diathesis. Autopsy of fatal cases of DHF reveals pleural and peritoneal effusions and widespread hemorrhagic lesions and petechiae. Paracentral hepatic necrosis is a common finding.

CLINICAL FEATURES

Dengue Fever

The onset of dengue in adults is usually accompanied by headache, backache, anorexia, chilliness, and malaise. Prodromal symptoms may precede the onset of fever by up to 12 hours or the onset may be abrupt, with severe headache, backache, myalgia, and ocular pain accompanying fever and chills. Nausea, vomiting, sore throat, and arthralgias may occur. Fever of 101° to 104° F persists for 3 to 6 days, usually without remitting; a diphasic "saddle-back" temperature curve sometimes occurs.

Early in the febrile period, a transient erythematous flush may be present over the face, neck, and upper trunk. In many cases, a distinct skin rash, usually macular or occasionally maculopapular, appears; it is more prominent on the trunk but can involve the face and extremities. It usually occurs between the third and fifth day of illness, lasting 1 to 3 days. Petechiae may be present in some patients, most commonly occurring on the lower extremities and usually appearing near the end of the febrile period. Generalized and frequently tender lymphadenopathy is a common physical finding early in the disease. The spleen is rarely enlarged. The conjunctivae are often injected and the eyes may be tender to pressure.

Leukopenia ($< 5,000$ per mm^3) is present in most cases, total leukocyte counts sometimes dropping as low as $1,500$ per mm^3 . Thrombocytopenia may also occur. Hematocrit, erythrocyte sedimentation rates, SGOT (serum glutamic oxaloacetic transaminase), and BUN (blood urea nitrogen) usually remain within normal limits (table 15).

TABLE 15.—Summary of clinical signs and laboratory findings in 55 dengue patients in Bangkok hospitals, 1971

Findings	Severity of disease ¹			
	Grade I (5 patients) percent	Grade II (14 patients) percent	Grade III (23 patients) percent	Grade IV (13 patients) percent
Fever	100	100	100	100
Hepatomegaly (2-5 cm)	100 (4/4)	91 (10/11)	100 (20/20)	100 (13/13)
Positive tourniquet test	50 (1/2)	92 (11/12)	84 (16/19)	62 (5/8)
Petechiae	0	100 (12/12)	52 (12/23)	69 (9/13)
Epistaxis	0	0	17 (4/23)	8 (1/13)
Hematemesis/melena	0	0	13 (3/23)	69 (9/13)
Hemoconcentration ²	60 (3/5)	71 (10/14)	91 (21/23)	69 (9/13)
Platelet counts:				
100-150 $\times 10^3/\text{mm}^3$	20 (1/5)	15 (2/13)	0	8 (1/13)
50-100 $\times 10^3/\text{mm}^3$	20 (1/5)	31 (4/13)	15 (3/20)	0
$< 50 \times 10^3/\text{mm}^3$	60 (3/5)	54 (7/13)	85 (17/20)	92 (12/13)

¹The following criteria (Nimmannitya et al. 1969) were used to grade the study population: Grade I: Fever accompanied by non-specific constitutional symptoms, with positive tourniquet test as the only hemorrhagic manifestation. Grade II: Fever and skin hemorrhage or other bleeding, such as epistaxis or gum bleeding. Grade III: Circulatory failure manifested by rapid, weak pulse with narrowing of the pulse pressure (< 20 mm Hg) or hypotension. Grade IV: Moribund patients with undetectable blood pressure and pulse.

²An increase in the hematocrit of > 20 percent.

Source: Pathogenetic mechanisms in dengue hemorrhagic fever: Report of an international collaborative study. *Bull. World Health Organ.* 48: 117-33, 1973.

Complications from a primary infection rarely occur in dengue fever. Epistaxis and menorrhagia have been reported, as has gastrointestinal bleeding, which is usually concomitant with a gastrointestinal disorder such as peptic ulcer. Prolonged convalescence with asthenia has been noted in some epidemics.

Dengue Shock Syndrome

Dengue hemorrhagic fever with shock or dengue shock syndrome is a distinct clinical entity which differs significantly from dengue fever. It occurs most frequently in children, rarely affecting adults. DHF and DSS occur in association with a second dengue infection. An initial febrile period lasting 2 to 5 days is characterized by headache, anorexia, vomiting, respiratory symptoms, and a maculopapular or petechial rash. Abdominal pain and marked lethargy in the first phase are poor prognostic signs presaging the onset of shock.

The shock phase may begin abruptly with lassitude, diaphoresis, and physical collapse. Patients appear severely ill with clammy extremities and peripheral vascular congestion. Cyanosis may be present, and petechiae and ecchymoses are common. The tourniquet test is usually positive. Pulse pressure is

narrowed and systolic and diastolic blood pressures may drop to undetectable levels, with a concomitant tachycardia. The liver is usually enlarged.

Untreated shock may result in coma, metabolic acidosis, and death. Bleeding may be marked, with epistaxis, hematemesis, or melena. Severe bleeding generally occurs after the onset of shock but sometimes happens during recovery from the hypotensive phase.

Marked hemoconcentration occurs as a result of increased capillary permeability; the hematocrit rises with the onset of shock. Leukocytosis occurs, in contrast to the leukopenia seen in primary dengue, and thrombocytopenia may be profound. The most marked depression of platelets occurs with the onset of shock. Serum albumin levels are low, as are serum sodium and bicarbonate, and terminal elevation of serum potassium levels has been noted in fatal cases. SGOT and SGPT (serum glutamic pyruvic transaminase) are elevated and parallel the severity of illness. The BUN is usually elevated. Serum C3 levels are markedly depressed, and the other early complement components are also low. Plasma fibrinogen levels are often low, and fibrin split products are present.

LABORATORY DIAGNOSIS

Conclusive diagnosis of a dengue infection requires isolation and serotypic identification of the virus. Virus usually can be recovered from the blood during the first 3 to 5 days of illness; success of isolation is highest on the first day. Fresh or frozen serum or plasma and cell culture systems such as LLC-MK₂ or *A. albopictus* cells are needed.

The HI, CF, and VN (virus neutralization) tests, using dengue antigens, can be of diagnostic value; however, antigenic sharing between group B arboviruses and the occurrence of broad cross-reactions with anamnestic antibody responses often make virus-specific diagnosis impossible by serology alone. The VN test is the most specific, the HI test the least. In some circumstances, separation of the IgM antibody for serologic testing may aid in providing a specific diagnosis.

In patients with primary dengue who have had no previous antigenic experience with a group B arbovirus, serum antibody becomes detectable on the fifth to eighth day, and titers rise for the next 2 to 4 weeks. The VN and CF tests may demonstrate type-specific antibody. Where previous exposure to a group B agent (including yellow fever vaccine) has occurred, antibody rises rapidly, as early as the fourth day. Titers in secondary antibody responses rise to very high levels, often within a few days, and extensive cross-reactions are seen, precluding a virus-specific diagnosis.

Demonstration of a significant (usually fourfold) rise in titer is necessary to serologically establish a recent infection; therefore, serum specimens collected early (day 1 to 4) and late (day 14 or later) are necessary.

PREVENTION AND TREATMENT

As of this writing, prevention of dengue depends on controlling or preventing exposure to mosquitoes; no dengue vaccine has been approved for use. *A.*

aegypti has been successfully eradicated from large areas of Central and South America, but vector control is ineffective or nonexistent in many tropical regions where dengue is endemic or hyperendemic.

A. aegypti breeds in and near human habitation, depositing its eggs in water storage vessels, ant traps, discarded tires, cans, and similar containers. Environmental cleanup and larvicide application can reduce vector populations. Insecticides such as malathion, delivered by fog or ultra-low-volume spray, are useful for short term control in limited areas, but residual spray techniques are no longer effective because of vector resistance. *A. aegypti* prefers to bite indoors during daylight; bed nets are therefore of little value. Screening of homes and billets effectively reduces exposure.

Treatment of dengue fever is entirely symptomatic as no effective antiviral therapy exists. DSS requires careful clinical observation and intravenous fluid therapy to maintain a satisfactory intravascular volume; patients may be dehydrated from vomiting and poor fluid intake before the shock phase. Plasma or plasma expanders can be lifesaving when shock occurs. A rising hematocrit is an indication for plasma replacement; whole blood transfusion may be required if bleeding is severe. Correction of acidosis is frequently required. There is no evidence that adrenocortical steroids, vasoactive agents, or antibiotics are of therapeutic value.

NEW ADVANCES

The Army Medical Department, as a result of U.S. involvement in the Vietnam war, made major contributions to the understanding of dengue in Southeast Asia in the areas of epidemiology, medical entomology, virology, immunology, and medicine. A research program on dengue and dengue hemorrhagic fever was initiated by the U.S. Army Medical Component, SEATO (Southeast Asia Treaty Organization), in 1962. Studies were carried out by the U.S. Army Medical Research Team, Vietnam, and by medical officers in several hospitals, including the 93d Evacuation Hospital at Long Binh, the 8th Field Hospital at Nha Trang, and the 3d Field Hospital at Saigon, in collaboration with the SEATO Laboratory in Bangkok, Thailand, the basic research facility (Deller and Russell 1967; Reiley and Russell 1969). Collaborative studies were also done in conjunction with l'Institut Pasteur in Vietnam.

Major epidemics of dengue fever did not occur among U.S. forces in Vietnam, undoubtedly because of the high level of environmental sanitation and the resulting absence of *A. aegypti* on most U.S. Army bases in Vietnam. Sporadic cases of dengue fever did occur and the disease was a significant cause of FUO (fever of undetermined origin); the FUO studies detailed in chapter 4 show that dengue was the cause of disease in 3.4 to 28 percent of patients hospitalized with FUO. Dengue was contracted mainly by support troops who had contact with civilian populations, as most mosquito transmission occurred in local communities. All dengue seen among U.S. military personnel was clinical dengue fever or mild undifferentiated febrile illness; although dengue hemorrhagic fever was not seen, epidemics did occur among Vietnamese children.

The first well-documented study of DHF in Vietnam, by Halstead and associates (1965), showed dengue-2 virus to be an etiologic agent; serologic tests demonstrated secondary antibody responses to the virus in eight patients (table 16). Epidemiological surveillance by Dr. Nguyen-Thi-Kim Thoa of l'Institut Pasteur indicated that annual epidemics of DHF occurred during the rainy season in the Saigon area from 1965 through 1973, and that DHF occurred occasionally in Vinh Long, Can Tho, Nha Trang, Qui Nhon, and Da Nang. A study of vector mosquitoes by Russell and associates (1969) showed that all four dengue virus serotypes were present in the Saigon area and confirmed *A. aegypti* as the major vector. An important observation in this study was that dengue in U.S. troops occurred at the same time as did epidemics of DHF in Vietnamese children; all four dengue serotypes were found to cause both dengue fever and DHF.

TABLE 16. — *Clinical and serologic findings in eight patients¹ with clinically diagnosed hemorrhagic fever, Saigon, 1963*

Item	Patient							
	1	2	3	4	5	6	7	8
Age _____	4	5	4	5	4	8	11	3
Sex _____	Male	Male	Male	Male	Male	Male	Female	Male
Day after onset when serum collected _____	21	22	27	31	18	² 4	10	30
Reciprocal of HI titer:								
Dengue _____	≥20,480	≥20,480	≥20,480	≥20,480	≥20,480	² 10,240	640	≥20,480
Chikungunya _____	< 20	160	< 20	< 20	< 20	² 320	320	< 20
Clinical findings: ³								
Days fever before admission _____	6	3	7	4	4	4	7	6
Vomiting _____	0	0	0	0	0	0	0	+
Abdominal pain _____	0	+	0	+	0	+	0	0
Positive tourniquet test _____	+	+	+	+	—	+	+	—
Lowest platelet count _____	20,000	50,000	50,000	10,000	160,000	80,000	36,000	—
Ecchymoses or petechiae _____	+	+	+	0	0	0	+	+
Gastrointestinal bleeding or epistaxis _____	+	+	+	+	+	+	+	+
Hepatomegaly _____	+	0	+	+	0	+	0	0
Shock _____	0	+	0	+	0	+	0	0
Coma _____	+	0	0	0	0	0	0	0

¹Patients 1 through 6 were hospitalized at Grall Hospital and 7 and 8 at Children's Hospital.

²Serum was also collected 14 days after onset with reciprocal of HI titer readings of ≥20,480 for dengue and 160 for chikungunya.

³(+) indicates presence of finding; (0) indicates absence; (—) indicates not known or not determined.

Source: Halstead, S. B. et al. 1965. Dengue hemorrhagic fever in South Vietnam: Report of the 1963 outbreak. *Am. J. Trop. Med.* 14: 819-30. © 1965, The Williams & Wilkins Co., Baltimore.

Section II. Japanese B Encephalitis

Brigadier General Andre J. Ognibene, MC, USA

Following the U.S. troop buildup in Vietnam in 1965-66, a number of cases of encephalitis occurred yearly between April and September (USARV-MC). During these months in 1969, 57 cases were evaluated by the U.S. Army. Most patients had acquired their disease in the Saigon-Long Binh area, although sporadic cases occurred in the coastal areas to the north. Diagnosis of JBE (Japanese B encephalitis) was definitively established by serologic study or viral isolation in 10; the available information on the remaining 47 was not as detailed as desired. The difficulties of conducting a study during wartime made a more comprehensive investigation impractical. A significant number of patients never came to the attention of the reviewers. However, the extent of the yearly epidemic and the possible future impact of mild or subclinical infections on U.S. troops in endemic areas direct that the available data be reported.

Twenty-four cases of JBE among U.S. personnel in I Corps were identified by the Naval Medical Research Team No. 2 in 1967 in a study of 295 febrile patients (Berman, Irving, and Kundin 1968). The seasonal period of occurrence was clearly demonstrated. Average rainfall and temperature in relation to identified cases are depicted on chart 3.

MATERIALS AND METHODS

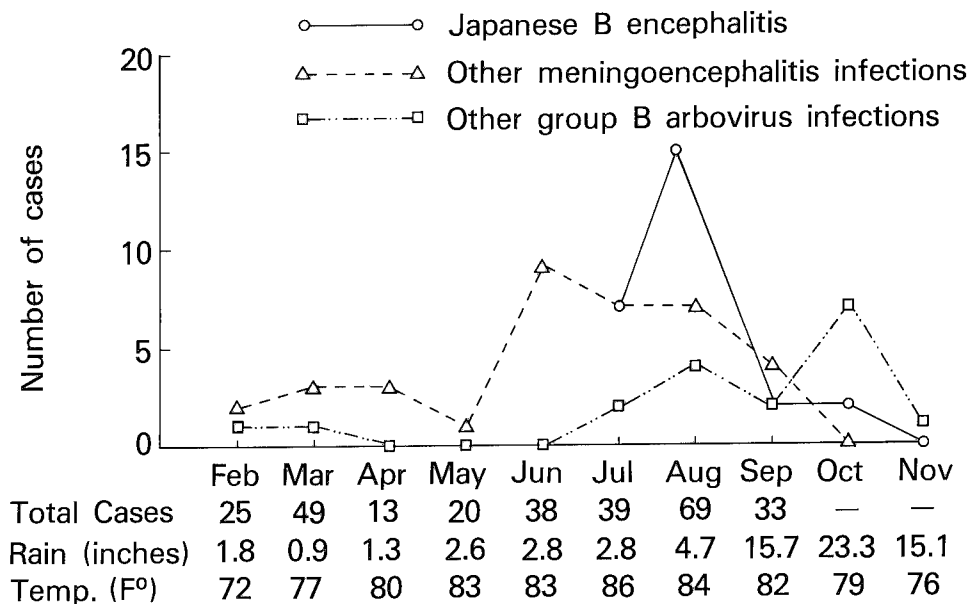
During the 1969 season, 57 patients with encephalitic manifestations were transferred to the neurology center at the 93d Evacuation Hospital in Long Binh for evaluation and therapy. They came primarily from the III and IV Corps areas, which included the Saigon-Long Binh complex. Nine patients with classical clinical signs were confirmed as having JBE by acute and convalescent serologic studies—CF, HI, and PRNT (plaque red neutralization test)—and an additional patient by virus isolation and identification from postmortem brain tissue at the SEATO Laboratory in Bangkok (table 17). A presumptive diagnosis was made in four others based on clinical observation and HI titers of 1:80 plus a fourfold titer rise in the convalescent specimen (table 18). In 43 patients, classical clinical encephalitis and abnormal C.S.F. (cerebrospinal fluid) were present and a probable diagnosis of JBE was made. Unfortunately, neither acute nor convalescent titers were available in this group, primarily because specimens were lost in the insecure and low priority transport system.

CLINICAL DATA

All of the 57 patients evaluated in this epidemic were males between 18 and 55 years of age, the majority under 25 years. Twenty-six were assigned to fixed

This section of the chapter is a revised version of an article by W. B. Ketel and A. J. Ognibene entitled "Japanese B encephalitis in Vietnam," originally published in *Am. J. M. Sc.* 261: 271-79, 1971.

CHART 3.—Seasonal occurrence of meningoencephalitis and group B arbovirus infections in Vietnam, 1967



Source: Berman, S. J.; Irving, G.; and Kundin, W. D. 1968. Infectious disease survey of U.S. personnel in I Corps, South Vietnam. U.S. Naval Medical Research Unit No. 2, Taipei, Taiwan, Mar. 68.

installations engaged in support activities; 12 of these had not left the confines of the large Long Binh military complex. Of the total group, 20 returned to duty in Vietnam after an illness not exceeding 2 weeks. Mental and neurological residuals warranting medical evacuation were noted in 36 patients; all were evacuated after the acute phase of the illness, and none returned to duty in Vietnam. Patients evacuated to Japan and then to the United States were lost to followup.

When initially examined, 86 percent of the patients were alert. They complained of several days of headache, fever, chills, vomiting, stiff neck, and photophobia or eye pain. The onset of fever heralded the most severe phase of the illness. Temperatures reached 104° to 106° F, rectally, remaining elevated from 3 to 6 days, then falling to normal within a few hours or over a 24-hour period. Changes in sensorium were most severe during the febrile period; many patients were extremely confused and combative. A semicomatose or comatose state occurred in 12 percent (chart 4).

Mental and neurological residua were not present at the time of discharge in the 20 patients returned to duty in Vietnam. During the acute phase in this group, alterations of consciousness were minor in degree, manifested primarily by lethargy, hypersomnolence, or confusion of time, place, or person. Otherwise, findings from neurological examinations were normal. Among evacuated patients, neurological residua varied from mild confusion to severe organic brain

TABLE 17.—*Clinical and laboratory data of ten confirmed Japanese B encephalitis patients in Vietnam, 1969*

Data ¹	Patient									
	1	2	3	4	5	6	7	8	9	10
White blood count (mm ³)	13,500	14,000	11,400	12,100	6,100	—	—	14,000	12,500	16,000
Cerebrospinal fluid:										
Pressure (mm H ₂ O)	—	160	210	190	—	—	210	—	180	190
Cells (mm ³):										
lymphs/polys	35/25	224/28	200/0	68/0	116/80	Elevated	31/21	144/0	2/8	196/4
Protein (mg percent)	92	48	95	80	84	—	60	40	45	172
Japanese B encephalitis titers (acute and convalescent):										
Hemagglutination inhibition	{ 640 1,280	{ 80 1,280	{ 160 2,560	{ 640 1,280	{ 160 320	{ 160 2,560	{ 160 640	{ 80 320	{ 80 1,280	{ (²)
Complement fixation	{ 32 128	{ 4 128	{ 8 32	{ 32 256	{ 16 32	{ 16 256	{ 32 128	{ 4 64	{ 16 128	{ (²)
Plaque red neutralization test	{ 160 640	{ 40 640	{ 40 160	{ 160 2,560	{ 160 2,560	{ 160 2,560	{ 160 640	{ 40 40	{ 40 160	{ (²)
Febrile days	10	6	5	6	5	5	4	6	4	9
Headache	+	+	+	+	+	+	+	+	+	+
Nuchal rigidity	+	+	+	+	+	+	0	+	+	+
Photophobia	0	+	+	0	0	+	0	0	+	+
Myalgia	+	+	+	+	+	+	0	0	+	+
Vomiting	+	+	+	+	+	+	0	0	+	+
Mental changes	+	+	+	0	+	+	+	+	+	+
Seizures	0	0	0	0	0	0	0	0	0	0
Abnormal neurological signs	—	0	0	0	0	0	0	+	+	+
Disposition	Evacuated	Evacuated	Evacuated	Duty	Evacuated	Evacuated	Evacuated	Evacuated	Evacuated	Died

¹(+) indicates presence of finding; (0) indicates absence; (—) indicates data unavailable.²Virus isolated from brain.Source: Ketel, W. B., and Ognibene, A. J. 1971. Japanese B encephalitis in Vietnam. *Am. J. M. Sc.* 261: 271-79.

syndrome with alterations in intellect, orientation, judgment, and memory. Abnormal neurological signs, such as reflex changes, positive Babinski signs, ataxia, weakness, and tremor, were noted infrequently, and two patients demonstrated an expressive aphasia.

Headache, a constant feature of the disease, was present in all patients and was usually described as frontal and bitemporal at the onset, becoming generalized. The pain markedly increased in severity with movement or walking and remained 48 to 72 hours beyond lysis of fever.

The severity of the nuchal rigidity which was present in 94 percent of the patients evaluated appeared to correlate with the severity of the clinical course. In most patients, nuchal rigidity was present on admission or developed within the first 48 hours. When it was moderate or severe, Kernig and Brudzinski signs were usually present.

Eye pain or sensitivity to light was a frequent initial complaint, noted in 45 percent of the patients. Increasing periorbital pain with exposure to light was characteristic; some patients stated that the light increased their frontal headache.

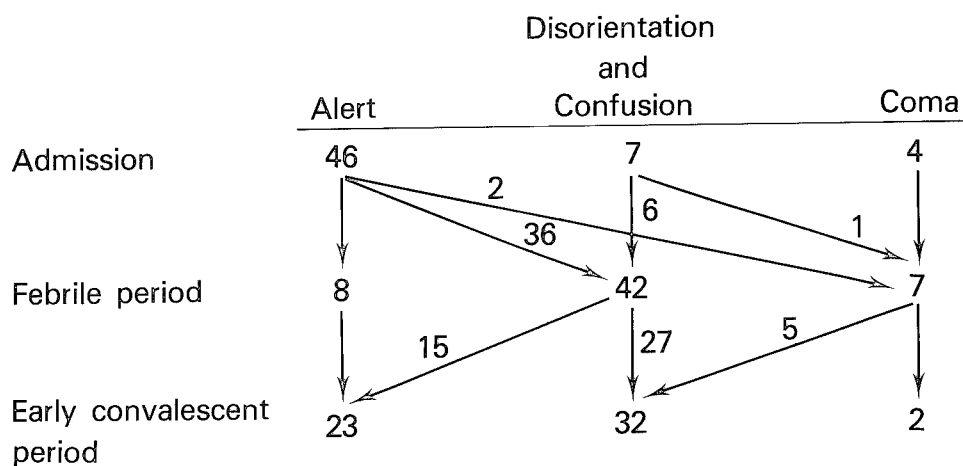
In 86 percent of the patients, mental status in the febrile period following admission deteriorated in varying degrees. In some patients, the symptoms were mild, consisting of a short period of confusion, poor orientation to surround-

TABLE 18.—*Clinical and laboratory data of four suspected Japanese B encephalitis patients in Vietnam, 1969*

Data ¹	Patient			
	1	2	3	4
White blood count (mm ³)	16,500	11,900	15,700	18,000
Cerebrospinal fluid:				
Pressure (mm H ₂ O)	—	210	—	—
Cells (mm ³): lymphs/polys	361/39	230/30	230/0	129/21
Protein (mg percent)	65	64	65	50
Japanese B encephalitis titers (acute and convalescent):				
Hemagglutination inhibition	20 320	20 160	40 160	20 80
Febrile days	6	4	4	5
Headache	+	+	+	+
Nuchal rigidity	+	+	+	+
Photophobia	+	+	+	0
Myalgia	+	+	+	+
Vomiting	+	+	+	0
Mental changes	0	+	+	0
Seizures	0	0	0	0
Abnormal neurological signs	0	0	0	0
Disposition	Evacuated	Evacuated	Evacuated	Duty

¹ (+) indicates presence of finding; (0) indicates absence; (—) indicates data unavailable.

Source: Ketel, W. B., and Ognibene, A. J. 1971. Japanese B encephalitis in Vietnam. *Am. J. M. Sc.* 261: 271-79.

CHART 4.—*Mental status of Japanese B encephalitis patients in Vietnam, 1969¹*

¹ Arrows indicate courses; numbers represent patients following them.

Source: Ketel, W. B., and Ognibene, A. J. 1971. Japanese B encephalitis in Vietnam. *Am. J. M. Sc.* 261: 271-79.

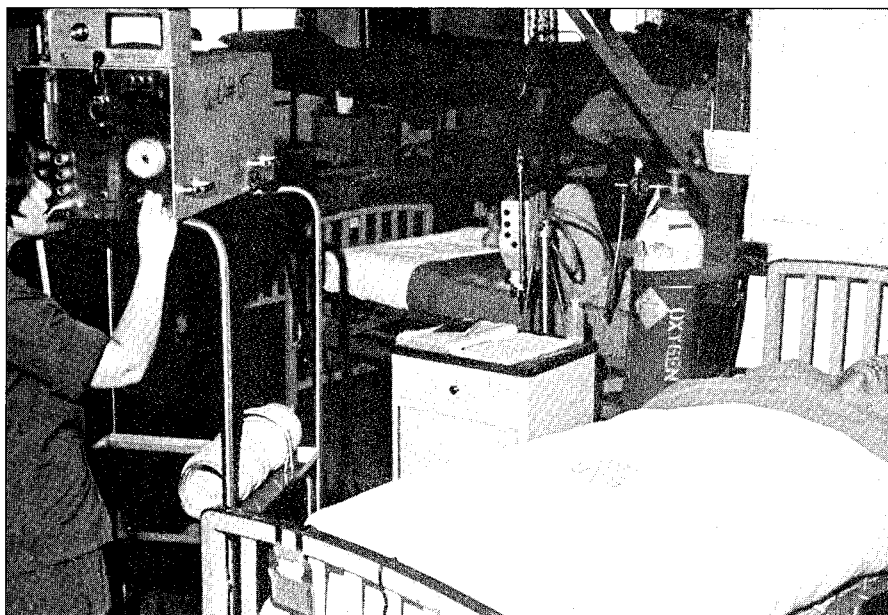


FIGURE 38.—Patient with Japanese B encephalitis under therapy at the 93d Evacuation Hospital with controlled hypothermia. Control of fever during the acute phase of illness was consistently practiced in the support of patients with Japanese B encephalitis in Vietnam.

ings, and lethargy. The remaining patients demonstrated moderate to marked mental status changes, which persisted in 32 (see chart 4). Severe disorientation to time, place, person, or surroundings, with confusion, hyperirritability, and belligerent behavior, occurred during the febrile period. Deterioration of mental functions generally appeared by the third or fourth day of illness. Coma or a semicomatose state on admission was indicative of severe morbidity and a slow recovery. Fifteen patients remained severely demented at the time of medical evacuation.

Paresis of the extremities occurred frequently during the acute phase but always resolved rapidly in the convalescent period despite persistence of mental changes. Ocular palsies and nystagmus occurred in three patients and rapidly cleared. Aphasia occurred in two and persisted as an expressive type. Mild alterations in coordination, clumsiness of gait, and mild tremor were frequently noted. Increased tone, hyperreflexia, spasticity, and positive Babinski signs were uncommon except in those patients who had a major motor seizure. The one patient who died was lethargic and aphasic and had spontaneous choreoathetoid movements of the right extremities and left hemiparesis on admission. He rapidly lapsed into deep coma with decorticate posturing which persisted through 9 hospital days.

Seizures have been reported infrequently in adults with JBE, although they are common in children (Lincoln and Sivertson 1952; Sabin 1947; Hüllinghorst et

al. 1951; Clarke and Casals 1965). Six patients in this study experienced seizures during the febrile phase of their illness (fig. 38). These were always generalized and major motor in type, and occurred during the first febrile day in five patients; one patient experienced a seizure on the third hospital day. Seizures were significantly correlated with persistent mental status abnormalities, reflex asymmetries, hemiparesis, or aphasia. This association has not been previously emphasized and may be explained by more extensive cortical inflammation and edema. Electroencephalograms were available for two patients and revealed diffuse slowing with predominant frequencies of 4 to 6 cycles per second. Epileptiform discharges were not noted. In five of the six patients, only a single seizure occurred.

The one death which occurred in this series represents a much lower mortality rate than those reported previously. In Korea, mortality as high as 53 percent occurred among local civilians during the epidemic of 1949 (Hullinghorst et al. 1951), and a rate of 8.5 percent was recorded in the epidemic involving American personnel in 1950 (Lincoln and Sivertson 1952). The low mortality in the present series may reflect the effect of more modern nursing and supportive care available to the patients. Vigorous efforts to reduce highly elevated temperatures, including controlled hypothermia, were made, and fluid balance was carefully monitored. Improvements appeared unrelated to the use of steroids or antibiotics.

The major persisting abnormality was in mental status. Present in 95 percent of evacuees, it usually took the form of any of a wide spectrum of persistent memory defects, poor orientation or attention span, or gross dementia. Abnormal neurological signs were not clinically prominent in this group; the most common neurological dysfunctions during the convalescent period were tremulousness and mild incoordination of the extremities or mildly ataxic gait.

Persistent alteration of mental status and ataxia correlate with microscopic findings. Throughout the cortex and cerebellum, cellular inflammatory nodules are present, consisting of increased numbers of oligodendroglia, microglia, and macrophages. Loss of neurons occurs in the cerebral cortex and in the Purkinje cells of the cerebellum (Greenfield 1963). It is therefore surprising that spasticity or other long tract signs were not observed.

The average white blood cell count in this series was 13,000/mm³ and varied from 5,500 to 18,000. A "shift to the left" was frequent.

A lumbar puncture was performed on all patients with clinical encephalitis. Opening pressure was generally mildly elevated. Only one patient had a pressure below 160 mm H₂O; 22 values above 200 mm H₂O were recorded. The cerebrospinal fluid was clear in those lumbar punctures performed at the neurology center. Cell counts ranged from 5 to 2,500/cm³. The predominate cell type was lymphocyte in all but four patients. C.S.F. glucose values were normal, cultures sterile, and Gram's stains negative in all patients. C.S.F. protein values were abnormal (above 45 mg percent) at the time of the initial lumbar puncture in 46 patients. Values ranged from 30 to 200 mg percent. There was no relationship between the number or types of cells or protein concentration in the spinal fluid and the clinical severity of the disease.

DISCUSSION

The typical patient presented with a symptom complex consisting of severe headache, fever, malaise, myalgia, nausea, vomiting, photophobia, and nuchal rigidity or pain. Confusion, disorientation, and combativeness dominated the febrile period.

A large percentage of patients infected with JBE do not develop clinical encephalitis (Halstead and Grosz 1962; Halstead and Sudie 1962; Scherer et al. 1959). Principal manifestations of the abortive form of the disease are mild headache, fever, and malaise of a few days' duration. The true incidence of low-grade or subclinical infections is difficult to assess; estimates have varied from 500 to 1,000 inapparent infections for each case of clinically apparent disease in one study (Southam 1956) to a ratio of 25 subclinical infections to 1 overt case of encephalitis during the Korean epidemic of 1958 (Halstead and Grosz 1962).

Serologic studies were performed on paired serum specimens (collected 1 year apart) from Australian soldiers deployed in Vietnam in 1966-67 (Russell et al. 1967). A significant serologic conversion establishing exposure to JBE virus occurred in 20.9 percent of those tested. These patients had been symptom-free. Only two cases of overt JBE had occurred among Australian troops during that same period; a ratio of subclinical to clinical infections of 210:1 was recorded. It can be estimated from this figure that during the epidemic of 1969 at least 11,970 American troops in Vietnam may have been infected with JBE virus and developed mild or subacute infections that did not come to the attention of medical personnel. Available information indicates that 61 clinical cases of encephalitis occurred among U.S. personnel in Vietnam in 1970, with two reported deaths (Edgett).

Considering the variable onset and often mild course of the abortive form of the disease, it is not surprising that the diagnosis is not established clinically. Therefore, it is strongly recommended that during an epidemic period lumbar punctures be performed on all persons with a suggestive history and symptoms of fever and headache. Serologic studies, when feasible, are mandatory. This recommendation is applicable to epidemics of other forms of encephalitis confined to the continental United States. It would surely have been of value to U.S. physicians in Vietnam, who were constantly challenged by patients with "fever of undetermined origin," for which lumbar punctures were not a routine procedure.

Incidence of late morbidity, such as personality changes, persistent memory loss, early dementia, Parkinsonism, and dyskinesias, in clinically overt cases of JBE is approximately 10 percent (Edgett 1971). Information concerning late morbidity in the much larger group with subclinical infection is not available. Minimal loss of intelligence and dexterity may accompany infections when both the functional loss and the infection itself remain entirely unrecognized. The continuing yearly epidemics in Vietnam and the still unresolved problem of late sequelae in subclinical infection (Weaver et al. 1958) warrant serious consideration of the development of protective immunization for individuals assigned to

endemic areas; this would be a realistic approach to recurring epidemics worldwide.

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Other Viral Diseases

Jay P. Sanford, M.D., and Colonel Adolf E. Rahm, Jr., MC, USA

Section I. Acute Respiratory Disease

Jay P. Sanford, M.D.

Acute infections of the respiratory tract constitute a major health problem not only for civilians and military recruits but also for seasoned troops, even in areas of the world where hygienic and climatic conditions predispose the troops to other illnesses such as gastrointestinal disorders and skin diseases. Such was the USARV (U.S. Army, Vietnam) experience, where rates for respiratory infections (based on soldiers reporting on sick call and confined to quarters or admitted to medical care facilities) varied between 315 and 617 cases per 1,000 troop strength per annum (USARV-CHR 1970).

In the past 20 years, virologists have made major advances in defining the etiologic agents of common respiratory diseases. More than 100 agents of human respiratory disease are now recognized (Ward 1973). The goals of this presentation are to review the current knowledge of the etiology and epidemiology of acute respiratory illness with special reference to military populations, to summarize observations in U.S. Army personnel in Vietnam, and to recommend types of data which are useful in developing methods for surveillance and control.

HISTORICAL PERSPECTIVE

As a result of the recognition of "primary atypical pneumonia, etiology unknown" at Camp Claiborne, La., in the winter of 1941-42, the Commission on Acute Respiratory Diseases was established by The Surgeon General of the Army. The objectives of the commission were to classify the acute respiratory diseases occurring among military personnel and to investigate their epidemiology. Fort Bragg, N.C., was selected for study because of its large size and because both relatively stable military units and recruits could be observed. The commission laboratory opened at Fort Bragg in October 1942. The epidemiological data were published in 1968 by Dr. John H. Dingle, commission director, and Dr. Alexander D. Langmuir, a member of the commission (1968). Despite a 25-year delay in publication the observations are brilliant, and they are directly pertinent to the problem of acute respiratory diseases in Vietnam. Furthermore, because specimens collected from 1942 to 1946 were stored well, recently developed laboratory techniques could be applied to them, enabling some of the epidemiological observations to be clarified.

The terminology and diagnostic criteria for classifying data were as follows:

For the entire post:

(1) Respiratory admissions: Daily admissions to the hospital with a diagnosis of some type of respiratory disease.

(2) Common respiratory diseases: Weekly admissions for respiratory disease as reported by the hospital's registrar. Similar reports from all Army posts in the continental United States were combined in the Office of the Surgeon General and were compared with the Fort Bragg data.

(3) Primary atypical pneumonia: The figures for this category were based on routine chest roentgenograms taken at the time of admission and on discharge diagnosis.

For the special studies:

(1) Acute undifferentiated respiratory diseases (also termed acute respiratory disease [ARD] of recruits): Acute illnesses, usually febrile, with respiratory or generalized constitutional symptoms, or both, ordinarily of less than 2 weeks' duration. 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.

(2) Nonstreptococcal exudative tonsillitis or pharyngitis: Respiratory illnesses characterized by exudative lesions on the tonsils, palate, or oropharynx without either beta-hemolytic streptococci or an increase in titer of antistreptolysin antibodies during convalescence.

(3) Primary atypical pneumonia: Respiratory illnesses 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: Diagnosed only when the illness was clinically compatible with such an infection and when beta-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. They were excluded from further consideration in this study.

The criteria employed in USARV Command Health Reports were essentially the same as those listed above except that CRD (common respiratory diseases) and acute undifferentiated respiratory diseases were interchangeable in Vietnam.

The first year of investigation at Fort Bragg led to a series of important observations. The most important respiratory disease, accounting for about 80 to 90 percent of hospital admissions, was ARD of recruits, so named because it was confined to newly inducted men. This disease occurred epidemically among both inductees in training centers and new recruits assigned to units composed of seasoned troops.

The epidemics began in the fall, usually in an irregular fashion. In mid-winter, they were sharp, distinct, and self-limited in newly arrived units, usually occurring within the first 4 or 5 weeks of training and not recurring in those units. In the spring, the epidemics were less severe; they were barely discernible or absent in summer. Units arriving in late summer, whose training period extended into the fall or winter, frequently experienced an epidemic at the end of their training period.

Susceptibility to ARD usually correlated inversely with length of military service. Geographic origin and age did not appear to be important factors. In general, the acute respiratory diseases occurred in association with primary atypical pneumonia in a ratio of approximately 10 to 1, regardless of season or length of service.

ARD OVERVIEW

Temperate Areas

Virtually all of the etiological and epidemiological studies of ARD which might serve as background upon which to assess the USARV experience are of troops based in temperate climates. The general pattern of occurrence of respiratory diseases in these areas is summarized, by specific agents, in table 19. The difficulty of extrapolating from such data is reflected in the following example. In the late summer and fall of 1968, an outbreak of coxsackievirus A21 occurred among marine trainees at Camp Lejeune, N.C., accounting for 60 to 86 percent of viral isolations; however, between February 1969 and February 1971, no isolations of this organism were made (Wenzel et al. 1971).

In addition to rates of occurrence, the severity and duration of illness are important considerations. For instance, while 89 percent of a group of Navy and marine recruits shed rhinoviruses on at least one occasion during 4 weeks of study in November 1965 and only 1 to 2 percent of them did not have symptoms

TABLE 19.—General pattern of the epidemiology of acute respiratory disease in U.S. military populations stationed in temperate climates

Etiology	Seasonal occurrence	Comments
Influenza A	Late fall-winter	Attack rates equal in recruits and seasoned troops.
Coxsackievirus A21	Late summer-early fall	Predominantly recruits.
Rhinovirus	Fall-late spring	Of the recruits, 89 percent shed virus, 1.2 illnesses/man, 5 weeks of recruit training.
Adenoviruses 4 and 7	Winter	Predominantly recruits.
<i>Mycoplasma pneumoniae</i>	Summer-early fall	Predominantly recruits, 20 to 44 percent of atypical pneumonia.

Sources: (1) Dingle, J. H., and Langmuir, A. D. 1968. *Am. Rev. Resp. Dis.* 97: 1-65. (2) Wenzel, R. P., et al. 1971. *Mil. Med.* 136: 873-80. (3) Rosenbaum, M. J., et al. 1971. *Am. J. Epidemiol.* 93: 183-93. (4) Griffin, J. P., and Crawford, Y. E. 1969. *Am. Rev. Resp. Dis.* 100: 206-12. (5) Mogabgab, W. J. 1968. *Am. Rev. Resp. Dis.* 97: 345-58.

of a common cold, these illnesses did not require loss of time from duty, although efficiency was undoubtedly impaired (Rosenbaum et al. 1971). In contrast, the average duration of hospitalization for ARD caused by adenovirus 4 or 7 was about 9 days, and for *Mycoplasma pneumoniae* illness the average was 20 days (Wenzel et al. 1971). While criteria for hospitalization and assignment to quarters probably differed, during an outbreak of influenza caused by A2/Hong Kong, the average time lost from duty was 2.6 days (Smith et al. 1970). Specific duties of afflicted personnel must also be considered. For example, a rhinovirus infection or otitis externa may be totally incapacitating in airborne personnel in whom aerotitis or aerosinusitis may occur, while these same entities merely decrease efficiency in ground support personnel.

Tropical Areas

The seasonal change of weather is one of the factors that influence the spread of respiratory viruses through a population. Several studies demonstrating this have been performed in tropical areas; however, these have primarily involved children, and applying the data to adults is difficult (Monto and Johnson 1967; Chanock, Chambon, et al. 1967; Bell et al. 1959).

In a study designed to define the etiology of severe viral respiratory infections in children, particularly in tropical areas, paired serums were collected from 528 children up to 5 years old admitted to hospitals in 10 countries (Chanock, Chambon, et al. 1967). The areas surveyed included Hong Kong, Singapore, and New Delhi. The findings indicated that the pattern of severe respiratory disease in tropical areas is similar to that which has been defined in temperate areas.

In a serological survey of both children and adults in Paraiso, Canal Zone (Panama), between May 1963 and January 1964, 41 individuals between the ages of 15 and 39 were included (Monto and Johnson 1967). Significant increases in antibody titer were noted in seven (17 percent): two in the parainfluenza 1 group, three in the parainfluenza 3 group, one in the respiratory syncytial virus group, and one in the adenovirus group; there were none in the parainfluenza 2 and *Mycoplasma pneumoniae* groups. No differences in antibody content were demonstrated when comparisons were made with serums obtained from a group of American adults. Respiratory disease accounted for more than two-thirds of the illnesses seen in Paraiso, with rates as high as 160 per 1,000 per month, so that lack of a winter season did not prevent dissemination of pathogens. An increase in illness was usually seen at the start of the rainy season, which coincided with the start of the school year.

These observations reflect a similarity between tropical and temperate climates. In contrast, in a study of adenoviruses isolated from conjunctival specimens in eastern Saudi Arabia, adenovirus types 1, 2, and 5, which are common in the United States, were never isolated; types 15, 16, 17, and several new types which were common in Arabia have not yet been reported in the United States (Bell et al. 1959).

Olson and associates (1973), in Thailand, observed that periods when specific agents were prevalent were independent of season, the only relevant weather variable being the presence or absence of rainfall. (The one possible exception was the 2-year period when coxsackievirus B2 was recovered only during January and February, months corresponding to the drier season.) Influenza A outbreaks were recognized in Hong Kong in April 1957 and July 1968 (Sanford 1969).

Thus, from the limited data available one could expect the patterns of seasonal occurrence in temperate climates to be absent or altered in tropical climates, where other factors would dominate the epidemiology. Furthermore, although viral respiratory diseases are widespread, the relative frequencies given for various pathogens in temperate climates only reflect observations in urban groups. In addition, differing serotypes may be encountered in different areas of the world, as with adenoviruses and possibly rhinoviruses.

ARD IN VIETNAM

Technical Considerations

Most of the data presented here, obtained from monthly USARV Command Health Reports (USARV-CHR) and from reports of selected units, have been reviewed not only for rates but also for the preventive medicine officers' comments. In these reports, rates are defined as follows:

$$\text{rate} = \frac{\text{new cases} \times 1,000 \times \text{days in year}}{\text{average morbidity strength} \times \text{days in month}}$$

The terminology used includes:

ARD—acute respiratory disease; cases requiring hospitalization or assigned to quarters.

CRD—common respiratory disease; used interchangeably with ARD.

URI—upper respiratory infection; includes outpatients with symptoms of upper respiratory infection as well as individuals requiring hospitalization or assignment to quarters, except for patients with pneumonia, influenza, and streptococcal sore throat.

Pneumonia—a separate category; a requirement for radiographic change was not defined.

Unfortunately, laboratory support for identification of respiratory disease agents was essentially limited to the detection of cold hemagglutinins. The 9th Medical Laboratory Activities Report for 1968 (ML9-AR, p. 19) stated that expanded studies of known agents of respiratory disease were projected and that attempts would be made to isolate antigenic variants of the principal groups being studied.

Materials reviewed for the statistics in this section include monthly reports from the unit surgeons of the 1st Cavalry Division (Airmobile), the 173d Airborne Brigade (Separate), and the 9th Infantry Division, to the USARV Surgeon, 1965-70 (CD1-HR; AB173-HR; ID9-HR). The data from these reports were used in the USARV surgeon's monthly reports to the USARV commander. Other sources are noted where appropriate.

Observations

The rates for URI varied markedly among units; for example, in March 1969 the rate in the 1st Infantry Division was reported as 2.2 cases per 1,000 average strength per year, while that of the 11th Armored Cavalry Regiment was 167 per 1,000 per year. Such discrepancies almost certainly reflect differences in reporting. Overall U.S. Army URI rates for 1968-70 fall in the range of 350 to 600 per 1,000 per year, which is remarkably close to the lowest rate from Fort Bragg in June and July 1944—520 per 1,000 per year (Dingle and Langmuir 1968).

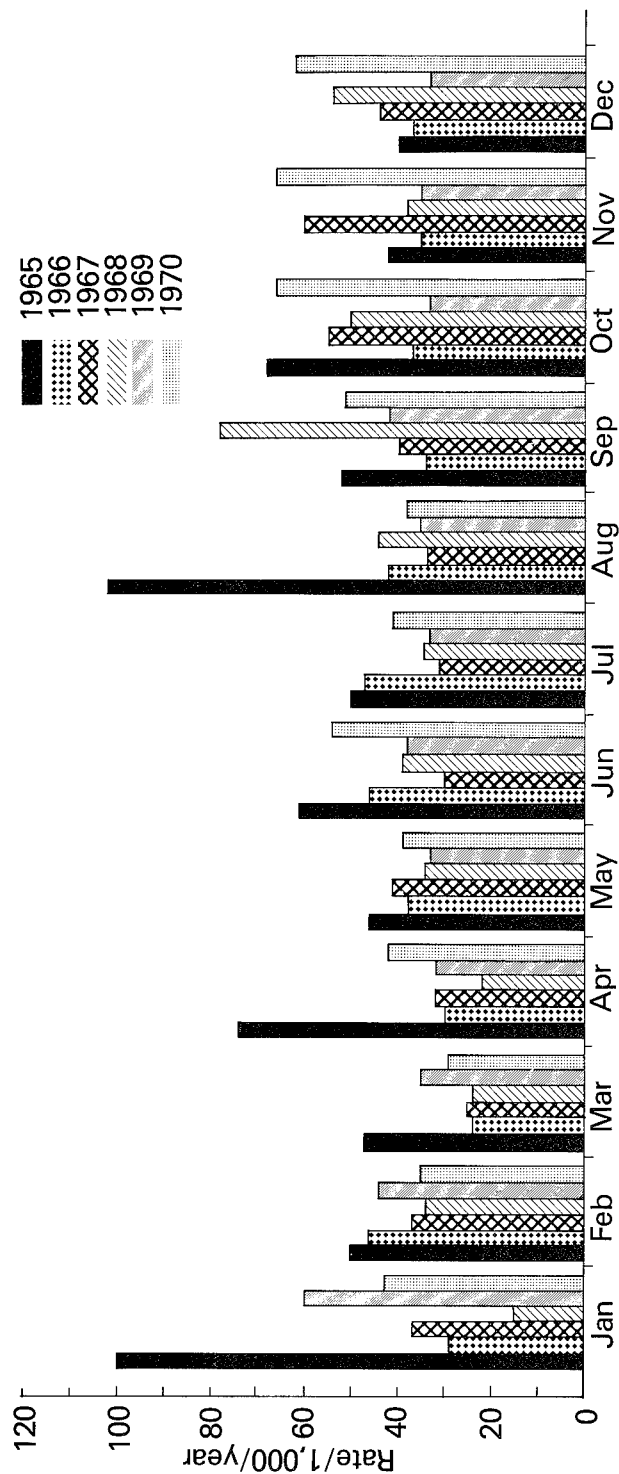
The ARD rates vary less and may reflect more accurately the total respiratory disease problem, although only 6.5 to 12 percent of all individuals with respiratory diseases were assigned to quarters or admitted to hospitals. Rates for USARV for 1965 through 1970 are plotted in chart 5. These rates (15 to about 105 per 1,000 per year) are comparable to the rates observed for the Army in the continental United States during 1944-45 (50 to 200 per 1,000 per year) (chart 6), especially since these latter rates included a proportion of recruits. The reason for the higher rates in USARV in 1965 is unknown.

A role of weather changes in the frequency of URI (and possibly ARD) was suggested by comments in the health reports of various units. An increase in URI between December 1968 and January 1969 in XXIV Corps tactical area, I CTZ (Corps Tactical Zone), was associated with the occurrence of rain and cooler weather, especially at night. A similar increase at Long Binh in April 1969 was associated with the monsoon. To better document these impressions, ARD rates for 1967 for the 9th Infantry Division at Dong Tam, in IV CTZ in the Mekong Delta, were compared with the rates for the 1st Cavalry Division (Airmobile) at An Khe and the 173d Airborne Brigade at Dak To, both in II CTZ in the Central Highlands (chart 7). The 9th Infantry Division was exposed to the summer monsoons and temperatures often exceeding 100° F at midday, while the 1st Air Cavalry Division (AM) and 173d Airborne Brigade were in the area of the winter monsoons (October to April), with temperatures in the 70's. No correlation could be made between ARD rates and season (dry or monsoon) or temperature differences associated with altitude. An isolated rate of 276.4 cases per 1,000 in the 9th Infantry Division in January is unexplained.

Rates for pneumonia were 8 to 10 percent of the ARD rates, varying between 1.3 to 6.8 per 1,000 per year, except for a rate of 10.5 per 1,000 per year in November 1967.

Confirmation of the specific etiologies which were responsible for ARD has not been possible. The occurrence of influenza A2/H3 N2/Hong Kong in the late summer and fall of 1968 is suggested by individual reports. In August, classical symptoms of an influenzal syndrome were noted in various units, including the 11th Armored Cavalry Regiment near Xuan Loc. In this regiment, rates for ARD increased from 98.8 per 1,000 in July to 386.1 per 1,000 in August. In December 1968, an increase in influenzal illness was reported in the Americal Division (23d Infantry Division).

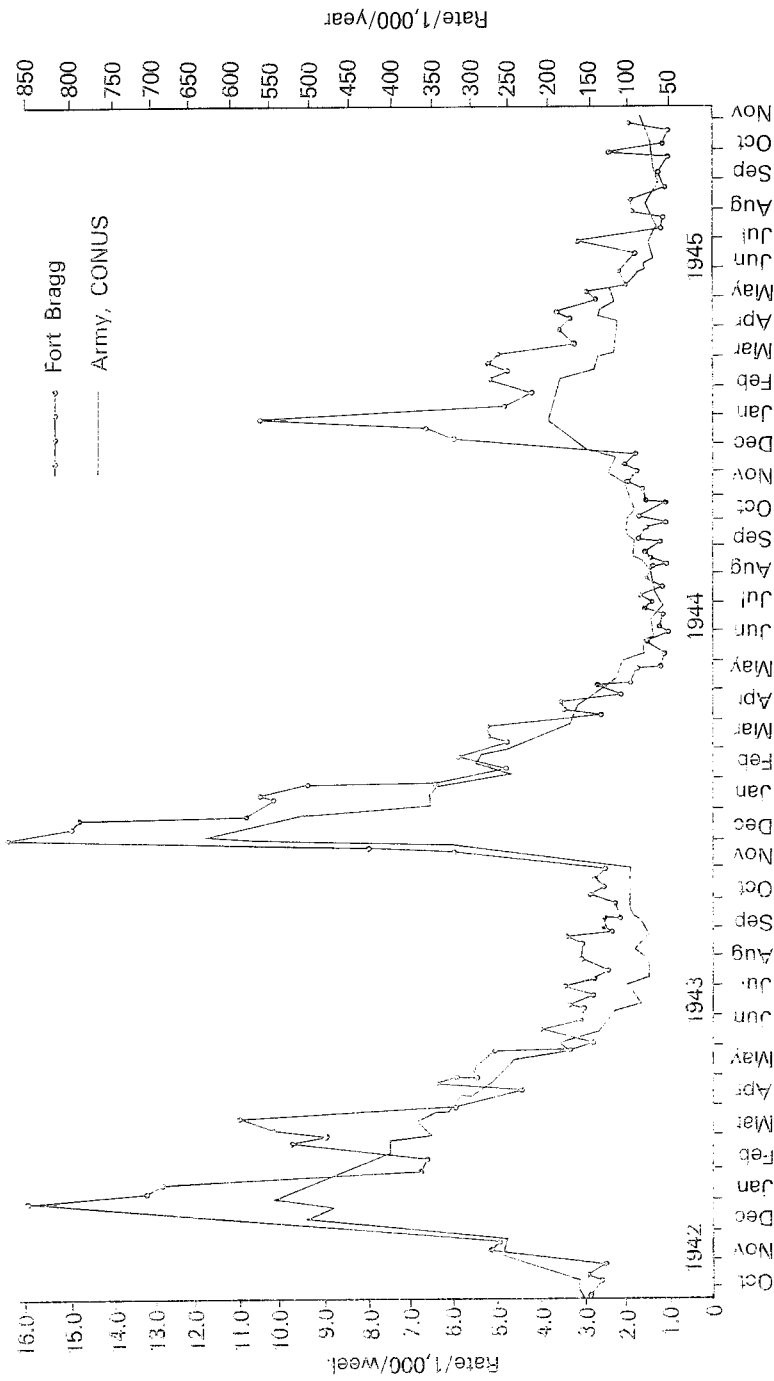
CHART 5.—*Reported incidence of acute (common) respiratory diseases in USARV, 1965-70¹*



¹ Rate for September 1968 reflects occurrence of A2/HK (Hong Kong influenza).

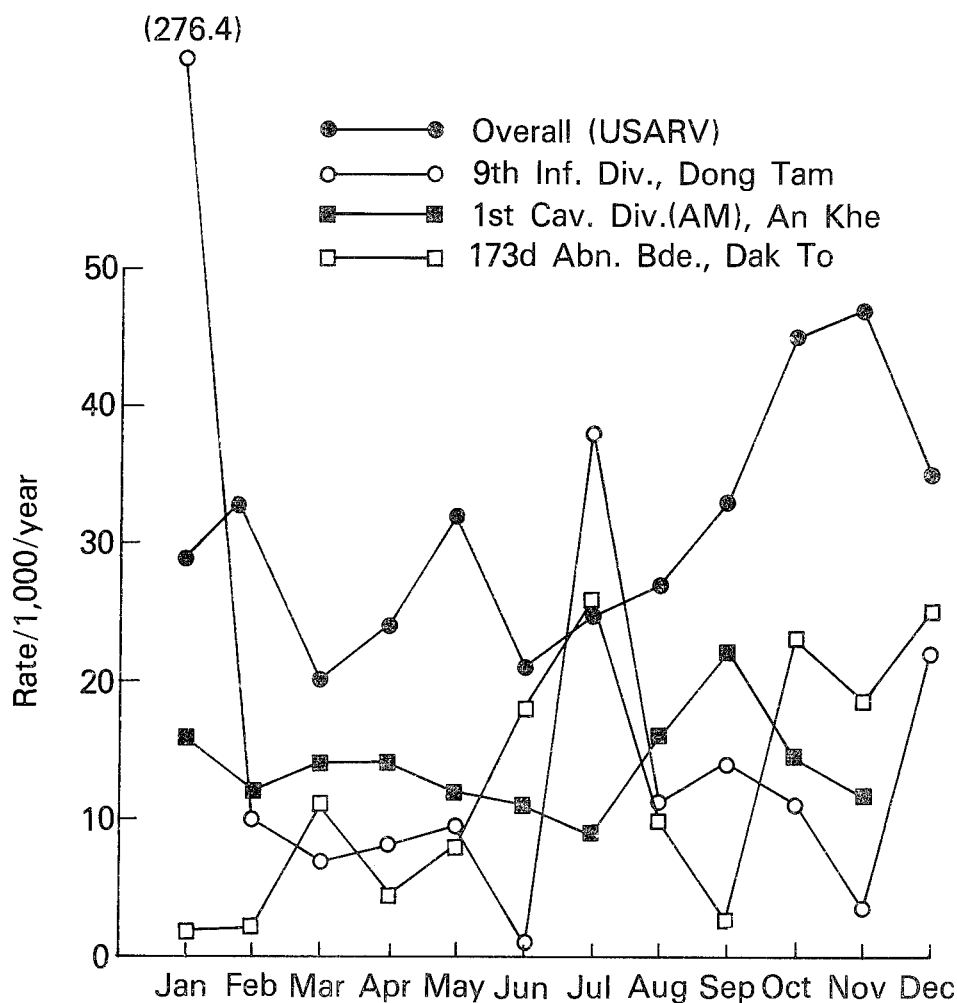
Sources: (1) USARV surgeon. Monthly Command Health Reports to USARV commander, 1965-70. (2) Office of the Surgeon General. Department of the Army. Health of the Army. May 1967 and May 1968.

Chart 8. Reported incidence of common respiratory diseases at Fort Bragg, N.C., and for the Army in CONUS, October 1942–November 1945



Source: Drigle, J. H., and Langmuir, A. D. 1968. Epidemiology of acute respiratory disease in military recruits. *Am. Rev. Resp. Dis.* 97: 1-6a.

CHART 7.—Incidence of acute respiratory disease in USARV, 9th Infantry Division at Dong Tam, 1st Cavalry Division (Airmobile) at An Khe, and 173d Airborne Brigade at Dak To, 1967



Source: Compiled from monthly unit health reports to USARV surgeon, 1967, by Jay P. Sanford, M.D.

These observations coincide with those reported by Smith and associates (1970) at the Korat Royal Thai Air Force Base, Thailand, where the initial peak of Hong Kong influenza occurred during the week of 19 August and the outbreak lasted through October. The duration of illness varied between 1 and 14 days (average 3.8 days), with an average of 2.6 days lost from duty. The attack rate was 8 percent based upon number of individuals off duty and 12.2 percent based upon a serological survey. The spread was slow, with no more than 1.5 percent of troops sick at any one time, and the outbreak subsided while a large segment of the population was still susceptible; thus, it was only slightly disruptive of activities. The relatively minor increase in ARD reported in Vietnam during the

fall of 1968 (see chart 5) may have been caused by the same virus, especially since the A2/Hong Kong influenza vaccine was not received until late 1968 or early 1969.

In a study of FUO (fever of undetermined origin) in Special Forces troops in 1963, Legters, Buescher, and Coppage* observed that infection with a respiratory agent, demonstrated by serologic evidence, was the most common etiology (table 20). Of particular interest in this study is the proportion of adenovirus group infections. One can only speculate that despite the fact that these men were seasoned troops they encountered adenovirus types with which they had not had previous contact; in view of the differences in adenovirus types encountered by civilians and the military in the United States and military groups elsewhere in the world, this seems plausible.

TABLE 20.—*Review of 553 Special Forces troops with fever of undetermined origin, Vietnam, 1963¹*

Manifestation	Cases	
	Number	Percent
Troops with one or more FUO episodes	97	17.5
FUO cases with one or more positive serologic results ²	49	50.5
FUO cases caused by respiratory agents:		
Adenovirus group	20	20.6
Influenza A	6	6.2
Influenza B	3	3.1
Respiratory syncytial virus	9	9.3
Q fever ³	3	3.1

¹All individuals had a 6-month tour of duty.

²Fourfold or greater increase in titer on paired specimens.

³These three individuals were assigned, respectively, to Nha Trang, Can Tho, and Loc Xinh.

Source: Compiled by Jay P. Sanford, M.D., from personal communication with R. L. Coppage.

The occurrence of RS (respiratory syncytial) virus in this group is also of considerable interest since almost all adults have RS antibody. RS virus primarily causes respiratory disease in infants and children (Chanock, Chambon, et al. 1967; Reilly et al. 1961), although a common coldlike syndrome can be produced in adult volunteers and acute lower respiratory illness has been observed in elderly patients (Kravetz et al. 1961; Fransen et al. 1967).

An unpublished study of a group of hospitalized patients by Arnold and associates** provides additional insight into the etiologic basis for pneumonia. Sixty-eight patients admitted consecutively to the 3d Field Hospital in Saigon between November 1969 and February 1970 with a diagnosis of pneumonia were studied. Bacteriological and virological isolation techniques (monkey kidney cells and WI-38 human diploid cells) and serological procedures (cold agglutinins, psittacosis, *Mycoplasma pneumonia*, respiratory syncytial, adenovirus group, influenza A, influenza B, parainfluenza 1 and 3, and melioidosis tests) were used.

*R. L. Coppage: Personal communication, based on data gathered by L. J. Legters, E. L. Buescher, and R. L. Coppage.

**K. Arnold: Personal communication.

Of the 68 patients, 59 were U.S. military personnel stationed within 50 miles of Saigon. Acute and convalescent serum specimens were obtained from 58 patients. Of these, 24 (42 percent) had significant increases in the complement fixation test for *M. pneumoniae*. (Cold agglutinins were elevated in eight patients, six of whom had a positive complement fixation test for *M. pneumoniae*.) Analysis of clinical features revealed no differences distinguishing the patients with *M. pneumoniae* infections from the others.

Among the infectious diseases diagnosed in 1969 in consultation with the 9th Medical Laboratory (ML9-AR 1969, p. 17) were 22 cases of primary atypical pneumonia. The following list of cases (incomplete for November and December) shows the facilities where probable and confirmed cases were seen:

3d Field Hospital.....	5	91st Evacuation Hospital.....	2
6th Clearing Company.....	2	93d Evacuation Hospital.....	2
24th Evacuation Hospital.....	5	95th Evacuation Hospital.....	1
3d Surgical Hospital.....	2	Other.....	2
67th Evacuation Hospital.....	1		

These diagnoses were based solely upon positive cold agglutinins; hence, they grossly underestimate the actual occurrence of *M. pneumoniae* infections. However, they do indicate that cases were encountered throughout Vietnam. These observations can be compared with observations in the United States, where *M. pneumoniae* is responsible for 20 to 44 percent of pneumonia hospitalizations (Chanock, Fox, et al. 1967; Griffin and Crawford 1969; Mogabgab 1968).

LESSONS LEARNED

Conclusions about ARD in USARV personnel in 1965-73 can be summarized as follows:

Upper respiratory disease was a major illness among U.S. Army personnel, ranking approximately equally with diarrheal disease as a cause of hospitalization or assignment to quarters.

The specific causal agents responsible for the acute respiratory disease syndrome in Vietnam were not defined. Limited studies suggest the occurrence of members of the adenovirus group as well as respiratory syncytial viruses. During the fall of 1968, influenza of the A2/H3 N2/Hong Kong strain was widespread but was not associated with marked increases in hospitalization or mortality.

Mycoplasma pneumoniae was the most common demonstrable causative agent in soldiers admitted to hospitals with pneumonia.

The following recommendations are made:

Standardized diagnostic and reporting criteria should be developed to improve surveillance.

Because of the prevalence of acute respiratory disease among even seasoned troops and the potential for developing means of immunoprophylaxis and chemoprophylaxis, clinical and laboratory support should be provided early to enable definition of specific disease problems.

Data on time lost from duty and reduction of unit effectiveness because of specific disease entities should be collected so that priorities may be established in the development of control measures.

Section II. Infectious Mononucleosis

Jay P. Sanford, M.D.

Infectious mononucleosis is a clinical syndrome which has been defined by clinical features, typical hematologic findings, and the presence of heterophil antibodies. The diagnostic criteria of Col. Robert J. Hoagland, MC (1967), have made possible more uniform diagnoses of the syndrome and have facilitated some astute observations on its epidemiology. Patients with clinically similar syndromes, in whom heterophil antibodies were absent, have been reported, resulting in the designation of a "heterophil-negative mononucleosis."

Henle, Henle, and Diehl (1968) reported the association of the EBV (Epstein-Barr virus), a herpes-like virus, with infectious mononucleosis. Subsequently persuasive evidence that EBV is causally related to heterophil-positive infectious mononucleosis was accumulated (Henle and Henle 1973). Studies based on serological evidence of infection with EBV have confirmed many earlier postulates, clarified aspects of the epidemiology, and modified some traditional clinical considerations. The experiences of the U.S. Army Medical Department in Vietnam will be reviewed and interpreted in light of this new knowledge.

ETIOLOGY

Since its earliest comprehensive descriptions, infectious mononucleosis has been strongly suspected of having a viral etiology, on the basis of clinical and epidemiological patterns and heterophil antibody responses. Hoagland (1967, p. 3) summarized the salient features of the syndrome: occurrence in young adults, usually between 15 and 23 years of age; a low degree of communicability, reflected by infrequent occurrence among roommates; prolonged duration of fever; sore throat, splenomegaly, and posterior cervical adenopathy; absolute and relative lymphocytosis, including the presence of atypical lymphocytes in the peripheral blood; and agglutinins for sheep erythrocytes (positive heterophil) which are not absorbed by guinea pig kidney extract.

The following observations support a causal association between EBV and heterophil-positive infectious mononucleosis. Infectious mononucleosis has been found to develop only in individuals whose serums lacked EBV antibody (Evans, Niederman, and McCollum 1968). EBV antibody has been absent in pre-illness serums of patients with infectious mononucleosis and has appeared during illness. The presence of EBV antibody has been regularly demonstrated in heterophil antibody-positive cases (Niederman et al. 1968; Evans, Niederman, and McCollum 1968; Smith and Bausher 1972). EBV is recoverable from washed leukocytes of patients with infectious mononucleosis (Diehl et al. 1968), which

may be transmitted by transfusion of whole blood or various blood components (Hoagland 1967, p. 25; Gerber et al. 1969; Blacklow et al. 1971; Turner, MacDonald, and Cooper 1972).

Throat washings from patients with infectious mononucleosis usually contain a filterable agent which is capable of transforming human umbilical cord leukocytes into lymphoblasts (Gerber et al. 1972; Miller, Niederman, and Andrews 1973; Golden et al. 1973) or converting an indicator lymphoid cell from negative to positive for EBV antigen (Golden et al. 1971). The transformed cells contain EBV-specific complement fixing antigens and EBV DNA (Gerber et al. 1972). The transforming capacity is neutralized by serums with EBV antibody (Miller, Niederman, and Andrews 1973).

EBV-specific IgM antibody responses suggesting primary infection have been demonstrated by special immunofluorescence techniques (Hampar, Hsu, and Martos 1971; Banatvala, Best, and Waller 1972; Schmitz and Scherer 1972). The inoculation of EBV-transformed autologous lymphoblasts in squirrel monkeys has induced both heterophil and EBV-specific antibodies (Shope and Miller 1973). Even though the last of the Koch postulates—the induction of infectious mononucleosis by the administration of EBV to susceptible volunteers—has not been fulfilled, the evidence for causal association between EBV and infectious mononucleosis appears convincing.

Some patients manifest many of the clinical features and hematologic signs of infectious mononucleosis but have negative heterophil agglutinations. Heterophil-negative mononucleosis syndromes have been associated with infections caused by *Toxoplasma gondii* (Remington et al. 1962; Beverley and Beattie 1958), adenoviruses, and cytomegaloviruses (Klemola et al. 1969).

In Western Europe and England, toxoplasmosis was estimated to account for 3 to 7 percent of heterophil-negative glandular fever (Beverley and Beattie 1958). In the United States, Remington and associates studied a group of 154 college students hospitalized with suspected infectious mononucleosis and found that, of the 85 students in whom other illnesses were not subsequently diagnosed, 34 had negative heterophil titers. Paired serums were obtained from 92 students; significant rises in toxoplasma dye inhibition titers or hemagglutination titers were demonstrated in 3 (Remington et al. 1962). Thus, toxoplasmosis may occasionally present as heterophil-negative infectious mononucleosis.

Infection with CMV (cytomegalovirus) can cause an illness hematologically resembling infectious mononucleosis but not associated with heterophil antibodies and often not associated with tonsillitis or cervical lymphadenopathy. Klemola and associates (1969) found that among 275 patients with infectious mononucleosis or a similar syndrome, 60 (22 percent) had negative heterophil titers. Recently, evidence for the occurrence of CMV and EBV was studied in 44 of these patients (Klemola et al. 1970). In 19 of the 44 cases, none of which involved tonsillitis or cervical lymphadenitis, CMV was implicated. Eight of the remaining 25 patients had high EBV antibody titers indicating current or recent infection, and 12 had titers compatible with either current or past infection. EBV and CMV seem to be the principal etiologic agents of heterophil antibody-

negative mononucleosis, but a proportion of cases is caused by as yet unidentified agents.

VIETNAM EXPERIENCES

Technical Considerations

The laboratory diagnosis of infectious mononucleosis during the later years of the Vietnam conflict was based upon the screening monospot or rapid slide test, using formalized horse erythrocytes. The correlation of this test with the Davidsohn differential test (used as the arbitrary definition of infectious mononucleosis) is 98.5 percent. Its sensitivity corresponds to that of sheep erythrocyte agglutination tests (Hoff and Bauer 1965). Some specimens diagnosed by the monospot test were forwarded to the 9th Medical Laboratory for confirmation by the Paul-Bunnell sheep erythrocyte agglutination and Davidsohn differential tests. The change from the traditional Paul-Bunnell technique to the monospot test apparently did not significantly modify diagnostic results.

Because infectious mononucleosis was not reported as a separate item in monthly USARV Command Health Reports, incidence figures are not available for the entire command. The major sources of data for this review were the Army Medical Service Activities Reports submitted by the 9th Medical Laboratory and its components, the 946th, 528th, and 406th Mobile Medical Laboratories (ML9-AR). However, the 9th Medical Laboratory data do not accurately reflect the number of cases of infectious mononucleosis in Vietnam since hospital laboratories and the mobile medical laboratories directly supported most of the hospitals and merely referred specimens to the 9th Medical Laboratory. The 9th Medical Laboratory did provide direct support to the 36th Evacuation Hospital near Vung Tau; hence, its data are mixed.

Observations

The data from the 9th Medical Laboratory are summarized in table 21. The proportion of positive tests to tests ordered ranges from 10 to 22 percent. Applying these figures, the estimated number of cases for 1968 is between 240 and 520. In 1967, approximately 480 serums at the 528th Mobile Medical Laboratory, Qui Nhon, had positive titers of heterophil antibodies if 10 percent of those tested were positive. Assuming U.S. Army troop strength at approximately 300,000 men during 1967 and applying the rate of hospitalization for infectious mononucleosis of U.S. marines in Vietnam—2.1 per 1,000 per year (Lehane 1970)—this figure reasonably approximates the anticipated incidence of infectious mononucleosis. Using the same rate and assuming the U.S. Army troop strength to be approximately 400,000 during 1968 and early 1969, the incidence of infectious mononucleosis is approximately two to four times the number of cases recorded in table 21.

In the FUIO studies summarized by Col. John J. Deller, Jr., MC, in chapter 4, infectious mononucleosis was not a significant diagnosis; among 892 patients in

TABLE 21.—*Heterophil and monospot tests for infectious mononucleosis performed by the 9th Medical Laboratory, Vietnam, 1966-69*

Unit and year	Number of serums examined	Positive	
		Number	Percent
<i>July-December 1966</i>			
9th Medical Laboratory ----- <i>1967</i>			22.0
9th Medical Laboratory -----	¹ 1,164	² 213	18.2
9th Medical Laboratory Detachment, 3d Field Hospital ----	210	22	10.4
946th Mobile Medical Laboratory -----		162	
528th Mobile Medical Laboratory ----- <i>1968</i>	865		
9th Medical Laboratory -----	³ 2,423		
<i>1969</i>			
9th Medical Laboratory -----	⁴ 895	96	10.7

¹Rate relatively constant throughout the year.

²Several cases identified when serums tested with melioidosis HA test. Figures include some Navy and Australian Forces members.

³1st quarter, 263; 2d quarter, 431; 3d quarter, 800; 4th quarter, 929 (includes 527 serums screened by monospot test).

⁴1st quarter, 155; 2d quarter, 442; 3d quarter, 150; 4th quarter, 148 (serums for all quarters screened by monospot test).

Sources: (1) 9th Medical Laboratory. Activities Reports, 1966-69. (2) Col. Hinton J. Baker, MC: Personal communication.

five studies, 6 had heterophil-positive infectious mononucleosis: 4 from I CTZ, 1 from Nha Trang in II CTZ, and 1 from Dong Tam in IV CTZ.

The increased frequency of requests for serological tests for infectious mononucleosis which occurred during the third and fourth quarters of 1968 is striking; it may be related to the allowance of leave following the January 1968 *Tet* offensive. Many cases of infectious mononucleosis occurred following leave to the United States and the disease was relatively frequent among soldiers about to be reassigned to Vietnam at the end of their home leave.

Lehane estimated the rate of seroconversion to EBV among susceptible Marine Corps recruits (14.3 percent of those studied) to be 166 per 1,000; the overall rate was 23.8 per 1,000 during a 13-month tour in Vietnam. This latter rate, contrasted with the hospital discharge rate of 2.1 per 1,000, suggests that the ratio of inapparent to apparent infection is approximately 10:1 (Lehane 1970). The application of these figures to U.S. Army personnel suggests a much higher EBV infection rate than is reflected in the available data. The ratio of inapparent to apparent infection among college students is much lower than the military figure, varying between zero and 1:2 (Sawyer et al. 1971; Niederman et al. 1970). A similar discrepancy between civilian adults and military population has been observed in another infectious disease, rubella, in which the ratio of inapparent to apparent disease is 1:1 or 2:1 for civilians but as high as 6.5:1 for military recruits (Horstman, Pajot, and Liebhaver 1969; Buescher 1965).

LESSONS LEARNED

Infectious mononucleosis must be anticipated whenever health plans include young adults. However, U.S. Army Medical Department data suggest that

the incidence of clinically apparent infectious mononucleosis in Vietnam was perhaps less than that encountered in military hospitals in the United States, that is, 3 to 4 cases per 100 admissions. It is unlikely that "heterophil-negative" mononucleosis is important in accounting for the difference. Bender (1959) discussed the relative lack of infectious mononucleosis in the Southwest Pacific Area during World War II. He attributed at least a portion of the decrease to the absence of women, but this was probably not the only factor.

Observations on EBV clearly demonstrate that persons of lower socioeconomic status acquire it at an early age as an asymptomatic or undifferentiated illness. Shedding of the virus in pharyngeal secretions may occur for considerable intervals but appears to become less common as the time since acquisition of infection increases. Thus, while the American soldier in Vietnam may have had considerable contact with women under circumstances conducive to the spread of EBV, most of his contacts probably had acquired it at so early an age that by puberty they only infrequently shed the virus in oral pharyngeal secretions. However, the susceptible soldier is at high risk and may acquire EBV while home on temporary leave or reassignment. Since almost all soldiers received leave and many were in the United States, including Hawaii, where they were probably exposed to infectious mononucleosis, this might account for the overall infection rate of 29.9 per 1,000 in susceptible (EBV antibody-negative) marines in Vietnam in comparison with a rate of 11.1 per 1,000 for susceptible college students (Lehane 1970). The apparent high rate of acquisition of EBV antibodies by susceptible individuals stationed in Vietnam may reflect not only experience in Vietnam but also greater opportunity for exposure during brief intervals out of country. Accepting this hypothesis, the problem that infectious mononucleosis poses to military effectiveness will be determined to a major extent by the socioeconomic conditions of the area in which troops are stationed. It is unlikely that epidemics will occur or that the disease will interfere with combat unit effectiveness as do many other infectious diseases in the Tropics.

Section III. Rabies

Colonel Adolf E. Rahm, Jr., MC, USA

Any warmblooded animal can carry rabies, a fact which fosters a serious problem whenever American troops are deployed overseas. Even in the United States, where most pets are immunized, some 30,000 Americans received vaccinations because of actual or possible exposure to rabies in 1967 (Plotkin and Clark 1971).

In a country like Vietnam where pets were not routinely immunized, the risk of exposure to rabies was much greater. In 1969, there were reports of 2,967 animal exposures; 1,628 individuals were treated prophylactically for rabies, and 76 were also given immune serum (USARV-CHR 1969). In 1970, 1,905 exposures were reported, 1,039 individuals were immunized, and 125 received serum (USARV-CHR

TABLE 22.—*Animal bite cases and antirabies treatment, USARV, 1969 and 1970*

Month	Number of bites		Duck embryo vaccine		Hyperimmune serum	
	1969	1970	1969	1970	1969	1970
January	278	308	90	218	17	17
February	234	277	63	170	0	6
March	269	125	137	49	10	1
April	213	138	100	52	10	1
May	214	133	79	68	10	3
June	253	105	141	28	4	10
July	193	206	118	128	0	40
August	279	191	161	91	1	7
September	246	93	130	43	5	2
October	251	63	99	22	3	5
November	275	150	130	134	10	22
December	262	116	380	36	6	11
Total	2,967	1,905	1,628	1,039	76	125

Source: USARV surgeon. Monthly Command Health Reports to USARV commander, Jan. and Feb. 1970 and Jan. and Feb. 1971.

1970). Table 22 shows the monthly breakdown of animal bite cases and antirabies treatment in USARV in 1969 and 1970.

An average of 352,755 individuals in 1969 and 289,964 in 1970 were eligible for primary medical care through Army Medical Department resources in Vietnam.* Contact with hostile forces during those years was more or less average and many troops who were not in direct combat activity had numerous opportunities to acquire pets. The disparity between the number of immunizations given and the number of exposures reported suggests that some of these pets were vaccinated, probably as a result of military pet control programs.

Some significant problems did arise. An 11-week-old female dog belonging to B Troop, 2d Squadron (Airmobile), 17th Cavalry, 101st Airborne Division, exhibited lethargy, staggering gait, and excessive salivation. Examination by a veterinary unit following her isolation and death revealed fluorescent antibody and histological evidence of rabies. During interviews 65 members of B Troop admitted to being licked, scratched, or bitten by the animal during her infectious period. Sixty-three individuals were treated with a 14-day series of duck embryo vaccine, and two were also given hyperimmune serum. One individual developed an allergic reaction to the duck embryo vaccine and was hospitalized and treated with Benadryl, and the immunization was continued. Later, a littermate of the rabid dog, which belonged to another unit, exhibited lethargy, staggering gait, and excessive salivation. Since the unit was now alert to the rabies threat, the dog was destroyed by repeated blows upon the head with a rifle butt, rendering examination of the brain inconclusive. It was necessary, therefore, to immunize an additional 27 individuals (USARV-CHR Feb. 1970, Tab I). While immunizing 90 individuals may not seem to be a great task, it involved 1,260 injections, requiring considerable expenditure of time and effort by medical personnel. Fur-

*Headquarters, 5th U.S. Army Surgeon's Office, Preventive Medicine Division. Inquiry, 2 Mar. 1973.

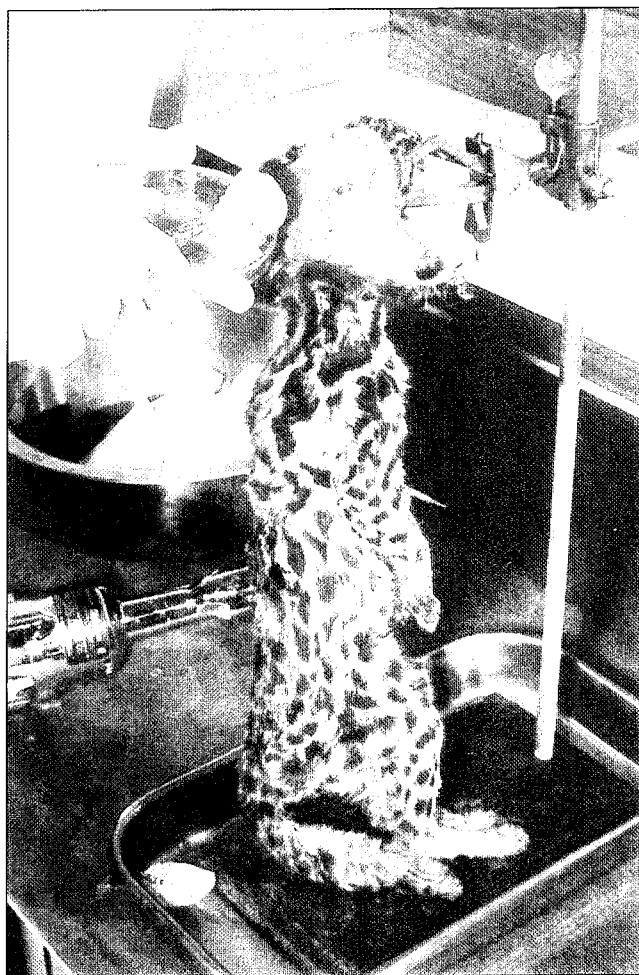


FIGURE 39.—Animal brain removed for examination in the 9th Medical Laboratory for evidence of rabies infection.

thermore, those 90 individuals could perform no activity in the field for 2 weeks while they received their immunizations.

Knowledge of which species carry rabies is of paramount importance in treating animal bite cases. A status report on rabies between January and June 1969, published in the USARV Medical Bulletin (Shroyer 1969), indicates that of 146 dogs whose heads were submitted for examination at the 9th Medical Laboratory, 26 were rabid; of 25 cats and 22 rats, none was (fig. 39). Monkey, mouse, bat, and chipmunk specimens were negative for rabies. One human specimen was positive.

In 1968, 300 rats examined at the laboratory were negative for rabies, as were 224 rats examined at the Navy Support Command Laboratory. The USARV medical consultant commented: "This report again reinforces the present policy of not administering rabies vaccine in cases of rat bite in Vietnam."

The question of whether or not to administer rabies prophylaxis following rodent bites is a thorny one, as rodents can carry rabies. The decision may depend on the circumstances of the bite. The USARV preventive medicine consultant in 1969 noted (USARV-CHR Dec. 1970, p. 13): "Although the 9th Medical Laboratory has not reported any positive specimens for rabies in rats, it is recommended that rabies advisory boards strongly consider initiation of rabies treatment following all *unprovoked* rat bites." Art must sometimes transcend science when making a decision regarding a disease which with rare exception has been 100 percent fatal (Rose, Schnurrenberger, and Martin 1971).

Rabies prevention programs during the Vietnam conflict were very effective; only one death occurred among Army troops, in Saigon in January 1973, just at the close of hostilities.*

Lt. Louis P. Dehner, MC, USN (1970), reported on the death of a young marine. The description of the case follows:

A 20-year-old white man was bitten on the right middle finger by a stray dog on the evening of September 4, 1967. The dog was killed immediately, but study of the brain was not possible because of improper handling. The wound was vigorously cleaned and the patient arrived at the U.S. Naval Support Activity Station Hospital, Da Nang, Vietnam, on September 6, 1967. The only pertinent physical finding was a painfully swollen and lacerated right middle finger. Results of the hemogram and urinalysis were normal. The wound was recleaned, and a dose of 1,000 IU of rabies antiserum (equine) was given locally about the wound. An additional 4,000 IU were given intramuscularly. Duck embryo vaccine was started immediately and administered daily for 21 consecutive days. Booster doses were given 10 and 20 days after the completed series.

The patient returned to his unit and did well until December 17, 1967, when he noted tingling and some pain in his right hand, which subsided. Two days later, the tingling sensation recurred and involved his entire right arm, chest, and face. He noted that the right side of his body perspired more than the left. Physical examination on December 19, 1967, showed an alert, cooperative young man with a temperature of 102° F. Hyperesthesia of the right scalp, right side of the face, and right upper extremity were prominent. The remainder of the findings from examination were unremarkable. The following day, the patient became extremely hyperactive and disoriented. A lumbar puncture disclosed an opening pressure of 140 mm of water, and the fluid was clear. The cerebral spinal fluid protein was 45 mg/100 ml, and the sugar was 91 mg/100 ml. No cells were noted. His condition remained stable for the next 24 hours.

His final 24 hours were characterized by marked clinical deterioration. Physical examination showed extreme restlessness, disorientation, increased motor activity, and hyperventilation. He was gasping and unable to swallow. He responded only to simple commands. The abdominal reflexes were absent; findings from neurologic examination were otherwise negative. The white cell count was 26,600/mm³ with 90% neutrophils. The hemoglobin was 17.4 g/100 ml. The cerebrospinal fluid protein on a repeat lumbar puncture was 200 mg/100 ml, and the sugar was 157 mg/100 ml. No cells were noted. The patient died during an episode of vomiting 108 days after the dog bite.

The autopsy was performed 7 hours after death. The pertinent findings at autopsy were acute congestion and edema of the lungs and slight congestion of the liver.

The brain weighed 1,300 g. The leptomeninges were clear, and the cortical convolutions were unremarkable. There were no signs of increased intracranial pressure. The vasculature at the base of the brain was normal. The consistency of the brain on palpation was unremarkable. The brain was sectioned in the fresh state, and blocks were taken from the frontal lobes, hippocampal gyri, midbrain, medulla, and spinal cord for imprints and mouse inoculation. Tissue from these areas was fixed in Zenker's formalin for histologic examination.

*Infectious Disease Branch, Preventive Medicine Division, Directorate of Health and Environment, Office of the Surgeon General. Inquiry, Jan. 1973.

Occasional eosinophilic intracytoplasmic inclusions consistent with Negri bodies were identified in Purkinje cells of the cerebellum. A moderate to marked perivascular inflammatory reaction composed predominantly of lymphocytes was present in the pons and medulla.

Homogenates from portions of the patient's brain were injected intracerebrally into suckling white mice. All animals became ill with central nervous system signs on the twelfth and fourteenth days after inoculation. Microscopic examination showed eosinophilic cytoplasmic structures in the neurons of the hippocampal gyri.

Although fluorescent antibody preparations showed equivocal results on portions of the patient's brain, they were positive on tissue from the infected mouse brains.

The key to a good control program is an appointed rabies advisory board or control committee within each hospital-size facility (USARV-Reg). The committee should consist of at least three physicians who can be called together in person or on the telephone to discuss the advisability of prophylaxis in each individual animal bite case; thus, more than one person makes the decision, and the individual physician is assisted and directed by a knowledgeable group. The loss of more than one well-informed individual through simultaneous transfer is unlikely. Guidance and current information should be given the widest dissemination. Local commanders must be stimulated to publish regulations on the control of animals. Pets should be limited to one per company-size unit and must be immunized since this procedure is approximately 95 percent effective in preventing rabies (Rose, Schnurrenberger, and Martin 1971). All animals must be penned or kept on a leash. Finally, stray or unwanted animals should be presented to the nearest veterinarian or veterinary unit for euthanasia.

In Vietnam, as noted earlier, postexposure prophylaxis was a large part of the rabies program, as was preexposure prophylaxis among veterinary personnel and others exposed to animals. The World Health Organization's recommendations were followed. Reporting of animal bites and numbers of prophylactic immunizations was mandatory. In addition to giving command surgeons information necessary to obtain adequate supplies of vaccines, bite incidence statistics provide a system of monitoring the animal control programs so that, if these measures are ineffective, command pressure can be applied to rectify the situation.

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Rickettsial Diseases and Leptospirosis

*Colonel O'Neill Barrett, Jr., MC, USA (Ret.), and
Colonel Fred R. Stark, MC, USA*

Rickettsial disease, especially epidemic typhus, has had an important effect on the outcome of military operations for centuries. Zinsser (1935, pp. 153, 283) noted: "Typhus had come to be the inevitable and expected companion of war and revolution; no encampment, no campaigning Army, and no besieged city escaped it." "Epidemics get the blame for defeat, the generals the credit for victory. It ought to be the other way around."

Beginning in the 16th century and continuing for the next 300 years, typhus was to play a prominent part in all major military campaigns in Europe. Remarkably, however, epidemic typhus has never been a serious problem for the U.S. Army. There was little or no typhus in the American Civil War; in World War I a worldwide total of only 42 cases occurred in American troops, and in World War II only 104 cases of epidemic typhus and 787 cases of murine typhus were recorded (MD-PM7, pp. 178-82). Scrub typhus, however, has had a significant—although geographically localized—impact on American military activities, especially since 1942. During World War II, 6,685 cases were recorded (Smadel 1952, p. 639).

Section I. Scrub Typhus (Tsutsugamushi Fever)

Colonel O'Neill Barrett, Jr., MC, USA (Ret.)

HISTORY AND MILITARY SIGNIFICANCE

Although a "disease caused by the bite of small red insects" was described in China as early as the 3d century, B.C. (Zdrodovskii and Golinevich 1960, p. 354), and a Chinese work from the 16th century discusses a "sand mite referred to as a fever carrier," the first detailed written description of scrub typhus is Japanese, attributed to Hakuju Hashimoto in 1810. The disease was subsequently described in Formosa and Pescadores Islands but, surprisingly, was not reported from China. The first report in English was written in 1878 by Theodore Palm, a medical missionary in Niigata. Occasional cases were observed in Malaya (now West Malaysia) in the early 1920's, but descriptions of the disease were primarily limited to Japan until the Allied involvement in Southeast Asia in World War II. Identification of the causative organism,

Rickettsia tsutsugamushi [orientalis], is attributed to Norio Ogata in the late 1920's, although claims for its discovery were made by other Japanese investigators. Nagayo, Kawamura, and Hayashi are also well known for their research on rickettsial diseases (Audy 1968, pp. 30-70).

The vector of scrub typhus in Japan was found to be a trombiculid mite (chigger), *Leptotrombidium akamushi*. The species name is derived from the Japanese terms *aka* (red) and *mushi* (mite). The vector is also referred to as the dangerous mite, *tsutsuga-mushi*; hence the name "tsutsugamushi fever." For at least two centuries, a *mushi-yaki* (mite burning) ceremony has been held every January at Haguro Shrine, where effigies of the tsutsugamushi mite are burned, the original purpose being protection of farmers from the disease (Audy 1968, pp. 30-40).

During World War II, three separate episodes of scrub typhus in U.S. Army forces were recorded, two of major significance. In the SWPA (Southwest Pacific Area), there were 5,718 cases, including 284 in troops who reoccupied the Philippines in late November 1944, and in the CBI (China-Burma-India) theater, 967 cases were documented. Cases of murine typhus were undoubtedly included in these figures, however, especially in the 125 cases reported from China. In the SPA (South Pacific Area), 32 cases were observed on Bougainville, New Georgia, and Espiritu Santo (MD-PM7, pp. 278-79).

The two most serious outbreaks in Army experience occurred in New Guinea following landings at Ow-Biak and Sansapor beachheads: by the end of 1944, there had been 2,500 cases in these areas. Although the case fatality rate was low (2 percent), morbidity was high as fever frequently lasted up to 20 days and convalescence was often prolonged (MD-PM7, p. 285). Another virulent outbreak occurred in 1944 on Goodenough Island, north of Papua, where Lt. Gen. (later Gen.) Walter Krueger had established the Sixth U.S. Army Headquarters. Approximately 40 cases of scrub typhus occurred among personnel of the 9th General Hospital who had helped clear an area of kunai grass (*Imperata cylindrica*) before construction of the hospital buildings. Several died, including one medical officer (MD-IM1, p. 524).

Although the typhus fevers, including scrub typhus, had been recognized in Burma as early as 1932, the first case of scrub typhus reported in the CBI theater was not from that country but from the 100th Station Hospital in Delhi, India. Still, Burma was the main focus of the disease in the theater (MD-IM1, p. 742). The five major peaks of scrub typhus there were primarily related to combat activities and not to a seasonal variation as had originally been supposed. The disease was widely distributed throughout the country, occurring along the entire length of the Ledo Road, most dramatically at Myitkyina, in the Fort Hertz district and around Lashio. The first cases were referred to as "CBI fever," although scrub typhus was suspected; this reluctance to diagnose FUO (fever of undetermined origin) as scrub typhus occurred even among Japanese medical officers who had greater experience with the disease, as evidenced by captured Japanese medical reports (MD-PM7, pp. 292-97; MD-IM1, pp. 743-44). Audy (1968, p. 110) wrote: "The dead hand of tradition, the clinical and

epidemiological mental picture of 'classical' tsutsugamushi disease along the rivers in Northwest Honshu" kept these "competent clinicians and epidemiologists from diagnosing a disease familiar at least by repute to every Japanese physician." Early confusion concerning diagnosis was resolved by a special team of the USATC (United States of America Typhus Commission) (MD-PM7, p. 297). A detailed report of the clinical and pathologic manifestations of the disease in Assam and Burma is given by Sayen and associates (1946) in their evaluation of 616 cases seen at the 20th General Hospital.

The psychological impact of scrub typhus on the combat effectiveness of American and Chinese troops in Burma was out of proportion to its actual statistical importance as a cause of mortality and morbidity. Still, American physicians knew little about the disease and almost nothing about its epidemiology or prevention, and they lacked a specific therapy for it. Furthermore, scrub typhus was a serious disease among the troops in Burma; mortality was higher there than in any other area, probably because of the frequent occurrence of other diseases, including malaria and dysentery, and the general debility of troops in continuous combat for prolonged periods (Stone 1969, pp. 123n-124n). The annual scrub typhus mortality rate of 14.6 per 100,000 in the CBI theater was the highest for an infectious disease in any World War II theater of operations (MD-PM7, p. 6). The mortality rate was approximately 4 percent among 113 American soldiers in Services of Supply units along the Ledo Road who developed the disease sporadically, and it was 16 percent among 105 patients evacuated by air from jungle combat in the mountains north of Myitkyina between March and May 1944 (MD-IM2, p. 128). The patient's pretyphus condition and the quality of early care were vital to the prognosis; patients given careful nursing and vigilant treatment of symptoms had the best chance of recovering.

Between 1945 and the beginning of hostilities in Korea in 1950, scrub typhus was not a significant problem for American military forces. However, one experience in Japan is noteworthy, primarily because of new epidemiological knowledge which resulted. Tsutsugamushi fever was thought to occur in grassy floodlands along river valleys in three prefectures of northwest Honshu. The disease had a definite seasonal occurrence, most cases being seen in July, August, and September, with a mortality rate greater than 20 percent (Smadel 1952, pp. 638, 647). However, during October and November 1948, 23 of 1,769 Army troops exposed to vectors in the military maneuver area at the foot of Mount Fuji were treated for scrub typhus, and it was estimated that an equal number of inapparent infections occurred (NAVY-MN). The vector for this outbreak was not definitely determined, but *R. tsutsugamushi* had previously been isolated by Wharton (1946) from *Leptotrombidium pallida*, a mite indigenous to the area.

Another outbreak in American military personnel in Japan occurred on the lower southwest slope of Mount Fuji in October 1953, where two regiments of the 3d Marine Division, Fleet Marine Force, Pacific, were undergoing training. Eleven days after entering the area, the first of 57 patients was admitted to the medical company dispensary. The clinical course was typical in these cases, including prompt response to Terramycin, and no complications or

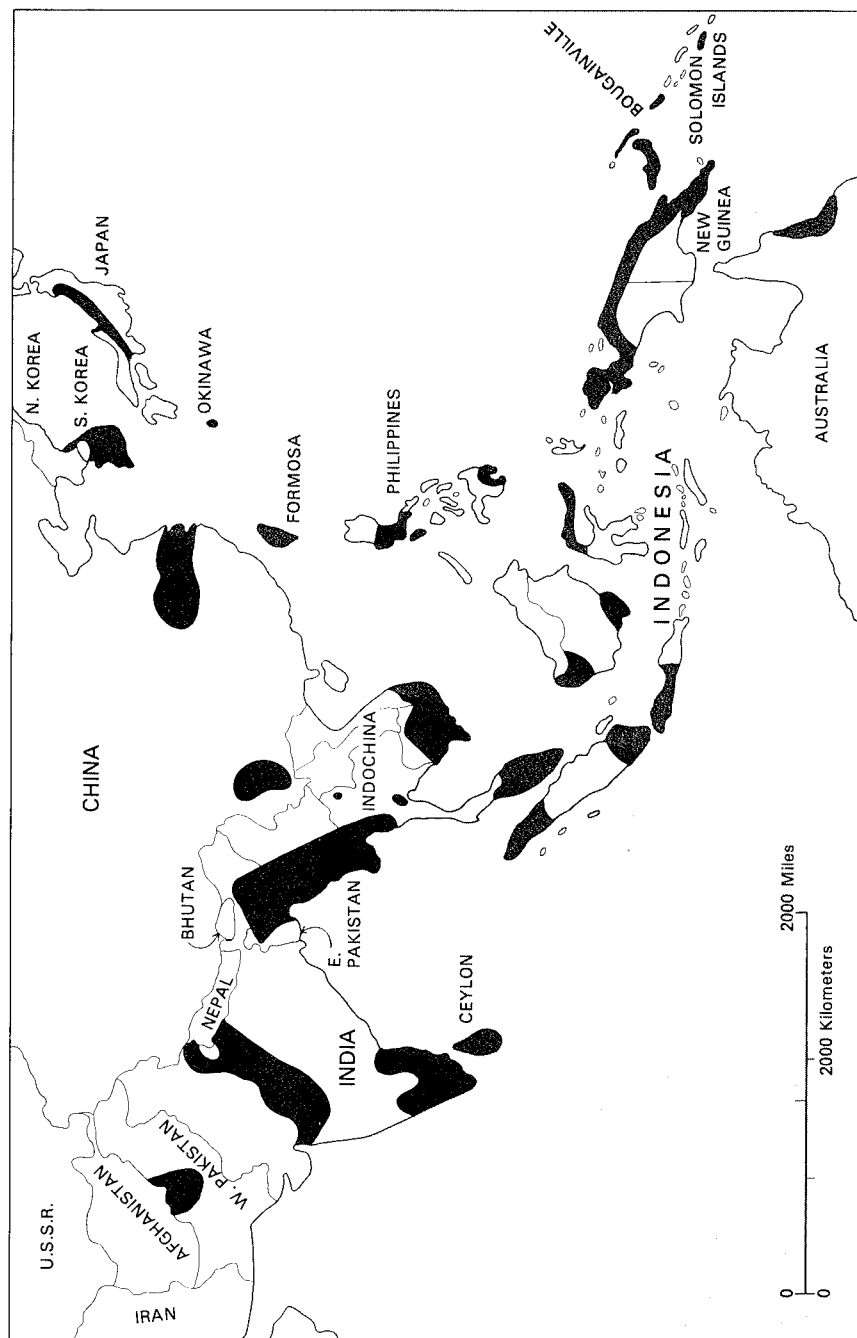
deaths occurred (NAVY-MN). Although the vector was not determined, the organism was isolated from patients' blood.

Tsutsugamushi fever was not a problem for American or allied forces during the Korean war. Only eight confirmed cases occurred among United Nations personnel from 1951 to 1954. This is not surprising since before 1951 there were only occasional unconfirmed reports of the disease (Ley and Markelz 1961). The first two documented cases were reported by Munro-Faure and associates (1951) from the BCOF (British Commonwealth Occupation Forces) 29th General Hospital in Korea. Jackson and associates (1957) later demonstrated *Rickettsia tsutsugamushi* in some of the Korean rodents they examined. The established vectors of scrub typhus are not known to occur in Korea or else are so rare that they have not been collected, although forms closely related to *Leptotrombidium akamushi* are plentiful. The absence or dearth of primary vectors is thought to be responsible for the low incidence of cases (Traub 1954).

EPIDEMIOLOGY

Although originally reported in Japan, scrub typhus now has been shown to exist throughout a large area of the Far East in a roughly triangular area bounded by Japan, India, and Australia (map 2). The term "scrub" is more of historical interest than of descriptive value, as the disease has a far wider distribution than along grassy islets and banks of fertile silt (as in Japan) or in scrub vegetation (as in West Malaysia); for instance, it was noted in suburban areas of Calcutta and in deep jungle in Burma during World War II (Audy 1968, p. 87). More recently, infective vectors have been found on the edge of sandy beaches and in deep jungle in Malaysia (Traub 1960; Traub, Frick, and Diercks 1950). Cadigan and coworkers (1972) demonstrated that over 73 percent of adult aborigines in West Malaysia's deep jungle had antibodies to *R. tsutsugamushi* despite the apparently infrequent occurrence of clinical disease among them; their exposure probably occurred in the deep jungle itself rather than in cleared areas. Although conditions are exacting for the maintenance of an endemic area, areas now devoid of the disease could become new foci if the infective vector were introduced; this seems to have already happened in Queensland, Australia, and the disease probably could be established in other sites in both Australia and Madagascar (Audy 1968, p. 116). Therefore, a more proper name for "scrub" typhus would be mite-typhus or tsutsugamushi disease.

Rickettsia tsutsugamushi is an organism which naturally infects mammals—including mice, rats, and voles—and probably some birds as well. Man is only an accidental host, becoming exposed and infected when he enters an enzootic area where the mammalian reservoir and a suitable ectoparasite are present. Basic requirements for maintenance of an endemic area include suitable cover for the reservoir host and moisture and temperature conditions favorable for growth of the vector (MD-PM7, pp. 302-21).



MAP 2.—Geographic distribution of scrub typhus, 1964. (Philip, C. B. 1966. Scrub typhus. In *A manual of tropical medicine*, ed. G. W. Hunter, W. W. Frye, and J. C. Swartzwelder, p. 106. 4th ed. Philadelphia: W. B. Saunders Co. Modified by Col. O'Neill Barrett, Jr., based on medical records for July 1964.)

Mites acquire the infection either transovarially or by settling on an infected host during the larval stage of development. The former mode is more important for perpetuation of the disease, since larvae settle on a potential host only one time (Zdrodovskii and Golinevich 1960, p. 367).

The disease is transmitted to man by a few species of larval trombiculid mites (chiggers) of the genus *Leptotrombidium*, the most important of which are *L. akamushi* and *L. deliensis*, two closely related chiggers. Other species including *L. tosa*, *L. scutellaris*, and *Schöngastia indica* also transmit the disease to humans (Smadel 1952, pp. 638-51; Faust and Russell 1964, pp. 773-76). The varying epidemiological host-vector patterns are shown in table 23.

These vectors represent a relatively small number of the many species of trombiculid mites found in enzootic areas. None of the others has been found to be naturally infected or to transmit the disease under laboratory conditions. A possible additional vector for human infection is *L. arenicola*, recently studied by Upham et al. (1971). This mite, which resembles *L. deliensis*, was found infesting rats trapped on a sandy beach during investigation of a scrub typhus outbreak near Singapore. *Rickettsia tsutsugamushi* was isolated from a significant number of pools of this species; to date it has not been described outside West Malaysia.

The epidemiology of scrub typhus in Vietnam is not well defined. Before World War II only an occasional, undocumented case was reported. On the basis of geographic considerations of proper terrain and humidity (fig. 40), Le Gac and Arquié (1964) suggested that endemic areas would probably include

TABLE 23.—Areas of known occurrence of scrub typhus with identified hosts and vectors

Area	Host	Vector
Japan:		
Niigata	Vole	<i>Leptotrombidium akamushi</i> .
		<i>Leptotrombidium tosa</i> .
Shikoku	Norway rat	{ <i>Leptotrombidium scutellaris</i> .
Shichito	Unknown	{ <i>Leptotrombidium akamushi</i> .
New Guinea	{ Bandicoot	{ <i>Leptotrombidium deliensis</i> .
	{ Brown rat	
Burma	Shrew, black rat	{ <i>Leptotrombidium deliensis</i> .
		{ <i>Schöngastia ligula</i> .
West Malaysia	Jungle rat	<i>Leptotrombidium akamushi</i> .
		<i>Leptotrombidium deliensis</i> .
		<i>Leptotrombidium arenicola</i> .
		<i>Leptotrombidium akamushi</i> .
Java	{ Domestic rat	<i>Schöngastia indica</i> .
	{ Wild rat	
Korea	Rodents	<i>Leptotrombidium pallida</i> .
Thailand	Field rat	<i>Leptotrombidium deliensis</i> .
Vietnam	{ Field rat	{ <i>Leptotrombidium deliensis</i> .
	{ Bandicoot	

Source: Compiled from (1) Faust, E. C., and Russell, P. F. 1964. *Craig and Faust's clinical parasitology*. 7th ed. Philadelphia: Lea & Febiger, pp. 773-74. (2) Upham, R. W., Jr., et al. 1971. *J. Med. Ent.* 8: 401-6. (3) Traub, R., et al. 1954. *Am. J. Hyg.* 59: 291-305. (4) Trishnananda, M.; Vasuvat, C.; and Harinasuta, C. 1964. *J. Trop. Med.* 67: 215-19. (5) Parsons, R. E., et al. Annual Progress Report, U.S. Army Medical Research Team (WRAIR) Vietnam and Institute Pasteur of Vietnam, 1 Sept. 1966-31 Aug. 1967, pp. 274-99.



FIGURE 40.—Terrain showing U.S. Army patrol in high grass in mountainous area of Vietnam. The trombiculid mite proliferated in these grassy areas, which accounted for the high incidence of scrub typhus in combat versus support troops.

Lang Son, Tan Hoa, and Son La in the North, Quang Tri, Dong Ha and “Cuvette Daden” in Central Vietnam, and Ben Cat in the South. Mountain jungles and areas around plantations were thought to be especially suitable areas; this speculation was partly confirmed by the experience of French forces fighting the Vietminh in Central Vietnam from 1949 to 1952. In 1949 and 1950, most of the fighting was along the coast or on the approaches to mountain areas and only 23 cases of scrub typhus were noted. From 1951 to 1952, however, combat moved into the Chaîne Annamitique and 248 cases were encountered. In the last phase of the French-Indochina War, 5,708 cases of scrub typhus were reported, with 158 deaths; these last figures are probably lower than the actual numbers since only cases in hospitalized patients are included. Although Le Gac and Arquie suspected that *L. deliensis* was the vector, they did not prove it. During studies at Ben Cat in 1969, Upham* identified *L. deliensis* as a parasite of several small mammal species but was unable to determine whether the mites were infected.

Data concerning the incidence of scrub typhus in American military personnel in Vietnam are approximate at best, although it was first seen as early

*R. W. Upham: Personal communication.

as 1962.* As was to happen frequently, the first case occurred simultaneously with falciparum malaria. Following clearing of the malaria parasitemia, the patient remained febrile and developed a typical rash, eschar, and positive OX-K titer. An estimated 6-percent incidence of scrub typhus occurred among patients hospitalized for malaria (USARV-MB, p. 17). During the early combat period, the only diagnostic laboratory method available was the Weil-Felix reaction, known to be positive in only 50 percent of proven cases (Bozeman and Elisberg 1963). Many clinically recognized cases were treated with tetracycline without serologic confirmation and, in some instances, without hospitalization.

Although the total number of cases which occurred in Vietnam is not known, some comparative data are available. For example, three FUO studies, each accomplished with sophisticated bacteriologic, virologic, and serologic support, were reported on. Two of them provide data from U.S. Army hospitals in 1966. At the 8th Field Hospital in Nha Trang, Reiley and Russell (1969) reported a 14-percent incidence of scrub typhus among 94 cases of FUO. Deller and Russell (1967) reported 110 FUO cases from the 93d Evacuation Hospital at Long Binh, with an 8-percent incidence of scrub typhus. Only those cases of scrub typhus which were diagnostic FUO problems were studied; therefore, while one can estimate that 10 percent of all FUO cases were scrub typhus cases, no extrapolation can be made concerning total numbers of cases of the disease. The third study of febrile illness in Vietnam was done by Deaton (1969) at the U.S. Air Force Hospital, Cam Ranh Bay. Of his 306 cases, only 1 percent were scrub typhus. The FUO data from these three studies are summarized in table 24, which also includes data from a study by Cottingham et al. of indigenous and U.S. troops in II and III CTZ's (Corps Tactical Zones) (discussed later in this chapter).

TABLE 24.—Incidence of scrub typhus among cases of fever of undetermined origin in Vietnam, 1966-67

Author and year of occurrence	Number of cases		Incidence of scrub typhus (Percent)
	Fever of undetermined origin	Scrub typhus	
Reiley (1966)	94	13	14
Deller (1966)	110	9	8
Cottingham (1967)	407	36	9
Deaton (1968)	306	3	1

Sources: Compiled from (1) Reiley, C. G., and Russell, P. K. 1969. *Mil. Med.* 134: 36-42. (2) Deller, J. J., Jr., and Russell, P. K. 1967. *Ann. Int. Med.* 66: 1129-43. (3) Cottingham, A. J., Jr., et al. Annual Progress Report, U.S. Army Medical Research Team (WRAIR) Vietnam and Institute Pasteur of Vietnam, 1 Sept. 1966-31 Aug. 1967, pp. 238-73. (4) Deaton, J. G. 1969. *Mil. Med.* 134:1043-8.

In a review of serological tests performed by the 9th Medical Laboratory, researchers (Baker, McKinney, and Huxoll) studied 190 cases with diagnostic titers for scrub typhus during a 12-month period. Specimens were received from the entire country, and diagnosis was based on a fourfold rise in specific antibody

*O'Neill Barrett, Jr.: Unpublished data.

titer. Admitting a possible sampling error in the first 3 months, a significant correspondence between occurrence of disease and the rainy season was found. Further analysis revealed that 93 percent of cases occurred among infantry and artillery troops rather than support troops. This distribution contrasts with that of murine typhus and confirms previous French data (Le Gac and Arquie 1964) indicating presence of disease primarily in mountain jungle terrain. Extrapolating from Baker, McKinney, and Huxoll's estimated sample source, approximately 2,000 cases of scrub typhus probably occurred during the 12-month period of observation.

ETIOLOGY, PATHOGENESIS, AND PATHOLOGY

The etiology and pathogenesis of scrub typhus are described in detail in several texts (Smadel 1952; Faust and Russell 1964). The etiologic agent, *R. tsugamushi*, is an obligate intracellular parasitic micro-organism appearing as short rods or diplococci, 0.3 to 0.5 μm long and 0.2 to 0.4 μm wide. In the electron micrograph, a well defined limiting membrane enclosing protoplasmic material that contains dense granules is seen. Although the rickettsiae are rendered noninfectious by 0.1-percent formaldehyde solution, they remain viable for long periods when stored at -70°C in appropriate protective media. They grow well in yolk sac tissue of embryonated eggs and in several types of tissue cultures (Smadel 1952, pp. 641-43).

In the experimental animal, rickettsiae initially multiply at the site of local inoculation and then become disseminated. The basic histologic lesion is a perivascularitis characterized by infiltration of monocytes, plasma cells, and lymphocytes with associated edema. Endothelial changes are uncommon except in the lungs where thromboses are frequently observed. In severe infections, focal necrosis of involved tissue may occur. In both experimental and human disease, lesions may be widespread, but they are most common in the skin, lungs, myocardium, and brain. In brain lesions, the focal perivascular reaction with proliferation of neuroglial cells is seen (Faust and Russell 1964, p. 774).

Recent studies concerning the pathogenesis of scrub typhus infection, especially in terms of latency and recrudescence, were performed by Kundin et al. (1964). They followed the course of infection in suckling and weaning mice, noting the effects of various routes of inoculation on the distribution of antigen, and also attempted to locate rickettsiae in mice at intervals after the initial infection. Their studies confirmed previous reports that susceptibility and length of survival varied with age of host, route of inoculation, and size of inoculum. An impressive finding was the observation that antigenic localization followed a characteristic pattern in all cases and that antigen was deposited in connective tissue of mesenchymal origin, especially loose areolar tissue, adipose tissue, and myeloid hematopoietic tissue. Infectivity titrations, however, showed that rickettsiae were present even in areas where antigen was not demonstrated by immunofluorescence. Tissue showing the highest degrees of infectivity included liver, kidney, brain, muscle, and spleen. In animals sacrificed 1 year after infection, organisms could be found in a similar distribution by infectivity titration

but not by immunofluorescence. Irradiated mice showed greater susceptibility to rickettsial infection with an increase in mortality, a short incubation period, and enhanced antigen deposition, supporting the hypothesis that X-radiation inhibits antibody response and renders cells more vulnerable to invasion.

The only two extensive pathological reports of scrub typhus in the literature represent experience from World War II. In the first study, done by Sayen et al. (1946) in conjunction with the clinical evaluation of disease at the 20th General Hospital in Burma, autopsies were performed in 28 of the 29 deaths caused by the disease. The second report, by Allen and Spitz (1945), reviews material collected by the Army Institute of Pathology and the USATC on 78 cases of scrub typhus in New Guinea.

The characteristic lesion, confirming the experimental data discussed above, was a perivasculitis involving arterioles, capillaries, and veins with eccentric infiltration by lymphocytes, plasma cells, and macrophages (Allen and Spitz 1945, p. 609).

Cardiac involvement was characterized by diffuse myocarditis, especially severe in the endocardium of the papillary muscles with the typical mononuclear infiltrate. There was no evidence of necrotizing arteritis, in contrast to a 17-percent incidence in epidemic typhus (Allen and Spitz 1945, pp. 611-13).

In 55 percent of scrub typhus cases, interstitial pneumonitis of varying degrees of intensity was found, characterized by marked dilatation of septal capillaries and interstitial infiltration by mononuclear cells as well as desquamation of alveolar epithelium and intra-alveolar hemorrhage in severe cases (Allen and Spitz 1945, p. 615; Sayen et al. 1946, p. 184).

Changes in the nervous system were seen in all patients and were characterized by diffuse meningoencephalitis with perivascular cuffing of arteries, degeneration of ganglion cells, and focal hemorrhages in parenchyma and meninges (Allen and Spitz 1945, p. 626).

Evidence of early but definite glomerulonephritis was found in 30 percent of the cases studied. The common finding was moderate to complete ischemia of the glomerular capillaries, often with obliteration by platelet thrombi or enlarged endothelial cells (Allen and Spitz 1945, p. 636).

There are no pathologic data on the cases of scrub typhus in Vietnam since no deaths from the disease were documented there.

CLINICAL MANIFESTATIONS

Scrub typhus is an acute febrile illness characterized by temperature elevation to 104° or 105° F, chills, malaise, and headache. The common but not invariable occurrence of an eschar and characteristic rash makes it more distinctive than other febrile illnesses seen in Vietnam. On the other hand, the disease may be atypical at onset, as evidenced by several FUO studies in which 1 to 14 percent of initially undiagnosed cases were caused by scrub typhus (see table 24). A comparison of the signs, symptoms, and routine laboratory studies from several detailed reports is given in table 25. The data of Sayen and associates are from the Burma experience in World War II; those of Cottingham et al. are

TABLE 25.—*Comparison of clinical manifestations of scrub typhus from five studies*

Manifestation	Author (and number of cases in series)				
	Sayen (200) Percent	Deller (9) Percent	Reiley (13) Percent	Cottingham (39) Percent	Hazlett (32) Percent
Fever	70	100	100	95	100
Chills	(²)	100	77	59	100
Bradycardia	(²)	(³)	(³)	(³)	97
Eschar	60	33	23	44	95
Rash	71	56	46	8	37
Adenopathy	97	100	70	44	75
Splenomegaly	35	(³)	31	36	19
Hepatomegaly	20	(³)	(³)	10	9
Headache	(²)	100	85	85	91
Eye pain	(²)	(³)	85	26	53
Myalgia	(³)	44	38	(³)	69
Cough	(²)	22	70	59	22
Pharyngitis	(²)	44	8	(³)	(³)
Conjunctivitis	38	56	0	(³)	(³)
Anorexia	(²)	56	(³)	(³)	28
Leukocyte count:					
> 10,000/mm ³	(²)	22	38	(³)	20
< 5,000/mm ³	(²)	0	0	(³)	16
Anemia	(²)	0	46	(³)	(³)
Elevated SGOT	(³)	11	57	(³)	(³)

¹Figure for spiking fever only.²Mentioned but no figure given.³Not recorded.

Sources: (1) Sayen, J. J., et al. 1946. *Medicine* 25: 155-214. (2) Deller, J. J., Jr., and Russell, P. K. 1967. *Ann. Int. Med.* 66: 1129-43. (3) Reiley, C. G., and Russell, P. K. 1969. *Mil. Med.* 134: 36-42. (4) Cottingham, A. J., Jr., et al. Annual Progress Report, U.S. Army Medical Research Team (WRAIR) Vietnam and Institute Pasteur, 1 Sept. 1966-31 Aug. 1967, pp. 238-73. (5) Hazlett, D. R. 1970. *Mil. Med.* 135: 31-34.

from indigenous Vietnamese units, including CIDG (Civilian Irregular Defense Group) forces; those of Deller and Russell and of Reiley and Russell from their respective FUO studies; and those of Hazlett from studies of an outbreak of 32 cases in a combat unit conducting search-and-destroy operations around an abandoned rubber plantation near Phan Rang.

Fever is almost invariably present and, by the third day of clinical illness, usually presents a classic spiking or "sawtooth" pattern with a return of temperature to normal or near normal between spikes (figs. 41 and 42). This characteristic pattern was seen in all 32 patients studied by Hazlett (1970). While a similar spiking pattern is seen in leptospirosis, the temperature in that disease rarely drops to 99° F between spikes (Reiley and Russell 1969, p. 38). Several authors report a relative bradycardia with the pulse rate disproportionate to the temperature elevations. However, a similar observation has been made both in dengue fever and malaria, and this finding is of little diagnostic value (Sayen et al. 1946; Hazlett 1970; Reiley and Russell 1969).

The eschar, when present, is an extremely valuable diagnostic aid. Classically it is a painless, nonpruritic lesion 1 to 2 cm in diameter with a black ne-

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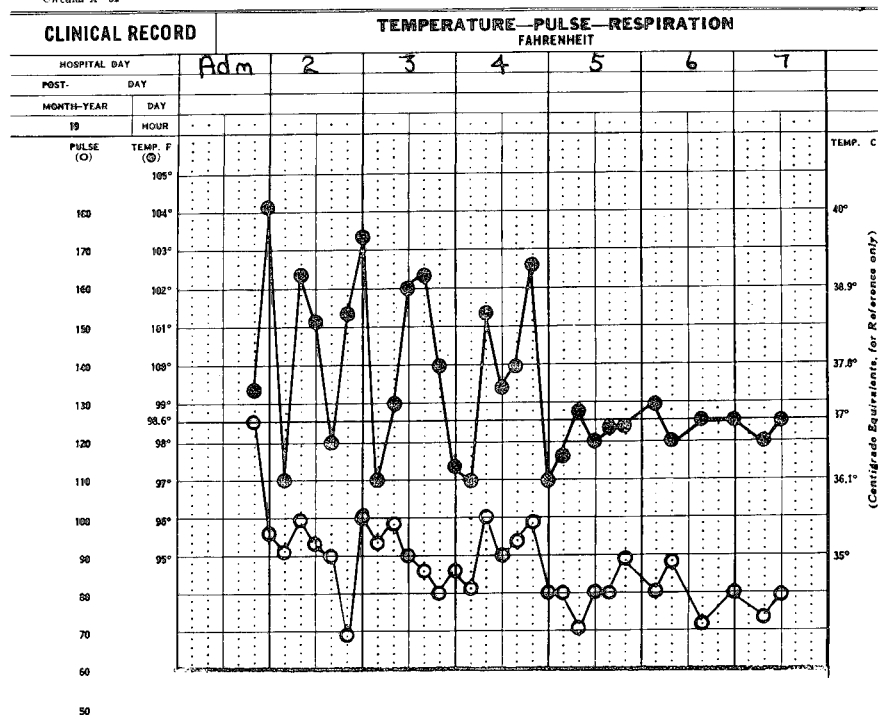


FIGURE 41.—Characteristic spiking or sawtooth temperature pattern in scrub typhus.
(Courtesy, Carlton Reiley, M.D.)

crotic center and halo of subacute inflammation (fig. 43). A typical eschar is seen in 33 to 85 percent of cases (Deller and Russell 1967; Hazlett 1970), but in some, because of perspiration and maceration, a crust may not form and the lesion appears only as a denuded papule. Eschars occur mostly on the extremities or trunk but may be found in either the axilla or genital area in about 20 percent of the cases (Hazlett 1970; Sheehy, Hazlett, and Turk 1973). A transient rash, macular or maculopapular, pink to red, nonconfluent and blanching, appears on the trunk after several days in about 50 percent of cases (fig. 44) (Reiley and Russell 1969). Lymphadenopathy occurs in almost all cases (Sayen et al. 1946, p. 171; Reiley and Russell 1969; Deller and Russell 1967; Hazlett 1970) and may be regional or generalized, usually appearing several days after onset of fever. The lymph nodes are usually tender and may be 1 to 3 cm in size. Splenomegaly is seen in about one-third of the cases but is generally mild. Hepatomegaly is not characteristic of the disease.

Headache is the most common symptom. The pain is usually severe and located in either the frontal or the retro-orbital area. Lumbar spinal punctures were not performed in any of the cases, so information concerning possible central nervous system involvement is unavailable. Cough, also a frequent

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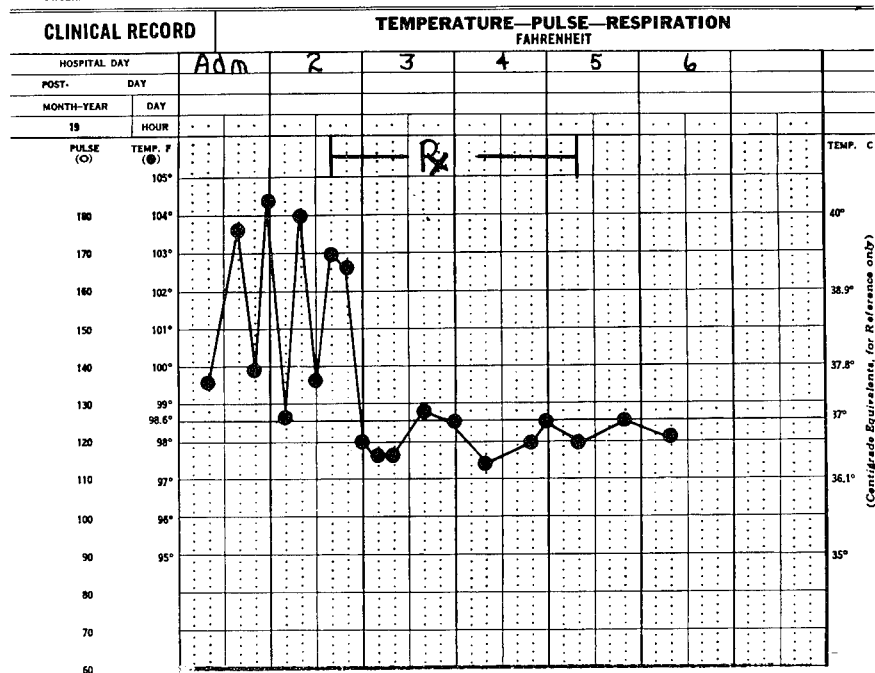


FIGURE 42.—Typical temperature response to tetracycline therapy in scrub typhus. (Courtesy, Carlton Reiley, M.D.)

symptom (Sayen et al. 1946, p. 168; Reiley and Russell 1969; Cottingham et al.), is generally mild and nonproductive and not associated with pneumonitis.

Complications of scrub typhus were remarkably uncommon in the cases reported from Vietnam and, as previously noted, there were no deaths from the disease in American troops. This is in striking contrast to the 5-percent mortality rate in Sayen's series and the 9-percent mortality rate in the CBI theater as a whole. In addition, clinical involvement of several organ systems was noted in the Burma experience: severe myocarditis was found in all cases at autopsy, about 12 percent of all patients had cardiomegaly, and 36 percent had definite electrocardiographic changes, including P-R interval prolongation and ST-T wave changes (Sayen et al. 1946; MD-PM7, p. 292). Only one case of myocarditis associated with scrub typhus was reported among American troops in Vietnam: Ognibene et al. (1971) described an 18-year-old white male who developed myocarditis which was self-limited, although it persisted well beyond the period of acute disease. The case was further complicated by the development of disseminated intravascular coagulation. This phenomenon had been described only once previously in an American in Vietnam. Chernof (1967) reported hypofibrinogenemia, prolonged prothrombin time, and mild thrombocytopenia in association with thrombophlebitis in a 22-year-old man with scrub

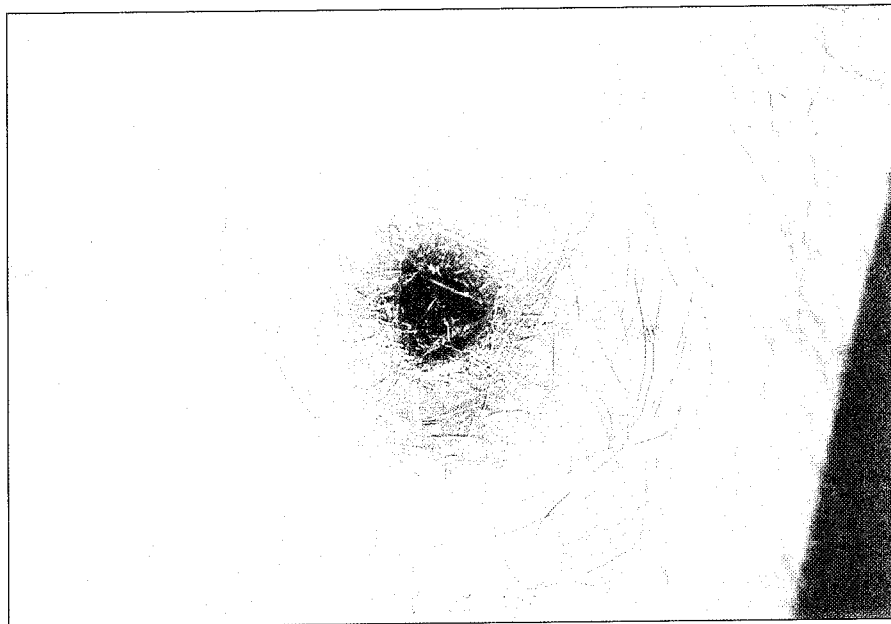


FIGURE 43.—Typical eschar seen in scrub typhus indicates site of infection by the trombiculid mite. The lesion, generally up to 1 cm in diameter, consists of a central tough black scab surrounded by a slightly elevated, dull red areola; it is neither painful nor pruritic. (Courtesy, Carlton Reiley, M.D.)

typhus. He was treated with heparin and recovered. The author properly presumed that the likely cause of this picture was "accelerated intravascular coagulation." This complication is well recognized in Rocky Mountain spotted fever and was probably a common occurrence in the lethal cases in Burma as suggested by the clinical and pathological evidence of widespread hemorrhages at autopsy (Sayen et al. 1946). There is also one case report of acute renal failure complicating scrub typhus in an individual with glucose-6-phosphate dehydrogenase deficiency (Whelton, Donadio, and Elisberg 1968). Mild renal involvement, characterized by a transient albuminuria and hematuria, was noted in 18 percent of the patients in Hazlett's series (1970). The serious pulmonary and central nervous system complications reported in the Burma study were not seen in Vietnam.

Routine laboratory data are not helpful in the diagnosis of scrub typhus. Sayen et al. (1946, p. 179) described anemia as occurring during the first 2 weeks of the disease but did not cite an incidence. Furthermore, the coexistence of malaria, amebiasis, and hepatitis makes the association between the anemia and typhus unclear. On the other hand, Reiley and Russell (1969) reported anemia (hematocrit below 40) in 6 of 13 cases. In only two was the hematocrit below 35 percent. No apparent cause was found; however, the evaluation was limited.

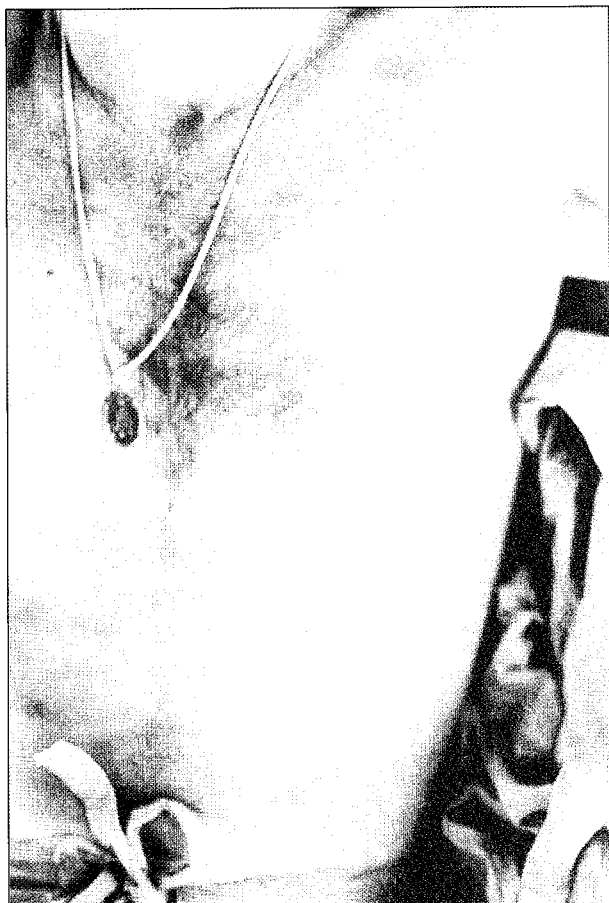


FIGURE 44.—Maculopapular rash showing dull red, discrete macular eruptions appearing first on the trunk and spreading to arms, legs, and face. (Courtesy, Carlton Reiley, M.D.)

The leukocyte count is generally normal although leukopenia and leukocytosis have been noted. Sayen and associates (1946, p. 179) found that the average total leukocyte count rose slightly during the second week and more definitely after the fourth week. Early leukopenias were observed in a few cases; a somewhat larger number of patients had considerable leukocytosis, with some counts as high as 20,000 in the second or third week. Associated disease and the lack of specific chemotherapy in this group may have affected the data. Reiley and Russell (1969) noted only five cases with leukocyte counts above 10,000 per mm^3 and only one of these exceeded 15,000. In Hazlett's larger series (1970) the leukocyte count varied in some patients from 2,750 to 26,000 per mm^3 at different stages of the disease. Leukopenia with relative lymphocytosis was noted in 16 percent of cases between the third and tenth day of illness. Leukocytosis

was seen in 20 percent and usually occurred between the 13th and 24th day of illness. Leukocytosis may, therefore, be a late manifestation of untreated scrub typhus, while leukopenia is less characteristic than in dengue and malaria (Deller and Russell 1967; Reiley and Barrett 1971).

LABORATORY DIAGNOSIS

The laboratory diagnosis of scrub typhus can be made either by immunological techniques or by recovery of rickettsiae from laboratory animals inoculated intraperitoneally with blood from infected persons.

Of the immunological tests available, one of the oldest, simplest, and most widely used is the WFR (Weil-Felix reaction). This agglutination test does not directly involve rickettsial antigens. Instead, it depends on the fact that, in the course of some rickettsial diseases, antibodies are formed which "react fortuitously" with the polysaccharide O antigens of the X strains of the *Proteus* bacillus, which are referred to as *Proteus* OX strains. The test was originally described by Weil and Felix, who because of this cross reactivity mistakenly suspected that *Proteus* was the cause of typhus fever (Davis et al. 1973, pp. 898-910).

Three *Proteus* strains are used in the WFR: *Proteus* OX-19 for the diagnosis of epidemic and murine typhus and Rocky Mountain spotted fever, OX-2 for the spotted fever group but not the typhus fevers, and OX-K (Kingsbury strain) for tsutsugamushi fever. A significant rise in titer is not often seen before the 10th day of illness; the maximal titer usually occurs by the fourth week and gradually falls to nondiagnostic levels by the eighth week.

Unfortunately, the WFR has three serious limitations. First, infections with *Proteus* organisms are fairly common and will give rise to elevated titers (Davis et al. 1973, p. 903).

Second, antibodies may also be detected in serums of patients infected with either louseborne relapsing fever or leptospirosis. Diagnostic titers have been reported in both of these spirochetal diseases, and both occur in the known geographic distribution of scrub typhus (Carley et al. 1955). Zarafonitis, Ingraham, and Berry (1946) studied 50 patients with louseborne relapsing fever in Cairo, all of whom had positive blood smears for *Borrelia recurrentis*; all patients demonstrated an OX-K titer of 1:40, and 60 percent had titers of 1:160 or greater. Therefore, caution is necessary in interpreting titer rises to OX-K in areas where these diseases may occur simultaneously. While louseborne relapsing fever has not been reported from Vietnam, leptospirosis is endemic and accounted for approximately 7 percent of FUO cases seen there (Reiley and Russell 1969; Colwell et al. 1969).

Finally, the Weil-Felix reaction is diagnostic in only 40 to 60 percent of cases of scrub typhus (Sayen et al. 1946; Blake et al. 1945; Bozeman and Elisberg 1963). In the study of Blake and associates in New Guinea, seven patients had classical disease but failed to show significant titer rises; *R. tsutsugamushi* was recovered from the blood of two of them by inoculation of mice. The same observation was made in Vietnam, in an epidemic setting, by Hazlett (1970), who

noted four individuals with clinical disease who failed to develop diagnostic titers. These factors, plus the availability of more specific serologic techniques, render the WFR of historical importance only.

The complement fixation reaction, also used for the diagnosis of scrub typhus, is unsatisfactory because of the high degree of strain specificity of soluble antigens and the marked antigenic heterogeneity among various strains of *R. tsutsugamushi* (Bozeman and Elisberg 1963). The test is also used for typing various strains of the *tsutsugamushi* organisms, especially in epidemiological studies, and remains a useful tool although it will likely be replaced by direct immunofluorescence techniques as described by Iida, Kawashima, and Kawamura (1965).

Various other diagnostic immunologic techniques are available but are not frequently used. Serums may be titrated for ability either to neutralize rickettsial suspension toxicity in mice or to protect chick embryos or laboratory animals from infection. Neutralization in both of these tests reflects activity of antibodies to type-specific antigens. The protection test is troublesome to perform because of the difficulty in obtaining standard suspensions and is hazardous because accidental human infection may occur (Davis et al. 1973, p. 902).

Currently, the most effective and specific immunologic means of diagnosing scrub typhus involves an indirect immunofluorescence reaction. The test was originally described by Goldwasser and Shepard (1959) in their studies of epidemic and murine typhus and was adapted by Bozeman and Elisberg (1963) for scrub typhus. Antigen is prepared by smearing dilute suspensions of rickettsial organisms on glass slides. Each antigen smear is ringed with a Vaseline-ether-Sudan black solution to prevent mixing of the applied serums. Fourfold dilutions of serums, prepared in normal yolk sac diluent, are applied to the smears and incubated. Serums are removed by rinsing the slide, and to each slide is added diluted fluorescein isothiocyanate-labeled antihuman horse globulin. The slides are again incubated and rinsed, and the intensity of immunofluorescence is recorded.

In Bozeman and Elisberg's study, antibody was regularly demonstrated in serums collected after the seventh day of illness; in a few, low levels of antibody were detected before the seventh day. Significant titers noted during the latter part of the second week increased to maximum levels between the third and fourth weeks. Only 6 of the 15 paired serums studied showed a significant rise in OX-K agglutinins, and no correlation was noted between the presence or absence of OX-K antibody and the fluorescent antibody titers. Nonspecific reactions did not occur when the scrub typhus serums were exposed to antigens of other rickettsial species, and no reaction occurred between *R. tsutsugamushi* smears and serums from other rickettsial infections or serums from patients with *Proteus* OX-K agglutinins of nonrickettsial origin.

The indirect immunofluorescence test of Bozeman and Elisberg is now used by laboratories throughout the world and is one of the most reliable serologic tests in use. However, the technique is difficult to apply when epidemiological studies or work in small animals is indicated because of the large

amounts of serum required. Gan, Cadigan, and Walker (1972) described a filter paper technique, requiring as little as 0.065 ml of blood, used in conjunction with the indirect immunofluorescence test. This technique is reliable and reproducible and works equally well with human, rodent, and primate specimens; it is particularly valuable since no special handling of the filter paper specimens is necessary.

Ideally, scrub typhus should be diagnosed by recovery of rickettsiae in mice inoculated with the blood of infected patients. Unfortunately, some strains of organisms cause disease in man but have only relative degrees of virulence in mice. For example, in the 15 cases of scrub typhus studied by Bozeman and Elisberg, 3 strains consistently killed all inoculated animals, 2 were mildly virulent, causing only occasional deaths, and 10 strains infected mice but did not kill them. In such instances, infection of test mice can be demonstrated only by their ability to survive challenge with a known pathogenic strain; this lengthy procedure requires 5 to 6 weeks to complete and is not applicable as a routine diagnostic study for scrub typhus.

TREATMENT

In 1945, the treatment of scrub typhus, as described by Sayen et al. (1946), consisted of "rest, nutrition, fluids and adequate nursing care." Although no effective specific therapy was available during World War II, two interesting treatment programs were evaluated. First, administration of immune blood and plasma was attempted. Blood was drawn from persons convalescing from the disease, usually during the fourth week and at a time when the Weil-Felix titer was maximal; six patients were treated with it, receiving from 500 to 2,000 cc of either whole blood or plasma. The authors found no evidence that the course of disease was alleviated by immunotherapy and did not believe that further trials of immune blood would be worthwhile.

Then, in the summer of 1944, penicillin became available in the China-Burma theater and was evaluated in the treatment of scrub typhus. Thirty-six patients were treated, receiving from one-half million to 6.5 million units (an average of 1.5 million units). Unfortunately, despite initial optimism, it became clear that "penicillin did not abort the disease, make its course milder, reduce the incidence of signs of major organ damage in severe cases, nor prevent patients from dying" (Sayen et al. 1946, p. 210). No other antibiotics were available for trial during this campaign. The disease remained a serious problem in Southeast Asia, with a significant mortality rate, prolonged clinical course with fever lasting 10 to 28 days, and protracted convalescence of 3 to 4 months before return to duty.

Within 3 years, this once dreaded infection was reduced to a nonfatal illness in which fever could be terminated within 30 hours. This dramatic reversal of the course of the disease resulted from the availability of Chloromycetin (chloramphenicol) and the work of Smadel and associates at the U.S. Army Institute for Medical Research in Kuala Lumpur, Malaya, and the Army Medical Department Research and Graduate School in Washington, D.C. The antibiotic

was first shown to have chemotherapeutic activity in a variety of experimental rickettsial and viral infections in 1946. Smadel and associates then undertook clinical trials of the drug in Malaya. In the initial report (Smadel et al. 1948), 25 treated and 12 control patients were compared. In a second study (Smadel, Woodward et al. 1949), results from a series of 30 treated and 19 control patients were reported. The individuals in these groups all had naturally acquired infection. The researchers also studied 37 volunteers who were exposed to scrub typhus in hyperendemic areas near Kuala Lumpur. These studies form the basis for the original chemotherapy of scrub typhus, and the observations of the authors have been reconfirmed by results from treatment of the disease in Vietnam.

The first important observation was that patients with naturally acquired scrub typhus who received chloramphenicol had a rapid resolution of fever, within 6 to 96 hours, and usually by about 30 hours, following institution of therapy. Total length of the febrile phase of the disease was shortened from 17 to 7 days, and the time between onset of symptoms and discharge from the hospital was shortened from 30 to 18 days. No relapses of the disease followed cessation of therapy in this group (Smadel, Woodward et al. 1949).

The experimental study confirmed the efficacy of the drug but raised some pragmatic problems and led to interesting and important immunologic conclusions. Of the 75 volunteers who were exposed, 37 developed clinical disease. Of these, 22 received no chemoprophylaxis and developed symptoms within 2 to 3 weeks of exposure. The remaining 15 received chloramphenicol prophylactically during exposure and for 2 succeeding weeks; they remained well until 2 weeks after the drug was discontinued but then developed clinical disease. The overall attack rate did not vary significantly between the prophylactically treated group and the control group (Smadel, Woodward et al. 1949).

An unusual and unexpected manifestation occurred among the volunteers who developed disease: 20 had relapses after they had apparently been cured by the initial course of the drug. This was especially disconcerting because there had been no relapses in the treated group with naturally occurring disease, nor had relapse been a part of the previously observed natural history of scrub typhus in man. An analysis revealed that the infecting dose in the volunteer group was probably heavier and was repeated over a several-day period, and that treatment in these individuals was invariably begun earlier than in those who acquired disease naturally. The ultimate conclusion was that Chloromycetin is rickettsiostatic rather than rickettsicidal (Smadel, Traub et al. 1949). When treatment was begun early in the course of disease, after a temporary interruption of growth of rickettsiae, the rickettsiostatic effect was dissipated quickly following discontinuance of the drug. At this early stage of infection, the immune mechanism of the host had not had time to respond adequately to the organisms. The patient's clinical and serologic response appears to depend on the mass of antigen which the pathogen releases in the body (Smadel 1954). Specific therapy may interfere with development of the usual mass of antigen and thus delay or diminish antibody production.

This observation was confirmed by the Vietnam experience. In Hazlett's

series (1970), all five patients who received treatment within 3 days of onset of symptoms had a relapse; among 24 treated 4 days or longer after onset of symptoms, there were no relapses. On the other hand, withholding therapy is unreasonable once the patient presents with symptoms. Furthermore, even with relapse, response to a repeat course of therapy is excellent. Smadel, Bailey, and Diercks (1950) suggested that relapses could be prevented by administering a 3-g dose of the antibiotic on the sixth to eighth day after termination of the original course of therapy. On the basis of these observations and data concerning total dosage, Hazlett recommended one of two possible regimens. If the patient is seen 4 or more days after onset of symptoms, he is given an initial dose of 3 g, followed by 0.5 g every 6 hours, to a total dose of 15-16 g. In treatment begun less than 4 days after onset of symptoms, an initial dose of 3 g is given, followed by 0.5 g to a total dose of 12 g, and an additional dose of 3 to 4 g is given 4 days after completion of the initial therapy for a grand total of 15 to 16 g. Because of the known serious hematologic toxicity of chloramphenicol, tetracycline, which is also effective (Smadel 1951), is the drug of choice for the treatment of scrub typhus at the present time. Recent data from Sheehy, Hazlett, and Turk (1973) suggest that tetracycline actually eliminates fever and other symptoms more rapidly than does chloramphenicol.

PREVENTION

Measures to prevent scrub typhus in endemic areas can be directed against the vector or toward active or passive protection of the human host from clinical infection (Smadel et al. 1952; Philip and Kohls 1945; Smadel et al. 1950). Control of the vector can be accomplished both by treatment of the terrain and by individual use of insecticides. Terrain control may be applicable to some military situations, but it is less satisfactory during peacetime because of cost and the need for treatment of large areas. Although controlled studies are not available, miticidal chemicals such as dimethyl phthalate, dibutyl phthalate, and benzyl benzoate clearly provide effective individual protection. However, M-1960 repellent, despite its availability in Vietnam (Hazlett 1970, p. 33), was used only infrequently by troops in the field because of the belief that the odor of the repellent could be detected by enemy forces.

Because chloramphenicol was extremely effective against clinical disease, attention was quickly directed to its possible use as chemoprophylaxis in individuals exposed to scrub typhus under natural conditions. Field studies by Smadel, Traub et al. (1949) clearly demonstrated that chloramphenicol given during and for 2 weeks after exposure prevented development of clinical disease only throughout the period of prophylaxis and the 5 ensuing days.

Attempts to develop a vaccine against scrub typhus began during, and continued after, World War II. Because of the postinfection immunity which apparently developed in man and was confirmed in animal studies, there was every reason to believe that such a vaccine could be developed, as had been done for

epidemic typhus. Several groups attempted to produce a noninfectious material and were successful in producing resistance against homologous strains of *R. tsutsugamushi* in laboratory animals. Preventive immunization against the disease in man was found to be extremely difficult, however, because of variations in the virulence of the organisms and the antigenic structure of various strains (Kekcheyeva 1968). Three field studies using killed scrub typhus vaccines failed to give encouraging results, and this approach has been abandoned (Smadel 1952, p. 644).

Subsequent studies evaluated the effectiveness of combining live vaccine and chemoprophylaxis to suppress clinical disease without interfering with the development of immunity. In their field trials, using both Gilliam and Karp strains, Smadel et al. (1950; 1952) noted that the level of immunity in persons treated in this manner was similar to that in patients following clinical infection. Immunity to the homologous strain was found to be complete and to persist for several years. On the other hand, resistance to heterologous infection was transient, lasting only a few months or less. Therefore, while the combined administration of live vaccine and chemoprophylaxis to produce homologous immunity is effective, it is of limited practical applicability.

Russian animal studies (Kekcheyeva 1968) suggest that live preventive vaccines made from virulent rickettsial cultures treated with tetracycline (antibiovacine) can produce both homologous and heterologous immunity in mice. However, immunity has been demonstrated only in short term studies, and no data from humans have been reported. Thus, at the present time, no practical vaccination program for the prevention of human scrub typhus is available.

SUMMARY

Placed in proper perspective, scrub typhus or tsutsugamushi fever does not enjoy a place of prominence in the medical history of Vietnam; rather, it will be best remembered as one of the several causes of FUO which always pose a diagnostic problem for physicians in the field. Early diagnosis was important because appropriate therapy allowed for rapid abatement of bothersome symptoms. On the other hand, in contrast to the World War II experience, no mortality was associated with its occurrence, probably because of the availability of adequate treatment and the good health of American troops, and perhaps because the form of the disease seen in Vietnam was less virulent than that in other areas of Asia.

No new therapeutic approaches were developed, although the efficacy of tetracycline as the drug of choice was confirmed. Previous epidemiological observations were extended to include Vietnam, but no new data were collected.

The refusal of combat troops to use the available repellents and the lack of an effective vaccine combined to assure that the exotic tsutsugamushi disease would provide an anamnestic stimulation to the intellectual titer of American medicine for another generation of physicians.

Section II. Murine Typhus

Colonel O'Neill Barrett, Jr., MC, USA (Ret.)

Although scrub typhus was recognized early during the American involvement in Vietnam, murine typhus was not recognized until July 1967 and, even then, was diagnosed only through an FUO evaluation using Weil-Felix OX-19 titers. It was never a serious clinical or epidemiological problem in Vietnam.

HISTORY AND MILITARY SIGNIFICANCE

In the mid-1920's, Maxcy (1926) suggested the occurrence of a disease similar to typhus fever but with a low mortality rate, milder clinical picture, and probably a different epidemiological pattern; this hypothesis was confirmed by the work of Dyer, Rumreich, and Badger (1931). By 1934, the differences among epidemic typhus, Brill's disease, and murine typhus were clearly defined (Zinsser 1934).

Statistics on U.S. Army experience with murine typhus before 1940 are not available because until that time all forms of typhus were recorded in a single figure. During World War II, 787 cases of murine typhus were reported in American troops; of these, 497 were acquired in the continental United States, primarily in the Southeast. The great majority of the 290 cases recorded overseas were in the Central and South Pacific Areas; only 34 cases were officially noted from the China-Burma-India theater, although other data suggest that more cases occurred there. A total of 15 deaths were attributed to murine typhus—a fatality rate of 19 per 1,000 cases. Fourteen of the fatal cases were acquired overseas; this comparatively high mortality might be attributed either to greater virulence of the disease in oversea areas or to the presence of associated diseases and the decreased resistance of the troops. Only 104 cases of epidemic typhus occurred in American troops during World War II, and no deaths were noted. The remarkably low incidence of this disease, which reached epidemic proportions in the surrounding civilian population, attests to extremely effective preventive measures (MD-PM7, pp. 178-79, 268-70). No cases of murine typhus were reported in American troops in Korea from 1950 to 1953.

The recognition of murine typhus in American troops in Vietnam was almost accidental. Statistical records from the Office of the Surgeon General on the incidence of rickettsial diseases in Vietnam show only 19 clinical cases of murine typhus from 1965 to 1970: 1 case was recorded in 1965, none in 1966 or 1967, 16 in 1968, 23 in 1969, and 10 in 1970 (PAD). Serologic and epidemiologic data, however, indicated that the occurrence of the disease was much more frequent than was recognized clinically. From July 1967 through 1968, 61 cases of murine typhus were serologically diagnosed, based on a fourfold rise in specific antibody titer, at the 9th Medical Laboratory (Baker, McKinney, and Huxoll). (In comparison, during the same period 190 cases of scrub typhus were

similarly diagnosed [Baker, McKinney, and Huxoll].) In the first reported clinical study in Vietnam, Deaton (1969) found 25 cases of murine typhus among 306 patients who presented with FUO at the U.S. Air Force Hospital, Cam Ranh Bay, from July 1967 to June 1968. Only the Weil-Felix reaction was available for the serologic evaluation in this study. As in scrub typhus, this test is less sensitive than other available serologic tests and probably underestimates the actual incidence of disease. Miller and associates (1974) described 58 cases seen at the same installation in the following year. In their study, both the Weil-Felix titers and fluorescent antibody techniques for specific antigens were used.

EPIDEMIOLOGY

Murine or urban typhus is a natural infection of rats and other rodents in many parts of the world. In the United States, this disease occurred initially in port cities and urban areas of the Atlantic seaboard and in the southeastern states, especially Texas, Georgia, Alabama, and Florida (MD-PM7, p. 269). It has since spread to rural areas, and for more than 20 years cases have been reported from California with increasing frequency (Adams, Emmons, and Brooks 1970).

Classically, the disease is transmitted by the oriental rat flea, *Xenopsylla cheopis*; the domestic rat, *Rattus norvegicus*, is the typical mammalian reservoir (fig. 45). However, a wide variety of naturally or experimentally infected animals and ectoparasites has been recorded, suggesting a more widespread distribution. Recent data indicate that the mammalian reservoir affecting man might also include the domestic cat and the opossum. Other species of fleas which readily bite man and domestic animals, especially the cat flea, *Ctenocephalides felis*, may transmit the infection from animal to animal and to man (Adams, Emmons, and Brooks 1970; Older 1970).

Murine typhus has been recognized in Southeast Asia since Lewthwaite and Savoor (1936) isolated *Rickettsia typhi* [mooseri] from rats and people in Malaya (now West Malaysia) and showed it to be distinct from other rickettsiae. Most of the animals harboring murine typhus were those closely associated with man in urban or other man-dominated habitats. The most common mammalian reservoir was *Rattus rattus diardi*, the house rat. Distribution of murine typhus in and around West Malaysia's urban centers is similar to that in other endemic areas and, while the cycle depends upon house rats in the cities and towns, the disease has been found in *Rattus rattus* in nonurban areas, indicating that rural foci may also exist (Marchette 1966). Similar experience has been reported from the Philippines (Woodward, Philip, and Loranger 1946).

In Thailand, *Rickettsia typhi* was first isolated in 1964 from rodents in the northern province of Chiang Rai. Since then, extensive surveys have indicated that murine typhus is widely endemic throughout the country, especially in the north and northeast regions. *Rattus exulans*, the Thai domestic rat, appears to maintain the enzootic cycle. The clinical significance of murine typhus

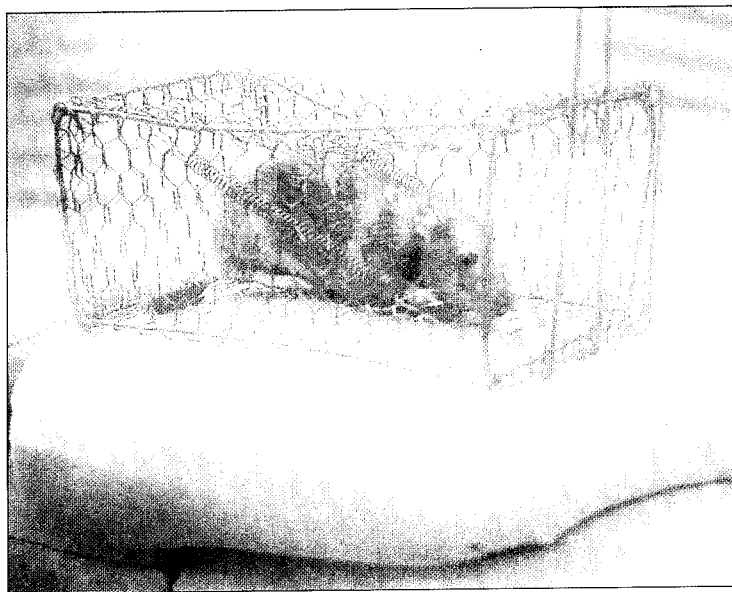


FIGURE 45.—*Rattus norvegicus*, the typical reservoir host for the Oriental rat flea, *Xenopsylla cheopis*, trapped in Vietnam.

in Thailand is unknown and to date the disease has been demonstrated there only twice in man (Sankasuwan et al. 1969).

Because the existence of murine typhus in Southeast Asia had been previously established, its discovery as a cause of FUO in American troops in Vietnam was neither surprising nor particularly disconcerting. The casual response to the disease was justified by its benign course and low morbidity. Data concerning the epidemiology of murine typhus in Vietnam are virtually nonexistent. Baker, McKinney, and Huxoll studied the distribution of rickettsial disease there by location and type of military activity. They found that 93 percent of the cases of scrub typhus occurred among combat troops, usually in infantry and artillery units; in contrast, only 45 percent of the cases of murine typhus occurred in this group, while 55 percent involved support troops, advisers, engineers, and U.S. contract civilians. This finding reconfirmed the urban distribution of the disease. Most cases of scrub typhus (60 percent) were noted in the Eastern II CTZ area, whereas most murine typhus cases (54 percent) occurred in the Western II CTZ area. No information regarding either the vector or the mammalian host is available.

CLINICAL MANIFESTATIONS

Although extensive clinical experience with murine typhus was not recorded during World War II, sufficient data were available to provide a summary of the clinical features of the disease, which mimicked epidemic typhus

TABLE 26.—*Comparison of clinical features of murine typhus from three studies in Texas and Vietnam*

Clinical features	Murine typhus studies ¹					
	Study 1 (Texas, 28 patients)		Study 2 (Vietnam, 25 patients)		Study 3 (Vietnam, 58 patients)	
	Number	Percent	Number	Percent	Number	Percent
Fever	26	93	25	100	58	100
Headache	18	64	20	80	51	88
Myalgia	12	48	19	76	² 10	17
Nausea	4	14	9	36	22	38
Cough	4	14	8	32	11	19
Rash	7	25	17	68	22	38
Splenomegaly			14	56	25	43
Lymphadenopathy			10	40	13	22

¹Studies represented by numerals are as follows: (1) Older, J. J. 1970. *J.A.M.A.* 214: 2011-17. (2) Deaton, J. G. 1969. *Mil. Med.* 134: 1403-8. (3) Miller, M.B., et al. 1974. *Mil. Med.* 139: 184-86.

²Arthralgia.

but tended to be less severe. Typically, the incubation period was from 8 to 16 days. Prodromal symptoms of nausea and malaise were common, followed by chills, headache, fever, and generalized myalgia. The total febrile course averaged 12 days with temperatures of 103° to 104° F. Rash occurred in 80 percent of the cases, typically appearing on the fifth day of illness. Lesions were first noted over the anterior chest wall, abdomen, lower back, and buttocks, generally sparing the face, scalp, palms, and soles; initially they were macular, becoming papular and confluent. As in epidemic typhus, a dry hacking cough usually developed, suggesting possible interstitial pneumonia. No specific laboratory changes were observed except for transient albuminuria (MD-IM2, pp. 221-23).

Three recent clinical descriptions of the disease confirm this picture. Older (1970) reported an outbreak of 28 cases in Texas in 1969; Deaton (1969) reported the first extensive experience from Vietnam—a total of 25 cases seen in 1 year at Cam Ranh Bay; and Miller et al. (1974) described 58 cases in the only other clinical study from Vietnam (table 26).

In the Texas series, symptoms were typical. The initial diagnosis in 22 of the 28 cases was influenza. The rash was generally mild and localized to the trunk and was observed in only a third of the cases. Rash was more common in Deaton's series, noted in 68 percent of the cases. In contrast to the experience in Texas and in the World War II study, splenomegaly was not uncommon in Vietnam; Deaton observed it in 56 percent of cases and Miller in 43 percent. Lymphadenopathy was a significant physical finding only in the studies from Cam Ranh Bay.

No consistent laboratory abnormalities have been defined in murine typhus. White blood cell counts have varied from low (4,600/mm³) to high (17,700/mm³); anemia, when noted, was mild. SGOT (serum glutamic-oxaloacetic transaminase) levels were abnormal in 11 of 20 measurements in Miller's series, but alkaline phosphatase, bilirubin, and BSP (Bromsulphalein) values were normal.

The diagnosis of murine typhus is made by standard serologic methods. The traditional Weil-Felix reaction using OX-19 antigen is useful but lacks sensitivity; of greater value are the complement fixation and hemagglutination or hemagglutination-inhibition tests (Wisseman et al. 1962; Zdrodovskii and Golinevich 1960, pp. 266-68). A toxin neutralization test, with high sensitivity and specificity, is available and useful in the diagnosis of epidemic typhus. Unfortunately in murine typhus, the toxin-neutralizing substance is nonspecific and can be found in a significant number (35 percent) of persons who reside in typhus-free areas and have not received typhus vaccine. Therefore, the test is not reliable as an indication of past infection with murine typhus or as a means of differentiating between murine and epidemic typhus fever (Bell et al. 1969). The fluorescent antibody technique is now the standard test for diagnosing murine typhus (Miller et al. 1974).

TREATMENT AND CHEMOPROPHYLACTIC MEASURES

Like other rickettsial diseases, murine typhus can be treated very effectively. While either chloramphenicol or tetracycline may be used, tetracycline is preferred because it does not pose the threat of aplastic anemia as does chloramphenicol (Older 1970; Miller et al. 1974; Wisseman et al. 1962). Both drugs are rickettsiostatic rather than rickettsicidal. The objectives of therapy are therefore to halt the growth of organisms as rapidly as possible and to prevent further proliferation until immune mechanisms are fully developed. When patients with either scrub or murine typhus are treated 7 or more days after onset of the disease, relapse is rare; when treatment is begun early, especially with a short course of chemotherapy, it is common. In murine typhus, the recurrence may be even more severe than the original infection. Furthermore, in murine typhus the interval between withdrawal of drug and return of clinical manifestations is only 2 to 3 days in contrast to 5 to 7 days in scrub typhus. These observations have led to the recommendation by Wisseman and others (1962) that the antibiotic be given until the patient is afebrile for 48 hours and then continued until 12 to 14 days after the onset of disease. Whether or not such a program is actually necessary is not clear, since neither Older (1970) nor Deaton (1969) comments on relapse following treatment of naturally occurring disease.

Although a vaccine against murine typhus was available during World War II, it was not used, in contrast to the vaccine for epidemic typhus, which was widely used and apparently effective (Gear 1969; MD-PM7, pp. 188-89, 267). There was no program for vaccination of troops against murine typhus during the Vietnam involvement, and commercial vaccines for the protection of laboratory workers were not available. However, the attenuated E strain of *Rickettsia prowazekii*, when used as a living vaccine, has been shown to provide cross-protection against the disease (Wisseman et al. 1962, p. 751). Prevention of the disease under naturally occurring conditions is best accomplished by control of the vector and the mammalian host.

Section III. Leptospirosis

Colonel Fred R. Stark, MC, USA

INCIDENCE AND EPIDEMIOLOGY

The conditions under which American ground forces operated in Vietnam predisposed them to intense local outbreaks of leptospirosis with considerable morbidity among field forces during the dry seasons. The absolute incidence of leptospirosis was unknown, but available data suggest that in certain regions for brief periods, up to 10 percent of combat troops who were inactive because of febrile illness suffered from leptospirosis (Berman, Irving, and Kundin 1968). The overall incidence of the disease, estimated from surveys of serums on medically evacuated wounded soldiers during the 1966-67 period, was approximately 1 percent.* In contrast, the rate of detection in Vietnam was only about one person per 1,000, based on confirmed cases reported from the 9th Medical Laboratory.**

Recognizing that about 1 in 10 febrile soldiers seen in the field at the battalion level reached a hospital, that only 20 percent or less of all soldiers in-country were in the field at any one time,*** and that leptospirosis in other outbreaks is often a mild self-limited disease (Heath, Alexander, and Galton 1965), a very high annual attack rate may be estimated, perhaps exceeding 100 per 1,000 combat soldiers per year. This is consistent with the experience of other forces operating in Panama (Mackenzie et al. 1966) and Malaysia (McCrumb et al. 1956). Although specific epidemiological research was not undertaken at the battalion level in Vietnam, reports from the 9th Medical Laboratory in 1969 (ML9-AR) indicate the larger number of serums positive for leptospirosis from such units.

There is no reason to believe that the pattern of leptospirosis transmission was unique in the Republic of Vietnam. A history of exposure to fresh water, often involving immersion, was usually elicited from patients there, as elsewhere. Excellent data accumulated under the direction of Lt. Col. (later Col.) Hinton Baker, MC, commander of the 9th Medical Laboratory from 1967 to 1969, revealed that the disease was widespread, seasonal (commencing with the end of the monsoon and peaking early in the dry season), and far more common in field soldiers than in support troops, and that it demonstrated a varied and nonspecific clinical picture.

*Personal observation by author, 250 random serums, Walter Reed General Hospital, 1966-67. Three serums possessed reciprocal hemolytic titers greater than 640 against *Leptospira biflexa*.

**Col. Hinton Baker: Personal communication. This figure inadequately reflects total incidence. In 1969, 169 cases of leptospirosis were serologically confirmed from among 3,300 serums (a 5.1-percent positivity rate) obtained from an estimated 22,000 FUO admissions (ML9-AR, pp. 14-17; Med Stat).

***Estimated by Lt. Col. Andre J. Ognibene, USARV Medical Consultant, 1969.

CLINICAL FEATURES

Generally leptospirosis presented as an FUO. As noted below, high fever, usually of 6 to 9 days' duration, persisting with or without antibiotic treatment was the rule. Headache, nausea, vomiting, and backache were common. The clinical features for 19 patients in one study (Allen, Weber, and Russell 1968) were as follows:

Fever	17	Nausea or vomiting	2
Headache	12	Lethargy or malaise	2
Chills	11	Abdominal complaint	2
Backache	9	Dizziness	2

Physical findings of conjunctival suffusion and liver tenderness were occasionally present in this group. Rash was uncommon. Mild degrees of liver and renal dysfunction were noted. Following are the physical findings in these patients:

Conjunctival suffusion	9	Petechiae (palate: 1; feet: 1)	2
Hepatic tenderness	9	Pharyngitis	1
Splenic tenderness	6	Palable spleen	1
Adenopathy	4	Flush of face	1
Muscle tenderness	3	No abnormal findings	1
Periumbilical tenderness	2		

Infrequently, more severe renal involvement requiring dialysis was documented. In many cases, high output renal failure occurred. High ambient temperatures contributed to the rapid development of hypovolemia and in some cases may have played a role in the production of oliguric rather than nonoliguric renal failure. In contrast to classical descriptions of the leptospiral disease syndrome, Weil's disease, jaundice, which is the most striking manifestation, was not characteristic of the leptospirosis seen in Southeast Asia.

In most cases seen by the author, mild proteinuria and many casts with infrequent red cells were present, but these findings were usually not striking compared to those in other patients with high fever. Marked hematuria was infrequent, few cases demonstrated cerebrospinal fluid abnormalities, and hemorrhagic complications were uncommon.

Neither autopsy studies nor antemortem tissue examinations are available from Vietnam. When fatal cases have been examined, myositis, hepatic inflammation or necrosis, marked inflammation of the kidneys, pneumonia, myocarditis, diffuse gastrointestinal hemorrhage, meningitis, transient transverse myelitis, and marked conjunctival suffusion have all been described; these findings are discussed in an excellent review of clinical experience with leptospirosis in the United States (Heath, Alexander, and Galton 1965, pp. 917-19).

The majority of leptospirosis patients in Vietnam had normal or modest elevations of the white blood count, moderate disturbances of liver function, with elevations of the serum glutamic-oxaloacetic transaminase and lactic dehydrogenase, and mild elevations of the alkaline phosphatase and bilirubin. BUN (blood urea nitrogen) elevations to 50 mg percent were common and were

associated with an element of prerenal azotemia, as described in studies on the Indian subcontinent (Sitprija 1968).

LABORATORY DIAGNOSIS

The bulk of cases were confirmed by serologic tests. Generally, *Leptospira biflexa* antigen obtained from Dr. Aaron Alexander, Walter Reed Army Institute of Research, was used to coat red cells for a nonspecific hemolytic assay. Between 1967 and 1969, fourfold titer rises in paired acute and convalescent serums, or single reciprocal titers of 1/400, with an appropriate history were taken as confirmation of leptospirosis. Few attempts at systematic isolation of the organism were made; some data comparing specific agglutination titers with the hemolytic assay were obtained from the I CTZ area laboratories (Berman, Irving, and Kundin 1968). These data from 297 cases suggested the presence of multiple species of leptospires, even in a single outbreak (Lipton and Legters), as follows (listed by serotype and number of cases):

australis	66	canicola	43
bataviae	68	grippotyphosa	35
icterohaemorrhagiae	47	hebdomidis	38

Multiple infections, simultaneously or serially, have been described in animals and man, from a single exposure source. Multiple species have been isolated from single samples of fresh water (Heath, Alexander, and Galton 1965).

PREVENTION AND TREATMENT

Few studies of the prevention of leptospirosis were undertaken in Vietnam by U.S. personnel, probably because early data on morbidity did not reflect the countrywide impact of the disease. Studies of polyvalent vaccines in animals have been impressive (Hanson, Tripathy, and Killinger 1972), and some preliminary data in man are available (Benoist and Lataste-Dorolle 1970). Measures such as prophylactic antibiotics, topical protection against immersion in fresh water, and vaccines were not evaluated during the Vietnam campaign. Studies of drug treatment of leptospirosis were not undertaken. Most patients treated received tetracycline because of the difficulty of differentiating the disease from scrub or murine typhus. Antibiotics did not appear to shorten the course of the disease, but the absence of mortality may have been related to the widespread policy of prompt administration of tetracycline at the battalion and hospital levels to severely ill febrile patients in whom leptospirosis or scrub typhus could not be excluded. In addition, the prompt use of parenteral fluids in most febrile patients may have prevented the oliguric renal failure known to be associated with the disease.

CONCLUSION

Significant gaps in the knowledge of leptospirosis persist. The relatively benign course in most cases in Vietnam blunted research efforts. In future operations in wet, tropical areas, this disease must be evaluated to determine its importance as a cause of combat man-days lost.

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Bacterial Diseases

Colonel Dan C. Cavanaugh, MSC, USA (Ret.),

Colonel Francis C. Cadigan, Jr., MC, USA, Major James E.

Williams, MSC, USA, Colonel John D. Marshall, Jr., MSC, USA,

Colonel William L. Moore, Jr., MC, USA, Carl R. Guiton, M.D.,

and Brigadier General Andre J. Ognibene, MC, USA

Section I. Plague

Colonel Dan C. Cavanaugh, MSC, USA (Ret.),

Colonel Francis C. Cadigan, Jr., MC, USA, Major James E.

Williams, MSC, USA, and Colonel John D. Marshall, Jr., MSC, USA

HISTORY AND MILITARY SIGNIFICANCE

Plague is an ancient disease, innumerable epidemics of which have resulted in a total mortality perhaps not exceeded by any other infectious disease. The persistence of plague in natural foci throughout the world and a succession of outbreaks during the past two decades present clear evidence that the technological advances of the 20th century are still inadequate to eradicate it.

W. J. Simpson (1905, p. 37) remarked that plague is brought in the train of armies or of commerce. The relationship of plague to warfare is not remarkable, as the devastation and disruption common to military operations often create favorable conditions for the proliferation of rats and fleas in areas where human beings are concentrated under unsanitary conditions. The history of plague is given extensive treatment in the works of various authors (Beasley 1969; Caten and Kartman 1968; Hirst 1953; MD-PM7; Pollitzer 1954, 1960; Simpson 1905; Wu Lien-teh 1911, 1926, 1959; Wu Lien-teh et al. 1936). Its impact on military operations is a matter of record.

The first plague epidemic which can be identified with some certainty was the Philistinian plague of 1320 B.C. in which the Philistines, returning from a war with the Israelites, were stricken with the disease; following this episode, plague became established in the Levant. Troops operating in the endemic region of Constantinople were considered by Procopius to be involved in the first

plague pandemic, the Justinian plague, which occurred in the 6th century (Hirst 1953, p. 10).

The second great pandemic, which resulted in the deaths of over 25 percent of the population of the Western World, was first noted in the city of Caffa on the Black Sea in 1346 (Hirst 1953, p. 11). The Tartar armies besieging the city experienced a devastating plague outbreak, and the victims' bodies were catapulted into the city, whereupon the disease appeared within its walls. Individuals fleeing the area in ships carried to Europe the "seeds of infection" that initiated a sequence of epidemics now known as the Black Death.

In the 18th century, the disease reappeared as a military problem. Frederick the Great, in 1745, was forced to conceal from his troops that the "foul fever" devastating the ranks was plague. Troops of Catherine the Great, returning from operations in the Balkans in 1769, initiated a destructive plague epidemic which ravaged Moscow for 2 years. French military operations in Egypt were impeded by plague epidemics, one of which caused them to abandon an attack on Alexandria in 1798 (Hirst 1953, p. 77).

The third and most recent pandemic, 1894-1920, began when Chinese troops were deployed in remote Yunnan Province, an endemic area, to suppress a Muslim rebellion. Military traffic to and from the area resulted in epidemics which quickly involved coastal cities. Aided by modern transport, plague was introduced into nearly every country in Asia. In India alone, an estimated 12 million people died before the disease retreated to its permanent foci (Hirst 1953, p. 145).

The third pandemic and the period following it have been characterized by intensive research on the etiology, epidemiology, treatment, and control of plague. The plague bacillus was isolated and described independently by Kitasato and Yersin in 1894. The association of the disease with rats and the incrimination of the flea as a vector were demonstrated by Liston, an officer of the Indian Medical Service and a member of the Indian Plague Commission from 1898 to 1914 (Liston 1903; Mollaret 1963, p. 1177). The vital concepts of rat and flea control emerged from the studies of this commission.

Haffkine, working in Bombay during this time, developed the plague vaccine that bears his name. The Haffkine vaccine was shown to be effective in reducing both morbidity and mortality and became an important feature of control programs. However, studies on pneumonic plague in Manchuria demonstrated the requirement for other techniques to control this fulminating form of the disease, which did not involve rats or fleas but rather direct man-to-man transmission from index cases infected by handling wild rodents. Changes in construction and fittings resulting in ratproof ships, together with the fumigation of premises and vessels with equipment developed by Clayton, were highly effective in reducing the territorial spread of the disease.

Although plague had subsided, World War II initiated renewed concern. A killed plague vaccine was developed and administered to U.S. troops deployed in endemic areas, and penicillin and the sulfonamides were studied to ascertain their value in treating the disease among indigenous people (MD-PM7, pp. 94-97). Fortunately, however, plague did not occur in U.S. troops in endem-

ic areas. DDT was developed and introduced during the war, and plague control became synonymous with flea control.

Following World War II, new concepts and technology contributed to a quantum leap in plague control. Improved bacteriological and serological techniques permitted the detection and delineation of plague foci in both commensal and wild rodents (Cavanaugh et al. 1965, 1970). Insecticides and rodenticides were developed which reduced the threat presented by these foci to manageable proportions (Pollitzer 1954, pp. 529-52; 1960, pp. 367-70). Advances in immunology led to the introduction of promising new vaccines (Meyer 1970, 1971). Of prime importance, the sulfonamides and, in particular, streptomycin and tetracyclines proved effective in the treatment of plague in all its clinical forms (McCrumb, Larson, and Meyer 1953; McCrumb et al. 1953; Simeons and Chhatre 1946; Smadel et al. 1952).

Plague has never posed a serious problem to the U.S. military thanks to an understanding of the epidemiology of the disease. Effective control measures have been incorporated into preventive medicine programs as rapidly as they have been developed. The prudence of this policy was amply demonstrated in Vietnam, where fewer than a dozen cases of plague were diagnosed in American personnel serving in an area of intense epidemic activity (Cavanaugh, Dangerfield et al. 1968; Feeley and Kriz 1965; Marshall et al. 1967; OM-PHD).

ETIOLOGY AND PATHOGENESIS

Plague results from infection with the gram-negative bacterium *Yersinia pestis* [*Pasteurella pestis*]. Clinical forms of the disease include bubonic plague, almost always initiated by the bite of an infective flea; primary septicemic plague, which bypasses massive involvement of the lymph nodes; and pneumonic plague, primary or as a complication of bubonic plague. Hematogenous dissemination of the plague bacillus results in pulmonary involvement. Primary pneumonic plague infection is obtained either by handling infectious material or by direct interhuman transmission of *Y. pestis* in aerosols.

Fleas, the biological vectors of *Y. pestis*, following a blood meal on a bacteremic rodent, develop a fibrinoid mass that retains plague bacilli in the proventriculus, an organ resembling a portion of the human esophagus. Growth of these plague bacilli gradually occludes the proventriculus and prevents the passage of food material into the stomach, resulting in a "blocked" flea (Bacot and Martin 1914; Cavanaugh 1971). Blocked fleas bite, suck blood into the proventriculus, and then regurgitate it along with plague bacilli into the host, initiating plague infection. Estimates of the number of bacilli introduced by the flea's attempts to feed range from 11,000 to 24,000 organisms (Cavanaugh and Randall 1959).

Epidemiological evidence indicates that the majority of bubonic plague cases occur when ambient temperatures are under 28° C, when, as shown by laboratory studies, *Y. pestis* organisms in the stomachs of blocked fleas are in a phagocytosis-sensitive condition (Bacot and Martin 1914; Cavanaugh and

Randall 1959). Therefore, the majority of plague bacilli introduced by fleabite are probably phagocytized. Phagocytosis-sensitive bacilli that are ingested by some mononuclear phagocytes, however, are not destroyed but reproduce within the cells, elaborating the factors that render them resistant to further phagocytosis and destruction by neutrophils at the time of their release from the infected cells (Cavanaugh and Randall 1959). Once established, the phagocytosis-resistant *Y. pestis* bacilli produce a rapidly progressing disease. Inter-human aerogenic transmission of phagocytosis-resistant *Y. pestis* explains the fulminating nature of epidemics of primary pneumonic plague.

Plague bacilli cultivated in vitro at temperatures under 28° C are sensitive to phagocytosis and destruction by neutrophils. Bacilli incubated at 37° C, however, produce at least three antigens which inhibit phagocytosis: the Fraction I antigen, which is the specific capsular antigen of *Y. pestis*, and the V and W antigens (Burrows 1955, 1957, 1960; Burrows and Bacon 1956). Fully virulent organisms have the capacity to produce these antigens, in vivo, in mammalian hosts (Burrows and Bacon 1954).

The plague bacillus contains several potent toxins or virulence factors other than those described above. A murine toxin, lethal for mice but not for rabbits, inhibits the respiration of heart mitochondria and induces alterations in the ST segments of electrocardiograms of susceptible rats inoculated with it (Rust et al. 1963). A lipopolysaccharide endotoxin of *Y. pestis* exhibits classical endotoxic biologic properties, in particular, the capacity to produce localized and generalized Schwartzman reactions in rabbits (Albizo and Surgalla 1970). A coagulase of *Y. pestis* produces firm clots in plasma when tests are conducted at temperatures under 28° C; above this temperature, fibrin apparently is destroyed rapidly by a fibrinolytic factor of *Y. pestis* (Cavanaugh 1971). Observations in patients indicate that several or all of the known virulence factors of *Y. pestis* may contribute individually or in concert to the pathophysiology of human plague.

Poland (1972, p. 1143) states: "Progressive heart failure may develop in severe infections, and sudden death from cardiac failure has occurred even during convalescence." Winter and associates (1971, p. 383) noted that occasionally patients succumb following apparently adequate therapy. *Y. pestis* cannot be isolated from tissues of these patients at autopsy; it is believed that the potent toxins of the plague bacillus may cause death in a manner analogous to the Herxheimer reaction. Clinical and postmortem observations indicate that a generalized Schwartzman phenomenon, mediated by the lipopolysaccharide endotoxin of *Y. pestis*, plays a major role in the pathogenesis of plague (Finegold 1968; Butler 1972).

Many patients display evidence of disseminated intravascular coagulation, such as low platelet counts, prolonged partial thromboplastin times, positive ethanol gelatin tests, fibrin thrombi in purpuric lesions, and, in some instances, acute cor pulmonale secondary to pulmonary thrombosis (Butler 1972, p. 274). At autopsy, fibrin thrombi found in the glomerular capillaries and elsewhere in the tissues of children have suggested that disseminated intravascular coagulation had occurred during the course of the disease (Finegold 1968; Finegold et al. 1968).

INCIDENCE AND EPIDEMIOLOGY

The risk of plague is greatest in concentrations of human beings living under unsanitary conditions in the proximity of large commensal or wild rodent populations infested with fleas that bite both man and rodents. If the climate is suitable and the plague bacillus is present or is introduced into the local rodent reservoir, an outbreak will ensue. The largest plague outbreaks have been associated with commensal *Rattus* species infested with the Oriental rat flea, *Xenopsylla cheopis*. This flea enjoys a cosmopolitan distribution, although the largest populations are found in tropical areas. It is wise to remember, however, that all fleas should be considered dangerous in plague endemic areas.

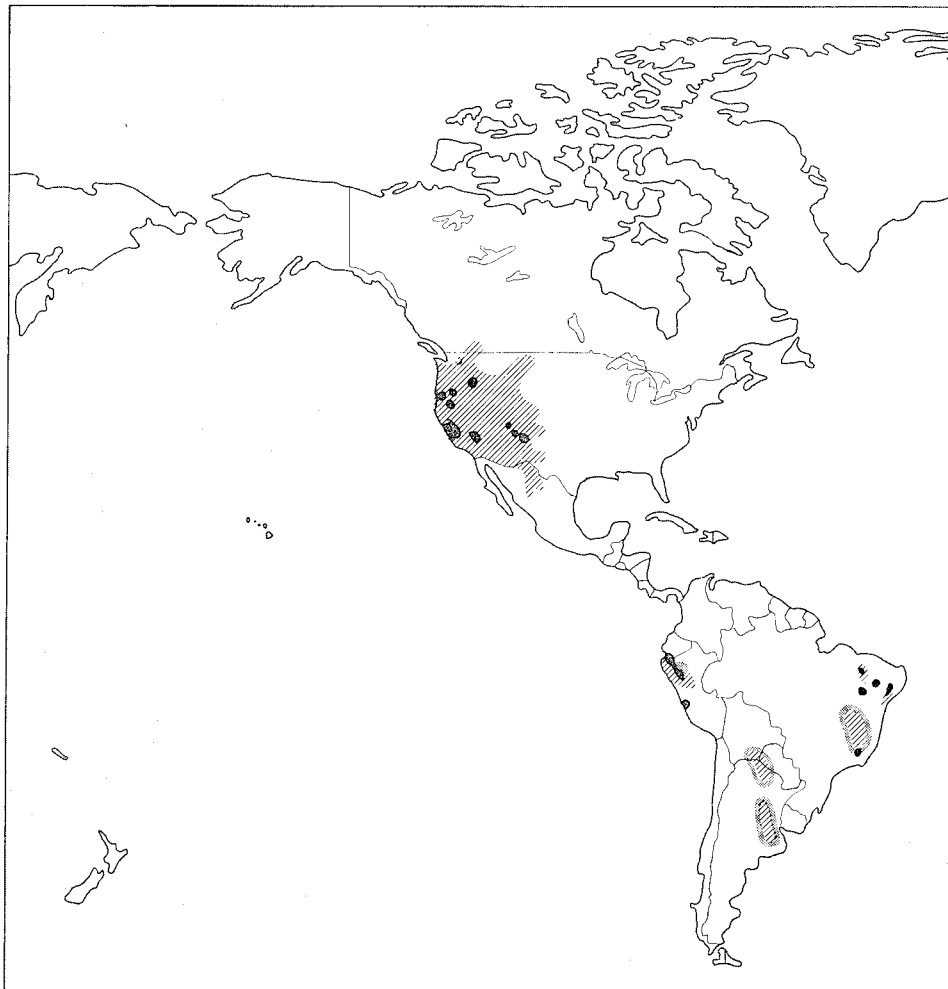
The basic epidemiology of fleaborne plague, which is essentially a disease of rodents, nearly always involves transmission of the plague bacillus from rat to rat and from rat to human being by the bite of an infected flea (Liston 1903, 1904, 1905; Lowson 1898, p. 247; Ogata 1897; Simond 1898). Interhuman infection or infection from fleas infesting bubonic plague patients is also possible (Swellengrebel 1967; Bahmanyar 1972; Pollitzer 1954, pp. 385-87).

Handling of infected rodents or exposure to droplets of infectious material produced by plague patients with pulmonary complications may lead to large, explosive epidemics of pneumonic plague (Wu Lien-tieh 1911, 1926; Pollitzer 1954, p. 245). Approximately 5 percent of bubonic plague patients develop a potential for the aerogenic transmission of the plague bacillus (Poland 1972, pp. 1141-48).

The epidemiology of primary pneumonic plague is not well understood. Most severe epidemics have occurred in areas where the climate is relatively cool. Primary plague pneumonia is rather rare in the Tropics, even in the presence of fulminating epidemics of bubonic plague, since high temperatures and humidities are unsuitable for the survival of *Y. pestis* in aerosol clouds. On the other hand, low relative humidity also is associated with the rapid death of plague bacilli in aerosols. Cool weather, moderate humidity, and close contact between susceptible individuals appear to be most favorable for epidemics of primary plague pneumonia (Burmeister, Tigertt, and Overholt 1962; Winter et al. 1971, pp. 377-87).

The observation that asymptomatic contacts may harbor virulent plague bacilli in their throats requires further evaluation to ascertain the role of such individuals in the epidemiology of plague pneumonia (Marshall, Quay, and Gibson 1967; Legters, Cottingham, and Hunter 1970). Future investigators also should consider the possibility that other respiratory infections superimposed on this "carrier state" might enhance the aerosolization of the plague bacillus and result in rapid dissemination.

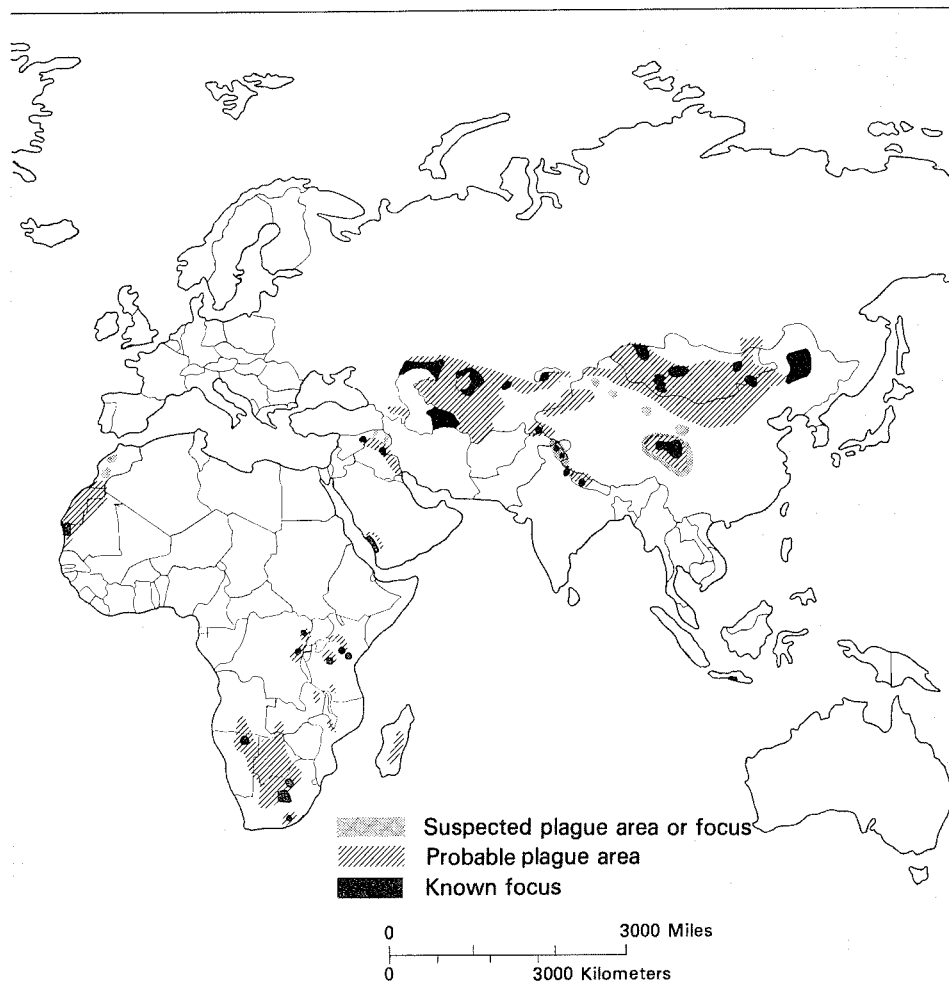
Wild rodents are now considered to be the principal reservoir of plague, serving as sources of infection for both human beings and commensal rodents. Widespread infection in numerous species of small rodents and other wild animals in the United States and elsewhere throughout the world is maintained in natural or temporary foci. The plague bacillus is transmitted among rodents by various fleas infesting the animals (Macchiavello 1954; Pollitzer 1954, p. 337;



MAP 3.—Known and probable foci and areas of plague, 1969. (Source: WHO Expert Committee

Pollitzer 1960, p. 357). Rodents may also become infected by digging burrows contaminated with infectious detritus (Mollaret 1963) or by cannibalism (Rust et al. 1972). *Marmota bobak* is a particularly notorious rodent, shown to be the initial source of infection in the great epidemics of pneumonic plague that occurred in Manchuria (Wu Lien-teh 1926; Wu Lien-teh et al. 1936).

Within a natural focus, the etiologic agent persists in wild rodents for considerable periods of time, and epizootics alternate with variable periods of quiescence. Temporary foci are territories that are seeded from permanent foci but, for unknown reasons, do not persist indefinitely. The epizootic process in each natural plague focus has its specific cyclic and periodic pattern, conditioned by the ecology of local rodent reservoirs and flea vectors. Each focus has distinct seasonal appearances of epizootic plague with characteristic peaks



on Plague, Fourth Tech. Rep. s. No. 447. Geneva: World Health Organization, 1970.)

of activity reflecting favorable local conditions (WHO-a).

Epidemics of disease in humans are also distinctly seasonal. The initial outbreak, which may or may not succeed in establishing a permanent focus, may occur at any season of the year; when the infection has secured itself in the rodent population of an area, characteristic plague seasons develop. In general, bubonic plague is a disease of the cooler months in hot climates and of the warmer months in cooler climates. Major epidemics occur at temperatures between 15° and 27.5° C associated with vapor pressure deficits not in excess of 7.6 mm Hg (Greenwood 1911, 1913, 1935; Brooks 1917; Cavanaugh and Marshall 1972).

The incidence of bubonic plague is directly related to the prevalence of the flea vector. Both cold and hot, dry weather cause the disappearance of *X.*

cheopis. If hot weather is associated with a vapor pressure deficit in excess of 7.6 mm Hg, the lifespan of adult *X. cheopis* is reduced (Hudson et al. 1973). If the relative humidity falls below 65 percent, *X. cheopis* larvae cannot maintain a water balance suitable for maturation (Knülle 1967). Rat fleas are not effective vectors when temperatures exceed 27° C (Kartman 1969; Cavanaugh 1971).

Data on the present distribution of known plague foci are shown on map 3. There is no evidence that new natural foci have been created in the recent past or that known natural foci have spontaneously become inactive or smaller in size, except for a few foci where intensive control measures have been employed. Many undetected foci may exist, particularly in Asia, Africa, and South America. Among known foci, those in Vietnam demonstrated the greatest activity in terms of human disease.

Rapid population growth and new development schemes are likely to bring more human beings into close contact with natural foci and create fresh problems in plague control, and military operations in such areas will probably create conditions favorable for the expansion of foci. Transportation of infected rodents and fleas from known foci may introduce the disease into plague-free areas. Although the ratproofing of ships has greatly reduced the risk of transporting infected rats and fleas to distant seaports, the new technique of shipping in containers poses a threat; transport of such containers by air may present a particular hazard.

CLINICAL FEATURES AND TREATMENT

Plague is a deadly disease which begins abruptly and can progress rapidly to death in a period of hours or of several days in 60 to 90 percent of patients unless therapy is initiated early (Poland 1971, 1972). Early recognition of the clinical syndrome is difficult because of the nonspecific nature of many of the early signs and symptoms, but delay of therapy while awaiting laboratory diagnosis might prove fatal because of the rapid progress of the disease.

The history of onset of symptoms is almost monotonously regular: virtually all patients have sudden onset of fever, chills, and headache (Butler 1972), usually followed within several hours by nausea and vomiting. The percentage of patients presenting with various manifestations follows:

Altered mentation.....	26-38	Chills.....	40
Headache.....	20-85	Vomiting.....	25-49
Chest pain.....	13	Cough.....	25
Prostration or severe malaise.....	75	Abdominal pain.....	18

Within 6 to 8 hours after onset, patients become aware of pain at bubo sites if buboes exist. The sudden onset of symptoms, characteristic of septicemic diseases, is the clinical picture in 95 percent of cases, according to Mathis and Pons (Pollitzer 1954, p. 411). Simpson (1905, p. 262) states: "no disease except cholera manifests * * * so rapid a development of its symptoms and overwhelms or

prostrates the patient to the verge of death in so short a time." (Meningococemia should probably also be excepted.)

Fever is variable, ranging from 99° to 106° F (37° to 41° C). Low fevers are not necessarily a sign of milder disease since the fever may never reach 100° F (38° C) in septicemic plague. Fluctuating levels of fever are of little value in the prognosis, except that it is unfavorable when the pulse rises as the temperature falls or when a sudden fall is accompanied by signs of collapse (Simpson 1905, p. 268). With successful antibiotic therapy, the temperature often falls precipitously but is accompanied by a slowing of the pulse and obvious improvement in the general condition of the patient.

Few acute infections produce a leukocytosis of such magnitude in adults as does plague. Counts are frequently in the range of 20,000 to 25,000/mm³, and even 50,000/mm³ is not unusual. Exceptions occur, however, and counts as low as 4,500/mm³ have been recorded, even in the presence of proven bacteremia; some evidence suggests that semi-immune individuals tend to have lower levels of leukocytosis than do fully susceptible individuals. Later in the course of disease, abnormalities are noted in the chest X-ray and, occasionally, in the electrocardiogram, blood chemistry, and urinalysis. Careful evaluation frequently reveals that disseminated intravascular coagulation is present. Cultures of sputum or blood, and aspirates or biopsies of buboes, will confirm the diagnosis in approximately 72 hours, but to reduce mortality, therapy must be initiated much earlier on the basis of clinical suspicion. Abundant plague bacilli may be observed in stained smears of material aspirated from buboes, in peripheral blood, or in sputum (Simpson 1905). These procedures are recommended. However, the hazardous nature of these clinical materials must be emphasized.

Buboes usually are found only when the infection is acquired by fleabite or mechanical irritation. Tularemia may also be suggested by the presence of buboes; in serological studies of suspected cases of that disease, 4.5 percent could be diagnosed retrospectively as cases of plague (Sites, Poland, and Hudson 1972). Buboes usually are heralded by severe pain in the area where they will appear. The bubo itself will usually become palpable or visible within 24 hours. The pain is intense, and even a nearly comatose patient attempts to reduce pressure on the area and shield it from trauma. The lightest touch may elicit exquisite pain, which is characteristic, but occasional patients have only moderate tenderness. The position of the body usually gives an immediate clue as to the location of a bubo—for example, hip partially flexed for groin buboes or patient supine with arm held away from body for axillary buboes.

The most common location for a bubo is in the groin, involving inguinal or femoral nodes (fig. 46) or both. These lesions comprise over half of those seen. Axillary and cervical glands (fig. 47) are next in frequency of involvement, accounting for another quarter to a third of cases. Virtually all lymph nodes of the body, including intrathoracic and abdominal nodes, are possible sites. Involvement of the latter may result in "acute surgical abdomen"; there are numerous records of patients operated on for this reason. As a bubo enlarges and suppurates, both pain and tenderness decrease. Swollen anterior cervical nodes and

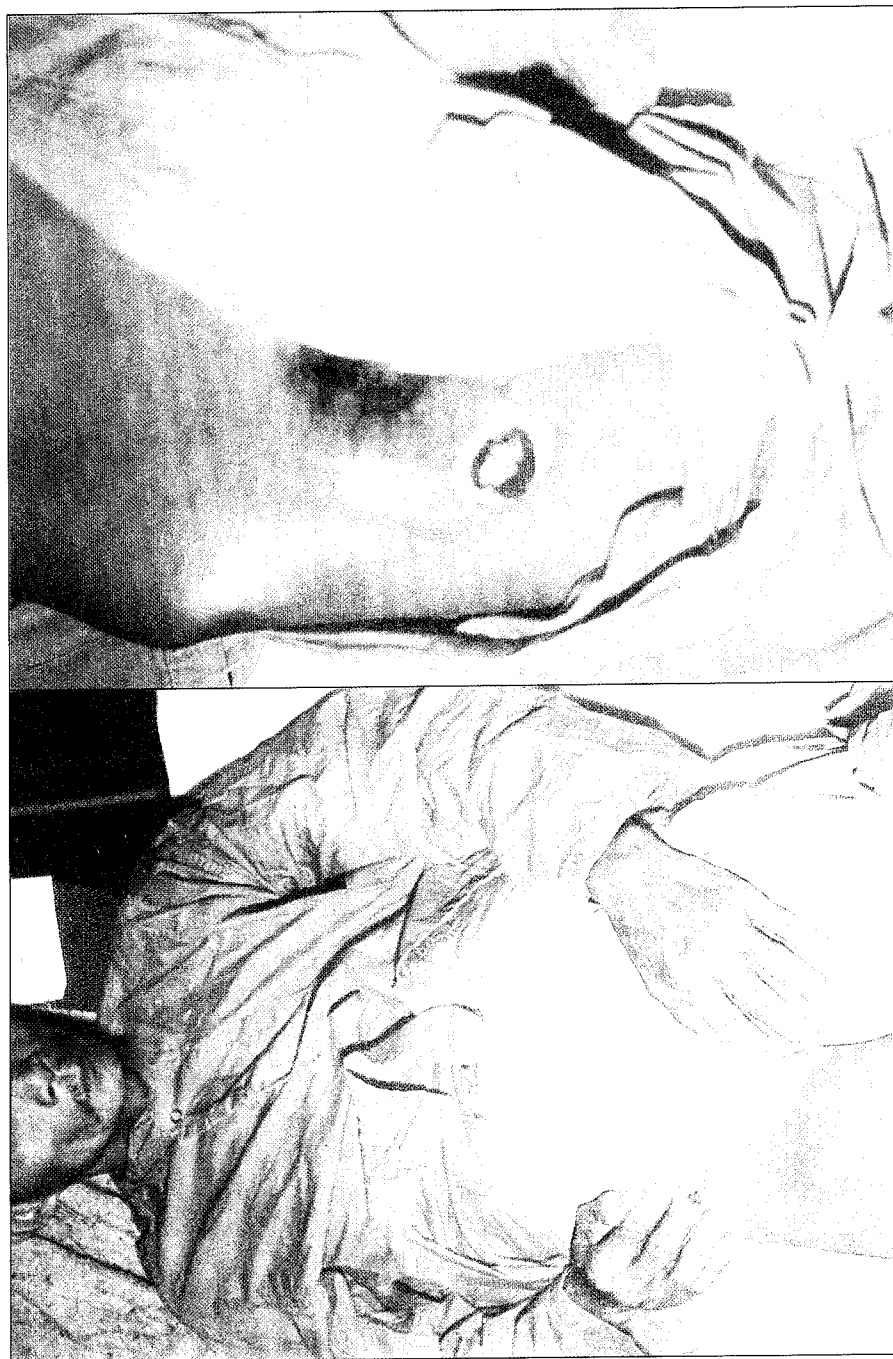


FIGURE 46.—Left: Typical femoral bubo as observed in Vietnam. Right: Femoral bubo showing drainage and early healing.



FIGURE 47.—Axillary bubo observed in acutely ill Vietnamese patient.

associated edema can cause sufficient pressure on the trachea to result in respiratory embarrassment or even death.

Multiple buboes are not uncommon, although they may not be obvious, as in the case of iliac buboes secondary to inguinal buboes. Buboes may appear simultaneously at widely separated sites or may develop secondary to a primary bubo along the line of lymph drainage. Bilateral cervical buboes suggest pharyngeal and tonsillar involvement. Pharyngeal or tonsillar plague may produce classical buboes or may result in large swollen nodes similar to those seen in other severe bacterial infections, in which case misdiagnosis may occur. A pseudodiphtheritic membrane can also occur and cases may be misdiagnosed as diphtheria (Simpson 1905).

Bubonic plague is observed in all degrees of severity ranging from pestis minor or ambulatory plague, which may be self-limited, to severe disease in which a febrile and relatively toxic, though alert, patient may be moribund in a few hours. The gravity of the case appears to be correlated with the degree of altered mentation and restlessness, depression, anxiety, and distress ("peste facies" or delirium and coma). Pneumonia and sepsis are grave manifestations. Observation of plague bacilli in smears of peripheral blood is a basis for a poor prognosis.

The most dreaded form of plague is that which involves the lungs. Pollitzer (1954, pp. 440-41) distinguishes three forms: one involving development of well-marked pneumonic foci with consolidation and all the signs of bacterial

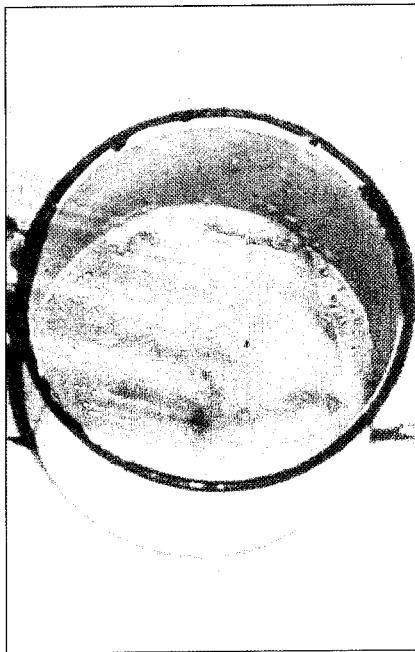


FIGURE 48.—Bloody sputum in advanced pneumonic plague. (Courtesy, Capt. F. R. McCrumb, MC.)

pneumonia; a transitory form with slight pneumonitis; and a form in which congestion and edema are marked and, although bacilli are found in the lower respiratory tract, no consolidation occurs. These are obviously partitions in a continuous spectrum of involvement but they are useful in classification. The first, the most severe form, is classic pneumonic plague. Primary pneumonic plague begins in the same fashion that severe bubonic plague does except that bubo pain does not appear. About 24 hours after onset of symptoms, a productive cough begins and a mucopurulent sputum rapidly changes to sanguinopurulent (fig. 48).

Hematogenous dissemination of the plague bacillus, as of any bloodborne pathogen, may result in the infection of any organ, leading to numerous complications. In some instances, especially in individuals receiving suboptimal therapy, purulent meningitis may develop. Primary plague meningitis without antecedent disease has occurred. Petechiae and ecchymoses can occur in such numbers and locations as to mimic severe meningococemia, and indeed the microscopic lesions (fig. 49) are almost indistinguishable. The pathogenesis is similar, probably involving a generalized Schwartzman reaction (Butler 1972, p. 274), and the prognosis is equally poor. Large ecchymosis or purpura, especially on the back, is a common feature of terminal pneumonic or septicemic cases. Purpura resulting in gangrene of the extremities has occurred in treated patients.*

*Col. Dan C. Cavanaugh, MSC: Personal observation.

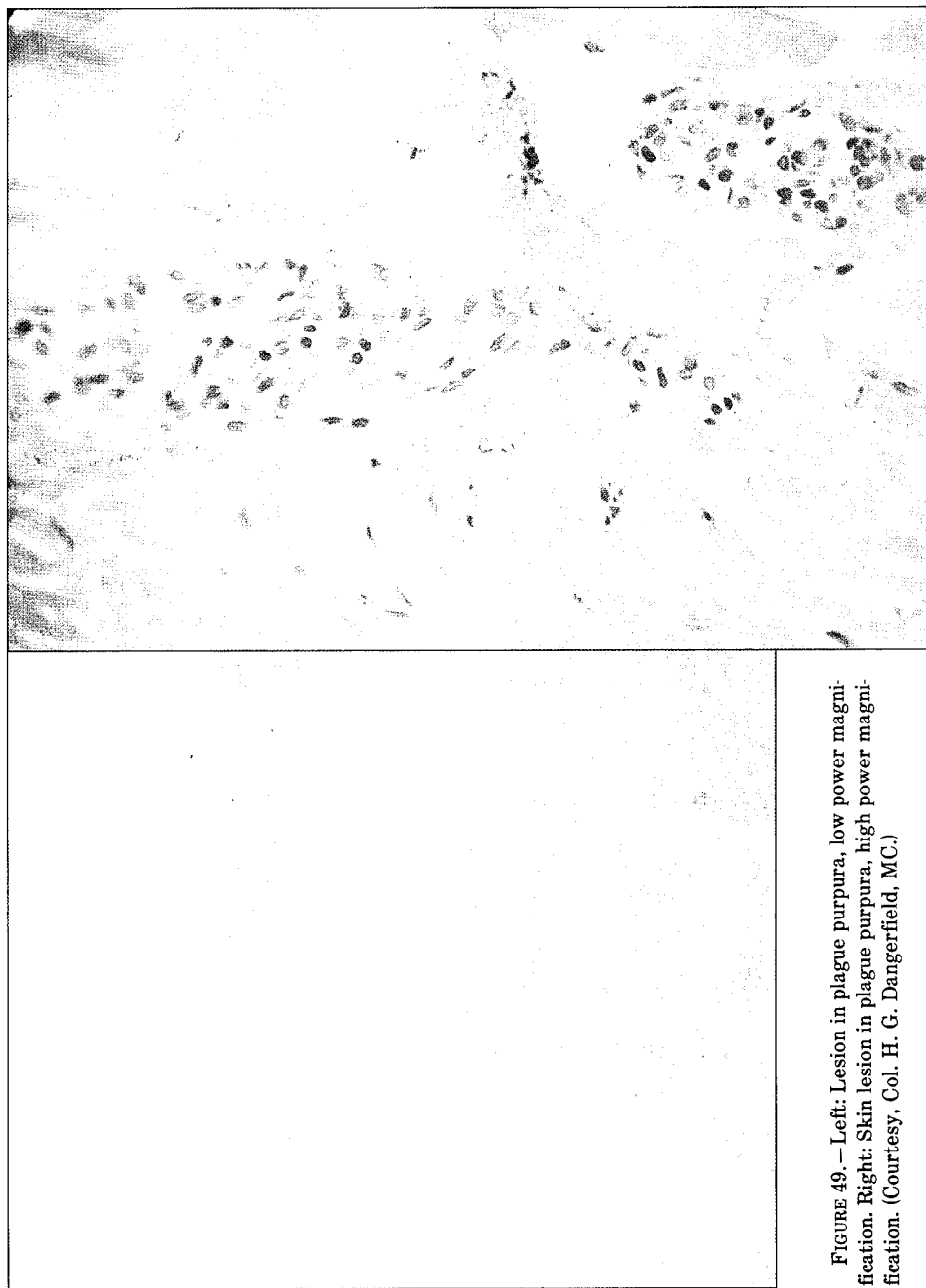


FIGURE 49. — Left: Lesion in plague purpura, low power magnification. Right: Skin lesion in plague purpura, high power magnification. (Courtesy, Col. H. G. Dangerfield, MC.)

At present, the preferred antibiotic therapy of the WHO (World Health Organization) Expert Committee on Plague is tetracycline. For the first 48 hours, this should be in large doses (4 to 6 g daily). It is better to use tetracycline in combination with streptomycin (0.5 g every 4 hours for 2 days, then 0.5 g every 6 hours until patient has improved). Chloramphenicol (50 to 75 mg/kg daily to a total dose of 20 to 25 g) can be substituted for tetracycline if indicated. The committee recommends sulfonamides not be used if any of the above antibiotics are available. This regimen should be followed for at least 10 days, and then throat and blood cultures should be repeated (WHO-a). Legters, Cottingham, and Hunter (1970, p. 651) have shown that, despite clinical cure and demonstrated sensitivity of the organisms to the drug used, bacterial cultures of the throat at 10 days may still be positive. Two reasons for therapy until cultures are negative are the possibility of a risk of spread from an asymptomatic carrier, and good evidence that plague meningitis not only occurs after "adequate" sulfonamide therapy for bubonic plague but may occur more frequently than in untreated cases (Landsborough and Tunnell 1947). There are not sufficient data to make the latter statement about meningitis following the antibiotic regimens suggested above, but the occasional persistence of *Y. pestis* in the throat certainly suggests the possibility of a similar situation.

Isolation procedures are probably unnecessary in bubonic cases without pulmonary involvement, except for care in handling blood and discharges from the buboes. Discretion is indicated, however, since early pulmonary involvement or throat infection may not be recognized. Except in epidemic situations, bubonic plague patients should be kept in a separate ward or room. On the other hand, rigidly enforced, strict isolation must be practiced for patients with pulmonary involvement until throat and sputum samples are free of *Y. pestis*. Many secondary cases of pneumonic plague have occurred in nursing and medical staff, despite precautions. Protection of the staff is not limited to gowns, masks, and gloves but should include a safeguard for the eyes; Pollitzer (1954, pp. 431-34) lists seven reported cases in which the eye seemed to have been the portal of entry. Eyeglasses may be sufficient, but a shield is preferable.

Personnel may become infected via broken skin, mucous membranes, or the respiratory tract through accidents in the laboratory or when taking specimens. Manipulations with pipettes or syringes are particularly hazardous. There is a particular requirement to keep laboratory animals free from ectoparasites, especially fleas. Adequate identification of *Y. pestis* can be carried out at the clinical laboratory level, but this is not recommended because of the hazard involved. Suspicious cultures or specimens should be forwarded as quickly as possible to laboratories that are completely equipped to accomplish timely identification. Immediate reports to public health authorities are mandatory.

LABORATORY DIAGNOSIS

The laboratory diagnosis of plague infection is made by the isolation of *Y. pestis* from buboes, blood, or sputum. In addition, epidemiological studies often require the isolation of *Y. pestis* from rodent tissue or from fleas.

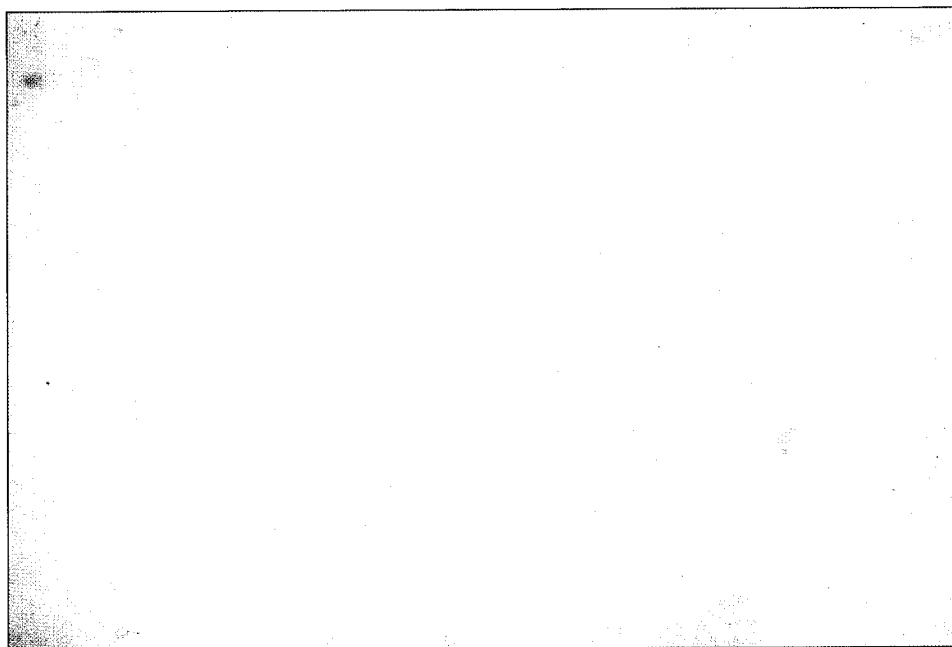


FIGURE 50.—Plague bacilli in clinical specimen of peripheral blood, Wayson stain. (Oil immersion.)

Smears of clinical material can be prepared under almost any circumstance, and the value of this procedure cannot be overemphasized. The plague bacillus can be demonstrated, often in great numbers, in specimens collected from patients. Smears of material aspirated from buboes, peripheral blood, and sputum are prepared, dried, fixed with alcohol (absolute methanol for 5 minutes), and then stained. While the Gram's stain is adequate to show the presence of gram-negative bacilli, Giemsa or Wayson stains are recommended for the demonstration of classical bipolar coccobacilli in the specimen (Poland 1972, p. 1141) (fig. 50). The organisms show pleomorphism.

In the laboratory, nutrient agar, blood agar and desoxycholate agar plates (particularly valuable when dealing with sputum specimens), and broth media should be routinely inoculated. Highly contaminated specimens, as well as most specimens of rodent tissues and fleas, should be given a preliminary passage through experimental animals before cultural isolation is attempted.

Following is a summary of the characteristics of *Y. pestis* which aid in the laboratory diagnosis of plague.

Microscopic Morphology

Yersinia pestis is a bipolar staining coccobacillus, 0.5 to 0.7 by 1.5 to 1.75 microns. Organisms usually occur singly or in pairs and are extremely pleomorphic. *Y. pestis* is gram-negative, nonacid-fast, and nonspore-forming. It is non-

motile in semisolid media. A capsule can be demonstrated in wet india ink preparations observed by dark field or by fluorescent antibody tests (Pollitzer 1954) when bacilli are incubated at 37° C. The demonstration of a capsule with fluorescent antibody tests (Moody and Winter 1959) is presumptively diagnostic, but absolute identification requires the cultural isolation of *Y. pestis*. Certain nonencapsulated variants of *Y. pestis* isolated from patients (Winter, Cherry, and Moody 1960) and some surface antigens of the closely associated *Y. pseudotuberculosis* (Quan et al. 1965) present problems and indicate that fluorescent antibody tests should be interpreted with some caution.

Animal Pathogenicity

The organism is virulent for white mice, white rats, guinea pigs, and other rodents by the cutaneous, subcutaneous (recommended), intraperitoneal, and intranasal routes. White mice should not be used for tests with sputum. Post-mortem examination of mice usually shows buboes and marked splenic enlargement with other nonspecific signs of generalized infection. The infection in rats and guinea pigs produces changes quite characteristic of plague: subcutaneous congestion, buboes in corresponding regional lymph nodes, enlargement of the spleen and liver with necrotic nodules, and pneumonic foci in the lungs (Baltazard et al. 1956). *Y. pestis* is observed in abundance in direct smears from all tissues. Certain strains of *Y. pestis* isolated from patients in Brazil are virulent for white mice but not for guinea pigs (Burrows and Gillett 1971).

Cultivation

Metabolism is aerobic or facultatively anaerobic. Optimal temperature is 28° C, with a range of 0° to 43° C; elaboration of the specific Fraction I capsular antigen requires incubation at 37° C. In broth, 24 hours at 37° C produces moderate growth with little or no turbidity. Floccular or granular deposit swirls up and disperses evenly, although not always completely, with shaking. Blood cultures should be subcultured on solid media after 48 hours. On agar media, 24 hours at 37° C produces very small 0.1- to 0.2-mm mucoid colonies, usually visible only in the initial streak. At 48 hours, colonies are considerably larger, 1 to 2 mm. With prolonged incubation, colonies continue to grow and assume a beaten copper surface. The center of the colonies is raised, and the periphery is flat with an umbonate edge. Older colonies often assume a "fried egg" configuration. Growth on desoxycholate agar does not appear until the second day, when small, reddish, pinpoint colonies are observed. Gelatin stab shows good filiform growth, confluent at top and discrete below, extending to the bottom of the stab line. No liquefaction occurs in 7 days at 22° C (Pollitzer 1954).

Biochemical Characteristics

No hemolysins are produced, although certain strains occasionally produce some "greening" of blood media. The organism is catalase positive and H₂S

negative, and indole is not produced. *Y. pestis* is coagulase specific, rapidly coagulating citrated rabbit and guinea pig plasma in tests conducted at temperatures less than 27° C. Fibrin clots are rapidly destroyed by *Y. pestis* incubated at temperatures in excess of 28° C. *Y. pestis* is oxidase negative, and variable results with nitrate reduction tests are used to differentiate variants. The organism is urease negative (one exception has been noted) and methyl red positive; methylene blue is not reduced (Baltazard et al. 1956, pp. 457-509). The Voges-Proskauer reaction is negative, and litmus milk remains unchanged (Pollitzer 1954).

Sugar Fermentation

Acid, but no gas, is produced from glucose, maltose, mannitol, and salicin. No fermentation of lactose, sucrose, rhamnose, and melibiose occurs. Variable results with glycerol are used to differentiate races.

Bacteriophage

The plague bacillus is lysed by a bacteriophage at temperatures ranging from 21° through 37° C. The lysis is specific for *Y. pestis* at 20° C; at temperatures in excess of 25° C, occasional strains of *Y. pseudotuberculosis* and *Escherichia coli* may demonstrate lysis in the bacteriophage tests (Cavanaugh and Quan 1953). Media containing blood should not be used in bacteriophage tests; some strains of *Y. pestis* are not lysed by bacteriophage when tested on blood agar plates. Plates of nutrient agar should first be seeded with *Y. pestis* before the application of individual drops of a bacteriophage suspension to the seeded area. Distinct plaques usually are visible in areas of otherwise confluent growth within 18 to 24 hours. Occasional variants of *Y. pestis* do not present a picture of complete lysis; scattered colonies of growth occur within the plaque.

Serological Identification

Demonstration of specific Fraction I antigen by gel diffusion precipitin techniques is diagnostic (Lawton, Fukui, and Surgalla 1960). Complement-fixing and hemagglutinating antibodies to the specific Fraction I antigen may be present in the serums of convalescent plague patients (Cavanaugh et al. 1970; Chen and Meyer 1954; Chen, Quan, and Meyer 1952). If available, specific Fraction I antiserums may be used in microslide agglutination tests to provide a rapid, presumptive identification of *Y. pestis* using selective colonies picked from blood agar as antigen.

PREVENTION

Plague is essentially an anthroponozoonosis, as the principal source of disease for man is contact with infected rodents and their flea ectoparasites. The attainment of a standard of living that allows the construction of ratproof buildings,

thus eliminating rat harborage, is the ideal means of long-term plague control. Unfortunately, this solution is not yet possible in many developing countries where urban plague exists.

Before World War II, the most important plague control measures were reducing the rat population and fumigating premises against fleas. A more rapid and direct method of flea control became feasible in the early 1940's with the introduction of chemicals such as DDT. The U.S. Army was the first to use DDT to control plague (in the African theater, 1944). A rational control program, however, should deal with both rodents and fleas. Specific actions for any area depend upon many factors, but in general, the control of bubonic plague involves interrupting the rodent-flea-man transmission cycle with pesticides and sanitation. By contrast, in pneumonic plague the man-to-man cycle of transmission by the respiratory route must be interrupted; therefore, casefinding, treatment of cases, and isolation and immediate treatment of contacts on the appearance of fever or other symptoms are the salient features of pneumonic plague control.

An epidemiological survey should be conducted to ascertain the source of the infection. Rodents and fleas should be collected and examined if possible. Serum surveys are particularly valuable in detecting plague foci in rodent populations (Cavanaugh et al. 1970, 1965; Rust 1971). Maps and graphs containing information derived from these investigations are valuable, but statistics of plague prevalence at district or state levels may be misleading. Study at the village level, block by block or house by house, may show that the disease is endemic throughout an entire area or that sharp, serious outbreaks are occurring in quite limited foci. The predominant clinical form of plague observed in the focus under consideration often is a valuable indication of possible sources of infection and thus of necessary preventive measures. For example, epidemics of bubonic plague usually are associated with commensal rats and fleas while epidemics of pneumonic plague often are associated with wild rodents or with individuals leaving wild rodent foci before the onset of clinical disease. A preliminary estimation of the number of patients involved and the total land mass or surface area of premises requiring control is logistically useful.

In controlling outbreaks of bubonic plague, the first and most important step is the selection of an effective insecticide. The spectacular success of insecticides such as DDT was short-lived; less than 10 years after their introduction, it became evident that fleas in many regions had developed resistance to them. Resistance to DDT may be anticipated where the pesticide has been employed for malaria eradication. The choice of insecticide is dictated by the results of susceptibility tests of the fleas in the area under consideration, but in emergency situations, an insecticide of known efficacy which has never been utilized in the area should be selected.

Insecticides are applied as dusts. Thorough coverage of rodent-frequented sites, particularly harborages and runways, is necessary. In houses, dust should be applied to the bottom of all walls and on floors for a distance of 15 to 30 cm from the walls. Where the wall-roof junction of the dwelling is open, it should be applied along the top of the walls and along rafters where rat runways are evident. Other areas which may provide food or shelter for rodents, both indoors

and outdoors, should be dusted. Retreatment may be required after a period of time, especially if nonresidual insecticides are used. The frequency of treatment cycles depends upon the insecticide and the conditions to which it has been subjected.

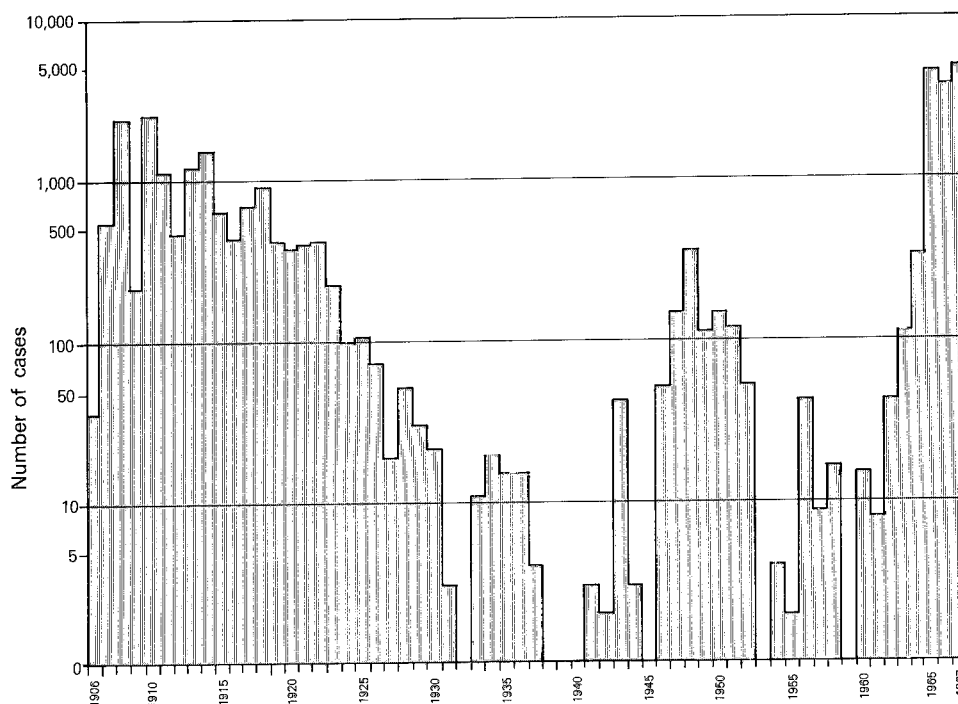
Rodents pick up insecticide dust on their feet, carry it back to their nests, and distribute it over their bodies through constant preening. Where the general application of dust may be hazardous, bait box techniques may be employed. Rodents entering locked bait boxes must pass through insecticide dust deposited in an outer foyer of the box to reach bait placed in an inner chamber. Both insecticides and rodenticides can be used (Kartman 1958, 1960).

Plague may persist in a rodent population in the absence of fleas by oral transmission, through cannibalism. Oral infection may play a significant role in the epidemiology of local plague epidemics by providing a mechanism for the persistence of the disease through interepidemic periods and may also account for sporadic cases of bubonic or pneumonic plague. Whenever possible, a coordinated program of rat abatement and flea control is recommended (Rust et al. 1972). Flea control, however, must be achieved before any rat poisoning activity, to prevent the appearance of large numbers of hostless rat fleas which may attack people and increase the prevalence of human plague.

In the control of wild rodent plague, the same considerations apply. The results of large-scale programs to eradicate or control the infection have been discouraging. Such programs demand large investments in personnel, equipment, and pesticides and, as a rule, while effective for short periods of time, do not achieve long-term control. Treated areas are soon repopulated with both rats and fleas and frequently demonstrate renewed enzootic or epizootic activity. Routine surveillance of such foci should indicate when control efforts are required. In some foci, in critical areas, routine control programs should be instituted either to reduce disease in man or to prevent the conveyance of infected rats and fleas into urban areas. Typical areas needing continual attention and control are: notorious foci in which index cases of large pneumonic plague epidemics were infected; environs of ports, airports, or towns; military camps; sites of large-scale construction of new settlements, roads, or railroads in endemic foci; and areas where a definite threat to agricultural or other workers exists.

An evaluation of the control program is mandatory. The incidence of bubonic plague should show a dramatic decline following a successful program. The rat flea population should be greatly reduced or almost eliminated within 48 hours, and a corresponding reduction in the prevalence of the disease in rats, estimated by bacteriological and serological evidence, should occur. Seasonal trends in individual foci should be taken into consideration to avoid interpreting normal seasonal declines as indicating a successful control program.

Modern means of transport, especially containerized cargo, provide new opportunities for fast and widespread dissemination. Fumigation with hydrogen cyanide or methyl bromide is useful in controlling rodents or ectoparasites which might be transported in various goods from infected areas. Complete kills of adult *X. cheopis* can be achieved within 24 hours by placing dichlorvos resin

CHART 8.—Incidence of human plague in the Republic of Vietnam, 1906 to 1 September 1967¹

¹ No data were available in 1932, 1938, 1939, 1940, 1945, 1953, and 1959.

Source: Cavanaugh, D. C.; Dangerfield, H. G.; Hunter, D. H.; Joy, R. J. T.; Marshall, J. D., Jr.; Quy, D. V.; Vivona, S.; and Winter, P. E. 1968. Some observations on the current plague outbreak in the Republic of Vietnam. *Am. J. Pub. Health* 58: 742-52.

strips (one per 9 m³) in each container before locking and sealing it for shipment. Rodents can be controlled by bait boxes containing anticoagulant rodenticides. Aircraft present special problems. Rodents should be trapped, as poisoned rodents may die in an inaccessible area vital to the function of the aircraft. Parking aircraft in rodent-free or ratproof areas and loading only disinfested cargo are helpful. Flea control on aircraft is best achieved through the use of aerosol insecticides (WHO-b).

Vaccination with one of the approved plague vaccines is recommended for individuals at risk of infection. The killed vaccines developed at the Haffkine Institute in Bombay and the USP vaccine developed at the George Williams Hooper Foundation of the University of California have proved to be effective in reducing the incidence of human plague; indirect evidence supports the conclusion that administration of the USP vaccine to troops in Vietnam was partly responsible for maintaining a remarkably low plague incidence there (Cavanaugh et al. 1974). Living, attenuated strains of *Y. pestis* used as vaccines in Java, Madagascar, and elsewhere have been credited with reducing plague morbidity and mortality. However, seed strains used in the preparation of these vaccines are subject to considerable variation when held in vitro, and vaccines

prepared from seed which is deficient in one or several antigens or virulence factors are likely to demonstrate diminished potency. Living plague vaccines prepared from seed having the requisite antigenic composition are also noted for reactogenicity (Meyer 1970).

VIETNAM EXPERIENCES

Vietnam has been recognized as a plague-endemic region for three-quarters of a century (chart 8). The period 1898-1920 was characterized by several sharp epidemics, with sporadic cases occurring between them. The incidence of the disease then declined, although plague was considered to be endemic in the coastal region around the city of Phan Thiet. During World War II, a recrudescence was observed when French Indochina was occupied by the Imperial Japanese Forces. Médecin General Roberts, of the French Medical Services, then considered Lang Bian Plateau to be an endemic area. The disease apparently had moved along the coast to the north of Phan Thiet and branched off in the general area of Phan Rang toward Da Lat (Cavanaugh, Dangerfield, et al. 1968).

Following the departure of the French forces from Vietnam as a result of the Indochina War, the political situation deteriorated. In all likelihood, public health also was neglected during this period, resulting in conditions favorable for the development of plague in territories surrounding previously established natural foci. After the cessation of monsoon rains in 1962, a disease characterized by fever, lymphadenopathy, and high mortality was reported near the cities of Nha Trang and Saigon. It soon occurred in the population of Nha Trang, and one American serviceman became infected in 1963. A suspicion that the disease was plague was confirmed when *Yersinia pestis* was isolated from the serviceman and several Vietnamese patients through bacteriological studies at l'Institut Pasteur in Nha Trang (Cavanaugh, Dangerfield, et al. 1968; Feeley and Kriz 1965).

A committee consisting of personnel from the South Vietnam Ministry of Health, the United States and Vietnamese military, and USOM (U.S. Operations Mission) was formed to evaluate and deal with the plague emergency. Personnel and facilities of the 7th Medical Laboratory, Nha Trang, under the command of Maj. Eugene J. Feeley, MC, were used in diagnostic and field studies. Control measures, chiefly vector control with DDT, were initiated in and around the plague foci by the appropriate Vietnamese authorities. The U.S. military promptly began standard plague control measures, including vaccination with a killed plague vaccine.

Correspondence between concerned parties led to a decision to deploy in Vietnam a medical research team from WRAIR (Walter Reed Army Institute of Research). The mission assigned to the team by Col. (later Brig. Gen.) William D. Tigertt, MC, Commandant, WRAIR, was to establish a laboratory which could support various investigations. In October 1963, the initial contingent arrived in Saigon. Led by Lt. Col. (later Col.) Paul E. Teschan, MC, the team rapidly developed protocols for the study of plague, as well as cholera, diarrheal

diseases, dengue, and hepatitis. A Joint Committee for Pathological Research was established, which brought together the Vietnamese health authorities, AID (Agency for International Development), and the U.S. military services. The protocol for proposed plague studies was presented to and accepted by this committee (Cavanaugh, Do-Van-Quy, and Ky-Vinh-Thai 1964).

In 1964, the only plague research laboratory in Southeast Asia was established. The joint facilities of l'Institut Pasteur of Vietnam and the WRAIR team were used in both field and laboratory studies. Various other agencies, American and Vietnamese, civilian and military, supported the program, particularly the Army 20th Preventive Medicine Unit, Saigon, and the Navy Preventive Medicine Unit, Da Nang. At the plague research laboratory, the extent and severity of plague in Vietnam were documented. Studies pertaining to plague control were actively pursued, and information was transmitted to military and civilian health officials as rapidly as it was generated. The disease did not become a major problem for U.S. military forces.

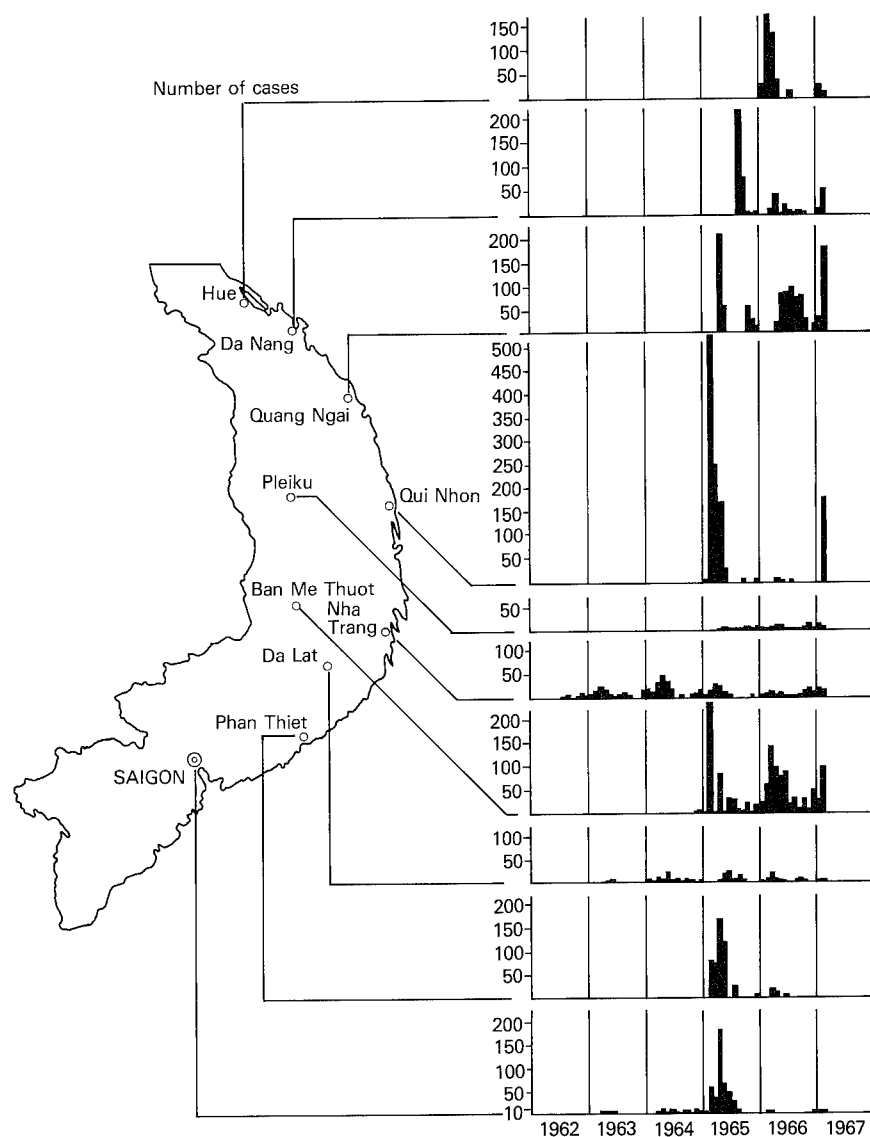
Control efforts in the Vietnamese sector were less successful. Plague continued to appear among the Vietnamese population in the city of Nha Trang during 1963, when *Y. pestis* was isolated from 85 of 186 patients tested (46 percent), and 1964, when it was isolated from 208 of 398 patients tested (52 percent) (Cavanaugh, Dangerfield, et al. 1968). Sporadic cases of plague occurred in and around Saigon during the same period. Succeeding years presented a picture of steady progression of the disease to new territories (chart 9 and maps 4 and 5).

Fortunately, broad spectrum antibiotics were available, and a majority of treated patients survived the infection (Cavanaugh et al. 1970; Cavanaugh, Dangerfield, et al. 1968; Marshall et al. 1967). The invaluable observations made by U.S. civilian and military physicians aiding the Vietnamese in the plague emergency provided a sound basis for the management of this fulminating disease (Cutting et al., pp. 1096-98; Burkle 1973; Butler 1972).

The predominant clinical form of the disease in Vietnam in the 1960's was fleaborne bubonic plague (Cavanaugh, Dangerfield, et al. 1968; Marshall et al. 1967; Nguyen-Van-Ai 1963). Brief, sporadic outbreaks of pulmonary plague were observed (Legters et al.; Pham-Trong, Tran-Quy-Nhu, and Marshall 1967). Virulent plague bacilli also were isolated, on occasion, from the throats of asymptomatic contacts of plague patients, providing evidence of the occurrence of asymptomatic pharyngeal plague (Marshall, Quy, and Gibson 1967). However, the epidemiological significance of the asymptomatic pharyngeal patient was, and is as yet, obscure, as no evidence of transmission of *Y. pestis* by such individuals has been obtained (Marshall, Quy, and Gibson 1967; Legters, Cottingham, and Hunter 1970, p. 651).

A localized outbreak of fulminant pulmonary infection was observed near Rach Gia in which the etiologic agent appeared to be either *Klebsiella pneumoniae* or *Y. pestis*, or perhaps both (Legters et al.). In another instance, pneumonic plague was diagnosed in an American AID employee. The individual had traveled throughout Vietnam as a member of a team vaccinating Vietnamese civilians with an attenuated, live plague vaccine. He had received multiple inoculations of both killed and living plague vaccines before the onset of symp-

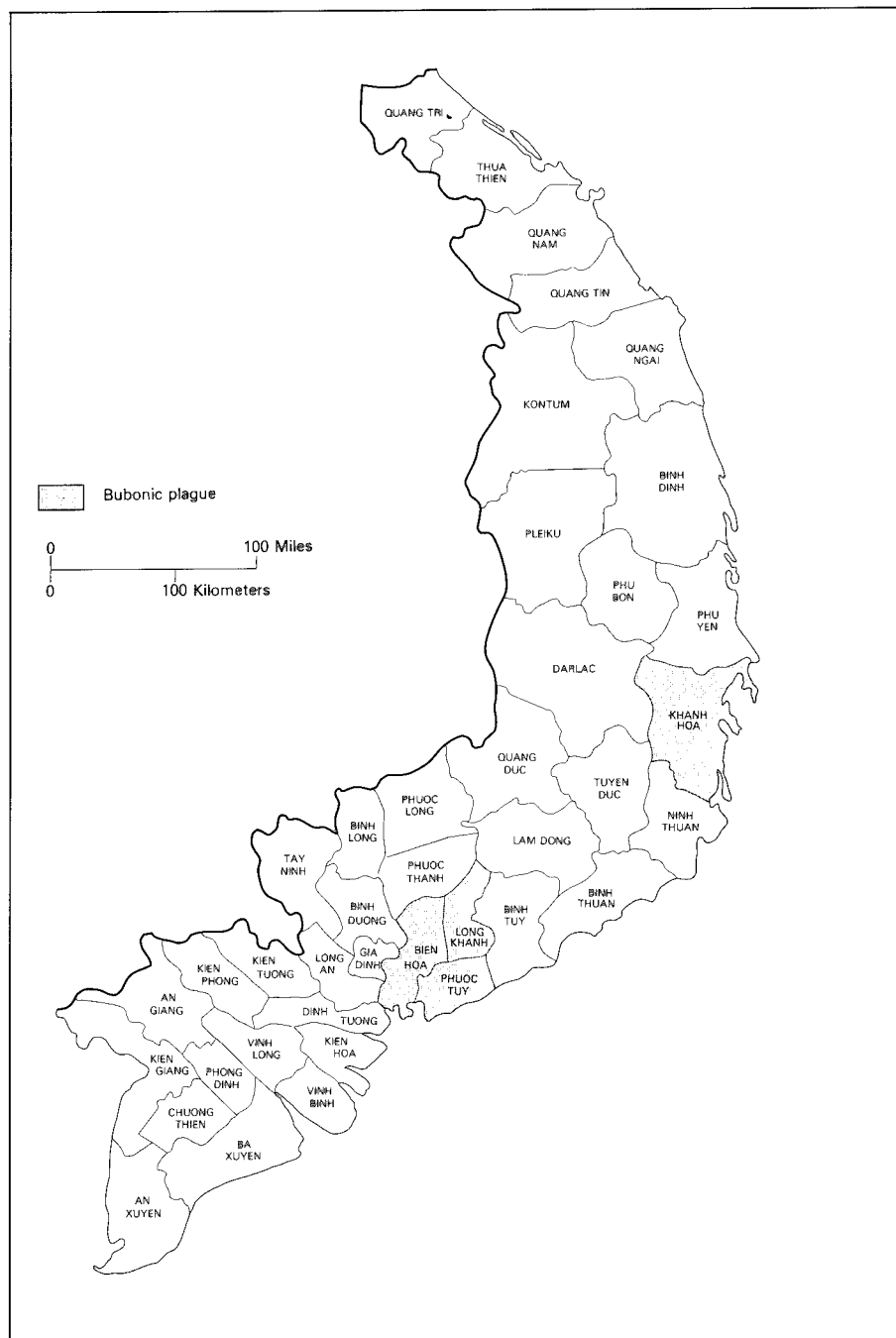
CHART 9.—Major plague outbreaks in the Republic of Vietnam, 1962-67



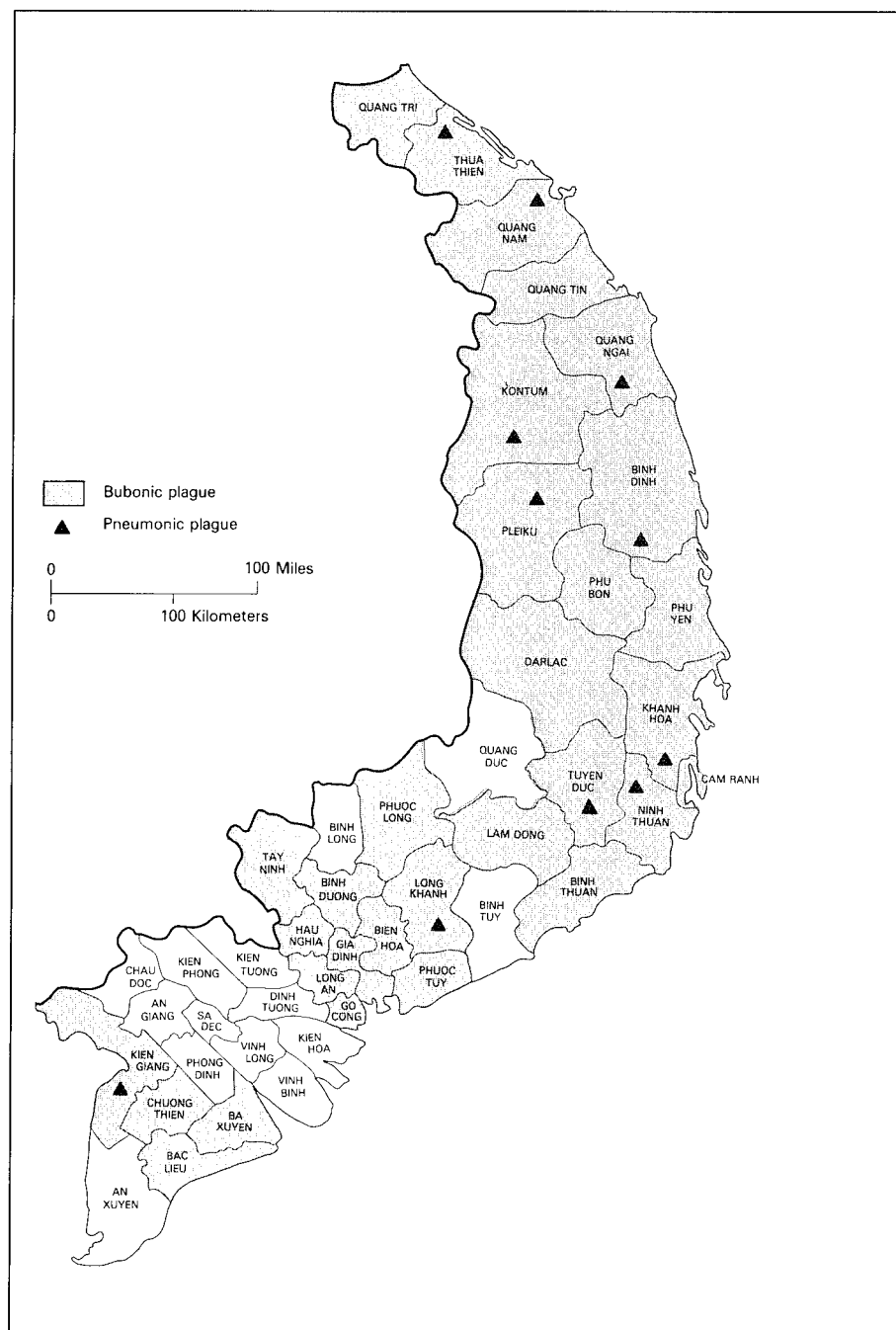
Source: Cavanaugh, D. C.; Dangerfield, J. G.; Hunter, D. H.; Joy, R. J. T.; Marshall, J. D., Jr.; Quy, D. V.; Vivona, S.; and Winter, P. E. 1968. Some observations on the current plague outbreak in the Republic of Vietnam. *Am. J. Pub. Health* 58: 742-52.

toms. His case history was not classical, in that the onset of serious symptomatology took several days, and he had an uneventful recovery following the administration of specific therapy (Cohen and Stockard 1967).

The broad spectrum antibiotics were freely available throughout South Vietnam, but numerous species of bacteria, in particular the enteric pathogens, had developed resistance to the majority of these drugs (Vivona et



MAP 4.—Extension of the human plague epidemic in the Republic of Vietnam, 1962. (Cavanaugh, D. C.; Dangerfield, J. G.; Hunter, D. H.; Joy, R. J. T.; Marshall, J. D., Jr.; Quy, D. V.; Vivona, S.; and Winter, P. E. 1968. Some observations on the current plague outbreak in the Republic of Vietnam. *Am. J. Pub. Health* 58: 742-52.)



MAP 5.—Extension of the human plague epidemic in the Republic of Vietnam, 1967. (Cavanaugh, D. C.; Dangerfield, J. G.; Hunter, D. H.; Joy, R. J. T.; Marshall, J. D., Jr.; Quy, D. V.; Vivona, S.; and Winter, P. E. 1968. Some observations on the current plague outbreak in the Republic of Vietnam. *Am. J. Pub. Health* 58: 742-52.)

al. 1966). Because of fear that heavy and sustained antibiotic pressure would result in the selection of antibiotic resistant *Y. pestis*, all plague strains isolated in Vietnam were screened to detect resistance as rapidly as possible. However, aside from a few strains, antibiotic resistant plague bacilli were not a problem (Marshall et al. 1967a). Moreover, strains which exhibited some resistance to streptomycin remained sensitive to other antibiotics (McCrumb, Larson, and Meyer 1953). Some problems in evaluating the clinical response to streptomycin therapy occurred; several patients remaining febrile following treatment were found to be suffering from concomitant typhoid fever which was then effectively treated with chloramphenicol.

Information was gathered on animal reservoirs of plague in Vietnam. Tissue pools from 22,144 small mammals and pools of their flea ectoparasites were examined for infection with *Y. pestis* (Cavanaugh, Ryan, and Marshall 1969). In addition, the serums of many rodents were tested for specific antibody to the Fraction I antigen. In coastal urban areas, four mammals were determined to be important in the epidemiology of plague: *Rattus exulans*, *R. norvegicus*, *R. rattus*, and *Suncus murinus* were infected at a frequency of about four *Y. pestis* isolations per 1,000 animals tested. A number of isolations and seropositives suggested that sylvatic rodents as well as urban rodents were involved (Cavanaugh et al. 1970; Cavanaugh, Dangerfield, et al. 1968; Marshall et al. 1967a, 1967b; Cavanaugh, Ryan, and Marshall 1969; Cavanaugh, Hunter, et al. 1968; Marshall, Currie, and Quy 1968; Van Peenen et al. 1970).

The Oriental rat flea, *Xenopsylla cheopis*, the classic vector of plague bacilli, was the principal flea ectoparasite. Over 99 percent of the fleas collected were *X. cheopis* (Cavanaugh, Dangerfield, et al. 1968, p. 748; Cavanaugh, Ryan, and Marshall 1969; Stark 1971). Other fleas collected included *Xenopsylla astia*, *X. vexabilis*, *Ctenocephalides felis felis*, *C. canis*, *C. felis orientis*, *Stivalius klossi*, *S. aporus* subspecies, *Leptopsylla segnis*, and *Macrostylophora* species (Stark 1971).

Bacteriologic and serologic studies performed on specimens collected from trapped rodents indicated that enzootic plague was present in the *R. norvegicus* population of Saigon for several years. Scattered and sporadic cases of plague occurred from 1962 to 1967, excepting the first half of 1965, which was characterized by a rather sharp epidemic of bubonic plague. DDT was used in control efforts in 1965, but by the time supplies of this insecticide were available, the epidemic (and rodent epizootic) was already in decline. Insecticide treatments did not prevent the reappearance of enzootic plague in Saigon, suggesting that DDT was not effectively controlling fleas (Hunter and Dangerfield 1967). Both bacteriologic and serologic evidence demonstrated that extensive enzootic plague could be present in an urban locale without overt human epidemics (Cavanaugh et al. 1970).

In contrast to Saigon, which experienced an epidemic only once in 6 years, Nha Trang experienced plague annually. In Saigon, isolations of *Y. pestis* were obtained more frequently from fleas than from rodent tissues during the epidemic year, while in endemic years, the reverse was true. The isolation rate for *Y. pestis* from rats collected in Nha Trang was approximately 10 times

greater than the rate in Saigon, and the isolation rate from fleas was approximately 20 times greater. While flea indices in Saigon were somewhat depressed during the endemic years, flea populations in Nha Trang were always high from January to May. Temperature conditions in Nha Trang were also more favorable for the flea transmission of *Y. pestis* from rat to man than they were in Saigon. As conditions for flea transmission were not always favorable in Saigon, studies were undertaken to determine how plague could persist in the rodent population. Cannibalism among rodents appeared to be a reasonable possibility, and was confirmed by subsequent experimentation (Rust et al. 1972).

DDT was initially used throughout Vietnam for flea control without apparent success. Aliquots of DDT from available stocks were submitted for analysis to Geigy, a Swiss chemical company, and found to be entirely as specified.*

When tested by WHO methods, the fleas collected in Saigon and Nha Trang were shown to be resistant to DDT but sensitive to other insecticides (Cavanaugh, Dangerfield, et al. 1968). These observations prompted a program to collect fleas in other plague foci and test them for insecticide resistance. Collecting trips often were possible only during periods when the flea population was at a seasonal low, so colonization of the new fleas that could be collected was required to provide sufficient numbers for the tests. A method for establishing flea colonies in the field was developed (Cavanaugh et al. 1972), and tests indicated that sensitivity to DDT varied from one focus to another.

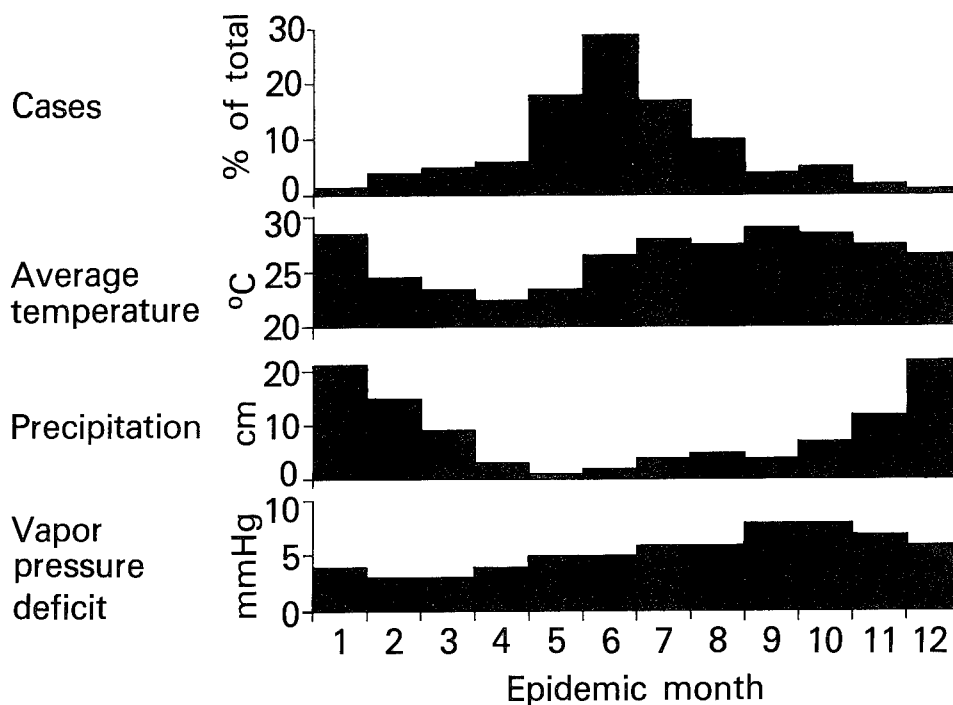
These tests resulted in the selection of the organophosphate insecticide diazinon for use in the plague control programs of the U.S. Army in Vietnam. This insecticide was used in a program in which results could be fully evaluated, and prompt control was achieved (Legters, Cottingham, and Hunter 1970, pp. 640-41). One difficulty in relying upon a nonresidual insecticide for flea control may have been elucidated by this study. A recrudescence of the infection occurred 3 weeks after the application of diazinon, indicating that the insecticide had a rather short half-life. New flea populations might have become infected by feeding on rodents which were bacteremic long after infection by fleabite or which had been infected by some other mechanism. Reinfestation of the area by the immigration of infected rodents was also a possibility. Reapplications of diazinon were required to control this second outbreak. Areas controlled with organochlorine insecticides, noted for their residual effects, had not experienced such problems.

As in epidemics of bubonic plague in India (Rogers 1928), distinct plague seasons were noted in Vietnam. However, the seasons varied from locale to locale and appeared to be related to climate (Cavanaugh and Marshall 1972).

The prevalence of plague in Vietnamese civilians and murine typhus in Americans showed a close relationship to the abundance of *X. cheopis*, the vector for both diseases in the coastal lowlands. Analysis of the climate in foci

*Col. Dan C. Cavanaugh, MSC: Personal communication to Dr. M. Giaquinto, 1965.

CHART 10.—Relationship between the occurrence of plague and various climatic factors in the coastal lowlands of the Republic of Vietnam, 1962-66



Source: Cavanaugh, D. C., and Marshall, J. D., Jr. 1972. The influence of climate on the seasonal prevalence of plague in the Republic of Vietnam. *J. Wildlife Dis.* 8: 85-94.

located in the coastal lowlands, where the majority of cases were reported, provided the composite shown in chart 10. The sixth month was the month of peak plague prevalence. Epidemics began at the end of the rainy seasons and later appeared to regress as temperatures exceeded 27.9° C. Periods of low plague prevalence were marked by high temperatures, high vapor pressure deficits, or high precipitation. Possibly many fleas were drowned when exposed to heavy rainfall in poorly drained locales. Definition of plague seasons in the various foci was useful in forecasting periods of high risk and in coordinating requirements for control programs.

Plotting the results of bacteriological examinations was useful. House-by-house or street-by-street plots showed that, in established foci, the disease occurred at random throughout the entire endemic districts, as, for example, in Nha Trang (Cavanaugh, Dangerfield, et al. 1968). In cities experiencing initial plague outbreaks, plotted data clearly showed pathways of dissemination and probable mechanisms of distribution. Such a pattern was observed in Hue, where canal boats apparently carried infected rats and fleas from one locale to another (Marshall et al. 1967). Retrospective epidemiological studies confirmed the dangerous potential of individuals infected with pneumonic plague who travel from one locale to another (Pham-Trong, Tran-Quy-Nhu, and Marshall

1967). The use of bacteriological data in this manner identified areas requiring immediate attention and areas requiring protection against the introduction of disease.

Inquiry into circumstances surrounding index cases of plague in newly established foci produced limited though convincing evidence that the transportation of infected rats and their ectoparasites contributed to the spread of plague in Vietnam. In the months just preceding the initial outbreak in Qui Nhon, the aftereffects of a devastating typhoon required emergency food shipments from Saigon, where plague was present. The rice received from that city, showing gross evidence of rat infestation, was stored in a warehouse where plague-infected rats were collected within a few days. Soon, cases of plague were noted in surrounding areas. In Ban Me Thuot, the index case was a merchant, just returned from Nha Trang with a load of goods. In Dak To, suspicion was directed toward a specific air shipment of rice for indigenous troops that was dispatched from Nha Trang. These observations and the fact that inspectors of the NCDC (National Communicable Disease Center) Foreign Quarantine Program began finding *R. exulans* in an increasing number of ships and aircraft returning to the United States from Vietnam (Pratt 1967) resulted in cargo fumigation for military materiel to prevent the introduction of the disease into other areas, including the United States.

Concern that new episodes of plague abroad arose as a result of the Vietnamese epidemics soon prompted intensive study. New outbreaks of plague occurred in Java in 1968 (Velimirovic 1972) and in Yemen in 1969. In the United States, the plague bacillus was isolated from tree squirrels in Denver, Colo., in 1968 (Hudson et al. 1968) and from rat fleas in Tacoma, Wash., in 1971 (Hudson et al. 1973). However, plague bacilli isolated in Yemen proved to be the classical variant for the area. Dr. B. W. Hudson and his associates (1973), using acrylamide gel electrophoresis, were able to demonstrate that bacilli isolated in the Javanese focus and in the United States were in many instances unique and separate from Vietnamese strains. Furthermore, the epizootic that occurred in Denver was in tree squirrels only, with the exception of one human plague case. Other species of carnivores and rodents in the same area remained uninvolved. In Tacoma, all evidence indicated that commensal rodents in only one small area were infected. Preventive medicine personnel on military installations adjacent to both Denver and Tacoma cooperated fully in these investigations, collecting and examining rodents on military properties for evidence of disease, with entirely negative results. Thus, it can be concluded that the measures taken to prevent dangerous infestation of military cargo returning from Vietnam were successful.

American personnel lived and fought in Vietnam under conditions which brought them into intimate contact with plague-infested rodents and fleas. On several occasions, the plague bacillus was isolated from rats and fleas collected in the cantonment area of Cam Ranh Bay, where numerous cases of murine typhus were encountered. While plague was diagnosed in fewer than a dozen Americans throughout Vietnam and documented only in eight (Cavanaugh et al. 1974), obviously exposure to plague occurred on numerous occasions. For exam-

ple, examination of acute and convalescent serums from a number of hospitalized murine typhus patients demonstrated rising titers to specific *Y. pestis* antigens in 7 of 58 patients. The infrequent occurrence of clinical plague in Americans in Vietnam inspired confidence in the killed plague vaccine used; there is, indeed, considerable evidence that killed plague vaccines are highly effective protection against bubonic plague (Bartelloni, Marshall, and Cavanaugh 1973; Meyer, Smith, et al. 1974; Marshall, Bartelloni, et al. 1974; Marshall, Cavanaugh, et al. 1974; Cavanaugh et al. 1974).

While the American authorities used a killed vaccine, the Vietnamese authorities employed the live, attenuated *Y. pestis* EV strain in their control programs. This vaccine, as developed and used by the French scientist, Girard (1963), was of extreme value in Madagascar, where it was credited with a great reduction in plague morbidity. Similar results were not obtained in Vietnam. Logistical considerations, including production and delivery on the scale necessary for use within a limited time frame, a requirement for careful refrigerated handling during shipment, and the coordination of vaccine campaigns, all made the mass utilization of the EV vaccine difficult. Facilities for the lyophilization of these vaccines probably would have obviated these difficulties; equipment could have been purchased and Vietnamese trained for the purpose. Unfortunately, numerous technical problems that could not be resolved on an emergency basis occurred, but a freeze-drying facility was completed just before the departure of the WRAIR team from Vietnam.

Subsequent laboratory studies revealed that several variants of the EV strain differed in their capacity to evoke a satisfactory immunogenic response in man and laboratory animals (Meyer 1971). Strains with the greatest immunogenic potential were also exceedingly reactogenic and, indeed, potentially dangerous (Meyer 1971; Meyer, Cavanaugh, et al. 1974).

Observations that were made in the course of the Vietnamese experience are still stimulating studies throughout the world. While the United States experienced little difficulty in suppressing the disease in American personnel, the picture in the Vietnamese population was far different. The many problems involved in plague control, which is very expensive, were aggravated by the war and civil unrest, by early failures of insecticides to limit the territorial spread of the disease, and by the need to develop policy on a day-to-day basis as facts concerning the complexity of the local situation emerged. The United States was indeed fortunate in having the disciplined, highly trained organization of Army Medical Department specialists capable of quick response in a wartime environment.

LESSONS LEARNED

In future plague emergencies, knowledge of the resistance of local fleas to various insecticides will be valuable, as will information on where adequate stocks of pesticide may be procured. Information on effective rat abatement procedures is also indicated; rat control might be of particular importance in a wartime situation such as existed in Saigon. Research on methods of rat con-

trol, other than improvements in local socioeconomic conditions, should be encouraged. Studies on the efficacy of various vaccines in preventing the pneumonic form of the disease should receive support. While the results on specific therapy for the plague patient are gratifying, the situation for those who procrastinate in seeking treatment is often hopeless. Studies on the pathophysiology of disease should continue to seek solutions to the problems encountered in dealing with these patients. Finally, surveillance, to alert authorities to the development of potentially hazardous enzootic or epizootic plague, should be continued in areas where the disease has occurred on previous occasions.

Section II. Melioidosis

Colonel William L. Moore, Jr., MC, USA

Melioidosis is an infectious disease of man and animals, endemic in tropical zones, particularly throughout Southeast Asia. It is caused by the gram-negative organism, *Pseudomonas pseudomallei*, a natural saprophyte which can be isolated from market produce, soil, rivers, ponds, drainage ditches, and rice paddies throughout endemic zones but is found more commonly in areas of human habitation (Chambon 1955; Strauss, Jason, and Mariappan 1967; Strauss, Groves, et al. 1969; Joubert and Phung Van Dan 1958; Fournier and Chambon 1958, pp. 7-24).

HISTORY AND MILITARY SIGNIFICANCE

In 1911, while looking for cases of human glanders in Rangoon, Burma, a British medical officer, Capt. A. Whitmore, and Assistant Surgeon C. S. Krishnaswami (1912) recovered a previously unrecognized organism from post-mortem specimens obtained from a morphine addict who had died 10 days after the onset of an infectious illness. Despite the apparent clinical, pathological, and bacteriological similarities of his disease to glanders, the epidemiological history made that an unlikely diagnosis. Subsequent bacteriological studies led to the recognition of a gram-negative, motile organism which had the morphological characteristics of *Pseudomonas mallei* but differed in several important respects (Whitmore 1912). During the ensuing 10 months, there were 37 more fatal cases from which the organism, now taxonomically classified as *Pseudomonas pseudomallei*, was isolated. In one case, the diagnosis was suspected before death, and the organism was recovered by guinea pig inoculation of the patient's blood. In only 1 of the initial 38 cases was the patient observed throughout the entire course of his illness (Whitmore and Krishnaswami 1912). In 1914, Fletcher observed the occurrence of fatal glanderslike illness in laboratory animals at the Institute for Medical Research in Kuala Lumpur, Malaya (Stanton and Fletcher 1921). The laboratory epizootic continued and it was not until 1917 that Stanton and Fletcher (1925) recognized

that the causative organism was identical to that which had been described by Whitmore and Krishnaswami.

Until 1925, the organism had been isolated and identified from animal and human sources only in Rangoon, Kuala Lumpur, and Singapore (Stanton and Fletcher 1925). That year Pons and Advier (1927) observed a case in a young pregnant Vietnamese woman near Saigon. Subsequently, human, animal, and environmental isolates have been reported from a number of tropical and subtropical areas, predominantly from Southeast Asia and the Western Pacific, but also in the Western Hemisphere. Krishnaswami (1917) claimed to have seen more than 200 cases between 1910 and 1915, but only 83 case reports could be found for a literature review in 1932 (Stanton and Fletcher).

Melioidosis has been, and remains, a disease of significance to military medicine. First, it was discovered by military physicians. Second, the occurrence of approximately 100 cases among the French Expeditionary Forces in the Indochina War between 1948 and 1954 led to the conclusion that it was a disease of some importance to military operations in an endemic area (Rubin, Alexander, and Yager 1963). Third, there is some justification for the view that the movement of personnel and supplies during and after World War II was responsible for dissemination of the organism from its original endemic home or, at the very least, that military interest in the disease resulted in its increased recognition throughout the world (Fournier and Chambon 1958). Finally, melioidosis became increasingly important to U.S. military forces operating in the endemic area over the past three decades.

Cox and Arbogast (1945) reported the first case in an American soldier in Burma. Sporadic cases occurred thereafter in military personnel, but the disease remained of interest primarily to epidemiologists and laboratory investigators. Rubin et al. prophetically labeled it a "military medical problem" in 1963, and the deployment of large numbers of troops to South Vietnam beginning in 1965 led to the fulfillment of that prophecy. The Melioidosis Registry of the U.S. Army Office of the Surgeon General (OTSG-MR) contains reports of 343 cases, among which there were 15 deaths directly caused by the disease and 21 others in which it was a contributing factor or secondary diagnosis. Anecdotal information from physicians assigned to Vietnam during 1968 and 1969 leads one to conclude that a significant number of diagnosed cases were not reported and that there must have been a number of undiagnosed cases as well.

Of what significance is a disease occurring in so few of the 2.5 million persons at risk (Clayton, Lisella, and Martin 1973) and resulting in so few deaths? First, despite the clairvoyance of Rubin et al., the disease was not anticipated by medical personnel on duty in Vietnam, and the occurrence of a number of fulminant, rapidly fatal cases in 1966 (Weber et al. 1969) was demoralizing to those who were already overwhelmed by diseases with which U.S. physicians generally lacked familiarity. Second, 1 in 10 of these cases was initially diagnosed as pulmonary tuberculosis, fostering unnecessary epidemiological concern and adding to the frustration of the medical officers involved. Third, at least 28 of these cases occurred in the continental United States or Hawaii following duty in Vietnam (OTSG-MR), causing some concern and leading to the disease's being called

a "medical time bomb." Two of these patients became ill while serving tours of duty in Germany, recalling the experience reported by European physicians after repatriation of French forces in 1954 (Jackson, Moore, and Sanford 1972). On the basis of serologic studies described below, it can be estimated that between 25,000 and 225,000 U.S. soldiers had subclinical infection with *P. pseudomallei*. There is adequate documentation that the disease can recur months or years after apparent cure or can first occur after many years of latency. Intercurrent illness, injury, or stress appear to be important factors in the latter circumstance (Jackson, Moore, and Sanford 1972, p. 271; Clayton, Lisella, and Martin 1973, p. 24).

INCIDENCE AND EPIDEMIOLOGY

Despite extensive study of the disease, the true incidence of melioidosis has not been established. Prevatt and Hunt (1957) were able to find only 300 cases in their review of the world's literature. If one includes all reports, substantiated or not, the number of recognized cases after more than 60 years does not exceed 1,000.

Despite the paucity of recognized cases, serological surveys indicate that mild or inapparent infection is not uncommon, suggesting that contact with the organism occurs frequently. Significant titers have been found in 6 to 20 percent of indigenous personnel in Vietnam, Thailand, and Malaysia (Brygoo 1953; Nigg 1963; Strauss, Alexander, et al. 1969). Similarly, 1.2 percent of Europeans living in Vietnam (Brygoo 1953) and from 1.1 percent (Spotnitz, Rudnitzky, and Rambaud 1967) to 2 percent* of healthy or nonwounded U.S. Army troops returning to the United States after spending 6 to 12 months in Vietnam had significant HA (hemagglutination) titers.

In a prospective serological study, Legters and coworkers** collected paired serums from 553 Special Forces personnel assigned to temporary duty in Vietnam for 6-month periods from 1961 to 1963. Of 97 individuals who had experienced one or more febrile illnesses, 2 demonstrated a fourfold or greater rise in HA/titer for melioidosis, representing infection in 0.36 percent of the population at risk. Sporadic cases occurred between 1960 and 1965, and following the troop buildup beginning in April 1965, the number increased sharply (table 27).

By August 1967, the 9th Medical Laboratory had begun to do HA tests for melioidosis on virtually all serum specimens submitted from a variety of sources. By January 1968, 66 cases had been identified by high or rising HA titers (ML9-AR). These represented approximately 9 percent of serum specimens submitted for an FUO (fever of undetermined origin) evaluation. Additional cases were identified from specimens submitted for cold agglutination titers from patients with suspected atypical pneumonia or tuberculosis. Unfortunately, demographic data on these patients are incomplete, and followup information is

*Sanders, C. V.; Moore, W. L.; and Sanford, J. P. Unpublished observation, 1969.

**Legters, L. J.; Buescher, E.; and Coppedge, R. L. Unpublished observations, personal communications, 1963.

TABLE 27.—*Melioidosis in Vietnam, 1965-71*

Month	1965	1966	1967	1968	1969	1970	1971
January		1	6	1	1	4	4
February			4	1	4	4	3
March		1	2	2	4	6	8
April			1	1	8	6	
May	1	1	1	9	3	3	1
June	1	3	6	5	15	6	8
July		6	2	4	8	10	2
August		4	3	9	5	2	2
September		5	9	16	12		2
October	1	4	9	10	12	4	
November	1	1	6	9	6	3	2
December	2	4	5	9	7	4	
Total	6	30	55	77	85	54	34

*Totals include cases not tabulated by month. Two additional cases were reported in 1972.

Source: Biostatistics Agency, Office of the Surgeon General, Department of the Army. Melioidosis Registry.

available on very few of them. Of the 66 cases, 25 (38 percent) came from the 25th Infantry Division (Johnson 1968). Nine cases of melioidosis in the 25th Infantry Division in 1966 were reported in detail (Weber et al. 1969). In 13 of the cases from this division reported through September 1968, the geographic location had been established (Johnson 1968). In one instance, the patient had been in Tay Ninh Base Camp for his entire tour. Significant HA titers (1:40 or higher) were found in 5.2 percent of 38 men from his unit. Most of the cases were from the Cu Chi area, and *P. pseudomallei* was cultured from several soil and water samples taken there (ML9-AR; Johnson 1968).

Positive serologies were noted in 0 to 9 percent of patients in various FUO studies (Deller and Russell 1967; Reiley and Russell 1969; Deaton 1969; Colwell et al. 1969; Kishimoto et al. 1971; ML9-AR, p. 43). In early 1969, a survey in the III CTZ (Corps Tactical Zone) disclosed 5 to 8 percent positive titers in tactical units (USARV-MB, p. 17). In later studies of troops returned to the United States, the percentage of significant titers was found to be related to the presence, and perhaps extent, of trauma in the patients. Seven (3.5 percent) of 200 patients with wounds of all types had HA titers of 1:40 or greater (Kishimoto et al. 1971) compared with 18 percent of patients with open orthopedic wounds* and 32 percent of burn patients.**

To determine if incidence was related to season, location, duty assignment, and length of time in Vietnam, a continuing FUO serologic study was conducted from the latter half of 1969 through early 1970 by the 9th Medical Laboratory in conjunction with a number of medical facilities throughout the country. Of 366 serological confirmations, 19 (5 percent) demonstrated probable or confirmed melioidosis (USARV-CHR). There were two positives in September and October, eight in November, one in December, two in January, none in February,

*Maj. Creed D. Smith, Chief, Microbiology, 6th U.S. Army Area Laboratory, Fort Baker, Calif.; Personal communication.

**Maj. Larry N. Dotin, MC, U.S. Army Institute of Surgical Research, Fort Sam Houston, Tex.; Personal communication.

three in March, and one in April. The seasonal occurrence of cases from retrospective review of the Registry reports is shown in table 27. Unfortunately, data on a large number of other variables which might have influenced these findings are not available for review.

Cowley found that 33 percent of cases had occurred in helicopter crewmen (Howe, Sampath, and Spotnitz 1971). In a subsequent study involving U.S. marines, no correlation could be established between elevated HA titers and any of the variables involved (Clayton, Lisella, and Martin 1973). While approximately 10 percent of the earlier cases had occurred in burn patients and 32 percent of such patients had significant HA titers,* by 1970 no cases were seen in the Institute of Surgical Research Burn Center at Fort Sam Houston and by 1971 there were no longer any positive HA titers found.** In all, 44 (12.8 percent) of the cases reported in the Registry occurred in burn patients (OTSG-MR).

Immunologically demonstrated exposure to the organism is far more common than clinical disease. Furthermore, there is an increased prevalence of disease and of asymptomatic seroconversion in patients with penetrating injury and burns, particularly when these wounds are contaminated with dirt and stagnant water from the environment.

The epidemiology of melioidosis has been investigated extensively. The organism is widely distributed around the world between 20°N. and 20°S. latitudes. Human, animal, and environmental isolates of *P. pseudomallei* have been reported from Burma, Malaysia, Singapore, Vietnam, Thailand, Cambodia, Laos, India, Celebes, Java, Borneo, Indonesia, Ceylon, New Guinea, Papua, Australia, the Philippines, Guam, Turkey, Panama, Ecuador, Africa, Madagascar, Germany, France, Italy, Aruba, England, and the United States (Redfearn, Palleroni, and Stanier 1966; Rubin, Alexander, and Yager 1963). However, the patients whose cases occurred in the United States and Europe, except the one in Turkey (Ertug 1961), acquired the infection while residing or traveling in areas of known endemicity.

Of the 38 cases reported by Whitmore and Krishnaswami (1912), 28 occurred in chronic morphine addicts, leading to the appellation, "morphine injectors septicemia" (Krishnaswami 1917), although evidence for a cause-and-effect association was circumstantial. Stanton and Fletcher (1925) believed that the laboratory epizootic in Kuala Lumpur resulted from fecal contamination of animal feed by infected rats, but subsequent studies have shown that rats rarely harbor the organism. Chambon (1955) and a number of others (Strauss, Jason, and Mariappan 1967; Joubert and Phung Van Dan 1958) have shown conclusively that the organism is a saprophyte in soil and water. There are numerous clinical examples of man acquiring the organism through contamination of wounds by dirt, mud, and water; this mode of transmission has also been demonstrated in the laboratory (Le Moine, Hasle, and Nguyen-Duc-Khoi 1937). Pulmonary infection has been seen following aspiration of contaminated water (Johnson 1968, p. 3) and experimental airborne infection has been demonstrated in hamsters

*Maj. Larry N. Dotin, MC: Personal communication.

**Robert L. Lindberg, Chief, Microbiology, U.S. Army Institute of Surgical Research, Fort Sam Houston, Tex.: Personal communication.

(Rosebury 1947, pp. 151-58). Mosquitoes and fleas have also been shown to spread the organism under experimental conditions (Blanc and Baltazard 1941a, b).

In the absence of trauma or known instances of ingestion, inhalation, or aspiration, there is little to suggest the specific means by which many patients become infected. In 209 of 343 case reports in the Melioidosis Registry (OTSG-MR), there is no evidence of trauma or other clear-cut exposure. No age, sex, or racial group is exempt from melioidosis. There is scanty evidence that chronic debility or preexisting disease (that is, diabetes mellitus) or intercurrent surgery predisposes one to the development of clinical melioidosis. Virtually all of the nontrauma-associated cases in U.S. Army personnel occurred in individuals who were otherwise healthy.

The distribution of cases in Vietnam may offer some epidemiological clue but, unfortunately, the available data do not permit firm conclusions. First, the disease was virtually unknown in the 9th and 4th Infantry Divisions, while there was an abundance of cases in the 25th Infantry Division, the 11th Armored Cavalry, and the 1st Cavalry Division (Airmobile). Second, at least 190 cases were seen in only nine medical facilities, while 99 others either had no medical unit designated or occurred in small numbers in numerous other field hospitals, evacuation hospitals, or surgical hospitals in Vietnam. The distribution of melioidosis among Army personnel, by facility, from 1965 to 1971 was as follows (OTSG-MR):

Evacuation Hospitals:	Field Hospitals:	
12th.....53	3d.....	21
24th.....24	8th.....	5
67th.....14	Other military, in Vietnam.....	99
85th.....12	Military, in continental United States or Hawaii.....	28
91st.....10	Military, in Europe.....	2
93d.....38	Civilian or Veterans Administration, in United States.....	7
95th.....13	Other facilities.....	17

Man-to-man transmission has been conclusively demonstrated only once; McCormick et al. (1975) recently reported a case of venereal transmission by a Vietnam returnee with prostatic infection. Prostatic melioidosis infection had been reported previously (Sollier and Boutareau 1937). Some epidemiological confusion has resulted from an account of a neonatal case in which the only apparent source of infection was the father, recently returned from Vietnam, who, however, had no opportunity for contact with the infant between onset of illness and the child's death (Osteraas et al. 1971).

The incubation period for melioidosis can be as short as 1 day (Johnson 1968) or as long as 26 years (Mays and Ricketts 1975). Clearly, although much is known, a number of interesting questions remain about the epidemiology of this often confusing disease.

ETIOLOGY, PATHOGENESIS, AND PATHOLOGY

Melioidosis is caused by the slender, motile, gram-negative bacillus

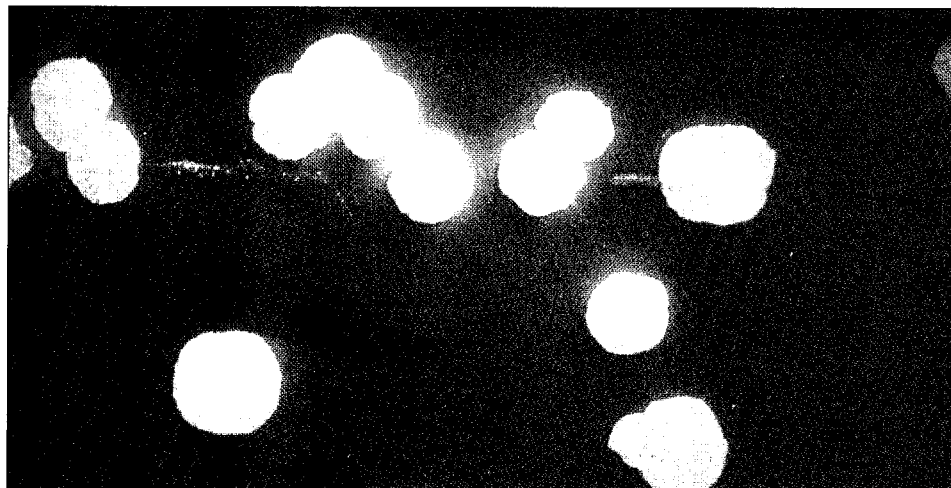


FIGURE 51.—Typical culture appearance of *Pseudomonas pseudomallei* on blood agar plate, 48 hours. Note typical rugose, umbonate morphology. (Courtesy, Col. John J. Deller, Jr., MC.)

Pseudomonas pseudomallei. It has previously been classified in several genera, including *Malleomyces*, *Loefflerella*, *Pfeifferella*, and *Actinobacillus*. It stains somewhat poorly with Gram's stain, showing irregular mottling and bipolar densities which are more prominent with methylene blue, Giemsa's stain, or Leishman's stain. In early culture, colonies may be indistinguishable from some strains of *Pseudomonas aeruginosa* and must be kept for 48 to 96 hours before developing the characteristic opaque, white, umbonate, rugose morphology (fig. 51). While the organism grows well at 25°C, 37°C, or 42°C, incubation at room temperature favors the development of the characteristic colonies. The organism causes alpha hemolysis in blood agar, a heavy, scummy surface pellicle formation in broth culture, and a musty, wet-earth odor in mature culture. On MacConkey's agar, the colonies are small, pink to red, and have a faintly visible metallic sheen. On EMB (eosin-methylene blue) agar, the colonies are lavender with a metallic sheen, and some investigators have used this feature as a means of early identification. The biochemical and serological confirmation of the identity of the organism has been described in detail (Moore, Hedberg, and Lindberg 1970).

Knowledge of the pathogenesis of melioidosis is derived from clinical and laboratory studies (Le Moine, Hasle, and Nguyen-Duc-Khoi 1937; Rosebury 1947). The incubation period is apparently related to a number of factors. Experimentally, highly susceptible animals—guinea pigs, hamsters, or rabbits—injected subcutaneously or intraperitoneally with large doses of virulent organisms may succumb within 24 hours. Animals exposed via scarification of skin, inhalation, or ingestion usually manifest symptoms within 2 to 7 days. A monkey which was infected by aerosol exposure to 130 organisms showed signs of illness only after 2 months and, when killed after 68 days, clearly had

meliodosis (Nigg and Johnston 1961).

Human disease has occurred within 5 to 10 days following burns (Flemma et al. 1969), within 1 day following aspiration of contaminated water (Johnson 1968), and within 3 days following aerosol exposure during a laboratory accident (Green and Tuffnell 1968). Prolonged latency after exposure to an endemic environment for from 5 months (Flemma et al. 1969) to as long as 26 years has been reported (Mays and Ricketts 1975). Latent infection has become manifest spontaneously (Spotnitz, Rudnitzky, and Rambaud 1967; Beamer et al. 1954; McDowell and Varney 1947) or in association with intercurrent medical or surgical illness (Jackson, Moore, and Sanford 1972; Alain, Saint-Étienne, and Reynes 1949). Apparently, the incubation period is variable, depending on the magnitude and mode of exposure and a variety of environmental and host-susceptibility factors (Dannenberg and Scott 1958a, b). It seems safe to assume in most cases of clinical illness the incubation period in health individuals is from 2 days to 3 weeks.

The disease mimics plague and tularemia in two major respects: septicemic dissemination frequently occurs in the course of primary pneumonia, and pneumonia, usually fatal, may develop after hematogenous spread from a localized infection or in the course of a primary septicemia. One can only speculate that the pathogenetic events in acute, systemic disease, in the absence of a primary infection, involve intracellular or extracellular hematogenous dissemination of the organism acquired from the environment through lungs, intestine, or skin. In recrudescence or late-occurring disease, the organism likely has lain dormant in intracellular sites, presumably in the reticuloendothelial system, but this has not been demonstrated clinically or experimentally. The factors which lead to active local or systemic infection in these cases are related to the complex interrelationships of humoral and cellular immune mechanisms and other poorly defined homeostatic systems.

In the acute and subacute forms of the disease, widely disseminated abscesses from 1 mm to 3 cm in diameter are seen. They are buff or yellow-gray and may be firm or rubbery or show central caseous necrosis with or without early cavitation. Larger lesions are hemorrhagic at the periphery and contain a mixed cellular infiltrate including polymorphonuclear leukocytes, mononuclear cells, and atypical multinucleated giant cells. There is a marked degree of karyorrhexis of involved cells, suggesting that a severe form of cytotoxicity results from a toxin or toxins produced by the organism. The lesions in chronic disease are larger and often cavitory, containing mononuclear cells, plasma cells, and granulation tissue.

CLINICAL MANIFESTATIONS

The clinical manifestations of melioidosis are sufficiently variable to preclude accurate diagnosis on the basis of symptoms, physical findings, and laboratory information short of bacteriological or serological confirmation. It was initially recognized as a severe, almost invariably fatal septicemic disease with involvement of the lungs and, often, widespread visceral dissemination

(Whitmore and Krishnaswami 1912; Whitmore 1912; Knapp 1915). Subsequent clinical and experimental investigations have disclosed its protean clinical spectrum of acute, subacute, chronic, and subclinical or asymptomatic infection.

Characteristically, the onset is dramatically abrupt, and the predominant symptoms are those of acute pulmonary infection. In the 38 cases originally described by Whitmore (1912; Whitmore and Krishnaswami 1912), most patients clearly presented the dominant picture of acute pulmonary infection, and most of the remainder had obvious lung involvement. Numerous other reports reflect the prevalence of pulmonary presentation. Most patients present with fever, chills, malaise, and a cough which usually produces purulent or bloody sputum, sometimes after the first 1 to 2 days of illness. The temperature usually varies between 99°F and 104°F, occasionally higher. Dyspnea, often moderate, may be out of proportion to the paucity of physical and radiographic findings in early disease. Anorexia, vomiting, and diarrhea are encountered frequently (Weber et al. 1969). Physical findings include fever, moderate tachypnea and tachycardia (consistent with fever), conjunctival suffusion, pharyngeal enanthema, rales, rhonchi, occasionally signs of consolidation, and, infrequently, a pleural friction rub. Pleural effusion and empyema are distinctly rare. The spleen and liver are not palpable in the absence of dissemination. Laboratory findings include normal to elevated leukocyte counts, rarely exceeding 20,000/mm³; polymorphonuclear cells comprise 85 to 90 percent of the total count. Mild, normochromic, normocytic anemia has been seen as early as the first week of illness. The organism has been seen in sputum smears in approximately 80 percent of the reported instances in which this test has been done. Radiographically, the most characteristic pattern is one of irregular nodular densities 4 to 10 mm in diameter scattered throughout the lung (James, Dixon, and Johnson 1967). Unilateral single or multiple lobe irregular confluence proceeding to consolidation is a less frequent finding. Cavitation occurs in some patients surviving beyond 1 week of illness.

The acute septicemic form of the disease is exemplified by cases 1 to 4 of Weber et al. (1969) and the five cases of Flemma et al. (1969). The first two cases began with cutaneous lesions which progressed rapidly and relentlessly through phases of cellulitis, lymphangitis, distal metastatic abscesses in skin and viscera, and diffuse involvement of the lungs. The third patient progressed from early symptoms of gastroenteritis to rapidly fatal diffuse pneumonia. The fourth had a very nondescript initial febrile illness which terminated in a fulminant pneumonia. All had high fevers, up to 106°F, and demonstrated evidence of toxicity with malaise and depressed mentation. Two of the four had normal total peripheral white blood cell counts and two had substantial leukocytosis. In none was there an associated history or evidence of trauma, while the five patients of Flemma et al. had suffered significant burns. The distressing features of these cases which are commonly noted in acute severe disease are lack of specific early signs and symptoms, rapidity and extent of progression, failure to respond to appropriate antibiotic administration, and a high case fatality rate.

Features of the acute pulmonary form of the disease are seen in case 5 of Weber et al. Characteristic are the sudden onset, with fever, chest pain (often pleuritic), productive cough, and a positive chest roentgenogram which, in this

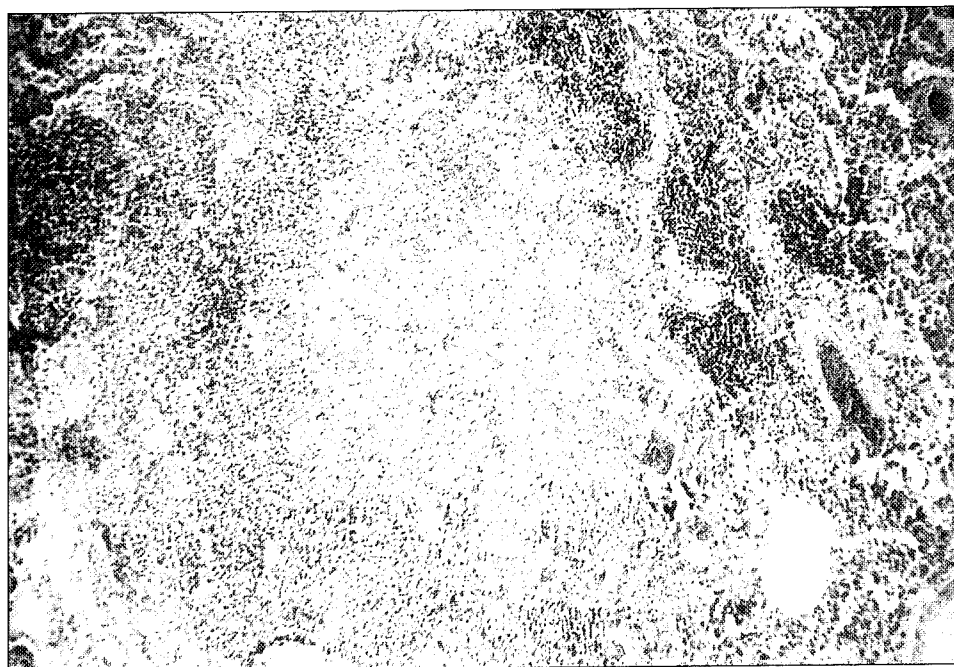


FIGURE 52.—Histopathologic material from a lung showing inflammatory cell infiltration in the area of an abscess. (Courtesy, Col. John J. Deller, Jr. MC.)

case as in many others, appears similar to a lung abscess (fig. 52) or cavitary tuberculosis. The white blood count may be normal or elevated. Response to therapy is more predictable and the case fatality rate, although estimated to be about 10 percent, is considerably lower than that of the acute systemic form of the disease.

The subacute or chronic pulmonary form of the disease is represented by the cases of Sweet, Wilson, and Chandler (1968). The first patient, a previously healthy, 23-year-old soldier, had a 2-month illness characterized by a dry non-productive cough, left pleuritic chest pain, intermittent fever, anorexia, malaise, weight loss, lymphadenopathy, and abnormal lymphocytes in a peripheral blood smear. His initial chest X-ray demonstrated a large, thin-walled cavity in the left upper lobe, and he developed a fever of 105°F accompanied by a modest leukocytosis without developing other evidence of acute disease (figs. 53 and 54). He was treated for tuberculosis and appeared to show some improvement but responded briskly after the diagnosis of pulmonary melioidosis was established and therapy with chloramphenicol, novobiocin, and streptomycin was begun. Case 2 had a remarkably similar course, as did two patients seen by the author who were diagnosed and treated at the pulmonary and infectious disease services at Brooke Army Medical Center. Spotnitz, Rudnitzky, and Rambaud (1967) reported two patients with pneumonitis who were clinically well and had a cavitary lung lesion discovered at the time of a routine chest X-ray.

Chronic melioidosis has been described by McDowell and Varney (1947),

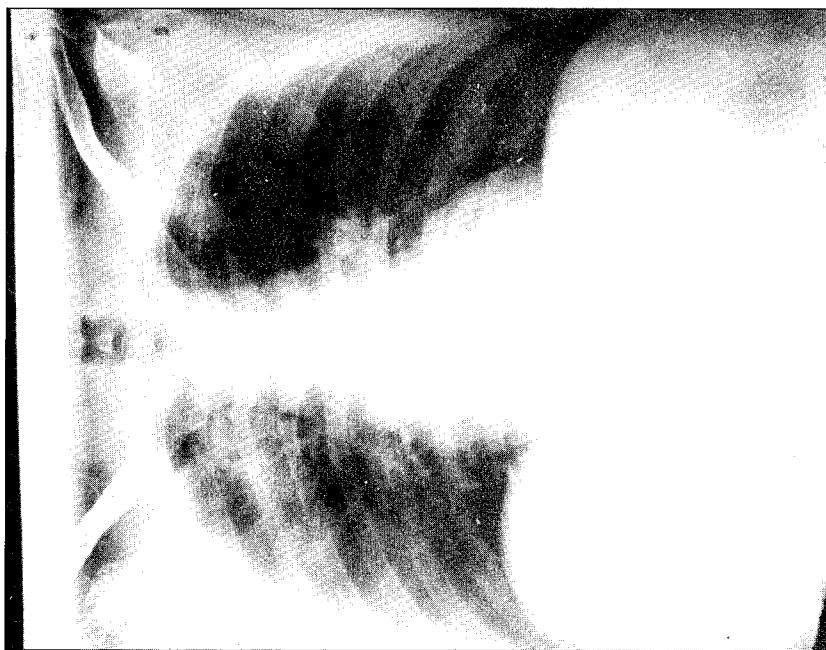


FIGURE 53.—Typical X-ray of cavitary melioidosis. Note the resemblance to tuberculosis. (Courtesy, Col. John J. Deller, Jr., MC.)

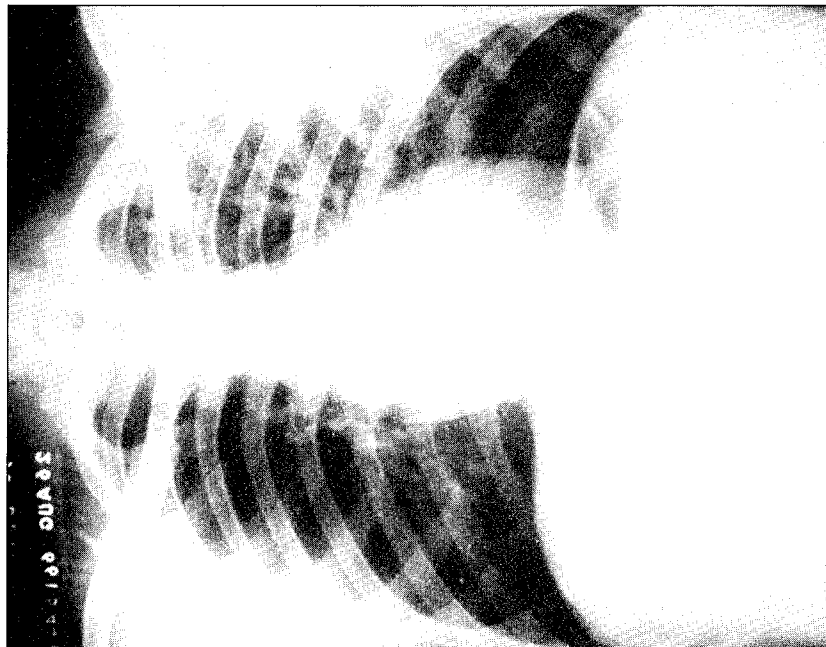


FIGURE 54.—Extensive pulmonary melioidosis of left upper lobe with widespread infiltration and multiple small cavities. Note similarity to pulmonary tuberculosis. (Courtesy, Col. John J. Deller, Jr., MC.)

Salisbury and Likos (1970), and Mays and Ricketts (1975). Chronic forms involve lungs (Everett and Nelson 1975), bone (Sutherland and Dahlstrom 1968; Borchardt, Stansifer, and Albano 1966), skin, and a variety of soft tissues (McDowell and Varney 1947).

Less common forms include localized acute lymphadenitis (Peck and Zwanenburg 1947), myocardial abscess (Baumann and Morita 1967) (fig. 55), meningoencephalitis (Schaeffer and Grant 1968) (fig. 56), and soft tissue or muscle abscess (fig. 57).

LABORATORY DIAGNOSIS

Confirmation of the diagnosis of melioidosis depends upon recovery of the organism from clinical specimens or a fourfold or greater rise in HA or CF (complement fixation) antibody titer associated with an episode of clinically apparent disease. Review of available data from the 343 Registry cases indicates that the diagnosis was based on serologic evidence in 24 cases, and that it was presumptive (dependent on a single high HA or CF titer) in 38 others who had either FUO (10 cases) or a clinical illness compatible with one of the forms of melioidosis. Cases not reported in the Registry include probable or presumptive diagnosis based on serologic tests done by the 9th Medical Laboratory and reported in a variety of sources.

Recovery of the organism from sputum samples in suspected cases is enhanced by digestion with 1 percent pancreatin for a half hour at 37°C, the pH adjusted to 7.5 with phosphate buffered saline, and addition of crystalline penicillin G and polymyxin B at a final concentration of 400 µg of each antibiotic per ml of specimen. This is then plated on NAGCV (nutrient agar [Difco]; glycerol 3 percent; crystal violet [1:200,000]; pH 6.7 to 7.0) medium and subsequently inoculated into hamsters. Blood cultures are collected in the usual manner, in standard broth media, and subcultured to NAGCV or standard laboratory solid media.* Pus, body fluids, and tissues may be handled as is sputum or inoculated directly onto solid media (blood agar plate, EMB, NAGCV, or MacConkey's) or in broth. The organism has been obtained from sputum, pus, blood, urine, feces, body fluids, tissue, and cerebrospinal fluid.

Agglutination tests with patient serums were used in serologic diagnosis in the past but are no longer considered helpful. Precipitin reactions have also been demonstrated but give false positive results with normal serums (Cravitz and Miller 1950).

The complement fixation test is most specific although less sensitive than others and, when the titer is elevated, suggests recent disease, since significant titers (1:8 or greater) do not persist for more than 2 years (Cook 1962). IHA (indirect hemagglutination) is convenient, relatively easy to perform, specific at titers of 1:40 or greater, and is the serologic test most often used. The titer is usually elevated in acute disease. An elevated titer in a single serum specimen in relation to a suspected case has less diagnostic significance than demonstration

*Department of Bacteriology and Immunology, SEATO Medical Research Laboratory, Bangkok, Thailand: Laboratory procedures, 1968.

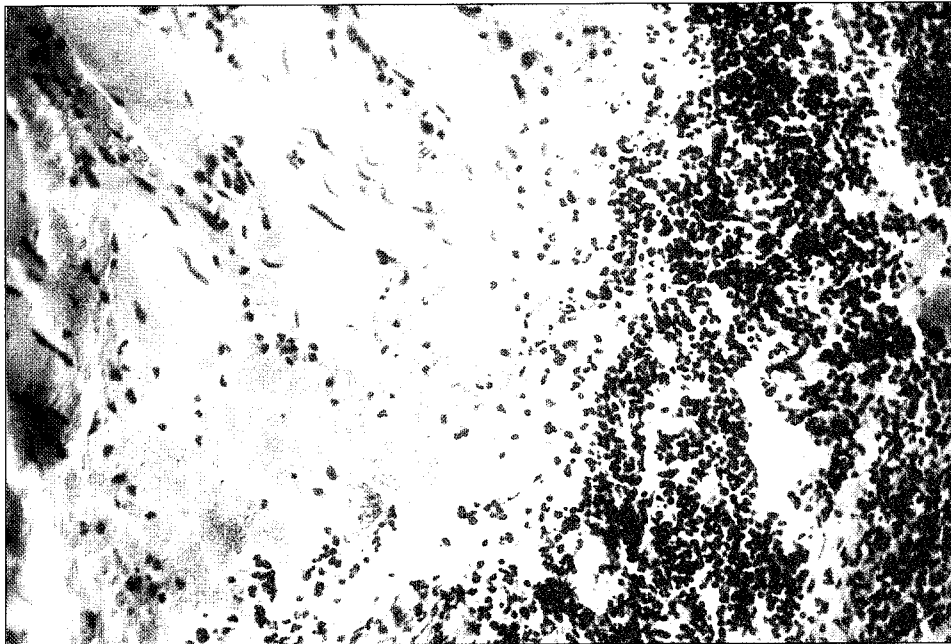


FIGURE 55.—Inflammatory cell infiltration causing microabscess formation in the myocardium.
(Courtesy, Col. John J. Deller, Jr., MC.)

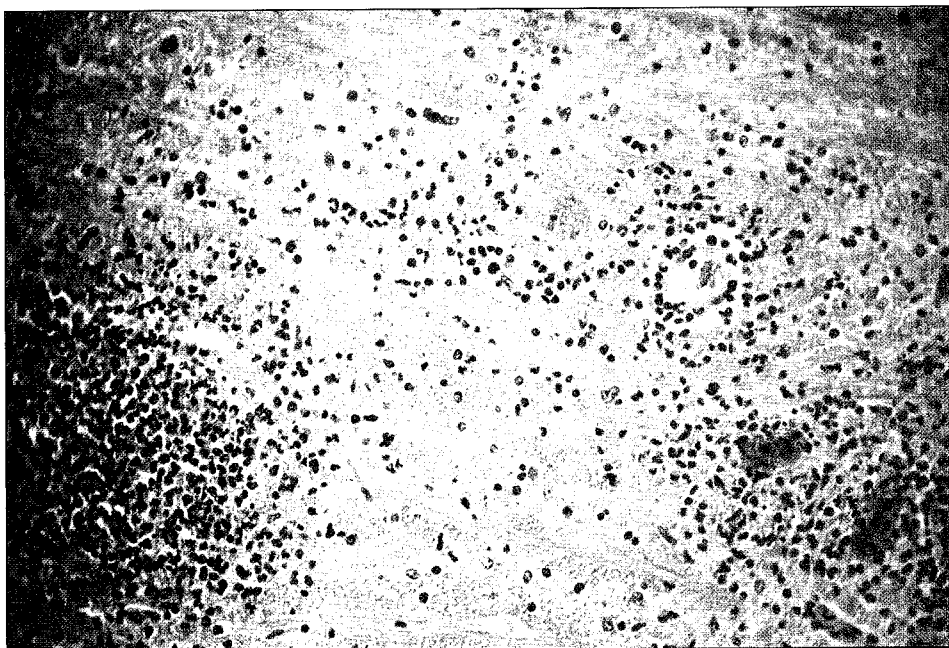


FIGURE 56.—Typical microabscesses in the brain. (Courtesy, Col. John J. Deller, Jr., MC.)

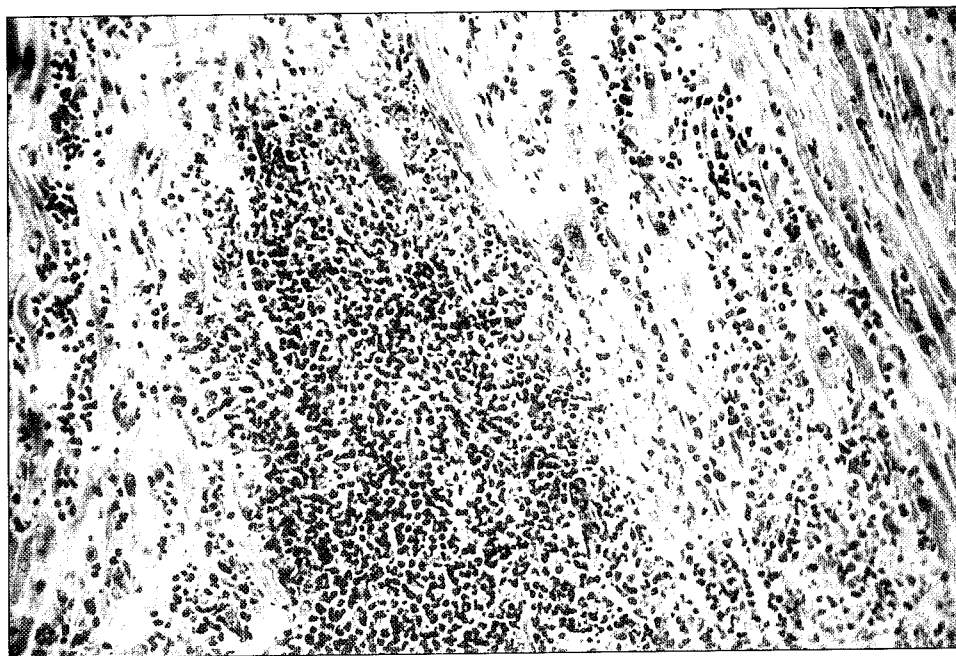


FIGURE 57.—Inflammatory cell infiltrate in the pectoralis muscle causing abscess formation. (Courtesy, Col. John J. Deller, Jr., MC.)

of complement fixing titer because indirect hemagglutinin may persist for many years after an immunogenetically significant encounter with the organism, whether or not clinical disease has occurred.

In view of the probable occurrence of false positive HA tests, Nigg (1963) recommended the combined use of complement fixation and hemagglutination tests in diagnostic and epidemiological studies. Paired serum samples are most helpful in establishing the diagnosis when cultures of appropriate clinical specimens are negative.

PREVENTION AND TREATMENT

There is no effective means of active or passive immunization against melioidosis. Data are not available to support the notion that early appropriate antibiotic treatment of wounded or burned individuals potentially exposed to *P. pseudomallei* would reduce the incidence of clinical disease; unfortunately, there is no demonstrable correlation between cases of melioidosis and the widespread use of penicillin, tetracycline, kanamycin, gentamicin, and chloramphenicol in various combinations among such patients in Vietnam. Since the organism is more common in areas of human habitation throughout the endemic zone, the only effective means of prevention appears to be avoiding exposure to the environment and that is, obviously, often impossible.

For a variety of reasons, the therapy of melioidosis remains a matter of mild

controversy. In vitro studies have shown that the organism is usually susceptible to clinically obtainable concentrations of sulfonamides, kanamycin, tetracycline, chloramphenicol, and novobiocin (Eickhoff et al. 1970), and synergism between novobiocin and tetracycline has been shown (Calabi 1973). Because of the high case fatality ratio associated with the acute septicemic and overwhelming pulmonary form of the disease, some authors have recommended combined therapy with chloramphenicol, 12 g per day; kanamycin, 4 g per day; and novobiocin, 6 g per day (Cooper 1967). The effectiveness of this regimen has not been demonstrated, and there have been several instances of severe bone marrow depression, ototoxicity, nephrotoxicity, and hepatotoxicity associated with this combination of drugs. In mild to moderate disease, tetracycline alone at 3 g per day or in combination with sulfisoxazole in standard or modestly increased doses is effective without significantly increasing the likelihood of toxic reactions (Cooper 1968; Spotnitz 1968) (figs. 58-60).

Studies in Vietnam in 1969 (chart 11) demonstrated significant sensitivity to tetracycline at low concentration, further emphasizing the importance of this drug as the mainstay of the therapeutic effort. Patients who succumb to acute disease have had positive postmortem cultures despite several days of therapy with antibiotics to which the organism appears to be susceptible in vitro. The response to antibiotic therapy is not so rapid as in many other bacterial infections, and relapse may occur after an asymptomatic interval of weeks to many months (Jackson, Moore, and Sanford 1972). The occasional occurrence of relapse has led some physicians to consider treatment for 3 to 6 months even for uncomplicated disease.

NEW ADVANCES

The experience with melioidosis resulting from military operations in Vietnam has not resulted in any major advances but has brought attention to observations made earlier.

First, early in its course, the disease is frequently mistaken for pulmonary tuberculosis, and when melioidosis is not considered in the initial differential diagnosis there may be considerable unnecessary delay in proper evaluation. Early diagnosis frequently depends upon a high index of suspicion and requires that, in addition to appropriate serological tests, the laboratory be advised to observe the cultures for a minimum of 4 days. Otherwise, the organism may be discarded before the characteristic morphological appearance develops.

Second, although in vitro antimicrobial susceptibility of the organism has shown no major changes since the discovery of chloramphenicol, in vivo response to drugs is variable and at times unpredictable. Therapy with appropriate antibiotics for less than 3 weeks has been accompanied by an unacceptable relapse rate; in the most extreme example, active disease has recurred after more than a year of continuous drug therapy (Jackson, Moore, and Sanford 1972). In fulminant cases, positive cultures have been obtained from postmortem specimens even after several days of therapy to which the organism shows in vitro susceptibility. On the other hand, high-dose multiple-drug therapy for fulminant

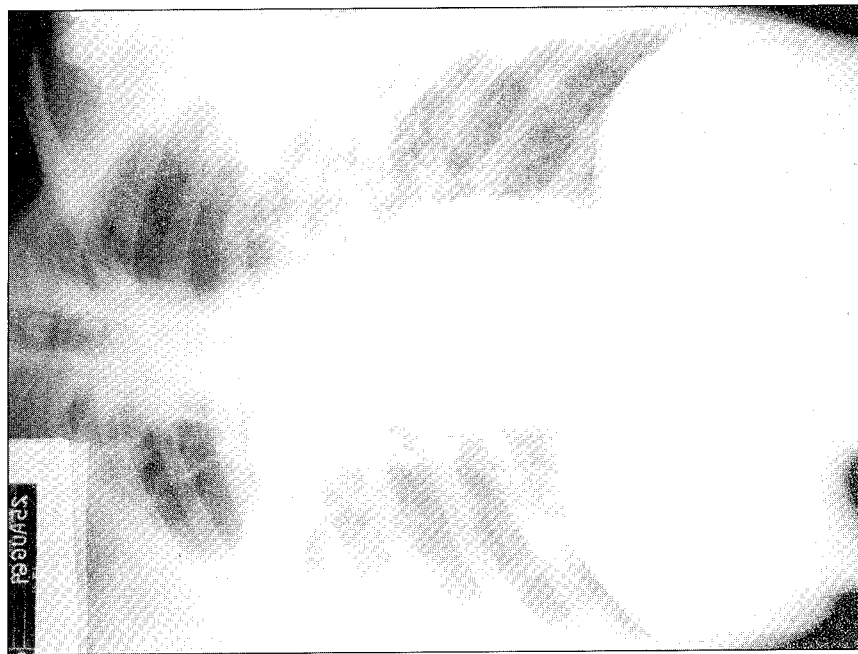


FIGURE 58.—Initial X-ray in a case of pulmonary melioidosis, untreated on 25 August 1969. (Courtesy, Col. John J. Deller, Jr., MC.)

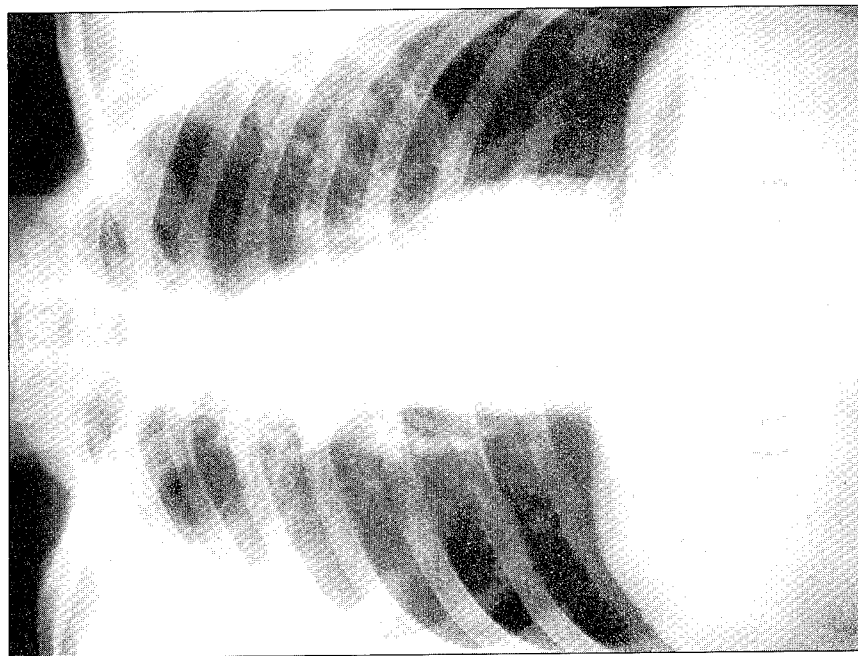


FIGURE 59.—X-ray showing sequential improvement in a case of pulmonary melioidosis, partially resolved on tetracycline therapy on 11 September 1969. (Courtesy, Col. John J. Deller, Jr., MC.)

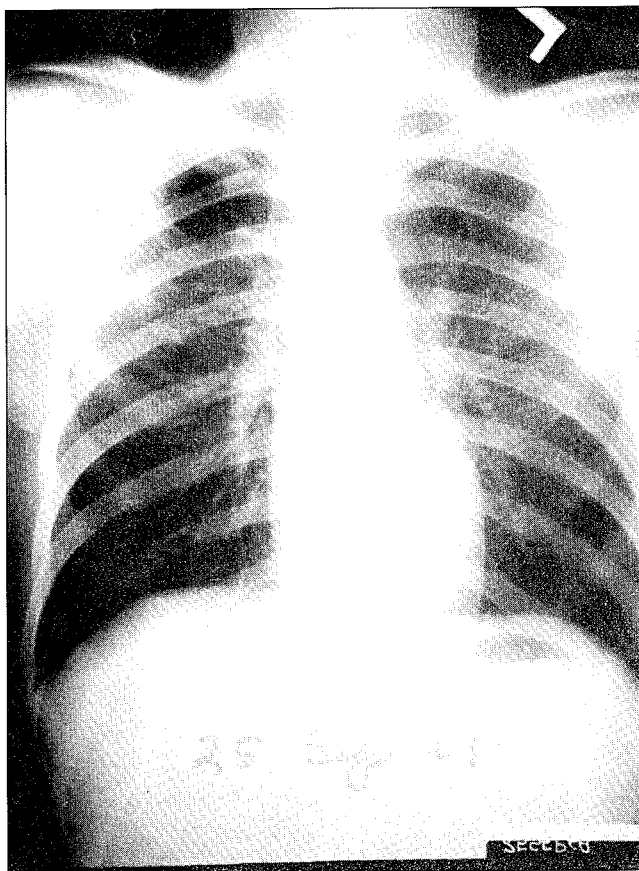
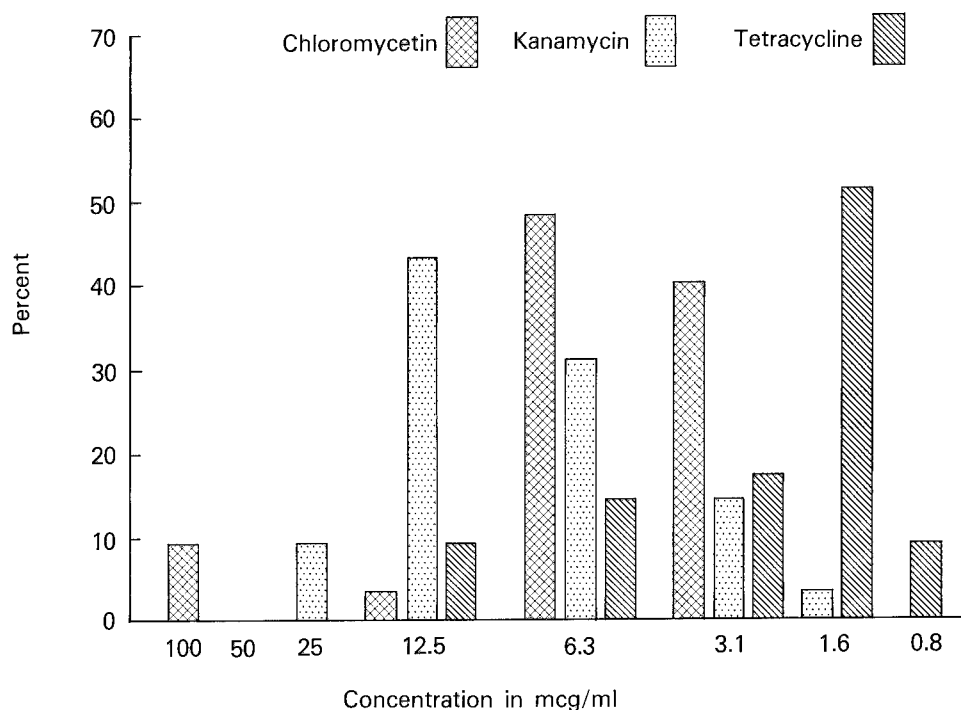


FIGURE 60.—Final X-ray showing improvement in a case of pulmonary melioidosis, near complete resolution following a course of tetracycline therapy, 25 September 1969. (Courtesy, Col. John J. Deller, Jr., MC.)

disease—specifically chloramphenicol, kanamycin, and novobiocin in combination—has not been shown to have increased effectiveness and the potential toxicity of this combination precludes its use.

Third, the experience in Vietnam points to the need for a central repository or registry for the maintenance of records and data on diseases of military or potential military importance, particularly for diseases that are not widely known or understood. It further emphasizes the importance of area medical intelligence and global epidemiology to military activities.

CHART 11.—Drug sensitivity of sixty-one *Pseudomonas pseudomallei* isolates studied in Vietnam, 1969



Source: Col. Andre J. Ognibene, MC, USARV Medical Consultant, 1969.

Section III. Tuberculosis

Carl R. Guiton, M.D., and Colonel O'Neill Barrett, Jr., MC, USA (Ret.)

HISTORY AND MILITARY SIGNIFICANCE

Tuberculosis has been a problem since antiquity and for centuries was a principal cause of death in men of military age. Records of hospital admissions and medical discharges from military service for tuberculosis have been maintained by the U.S. Army since the Civil War. During that conflict, there were 13,499 tuberculosis admissions and 5,286 deaths from the disease among white soldiers. The mean annual rate of discharge for tuberculosis was 8.6 per 1,000 in white troops and 3.1 per 1,000 in black troops. However, in neither the Civil War nor the Spanish-American War was the disease frequent enough to prompt any unusual comment in the analyses recording the medical aspects of military operations.

Unless otherwise noted, material under "History and Military Significance" in this section is derived from Medical Department, United States Army. *Infectious diseases*. Internal Medicine in World War II, vol. 2. Washington: Government Printing Office, 1963, pp. 329-407.

During World War I, persons with tuberculosis were detected and excluded from military service almost entirely on the basis of the physical examination since roentgenology was in its infancy and screening skin testing resources were not available. There were 22,812 disability separations because of tuberculosis during the war, or 5.52 per 1,000 average strength per annum. The disease was the leading cause of disability separation, accounting for 11.1 percent of the total (MD-WW15, pp. 166-82, 1022). Furthermore, the full magnitude of the problem did not become evident until several years after the war. Goldberg (1941) calculated that the approximate expenditure by the Veterans Administration for service-connected tuberculosis from the close of World War I through 1940 was \$1,186,000,000. The number of hospitalized tuberculosis beneficiaries peaked in 1922, at 44,591 (Wolford 1944).

At the beginning of World War II, the Office of the Surgeon General recognized that drastic revision of the physical standards in the existing Mobilization Regulations was necessary because of technical developments in tuberculosis control. In April 1939, a chest X-ray was required before applicants could be commissioned. As early as 1940, routine screening chest X-rays for all inductees were considered, but they were not made a mandatory part of all physical examinations at induction stations until 3 June 1941. While approximately 10 million men had chest X-ray examinations, about 1 million men were inducted without them (MD-PS, pp. 30-33).

The average incidence rate of tuberculosis for World War II from 7 December 1941 to 14 August 1945 was 1.2 per 1,000 per annum (MD-IM2, p. 334). Tuberculosis accounted for 1.9 percent of all discharges for disability from disease between 1942 and 1945, ranking 13th on the list (HOA-46, pp. 22-23). Among Americans who had been prisoners of war, the rates were higher. Prisoners from the European theater had an incidence five to seven times that of the Army in general (MD-IM2, p. 346). Figures on those returned from the Pacific area were more difficult to obtain, but a special study of repatriated prisoners at West Coast debarkation hospitals, directed by The Surgeon General, showed that 2.7 percent of 3,742 individuals studied with chest X-rays had evidence of active pulmonary tuberculosis (Morgan, Wright, and Van Ravenswaay 1946).

As a means of standardizing therapy and of studying the disease in more detail, three specialty centers for the management of tuberculosis were established: Fitzsimons General Hospital in Denver, Colo., Bruns General Hospital in Santa Fe, N. Mex., and Moore General Hospital in Swannanoa, N.C. Fitzsimons Hospital has remained the Army center for tuberculosis.

While specific incidence rates are not available for the Korean conflict, tuberculosis continued to be a problem for the Army, as reflected by the approximately 600 admissions per year to Fitzsimons General Hospital during that period (HOA-52, p. 11; HOA-53, p. 11; HOA-54, p. 25).

INCIDENCE AND EPIDEMIOLOGY

Rightful concern was expressed about the exposure of American troops in

Vietnam to a population with a high tuberculosis infection rate. The conflict in Vietnam placed an estimated 500,000 American military personnel annually in varying degrees of contact with a highly infected population. While detailed statistics were initially lacking, several U.S. studies done there highlight the seriousness of the problem. In 1968, a chest X-ray survey by Siegler et al. of Vietnamese civilians showed that 31.7 percent over the age of 15 had definite radiologic evidence of active pulmonary tuberculosis (Cowley 1970). Another study demonstrated that nearly 100 percent of the adult population was tuberculin skin test positive (Houk 1967). Poffenbarger (1972) performed tuberculosis skin tests on 631 children, ages 1 through 18, and showed an increasing number of positive reactions with age. Of the 17- to 18-year-old group, 47.5 percent reacted. Furthermore, tuberculin-negative children retested 9 months later showed increasing conversion rates, with a 17-percent chance annually of acquiring infection.

Among American troops, approximately 95 percent had had no previous exposure to tuberculosis and were tuberculin-negative upon arrival in Vietnam (Stead and Bates 1969; Edwards 1969). Data from the 20th Preventive Medicine Unit indicated that only 6.2 percent of 901 first-time personnel were tuberculin-positive on entering the country, whereas 13.7 percent of 190 personnel with a previous tour in Vietnam were positive (PMU-20). In the first-tour group, breakdown by race showed that 3.2 percent of whites, 7.4 percent of blacks, 9.1 percent of Orientals, and 15.6 percent of Spanish-surnamed persons were positive; a similar racial distribution was noted in the group with previous tours in Vietnam (table 28).

In a review of 334 patients evacuated from Vietnam because of injury, who had had negative tuberculin tests immediately before arrival in Vietnam, 11 (or 3.3 percent) showed conversion. The average length of stay in Vietnam for these individuals was only 7 months. The author speculated that the conversion rate would have been higher with a full 1-year tour (Cowley 1970).

This suggestion was confirmed in a larger study done by Sowell, Russell, and Ionata (1973). This group studied U.S. Army enlisted men rotating to the United States from field units within the III Corps Tactical Zone, including the 1st Air Cavalry Division, 25th Infantry Division, 20th Engineer Brigade, and 11th Armored Cavalry Regiment. Among the 711 individuals studied, 35 (4.9 percent) demonstrated conversion. There was no difference in conversion based on age, rank, or MOS (military occupational specialty). However, a significant difference was found between whites and blacks. Whites had a 3.4-percent conversion rate (21 of 620) compared to 17.1 percent (12 of 70) in blacks. Overall distribution of troop strength for the U.S. Army in Vietnam by race was 87 percent white, 11 percent black, and 2 percent other.

These data are similar to those obtained in a U.S. Navy study at St. Albans Hospital in New York, which revealed a 4.7-percent conversion rate among Vietnam evacuees (Elliot, Miller, and Sachs 1970). The rates in both studies are higher than the 2.5 percent per annum conversion rate in Europe and the 1.0 percent per annum rate for Army personnel in the United States (Cowley 1970).

While the rate of tuberculin skin test conversion in U.S. servicemen in Viet-

TABLE 28.—*Incidence of positive tuberculin skin test in personnel on first tour in Vietnam and personnel who had previous tours, 1970*

Racial group	Personnel on first tour			Personnel who had previous tours		
	Number tested	Positive skin test		Number tested	Positive skin test	
		Number	Percent		Number	Percent
White	709	23	3.2	143	10	7.0
Black	136	10	7.4	40	12	30.0
Spanish-surnamed	45	7	15.6			
Oriental	11	1	9.1			

Source: 20th Preventive Medicine Unit, USARV, Annual Report, 1970.

nam seems reasonably well established, the incidence rate for the development of active pulmonary tuberculosis is not known, although apparently it was small. Data from the USARV (U.S. Army, Vietnam) medical consultant for 6 months in 1969 reveal that only 28 patients were evacuated from Vietnam because of active pulmonary disease.*

Early data suggested an increased incidence of primary drug-resistant tuberculosis in soldiers returning from Vietnam (Cowley and Briney 1970). This conclusion, however, was based on the discovery of only five cases of drug-resistant disease among servicemen recently returned from Vietnam and on the supposition that there was an increased incidence of drug resistance in countries where administration of antituberculosis drugs is uncontrolled. There were no data on the incidence of drug-resistant strains in the local population in Vietnam. Primary drug resistance in developed countries has been reported to be 4 to 6 percent in the United States, 3.8 percent in Great Britain, 4.9 percent in Canada, and 9.8 percent in France (Fox 1968; Canetti 1965).

A Veterans Administration study of 3,183 strains of *Mycobacterium tuberculosis* from veterans in the United States showed no change in the susceptibility of the strains to streptomycin or isoniazid during the period 1962-69 (Hobby, Johnson, and Boytar-Papirnyik 1970). These findings are in accord with those of the Bureau of Tuberculosis, Department of Health, City of New York (Chaves 1970), and of the USPHS (U.S. Public Health Service).

Dantzker, Steinborg, and Kmiecik (1972) reported on the only large study dealing specifically with the problem of drug-resistant strains of tuberculosis in troops returned from Vietnam. They reviewed the records of 501 consecutive active-duty male tuberculosis patients who were discharged from the Army during 1967-70. The patients were divided into two groups: 201 who had had a tour of duty in Vietnam within 3 years of admission, and 300 who did not. Culture-proven disease was present in 127 patients in the Vietnam group and 154 in the non-Vietnam group. The percentage of resistant strains was 9.5 to 7.8, respectively, indicating no statistical evidence of increased drug resistance in the Vietnam group.

*Andre J. Ognibene: Unpublished data on hospital discharges of patients evacuated to Japan from Vietnam, 1969.

CLINICAL FEATURES, COMPLICATIONS, AND TREATMENT

The clinical course of tuberculosis was apparently no different in American servicemen in Vietnam than it was in patients in the United States. Extrapulmonary forms and pleural effusion were uncommon.* Cavitory disease of the lung due to melioidosis caused confusion in early diagnoses at times, but this disorder was easily distinguished from tuberculosis with appropriate culture techniques (Weber et al. 1969).

Treatment of tuberculosis with chemotherapy at the present time is highly successful because of the variety of drugs which are effective against the organism. Primary or major drugs include isoniazid, para-aminosalicylic acid, ethambutol, streptomycin, and rifampin. Currently isoniazid is used in conjunction with either ethambutol or rifampin. Triple-drug therapy is recommended for extrapulmonary and far advanced pulmonary disease. The duration of treatment in Vietnam was 18 months for minimal pulmonary tuberculosis and pleural effusion and at least 24 months for extensive disease, cavitory disease, and extrapulmonary forms of the disease. When tubercle bacilli are found to be resistant to the primary drugs or when toxic symptoms preclude their use, so-called "secondary" drugs are available, including ethionamide, pyrazinamide, kanamycin, and cycloserine. Ideally, drug combinations are selected on the basis of sensitivity studies, and a combination of two or more effective drugs, either primary or secondary, must be used (TB MED).

SUMMARY

Despite the large numbers of troops who served in Vietnam and the potential threat posed by an indigenous population with a high incidence of active disease, tuberculosis was not a major military medical problem for U.S. forces stationed there.

Section IV. Gram-Negative Infection

Brigadier General Andre J. Ognibene, MC, USA

The occurrence of nosocomial infections in Vietnam in the early years of the war was accorded little interest. Hospital-acquired infection was not a primary problem in the early management of patients, and evacuation policy was such that the susceptible patient was moved out of country rapidly. The continuing interest of the surgical staff in primary sepsis is recorded in their attempts to identify wound flora and analyze the effects of surgery in relation to the reduction of

*Carl R. Guiton: Unpublished data.

Except where otherwise noted, this section is derived from the personal experience of the author and from the following article by him (1971): Newer patterns of infection encountered in Vietnam. In *Symposium on changing patterns of bacterial infections and antibiotic therapy*, ed. H.C. Neu. *Excerpta Medica International Congress Series*, no. 228, pp. 121-27.

infection rates (Pruitt and Baker). Nosocomial infection became a problem for study when in-country hospitals stabilized.

The development of relatively fixed installations and of increasing surgical capability, resulting in longer retention of patients in hospital, was a distinct feature of the later years of the war. This development, coupled with a capability for adequate specimen transport and bacteriologic support by the 9th Medical Laboratory, allowed a more specific diagnostic and therapeutic approach to gram-negative infections in Vietnam. In 1969, documentation of nosocomial infection was clearly obtained.

SERRATIA MARCESCENS

Before 1968, confirmed isolations of *Serratia marcescens* in Vietnam were rare. However, in late 1968 and early 1969, the organism was cultured from wounds and from the sputum of 12 patients and the blood of 8 of these 12. Of those with positive blood cultures, five died (table 29).

Because of experience with this initial group of patients, 2,600 blood cultures were subsequently examined at the 9th Medical Laboratory (Mobile) in Long Binh, with particular attention to Enterobacteriaceae. Of the 321 positive blood cultures, 100 (31 percent) were confirmed as *S. marcescens*. These 100 isolates were obtained from 40 patients at three hospitals in the vicinity of the laboratory.

This striking increase in the incidence of *S. marcescens* in blood cultures in Vietnam prompted attempts to isolate the source of the organism. Hospital infection committees were established for the first time in combat hospitals. Routine culturing practices in wards and operating rooms were undertaken. Initially *S. marcescens* could not be cultured from respirators or operating rooms, but a significant number of other pathogens were isolated, including both *Klebsiella* and *Pseudomonas* species.

Results of bacteriologic studies of the antibiotic sensitivity of 100 *S. marcescens* isolates in Vietnam were as follows:

Kanamycin.....	43%	Cephalothin.....	23%
Chloramphenicol.....	41%	Tetracycline.....	12%
Polymyxin B.....	34%	Streptomycin.....	5%
Colistin.....	25%	Ampicillin.....	5%

Of particular importance is the striking finding that half of the strains isolated were resistant to all antibiotics. Gentamicin had not yet been used extensively and still enjoyed a place in the treatment of *S. marcescens* infections. This drug, however, was not available in Vietnam until late in 1969 and was not used for testing sensitivity of *Serratia* isolates.

Serratia marcescens is a short, almost spherical gram-negative rod. About 17 percent of isolates produced the pigment prodigiosin at room temperature. Nonpigmented forms present in Vietnam have also amply demonstrated their pathogenicity, as noted in the United States (Sanders et al. 1970; Clayton and von Graevenitz 1966). In the past the organism was confused with organisms of

TABLE 29.—*Serratia marcescens* infection in eight patients in Vietnam

Patient	Wound	Operation	Course
20-year-old, Viet Cong.	Gunshot wound of abdomen.	Repair of multiple bowel perforations. Diverting colostomy.	Penicillin and chloramphenicol for fever. Colostomy closed. Fever persisted. Keflin added. Marked sepsis and death.
23-year-old, Vietnamese.	Multiple fragment wounds of abdomen. Penile wound. Lower extremity wounds.	Repair of bowel perforation. Colostomy, cystotomy, left orchiectomy. Left knee disarticulation.	Postoperative fever. Ileus. Transferred and lost to followup.
18-year-old, U.S. Army.	Massive buttock, sacrum, perineum, abdominal and extremity fragment.	Amputation of right leg, debridement of buttocks and perineum, colostomy, wide pelvic drainage.	Complicated by shock (50 units whole blood), gastrointestinal hemorrhage, pelvic abscess. Given multiple antibiotics. Eventually died with <i>S. marcescens</i> sepsis.
20-year-old, U.S. Army.	Gunshot wounds of abdomen, left hip and buttocks.	Inferior vena cava repair, debridement and packing of liver, T-tube, colostomy, left hip disarticulation.	Developed intrahepatic abscesses, pelvic abscess. Death from sepsis.
21-year-old, U.S. Army.	Gunshot wound of right hip and left thigh.	Extensive debridement.	Postoperative fat emboli. Gangrenous cholecystitis. Sepsis with <i>S. marcescens</i> . Large pelvic abscess. Died.
31-year-old, U.S. Navy physician.	Multiple fragment wounds of left leg.	Left knee arthrotomy	Fat emboli. Recovered. Evacuated to Japan. <i>S. marcescens</i> in blood cultures. Recovered.
20-year-old, U.S. Army.	Punji stick in left popliteal space.	Debridement	Progressive pneumonia. Unresponsive to therapy. <i>S. marcescens</i> grown from both lungs at autopsy.
19-year-old, U.S. Army.	None	None	Malaria. 3d day fever, chills. <i>S. marcescens</i> grown from the blood. Recovered.

Source: Ognibene, A. J. 1971. Newer patterns of infection encountered in Vietnam. In *Symposium on changing patterns of bacterial infections and antibiotic therapy*, ed. H. C. Neu. *Excerpta Medica* International Congress series, No. 228, pp. 121-27.

the chromobacterium group because of its pigment production. However, the pigment has been clearly identified as prodigiosin and is not related to the viola-

cein pigment of the chromobacteria. *S. marcescens* has been properly classified as a member of the family Enterobacteriaceae. Formerly it had been regarded as a saprophyte; it has now been incriminated as a cause of endocarditis, lung abscess, pneumonia, and a variety of urinary tract infections (Alexander, Reichenbach, and Merendino 1969; Cabrera 1969). Epidemics related to the contamination of hospital respirators have been reported (Sanders et al. 1970).

Additional review of the initial hospital surveys in Vietnam showed that the organism could not be found in jugs of saline used for irrigation and cleansing of wounds as previously reported by Cabrera (1969). It was probably carried in the air. Cross-contamination of patients using nebulizers was possible before the use of disposable reservoir nebulizers, manifold tubing, and mouthpieces on all equipment. Such disposable parts are of prime importance in a combat area where patients with severe injuries often require prolonged periods of assisted ventilation and are particularly prone to contamination with *S. marcescens*.

The possible virulence of this particular organism demanded frequent blood cultures and meticulous care of wounded patients on assisted ventilation. Basic requirements included a more discriminate use of broad spectrum antibiotics initially, greater attention to infection control procedures, and avoiding contamination of ventilation equipment.

The internist was not often involved in the care of the patient with a superinfection following wounding. The appearance of sepsis with *S. marcescens*, however, fostered an exchange in expertise between medical and surgical staffs in the prevention and management of such infections. It became clear that infection control in the hospital was of primary importance in the early management of the wounded patient, especially when combat support hospitals became fixed installations. Provision for effective bacteriologic analysis is critical to medical support of combat operations and must be available early if the establishment of relatively fixed support hospitals is contemplated.

CHROMOBACTERIUM VIOLACEUM (JANTHINUM)

Unusual gram-negative infections were not limited to surgical patients in Vietnam. In 1968, two isolates of *Chromobacterium violaceum (janthinum)*, a gram-negative rod which characteristically produces an indigo pigment on culture, were reported on by the 9th Medical Laboratory (ML9-AR, p. 29). No details of patient status, source of infection, or other clinical data were obtainable. Fatal infection by this organism was first reported from Malaya in 1927 (Sneath et al. 1953). Of the 16 known human cases in the world, 9 came from that country. The most recent cases have been described in the southeastern United States (Dauphinais and Robben 1968; Nunnally and Dunlop 1968).

Two patients died of *C. violaceum (janthinum)* infection in Vietnam in 1969. The first, a 21-year-old soldier, entered the hospital with chills, fever, and a temperature of 105°F. He had lost 15 pounds over 2 weeks and appeared moderately ill, although his physical examination was unremarkable. The white blood count was elevated. He developed sudden cyanosis followed by respiratory arrest and died 8 hours after admission. Chest X-rays showed bilateral

pulmonary infiltrates. At autopsy, the lungs were studded with multiple small yellow abscesses, and necrotizing pneumonia was present. *C. violaceum (janthinum)* was grown from the premortem blood and tracheal cultures as well as from both lungs at autopsy.

The second patient was a 19-year-old soldier who had marked vomiting, diarrhea, and abdominal cramps for 3 days. He was noted to be markedly jaundiced and was thought to have fulminant hepatitis. His temperature rose to 105°F, and he was hypotensive. Hepatomegaly was the sole abnormal physical finding. Although kanamycin and cephalothin were begun, he died on the first hospital day. All blood cultures grew *C. violaceum (janthinum)*. At autopsy, there were abscesses in the liver, a thickened gallbladder, and evidence of a necrotizing infection in the biliary tree and the liver.

Septicemia with liver abscess is characteristic of the infection. A number of patients had skin lesions which disseminated up to 15 months later, resulting in death (Dauphinais and Robben 1968). A patient with a positive culture from a skin lesion was identified in Vietnam in 1969. Unfortunately, followup could not be achieved.

The infection was first described in water buffalo from Malaya (Sneath et al. 1953). The organism displays a predilection for tropical and semitropical areas. Because of previous reports of its isolation from water supplies, samples of a number of water supplies in Vietnam were cultured and the organism was grown from the main water supply of a village in central Vietnam. Positive isolations were not obtained from the rectal swabs of 50 water buffaloes.

Studies of four isolates (from two autopsies, one skin lesion, and the water supply) showed that sensitivity existed to tetracycline and chloramphenicol, but there was resistance to cephalothin, kanamycin, ampicillin, and colistin.

Because of the latent period, reported by some, between appearance of a skin lesion and later dissemination, one must speculate about the probability of importation of this disease from Vietnam to the United States by returning servicemen. In five cases reported from Florida and Louisiana, no mention was made of military service or other exposure in Southeast Asia. However, experience with melioidosis suggested that an indolent *C. violaceum (janthinum)* infection should be considered in the differential diagnosis of infectious disease in returning servicemen.

NEISSERIA MENINGITIDIS

While the occurrence of unusual gram-negative infection was recognized, some gram-negative infections of worldwide distribution did not cause significant problems. For example, the development of meningococcal disease in U.S. troops was not a feature of the Vietnam war. However, in 1967, 15 strains of meningococci were recovered from North Vietnamese carriers in a prisoner-of-war camp after there had been seven cases and one death. These were later characterized as only nine strains—seven Type B, one Type C, and one Type A*

*Malcolm S. Artenstein: Personal communication.

(table 30). Meningococcal meningitis also occurred in Vietnamese troops, but their length of service and the extent of the problem were not clear.

TABLE 30.—Sensitivity characteristics of *Neisseria meningitidis* strains from Vietnam

Strain number	Serotype	Sulfadiazine sensitivity (mg%)	Penicillin sensitivity (μg/ml)
476-1	B	0.5 - 1	< .031
478-1	B	1 - 2	< .031
480-1	B	0.5 - 1	< .031
482-2	B	1 - 2	.062
483-6	B	1 - 2	< .031
484-1	B	0.5 - 1	< .031
489-3	B	0.5 - 1	< .031
481-1A	C	1 - 2	< .031
485-4	A	2 - 5	< .031

Source: Dr. Malcolm S. Artenstein, June 1970.

Studies done at Fort Dix and Fort Benning in 1966 and 1968 (Goldschneider, Gotschlich, and Artenstein 1969b) demonstrated that 92 percent of tested recruits developed serum bactericidal activity against acquired strains of meningococcus. On the basis of this information, it might be speculated that the American soldier arriving in Vietnam had been "seasoned" in basic training in relation to the meningococcus organism.

Goldschneider and coworkers believed this to be a reasonable explanation for the universal observation that seasoned military personnel are much less susceptible to meningococcal disease than are basic recruits. Such seasoned troops have apparently been immunized during basic training by means of the meningococcal carrier state. This is corroborated by a study in which 67 to 86 percent of a susceptible population of military recruits become carriers of meningococci other than the prevalent disease-producing strains (Goldschneider, Gotschlich, and Artenstein 1969a). Such individuals subsequently developed bactericidal antibodies to the pathogenic organisms.

The recognition of this fact was imperative in the reeducation of the physician new to the Army and to Vietnam who placed meningitis high in the differential diagnosis of the comatose and febrile young soldier and neglected falciparum malaria and Japanese B encephalitis. This was especially true when the encephalitis patient demonstrated a predominance of polymorphonuclear leukocytes in the spinal fluid. The change in the order of probability of these diseases to fit the Vietnam experience was ultimately accomplished and improved the practice of internal medicine in the Vietnam conflict.

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Venereal Diseases

Colonel John J. Deller, Jr., MC, USA (Ret.), Dallas E. Smith, M.D., David T. English, M.D., and Edward G. Southwick, M.D.

HISTORY AND INCIDENCE

Venereal diseases have always played a major role in the history of military medicine. In the U.S. Army during World War I, they ranked second only to influenza as a cause of disability and absence from duty, being responsible for the loss of 6,804,818 days and the discharge of more than 10,000 men (Dunham 1923). During World War II, the incidence of VD varied widely among the theaters of operation. Between 1941 and 1945, worldwide incidence in the Army averaged 42.9 per 1,000 strength per year. This figure doubled during the postwar period (1946 to 1950) to 82.3 per 1,000 strength per year. With the troop buildup in Korea, the case rate once again doubled, to 184.0 per 1,000 average strength per year for the period 1951 to 1955. The incidence in American troops in Korea remained at a consistently high rate in the ensuing 10 years, exceeded only by that of American troops in Thailand (Greenberg 1972).

Similar high rates of venereal disease appeared in Vietnam as substantial troop concentrations occurred in 1963. The overall average incidence was 261.9 per 1,000 strength per year during the period of 1963 to 1970 (Greenberg 1972, p. 1095). In comparison with other common diseases, venereal disease was the number one diagnosis from 1965 to the conclusion of the war, as reflected in monthly morbidity reports. Table 31 shows the incidence rates of all venereal disease in the Army, worldwide, in CONUS (continental United States), and in Vietnam, from 1963 to 1972. Table 32 gives the rates for the three general categories of venereal disease (gonorrhea, syphilis, and "other") as reflected in the USARV (U.S. Army, Vietnam) monthly morbidity reports.

These data reveal that approximately 90 percent of all venereal disease cases reported were cases of gonorrhea, as were the majority of hospitalized cases. However, despite the high prevalence of venereal disease, and especially of gonorrhea, only about 1 percent of all cases required hospitalization for treatment. The admission rates for all venereal diseases among Army personnel in Vietnam, compared with those worldwide and in CONUS, are shown in table 33. Most venereal disease cases were managed at division-level medical facilities, but the magnitude of the problem was such that significant numbers of patients required hospitalization for primary treatment of venereal disease or its complications.

TABLE 31.—*Incidence rates for all venereal diseases among U.S. Army personnel, 1963-June 1972*

[Rates per 1,000 average strength per year]

Year	Worldwide	CONUS	Vietnam
1963	47.6	26.9	354.1
1964	47.1	26.2	333.4
1965	53.7	26.9	277.4
1966	81.3	27.4	281.5
1967	89.6	30.6	240.5
1968	86.2	31.8	195.8
1969	87.7	33.2	189.7
1970	101.0	36.1	223.0
1971	105.3	36.1	326.4
1972 ¹	120.6	42.0	698.9

Note: Based on cases excused from duty (admitted to hospital or quarters) and not excused from duty (CRO—carded for record only—that is, treated on outpatient status).

¹January-June.

Source: Patient Administration Division, Health Services Command, Department of the Army.

TABLE 32.—*Incidence rates for types of venereal disease among U.S. Army personnel in Vietnam, 1963-June 1972*

[Rates per 1,000 average strength per year]

Year	Total	Gonorrhea	Other	Syphilis
1963	354.1	281.5	66.7	5.3
1964	333.4	284.4	45.8	3.2
1965	277.4	244.1	28.5	4.9
1966	281.5	251.6	25.5	4.4
1967	233.9	222.4	9.5	2.0
1968	195.8	175.3	18.6	1.9
1969	189.7	171.4	16.6	1.7
1970	239.7	217.6	19.1	3.0
1971	326.4	283.2	41.1	2.1
1972 ¹	698.9	605.7	90.6	2.6

Note: Based on cases excused from duty (admitted to hospital or quarters) and not excused from duty (CRO—carded for record only—that is, treated on outpatient status).

¹January-June.

Source: Patient Administration Division, Health Services Command, Department of the Army.

Although the medical aspects of the venereal diseases will be emphasized in this chapter, it seems appropriate first to review the basic problems predisposing to high venereal disease rates—the obvious failure of adequate control measures.

CONTROL OF DISEASE

The control and management of venereal disease in the U.S. Army in recent years have been based upon five principal measures: education, prophylaxis,

TABLE 33.—*Admission rates for all venereal diseases among U.S. Army personnel, 1963-June 1972*

[Rates per 1,000 average strength per year]

Year	Worldwide	CONUS	Vietnam
1963	0.9	0.4	
1964	0.8	0.4	
1965	0.9	0.4	3.6
1966	1.1	0.3	3.9
1967	1.1	0.4	2.6
1968	1.0	0.3	2.3
1969	0.7	0.3	1.0
1970	0.8	0.3	1.4
1971	0.5	0.3	0.8
1972 ¹	0.7	0.4	1.7

Note: Based on cases excused from duty (admitted to hospital or quarters). Does not include cases not excused from duty (CRO—carded for record only—that is, treated on outpatient status).

¹January-June.

Source: Office of the Surgeon General, Department of the Army. Health of the Army, May 1963, May 1964, May 1965, May 1966, May 1967, May 1968, May 1969, May 1970, May 1971, May 1972.

detection, early treatment, and suppression of prostitution. The earlier emphasis on punishment of the individual soldier or the unit commander has not in recent years been an acceptable policy.

The basic venereal disease policy of the armed forces at the time of the Vietnam war was published in a technical bulletin (TB MED). The degree to which the measures set forth in this document could be effected during a combat situation, however, remained a critical problem throughout the war. The overall case rate in Vietnam during the conflict was reportedly higher than that of any previous war (Greenberg 1972, p. 1095).

One of the best documented studies attempting to resolve some of the problems of venereal disease control within a combat division was carried out in the 25th Infantry Division early in 1970 by Happer, Kerschbaum, and Reid.* The basic principles of venereal disease control, as set forth in Technical Bulletin 230 (TB MED), had been adhered to by personnel of the division. Troops were exposed to education programs on at least three separate occasions during their tour: an initial briefing upon arrival, an intensive lecture series from unit surgeons once they reached their unit assignment, and a subsequent briefing before departure on R&R (rest and recuperation) or leave. Despite this approach, venereal disease remained at a high level. To investigate the failure of VD control, questionnaires were completed for every case within the division during a 4-month study period; 465 cases were then reviewed. The distribution of types of venereal disease was comparable to that throughout the country (USARV-CHR): gonorrhea accounted for nearly 92 percent of the cases, syphilis for slightly less than 1 percent, and other venereal diseases for the remaining 7 percent. The study also revealed that 88 percent of all venereal disease oc-

*Lt. Col. Robert L. Reid, MC: Personal communication to Lt. Col. Andre J. Ognibene, MC, 1970.

curred within the 18- to 24-year age group (which was the peak age range for assigned personnel). The risk of acquiring venereal disease increased with the length of time in the Republic of Vietnam, and combat support units were at highest risk. Within this particular division, Saigon and two base camps accounted for nearly 50 percent of the cases, while out-of-country R&R centers accounted for over 20 percent. Thus, not unexpectedly, the areas nearest large cities and of greatest troop concentration and least combat activity had the highest venereal disease rate.

Perhaps of greatest significance is that in this study venereal disease education was clearly shown to be ineffective. Only 12 percent of the patients claimed never to have been exposed to a VD education program. Nevertheless, 88 percent did not use prophylactic measures in their index case and 25 percent never used prophylaxis. What the VD incidence would have been without any education program is impossible to predict. Obviously, well-organized programs do get information to nearly 90 percent of the troops; the problem is how to get the troops to apply the information which is imparted. Education alone apparently is insufficient and other means of control applicable to combat situations must be seriously considered.

In fact, careful evaluation of whether attempts to control venereal disease are worthwhile at all in combat situations is necessary before a future course can be decided upon. A brief review of the history of venereal diseases to date suggests that, despite advances in knowledge and therapies over recent years, the acquisition rate has doubled with each war since World War II. Yet, more importantly, the problem of noneffectiveness has been reduced with each war. From 1929 to 1939, the average time lost because of gonorrhea was 38 to 50 days per case (Greenberg 1972, p. 1099) while today the average time lost because of gonorrhea is but a few hours and only the rare case is complicated.

If continuing to "control" the incidence rate of venereal disease is deemed desirable, then more emphasis must be directed at the ultimate problem, the infected "camp follower," placing importance on regulation of prostitution. This course was attempted on occasion by a number of units in Vietnam but never received overt support and was carried out almost surreptitiously. Thus, data on the results of such an approach in recent times are not available. In the early 1900's, control of prostitution was officially sanctioned in Cuba and the Philippines, but a change in the VD rate was not effected (Greenberg 1972, p. 1089). Yet, such an approach could be possible in the future, using modern techniques and stripped of the moral encumbrances of the past. Whether this would provide more effective control than the current method is unknown. These and other considerations must be realistically examined if we are not just to record history but to learn from it.

CLINICAL SPECTRUM

The method of recording venereal disease problems in the U.S. armed forces has generally been to divide them into three broad categories: gonorrhea, syphilis, and other venereal diseases. The category of other venereal diseases is

one of great interest and importance, but gathering exact incidence figures is difficult because a number of diseases were reported together. The venereal diseases are discussed here in two general groups. Group 1 consists of those conditions which are primarily manifested by urethritis: gonorrhea, postgonococcal urethritis, nonspecific urethritis, and Reiter's syndrome. Group 2 consists of those conditions in which urethritis is not a principal manifestation but in which penile lesions and/or inguinal adenopathy are the major presentations; within this group are lymphogranuloma venereum, chancroid, and syphilis.

Section I. Urethritis Syndromes

Colonel John J. Deller, Jr., MC, USA (Ret.), and Dallas E. Smith, M.D.

GONORRHEA

Etiology

The causative organism of gonorrhea is *Neisseria gonorrhoeae*, commonly referred to as the "gonococcus." This gram-negative diplococcus belongs to the same genus as the meningococcus. Although the organism is aerobic, it grows best when stimulated with carbon dioxide. Its requirements for growth and survival are stringent, making confirmation by culture techniques difficult, especially under conditions of field medicine. When the gonococcus dies, a highly irritant endotoxin is liberated, producing the purulent discharge and erosive balanitis which are the hallmarks of the clinical infection. Early in the course of infection, the organisms can be seen extracellularly in the urethral discharge and later within the polymorphonuclear leukocytes (Fiumara 1972).

Clinical Features

Clinical manifestations may occur from 1 day to 2 weeks following sexual contact, with an average incubation period for males of 3 to 5 days. The individual usually reports a penile "drip" as the first symptom, although on careful questioning, descriptions of variable sensations in the penis followed by frequent urination, with or without dysuria, are elicited. The discharge is generally cloudy white to creamy (fig. 61). Constitutional symptoms are usually absent in the early, uncomplicated case.

This overt presentation in the male is contrasted by the often silent disease (75 percent of cases) in the female. Early recognition and treatment are therefore more likely in the male. If the urethritis is neglected or inadequately treated, serious complications may occur. The infection may spread locally to involve the prostate, seminal vesicles, and epididymis, or it may produce septicemia with occasional gonococcal arthritis. This latter complication, seen frequently in general hospitals in CONUS, was rarely recorded in Vietnam (Deller 1968). Gonococcemia can produce vesicular and pustular eruptions followed by



FIGURE 61.—Typical urethral discharge, gonococcal urethritis. (Courtesy, Col. John J. Deller, Jr., MC.)

petechiae similar to those seen in meningococcemia (Fiumara 1972). Meningitis also may occur but is quite rare and was not a recorded complication of gonococcal infection in Vietnam.

Laboratory Diagnosis

In the male with purulent urethral discharge, the diagnosis is not difficult. Gram's stain of the urethral discharge will show the typical organism within polymorphonuclear leukocytes in nearly 98 percent of cases. Few laboratory procedures have such a fine record.

Ever since the recognition and designation of a group of organisms known as the tribe Mimeae (De Bord 1943), so named because of their similarity to the tribe Neisserieae in clinical, smear, and culture characteristics, concern has arisen that the "nonsophisticated" smear may be an inadequate means of diagnosing gonococcal urethritis. Moreover, since these organisms are not sensitive to penicillin (but rather to tetracyclines), "misdiagnosis" may account for some of the increasing resistance of *Neisseria gonorrhoeae* to penicillin. In 1967, 376 cultures of material from urethral discharges were performed at the 9th Medical Laboratory. (The results of the fresh Gram's stains were not reported and no mention was made as to whether an appropriate "transgrow" medium was used to support the fastidious gonococcus during transport to the laboratory.) Two percent of these cultures grew members of the tribe Mimeae (Smith 1968a).

Most recent studies (Schroeter and Pazin 1970; Holmes et al. 1967) fail to support the contention that these organisms constitute a serious problem in differential diagnosis and thus in accounting for "penicillin-resistant gonococci."

Treatment

After a quarter of a century of antibiotic therapy for *N. gonorrhoeae* infections, penicillin remained the drug of choice during the Vietnam conflict despite clear documentation of a slowly developing bacterial resistance to the drug. The average sensitivity of gonococcal strains from treatment failures was 0.1 units/ml in 1954; by 1969 it was 0.5 units/ml. During the same period, the MIC (minimal inhibitory concentration) of the most resistant gonococci increased from a high of 0.2 units/ml to 3.5 units/ml (Schroeter and Pazin 1970, p. 555).

This change in sensitivity of the gonococcus to penicillin required a gradual increase in single-dose therapy from 100,000 units before 1950 to 4.8 million units or more in Vietnam in 1970 (Schroeter and Pazin, p. 555). Concern over this problem, augmented by reports indicating that Southeast Asian strains of the gonococcus had even greater resistance than strains isolated from other geographical areas, led to several clinical trials of alternative methods of therapy (table 34).

TABLE 34.—Gonorrhea treatment schedules given clinical trials by the U.S. Army in Vietnam

Drugs	Dose	Number of cases	Percent of cure
I. Penicillin, I.M.	2.4 million units	1,029	93.2
and probenecid	1.0 g stat, 0.5 g at 6 and 12 h		
II. Penicillin, I.M.	4.8 million units	169	99.0
and probenecid	1.0 g stat, 0.5 g at 6 and 12 h		
III. Tetracycline	Three groups:	109	
	A. 2,500 mg, repeat after 12 h	}	87.2
	B. 2,500 mg, repeat after 24 h		82.6
	C. 3,500 mg, one time only		77.4
IV. Tetracycline (recommended)	1.5 g stat, 0.5 g every 6 h x 4 days	(3)	(3)

¹Treatment failures from schedule I.

²Cumulative, schedules I & II.

³No reliable data.

Sources: (1) Schedules I, II, and IV: Commander, U.S. Army Medical Command, Vietnam, 1969. Army Medical Department Activities Report to The Surgeon General, p. 15. (2) Schedules I, II, and IV: personal records of Lt. Col. Andre J. Ognibene, USARV Medical Consultant, 1969. (3) Schedule III: Scherman, B. M.; Dunkelberg, W. R., Jr.; and Conte, N. F. In Annual Progress Report, U.S. Army Medical Research Team (WRAIR) Vietnam and Institute Pasteur of Vietnam, 1 Sept. 1967-30 June 1968, pp. 161-65.

From these data and studies done elsewhere, it appeared that a single large injection of procaine penicillin G (aqueous), 4.8 million units, plus probenecid to

retard renal excretion of the penicillin, assured bactericidal blood concentration sufficient to eradicate 99 percent of the organisms. Evidence of even greater resistance did not develop until after cessation of hostilities.

Although only penicillin and tetracyclines received wide usage in Vietnam, other alternatives were available, such as erythromycin and cephaloridine. Recently two new treatment programs were added: doxycycline or minocycline given as a 100-mg capsule twice a day for 3 days; and spectinomycin given intramuscularly in a single dose of 4 g. This latter drug may be the alternate choice in penicillin-sensitive individuals and for penicillin-resistant organisms.

The treatment of the patient with gonorrhea cannot be considered complete unless the patient is reexamined immediately to detect primary treatment failures. Since a few patients in Vietnam with gonorrhea were also found to have syphilis (which may not be eradicated by some gonorrhea treatment schedules), a serologic test for syphilis should have been performed on every patient. Those with positive tests should have received appropriate therapy for syphilis and those with negative results should have had a repeat serologic test at the end of 4 to 6 weeks. Unfortunately, these ideal measures were difficult to effect in combat situations. The practice of providing 2.4 to 4.8 million units of procaine penicillin to patients with gonorrhea, however, effectively eliminated concomitantly acquired syphilis (table 35). The practice of self-administration of tetracycline, however, did little to abort late onset syphilis. Continuous education was needed at all levels to ensure that treatment was obtained from the appropriate medical authority.

TABLE 35.—*Relative efficacy of various schedules of therapy in aborting incubating syphilis*¹

Treatment	Dose	Total cases		Developed syphilis		Relative efficacy (percent)
		Treated	Observed ²	Number	Percent	
Penicillin G benzathine	2.4 million units	84	79	0	0	100
Aqueous penicillin G procaine	4.8 million units	72	66	0	0	100
Aqueous penicillin G procaine	2.4 million units	55	51	0	0	100
Penicillin G procaine with aluminum stearate	2.4 million units	13	10	0	0	100
Penicillin G procaine with aluminum stearate	3.0 million units	11	9	0	0	100
Tetracycline phosphate	3.0 g	76	73	9	13.3	56
Tetracycline phosphate	1.5 g	28	28	6	22.1	27
Placebo		61	57	16	30.3	0
Total		400	373	31	9.0	

¹Cases exposed within preceding 30 days.

²Observation for 90 days after treatment.

Source: Schroeter, A. L.; Turner, R. H.; Lucas, J. B.; and Brown, W. J. 1971. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. *J.A.M.A.* 218: 711-13. © 1971, American Medical Association.

POSTGONOCOCCAL URETHRITIS

The syndrome of PGU (postgonococcal urethritis) has received little attention, despite its high prevalence, and very little was recorded about its incidence in the Army Command Health Reports from Vietnam. This was perhaps because of the imprecision of diagnosis and the lack of a firm definition of the syndrome. It remains unclear whether PGU represents persisting gonorrhea, a normal, gradual resolution of urethral inflammation after gonorrhea has been adequately treated, nongonococcal urethritis acquired coincidentally, or secondary infection by the normal urethral flora (Holmes et al. 1967).

Recent Studies on Possible Pathogenesis

The study by Holmes and coworkers (1967) raised two significant considerations concerning the possible etiology of this syndrome. First, a far greater number of cases of PGU were found in patients whose original gonococcal organisms demonstrated in vitro resistance than in patients whose organisms showed a more "normal" sensitivity pattern. Such an association could be taken as evidence that, although all the patients were treated "successfully" for their acute gonococcal urethritis with penicillin, a suboptimal dose (for the more resistant strains) could induce gonococcal L-forms which then might be responsible for the PGU syndrome. The second finding was that a definite relationship could be shown between PGU and the presence of urethral mycoplasma in patients initially treated with penicillin. It might thus be concluded that the simultaneous acquisition of mycoplasma and gonococcus organisms is frequent and that mycoplasmas may produce postgonococcal urethritis as a direct consequence of the concomitant urethral mucosal damage produced by gonorrhea itself. The accumulating evidence that much nonspecific (nongonococcal) urethritis may be caused by mycoplasma supports this contention.

Therapeutic Implications

If gonococcal L-forms are responsible for PGU, then low-dose penicillin regimens may induce the syndrome, especially when dealing with relatively resistant strains of *N. gonorrhoeae*. If mycoplasmas are acting as secondary invaders and are responsible for PGU, no penicillin regimen, without a tetracycline, will be effective in eradicating this syndrome. More careful scrutiny of the cases during the immediate followup period will be required before the magnitude and importance of this syndrome can be clarified.

NONSPECIFIC URETHRITIS

Etiology and Incidence

Data from the Army monthly morbidity reports are insufficient to define

either the magnitude of the problem of NSU (nonspecific urethritis) or its etiology. Since Guiard's original description (1897), there have been many studies in search of a cause of nonspecific urethritis, and a number of agents have been implicated. These include various bacteria and mycotic agents, *Trichomonas vaginalis*, TRIC (trachoma inclusion conjunctivitis) agent, and mycoplasma (King 1972). Studies in England and in U.S. naval personnel in the Philippines suggest that the incidence of NSU is at least equal to, if not greater than, that of gonococcal urethritis (Frederick 1972).

Clinical Course

Nonspecific urethritis usually presents in the male in "subacute" form, with a low-grade urethritis, variable dysuria, and a scanty mucopurulent discharge. The "acute" form is clinically indistinguishable from gonorrhea when a profuse urethral discharge, urinary frequency, and dysuria occur. The symptoms usually appear within 5 to 14 days after intercourse. Subclinical infection is thought to be common. Prostatitis is an infrequent complication. Association with Reiter's syndrome will be discussed separately.

Diagnosis and Treatment

The diagnosis of NSU is one of exclusion. The Gram's stain of the NSU exudates should reveal abundant polymorphonuclear leukocytes without gram-negative intracellular diplococci and should be free of trichomonads and yeasts.

Nonspecific urethritis does not respond to penicillin therapy at any dose level. Most cases are treated with tetracycline, but as the entity probably has more than one causative factor, response to therapy is not always dramatic. Search for a specific agent is required. Many studies have attested to the superiority of tetracyclines over penicillin, placebo, and spontaneous remission with "cure rates" ranging from 59 to 94 percent (Frederick 1972). Both dosage and duration of therapy appear to be important in achieving a "cure": a minimum of 1 g per day in divided dosage for a minimum of 10 days is necessary. The best results from a particular treatment program were reported by John (1971). In a comparative study using 500 mg of oxytetracycline three times daily for 5 days, 500 mg four times daily for 10 days, and 250 mg four times daily for 21 days, he reported successes of 55 percent, 72 percent, and 87.5 percent, respectively, after 3 months. The longer the duration of therapy, the lower is the relapse rate.

The proven value of tetracycline therapy in the treatment of both PGU and NSU seems to strengthen the contention that mycoplasmas (cultured from significant numbers of patients with both these syndromes) may well be the major etiologic agent in these infections.

REITER'S SYNDROME

History and Military Significance

Hans Reiter (1916) first described the triad of urethritis, arthritis, and conjunctivitis in young males in the German Army. Other manifestations, such as distinctive lesions of the buccal mucosa, of the glans penis (circinate balanitis), and of the skin (keratoderma blennorrhagicum) may also occur, singly or in varying combinations. Although the syndrome may appear following epidemics of shigella dysentery (Noer 1966), the vast majority of cases appear to be venereally transmitted.

Despite the importance of Reiter's syndrome, it was rarely diagnosed in Vietnam. It was usually considered to be nonspecific urethritis and lumped into the "other venereal disease" category or was diagnosed as "nonspecific arthritis." Nevertheless, the syndrome was seen frequently in general hospitals to which patients were referred during the war years. Records kept by the medical consultant in 1969 revealed that up to 13 patients in a single month were evacuated because of manifestations of this syndrome.*

Etiology

Because of the clear epidemiological evidence, an infectious cause of Reiter's syndrome has long been sought. Reiter himself believed it was caused by a spirochete; later, mycoplasma seemed to be the most likely etiologic agent. More recently, evidence has suggested that a *Bedsonia* [*Chlamydia*] organism may be the agent (Schachter et al. 1966). However, precise data indicating the exact etiology (if a single agent is responsible) are not yet available. The common occurrence of mycoplasma in the normal urethra and its increased occurrence in patients with "pure" NSU suggest that this agent might be found in patients with Reiter's syndrome, but whether it is causative remains questionable. The failure of tetracyclines to eradicate the disease can be used as evidence against this etiology. The theory that *Bedsonia* organisms cause the syndrome is supported by the fact that other *Bedsonia* infections may be transmitted venereally (TRIC agent urethritis and conjunctivitis, and lymphogranuloma venereum).

Most of the material under "Reiter's Syndrome" in this chapter is derived from the following article by the author (1968b): Reiter's syndrome. *Present Concepts Int. Med.* 1:46-50.

*Lt. Col. Andre J. Ognibene, MC, USARV Medical Consultant 1969. Unpublished data.

Clinical Features

The classic case of Reiter's syndrome consists of the triad of arthritis, urethritis, and conjunctivitis, but most authorities agree that the diagnosis may be made in the absence of the complete triad, especially when mucocutaneous or other manifestations are present. The disease tends to be self-limited, with the average duration of the initial attack being 3 months. However, recurrence in 50 percent of cases studied has been reported by Csonka (1965), and a small percentage of these patients may develop permanent joint and visual disability.

Transient or recurrent nonspecific urethritis may be the initial manifestation. However, gonococcal urethritis is frequently seen in association with Reiter's syndrome and the diagnosis must be suspected in the patient with arthritis and gonorrhea in whom urethritis and arthritis fail to respond to adequate penicillin therapy. The entire genitourinary tract may be involved, leading to simple cystitis, hemorrhagic cystitis, prostatitis, prostatic abscess, and, rarely, hydronephrosis and nephritis.

A mild, self-limited, bilateral conjunctivitis is the usual ocular manifestation. However, eye symptoms may be minimal and may not be readily volunteered by the patient. Anterior nongranulomatous uveitis may be the first indication of Reiter's syndrome, but it usually follows repeated episodes and, in this setting, may be severe. Keratitis, corneal ulcerations, and cataracts have also been reported.

Arthritis is the most disabling aspect of the syndrome. It is an asymmetric polyarthritis most commonly involving joints of the lower extremities, although almost any joint in the body may be involved. Knees, ankles, toes, heels, and the Achilles tendon insertions are frequent sites. Swelling in the phalanges, similar to that seen in psoriatic arthritis, tends to involve the distal as well as the proximal joints and soft tissues, which gives rise to the phrase "sausage-like swelling." The true incidence of sacroiliac involvement is not known, but it has been reported in up to 50 percent of cases (Csonka 1965, p. 147) and tends to be bilateral.

Mucocutaneous lesions are of great diagnostic importance and must be carefully looked for. Circinate balanitis is considered the most diagnostic of all lesions in this syndrome. This consists of discrete, round, shallow ulcers or hyperkeratotic lesions on the head or shaft of the penis (fig. 62). The lesions are asymptomatic and do not tend to become secondarily infected. A nonspecific stomatitis is also quite common. Finally, keratoderma blennorrhagicum, consisting of erythematous based vesicles or pustules, may appear anywhere on the skin but is most common on the palms and soles. Nail changes consisting of subungual accumulation of keratin, which makes the nail appear yellow, opaque, and elevated, may be seen and may result in loss of the nail. The pitting of the nail seen in psoriasis is absent, however (fig. 63).

Involvement of other organ systems has been covered in Csonka's excellent review. Manifestations include cardiac conduction defects, aortic insufficiency, thrombophlebitis, pulmonary infiltrates, and peripheral neuritis, all of which are quite rare.

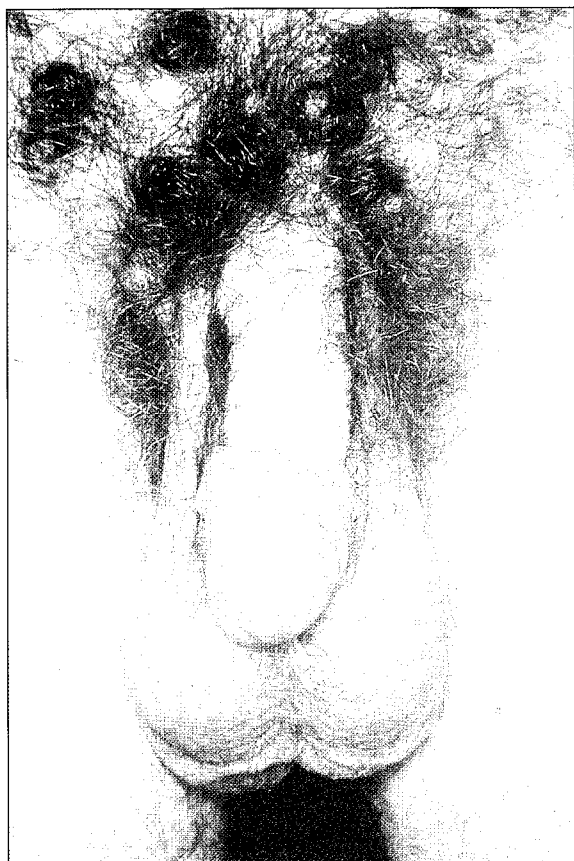


FIGURE 62.—Typical desquamation of the scrotal and penile areas in Reiter's syndrome. (Courtesy, Col. John J. Deller, Jr., MC.)

Laboratory Findings

There are no characteristic laboratory findings in Reiter's syndrome although an association with HLA-B27 (histocompatibility leukocyte antigen) has been demonstrated. The white blood count may be normal or show slight leukocytosis. The E.S.R. (erythrocyte sedimentation rate) may or may not be elevated. Sterile pus in the urine is found when urethritis or cystitis is present. Analysis of joint fluid shows acute inflammatory cells in the early stages and chronic inflammatory cells in the later stages of synovitis. The white blood cell count is seldom above 20,000 cells per cubic millimeter, and synovial fluid glucose is not markedly reduced as in bacterial pyarthrosis. Complement fixing antibodies to *Bedsonia* group antigen ("psittacosis titer") may be present in 37 percent of cases, and isolation of *Bedsonia* from urethra, conjunctiva, synovial fluid, and synovial membrane has been reported.

Roentgenograms of the feet and sacroiliac joints may be helpful. Erosions



FIGURE 63.—Typical scaling and nail changes of Reiter's syndrome. Top: Feet. Bottom: Hands.
(Courtesy, Col. John J. Deller, Jr., MC.)

about the os calcis at the region of the Achilles tendon and plantar fascia insertion, and periosteal new bone formation about the metatarsal shafts of the proximal phalanges are common. Loss of cortical margin of sacroiliac joints is an early sign of involvement of the joints and may precede by a considerable period of time the gross bony sclerosis and ankylosis characteristic of the later stages.

Treatment

Treatment, in the absence of a confirmed etiology, must be directed at symptomatic relief. Tetracycline has occasionally been beneficial in controlling urethritis, but the arthritis is not responsive. Salicylates, indomethacin, and phenylbutazone may be helpful in controlling acute synovitis, but because of spontaneous remissions, therapy is difficult to evaluate. The use of corticosteroids has given disappointing and irregular results and should be reserved for exceptional cases. Methotrexate has been reported to be effective in some cases (Jetton and Duncan 1969). Iritis, which may result in permanent visual impairment, should be treated by an ophthalmologist. The prognosis in Reiter's syndrome is generally excellent and, despite even severe involvement, relatively few patients develop permanent disability.

Section II. Nonurethritis Syndromes

*David T. English, M.D., Edward G. Southwick, M.D., and
Colonel John J. Deller, Jr., MC, USA (Ret.)*

LYMPHOGRANULOMA VENEREUM

Incidence and Etiology

LGV (lymphogranuloma venereum) is a systemic venereal disease caused by a member of the *Bedsonia* group, *Miyagawanella [Chlamydia] lymphogranulomatosis*. Incidence of LGV is increasing in the United States. Although no accurate statistics are available, recent studies (Abrams 1968; Schachter et al. 1969) indicate that part of this increase was caused by dissemination of the disease by soldiers returning from Southeast Asia. Of 20 patients studied at Letterman General Hospital in 1967-68, 18 were recent Vietnam returnees (Abrams 1968).

Clinical Features and Course

After an average incubation period of 10 days, a small papule commonly develops on the external genitalia. This primary chancre is inconspicuous and is



FIGURE 64.—Typical inguinal bubo in a patient with lymphogranuloma venereum. (Courtesy, Col. John J. Deller, Jr., MC.)

noticed in less than one-half of the cases (Costello and d'Avanzo 1948).

After a highly variable interval, from 1 week to 6 months, several syndromes ensue. The inguinal syndrome is most frequent in men and is the most common clinical picture of LGV. It is characterized by tender inguinal lymphadenopathy and systemic signs and symptoms. Some nodes have been misdiagnosed and surgically excised as hernias. The tender bubo is irregularly fluctuant. Its long axis is parallel to the inguinal ligament, which occasionally may separate matted groups of glands forming the pathognomonic "groove sign." Spontaneous rupture of fluctuant areas may occur through the overlying violaceous skin and form multiple fistulas (fig. 64).

The rectal syndrome, seen most often in women and male homosexuals, is characterized by a bloody mucopurulent discharge. Abdominal pain and constipation or diarrhea may coexist.

Systemic signs and symptoms accompany the inguinal more frequently than the rectal syndrome; these include fever, headache, weight loss, arthralgia, arthritis, meningismus, conjunctivitis, urethritis, hepatitis, and pneumonitis. Skin manifestations include erythema multiforme, erythema nodosum, scarlatiniform eruptions, and a peculiar photodermatitis (Canizares 1954, pp. 62-96; Abrams 1968, pp. 201-2).

Untreated cases of LGV may resolve spontaneously in 8 to 12 weeks. However, the majority of untreated patients develop chronic complications. The

rectal syndrome may progress to rectal fistulas, abscesses, or strictures. Such lesions are far more common in the female (Abrams 1968, p. 201). Strictures are associated with an increased incidence of carcinoma of the rectum (Levin et al. 1964). Both rectal and inguinal syndromes may lead to genital elephantiasis.

Laboratory Diagnosis

There may be a mild leukocytosis with a relative lymphocytosis or monocytosis. The E.S.R. is elevated and there may be reversal of the albumin-globulin ratio. A high incidence of false positive serologic tests for syphilis has been noted (Canizares 1954, pp. 70-71, p. 82).

A positive Frei test (greater than 6 mm induration) occurs in 12 to 40 days and usually remains positive for many years and sometimes for life (Greenblatt, Dienst, and Baldwin 1959). A recent study (Schachter et al. 1969) revealed the Frei test to be insensitive compared to the CF (complement fixation) test (36 percent positive compared to 83 percent). There appears to be no correlation between the skin test reaction or the CF test and the severity of the disease (Abrams 1968).

Treatment

Drugs recommended include tetracyclines, sulfonamides, or both. Tetracycline 500 mg every 6 hours and sulfisoxazole 4 g loading dose and 500 mg every 6 hours were used for therapy in Vietnam. Bed rest and cool compresses offer supportive therapy (Abrams 1968). If bubo aspiration is necessary, an indirect lateral approach through adjacent normal skin greatly lessens the likelihood of the development of a persistent draining sinus. Surgery is required for chronic sequelae, but surgical drainage of the acute bubo is to be avoided.

CHANCROID

Etiology and Incidence

Chancroid is an ulcerating venereal infection caused by the gram-negative bacillus *Haemophilus ducreyi*. The disease is endemic in tropical climates and therefore was common in U.S. Armed Forces in South Vietnam. Because of the short incubation period of chancroid (2 to 5 days) and the short lapse in travel time from South Vietnam to CONUS (sometimes within 30 hours), many men who acquired the disease during the last few days or hours of their tour first presented with it in CONUS. The disease was second only to gonorrhea among venereal infections early in the war (Kerber, Rowe, and Gilbert 1969). Similar reports during the Korean war suggest that this experience was not unique (Asin 1952).

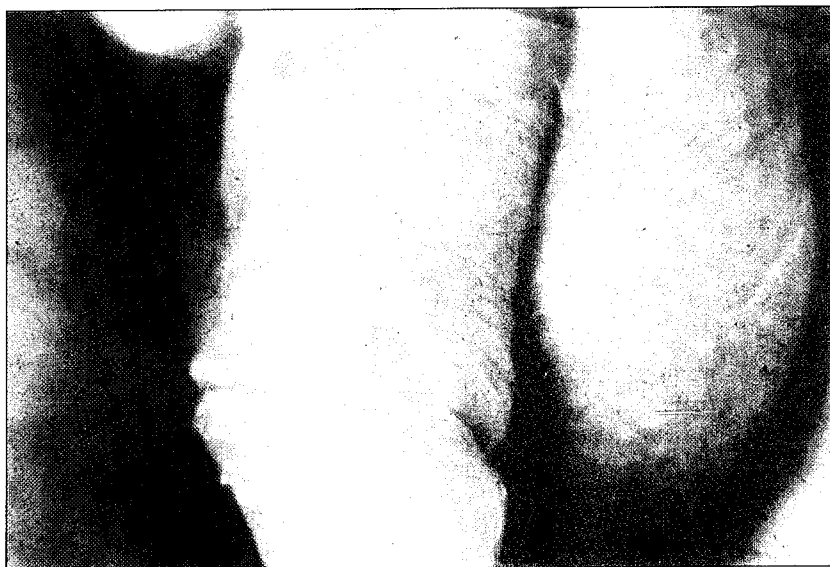


FIGURE 65.—Typical penile ulcer in a patient with chancroid. (Courtesy, Col. John J. Deller, Jr., MC.)

Clinical Features

The initial sign of chancroid is a small, red papule which rapidly becomes pustular and then ulcerates (Rook, Wilkinson, and Ebling 1968, pp. 629-30) (fig. 65). Often there are several ulcers. These ulcers are characteristically covered with a necrotic grayish exudate and surrounded by an erythematous halo. They are usually tender and painful, in contrast to those of syphilis. In order of frequency, the lesion occurs in the male in the prepuce, frenulum, penile shaft, and anus. In the female it occurs in the labia, clitoris, fourchette, vestibule, anus, and cervix. In about one-half of the cases, inguinal adenitis occurs about 1 week after the appearance of the ulcer. Typically, this is unilateral and painful and may suppurate (Olansky and Norins 1971, pp. 1978-80).

Diagnosis

The diagnosis of chancroid is usually made on a clinical basis rather than by attempting to demonstrate *H. ducreyi* because of the sometimes misleading or unreliable results obtained from the smears or cultures. Heyman, Beeson, and Sheldon (1945) consider the disease to be most easily and accurately diagnosed by biopsy. A granulomatous reaction is usually sufficiently distinct to permit a diagnosis of chancroid. Biopsy, however, is impractical in many situations. Furthermore, in 50 percent of the cases, a diagnosis can be made by staining a smear of material from an ulcer. Exudate from the undermined border of the ulcer is obtained on a sterile cotton-tipped applicator stick (Borchardt and Hoke 1970). By carefully rolling the stick 180 degrees in one direction (never back and forth)

onto a glass slide and staining with Gram's or methyl green-pyronine (Unna Papanheim) stain, one can see the organisms. They are shown to occur in pairs and short chains and often are parallel to shreds of mucus. A positive culture, when it can be obtained, is the most reliable criterion for the diagnosis; however, this procedure is rarely used.

Kerber, Rowe, and Gilbert (1969) cultured lesions on rabbit and human blood, on EMB (eosin-methylene blue) agar, and on thioglycolate broth. In no instance could they specifically identify *H. ducreyi*. Deacon et al. (1956) used fresh human clotted blood as a culture medium and obtained positive results in only 18 of 62 patients. Borchardt and Hoke (1970) used heat inactivated serum obtained from a patient as the culture medium and obtained positive results in 21 of 24 patients. Formerly, the Ito-Reenstierna vaccine for skin testing was considered helpful in establishing a diagnosis, but this vaccine is no longer available. It consisted of killed *H. ducreyi* and, when injected intradermally, produced a reaction in active and remote cases.

The differential diagnosis includes herpes progenitalis which has become secondarily infected, traumatic ulcerations, and primary syphilis. Because syphilis infections may occur simultaneously with chancroid (the mixed ulcer) or subsequent to it, repeated darkfield examinations for *Treponema pallidum* are indicated in every genital ulcer, even when the diagnosis of chancroid has been established. Followup serological tests for syphilis are also indicated (Borchardt and Hoke 1970).

Treatment

The sulfonamides are effective and specific for chancroid. A dose of 4 g daily in divided doses for 7 to 14 days is generally adequate. Tetracycline has also been effective. However, in a study conducted on 90 consecutive patients at the 9th Medical Battalion, Bearcat, Vietnam, in 1968, Kerber, Rowe, and Gilbert (1969) found sulfisoxazole to be more effective than tetracycline, which was inadequate alone. They evaluated the combination of tetracycline and sulfonamide and concluded that it was effective as primary therapy or for the occasional patient who failed to heal promptly on sulfonamide alone.

Based on the study of Kerber et al., the basic regimen used through 1970 consisted of sulfonamide or sulfonamide-tetracycline combination. Marmar (1972), at the 24th Evacuation Hospital in 1970, treated 67 patients who were resistant to these drugs. These patients presented coronal or foreskin ulceration, inguinal adenopathy or abscess, and/or abscess of the penile shaft. Treatment consisted of kanamycin 500 mg twice daily for 6 to 14 days. The lesions were cleansed daily with povidone-iodine surgical scrub, and abscesses were drained by sterile aspiration. All patients responded, but the various lesions healed in differing periods of time. Storey, at the 93d Evacuation Hospital, utilized sodium cephalothin for a similar group of patients.

Resistant chancroid did not become a major disease problem. However, the potential of this disease for significant impact in tropical military operations remains.

SYPHILIS

Incidence

The available data from the 10 years of the Vietnam conflict indicate an overall incidence rate of approximately three cases of syphilis per 1,000 average strength per year. During the last 3 years of U.S. involvement (1970 through 1972), the hospital admission rate for syphilis was only 0.2 per 1,000 average strength per year (PAD) which is probably a fair estimate of the total admission rate for the 10 years based on the incidence rates. Thus, syphilis was not a significant medical problem, despite the high rate of gonorrhea and other venereal disease. Why this should have been remains somewhat of a mystery. This is not unique to Vietnam, however, for despite the rapid upswing in gonorrhea worldwide, the incidence of syphilis has barely risen.

Diagnosis

The classic features of primary and secondary syphilis are well recorded and need no further elaboration here. The important aspect to consider is that all patients with genital lesions of any type should have serologic tests to rule out the possibility of syphilis and repeated darkfield examinations (3 consecutive days) before institution of penicillin or broad-spectrum antibiotic therapy. One should suspect syphilis when a typical clean, well-demarcated chancre is found; however, there are many mixed infections (chancroid being the most common associated disease), and in tropical climes, there is often a secondary bacterial infection which masks the typical chancre. A similar alertness to the possibility of secondary syphilis must be maintained when one is confronted with almost any type of generalized skin eruption and, again, a serologic test for syphilis must be obtained (fig. 66).

The serologic screening tests in general usage in Vietnam were the VDRL (Venereal Disease Research Laboratory) slide test and the RPR (Rapid Plasma Reagin) test. In primary syphilis, the VDRL test usually becomes positive about 30 days after infection (7 to 10 days after appearance of a chancre), while the RPR test usually is positive about 14 days after infection.

Two problems may occur in the serodiagnosis of syphilis. First, if the test is done too early and not repeated, the diagnosis may be missed. Second, BFP (biologically false positivity) may occur with the commonly used reagin tests. If a specific treponemal antigen test is not employed for confirmation, a false diagnosis of syphilis may be made, and the disease inducing the BFP may be missed.

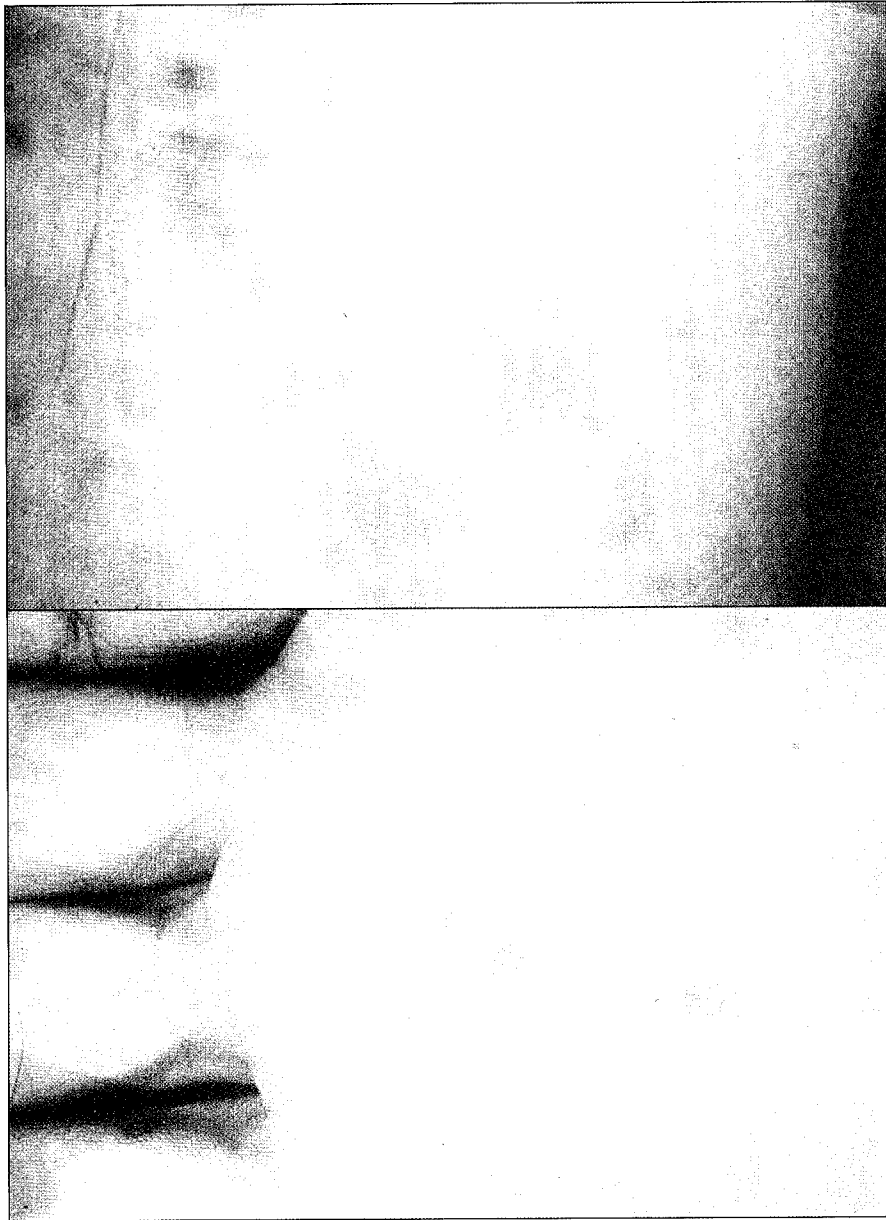


FIGURE 66.—Top: Typical cutaneous lesions of secondary syphilis. Bottom: Typical palmar lesions of secondary syphilis. (Courtesy, Col. John J. Deller, Jr., MC.)

In secondary syphilis, there is less problem with diagnosis, since the serologic test is always reactive. The problem of biological false positive reactions remains but can usually be clarified by a treponemal antigen test.

Treatment

The treatment of syphilis remains unchanged from the established therapeutic regimens outlined in Technical Bulletin 230 (TB MED, pp. 7-13). The area of greatest concern is whether the low incidence of syphilis in association with the high incidence of gonorrhea in Vietnam can be partially attributed to inadequate followup practices leading to missed diagnoses. Although it has been reported that in general the treatment schedules used in gonorrhea may also be curative for incubationary syphilis (Schroeter et al. 1971), this remains questionable, especially in view of the variety of therapeutic regimens used in treating gonorrhea.

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General Medicine

Brigadier General Andre J. Ognibene, MC, USA

The classic confrontation between diseases inherent in large populations and men of science and knowledge surfaces in times of war. In November 1888, in his address at the opening of the institute which bears his name, Louis Pasteur said (Hume 1943, pp. 216-17):

Two opposing laws seem to me now in contest. The one law of blood and death, opening out each day new modes of destruction, forces nations to be always ready for battle. The other, a law of peace, work and health, whose only aim is to deliver man from the calamities which beset him. The one seeks violent conquests, the other the relief of mankind. The one places a single life above victories, the other sacrifices hundreds of thousands of lives. The law of which we are the instruments strives even through the carnage to cure wounds due to the law of war. Treatment by our antiseptic methods may preserve the lives of thousands of soldiers. Which of these two laws will prevail, only God knows. But of this we may be sure, that science, in obeying the law of humanity, will always labor to enlarge the frontiers of life.

The medical effort in Vietnam was dedicated to enlarging "the frontiers of life" for American soldiers there. Medical experience in Southeast Asia encompassed the breadth of internal medicine and provided the internist with a challenge equivalent to his skills and ingenuity. It would be impossible to review in depth the difficult and complex parade of patients, both American and Vietnamese, who passed through the portals of medical wards in Vietnam. Many physicians were exposed for the first time to the rigors of tetanus and rabies on the one hand and the management of an acute myocardial infarction without a CCU (coronary care unit) on the other. The challenge was immense and the response genuine. Those returning from a year of medical service in Vietnam felt a significant sense of fulfillment and contribution. Some left newfound knowledge in publications and theses to those who followed. In all, it was an effort characterized by rewards and successes in a time and place where rewards were few indeed.

DISEASES OF GENERAL MEDICAL SIGNIFICANCE

Under the pressure of combat casualties, malaria, and hepatitis, the continued presence of general medical diseases in a large troop population often is forgotten. A review of the medical consultants' reports gives testimony to the broad range of problems encountered in internal medicine practice in Vietnam. Reports in 1965 and 1966 were preoccupied with the serious threat to field

operations posed by malaria. However, in late 1966, indications appeared that the practice of internal medicine in Vietnam was not limited to malaria, typhus, and other exotic diseases. For example, a report in November 1966 referred to a merchant marine seaman with severe emphysema and pneumonia who developed bronchospasm unresponsive to steroids; he ultimately bled from a stress ulcer and died at the 3d Field Hospital (Blohm 1966).

In the ensuing years, reports were filled with references to complex and catastrophic disease states encompassing all subspecialties of medicine. The 3d and 8th Field Hospitals in successive weeks admitted two patients with acute myelogenous leukemia. Both patients died from subarachnoid hemorrhage before further evacuation (Ognibene 1969a-Jan.) Hemolytic anemia caused by G6PD (glucose-6-phosphate dehydrogenase) deficiency and agranulocytosis related to dapsone usage were also part of the large group of hematologic disorders occurring in the troop population.

Intravascular coagulopathy was an ever-present problem in infected and wounded patients. The laboratory support necessary to delineate specific clotting disturbances was not available, and documentation of diagnosis was impossible. Heparin was given empirically to patients with infection and thrombopenia (Ognibene 1969b). Patients with oozing and bleeding wounds were given fresh frozen plasma and heparin in the hope that dilution of clotting factors and consumption could be corrected concurrently. The need for organized hematologic interest in coagulation problems of infection and wounding was obvious. Belated efforts by the renal unit in Saigon in 1969 and the surgical research unit in Long Binh in 1970 did not produce tangible results before the withdrawal of troops and the cessation of hostilities.

The major endocrine dysfunction addressed by the internist was diabetes. As was noted in World War II, those diabetic patients who were encountered, although relatively few in number, presented significant problems in diagnosis, treatment, and disposition. In Vietnam, increased exposure to skin infections, fungus disorders, and infectious diseases of many varieties posed additional risks for the diabetic patient. In January 1969 the 93d Evacuation Hospital reported a patient with diabetic ketoacidosis who had been serving in Vietnam while on insulin. Studies of the dark mucoid material which drained from his nose revealed hyphae and spores of mucormycosis. He died despite surgical and medical therapy (Koch 1969).

Diabetes per se did not disqualify one from military service in Vietnam, and many individuals were retained on active duty despite significant insulin requirements. Most insulin-dependent patients found it difficult to maintain control because of the variability of diet and activity; in addition, the requirement for refrigeration of insulin supplies was often neglected. It became quite clear that insulin-dependent patients should have been excluded from service in a combat zone and that the exclusion of all diabetic patients from tropical combat theaters should have been seriously considered.

The neurologist encountered Japanese B encephalitis, ingestion of C-4 plastic explosive (cyclonite, 91 percent; polyisobutylene, 2.1 percent; motor oil, 1.6 percent; and di(2-ethylhexyl) sebacate), cerebral malaria, and drug overdose,

all characteristic of Vietnam experience. In addition, however, patients presented for therapy with disorders unrelated to the tropical environment. Stroke, epilepsy, and unclassified seizure disorders were common. In 1969, the 93d Evacuation Hospital reported a 23-year-old soldier with periodic hypokalemic paralysis (Koch 1969) and, in 1971, a 20-year-old soldier died of Guillain-Barré syndrome at the same hospital (Davis 1971). All of the acute neurologic emergencies which a population of 500,000 can generate were seen at the medical services in Vietnam.

The neurologic centers at Long Binh and Nha Trang were barely adequate to provide the consultative support required. Most basic neurologic practice was handled by the internist at fixed USARV (U.S. Army, Vietnam) hospitals but, because of the ever-present difficult or unusual case and the requirement for EEG interpretation, the neurologist had a critical role. The allocation of one neurologist to each medical group was a realistic and effective solution. Ready consultation for hard-pressed medical services was maintained within medical group hospitals and patients with significant neurologic dysfunction were concentrated at a neurology center where subspecialty expertise could be focused.

As evacuation channels developed and more patients were taken to USARV hospital facilities, field and evacuation hospitals had to modernize. In the early years of the war, portable field defibrillators were found only in large hospitals. In addition, most internists in USARV hospitals were handicapped by the absence of cardiac monitoring equipment, a facility for blood gas analysis, and rapid serum and urine electrolyte determinations. By 1969, these impediments had been surmounted. All medical services in USARV hospitals were required by the USARV medical consultant to have monitoring and defibrillating equipment. In addition, a six-bed centralized CCU was established at the 3d Field Hospital. This facility was required because a large population of MACV (Military Assistance Command, Vietnam) Headquarters personnel was being supported and because the average age of the troop population supported was thus raised. With the opening of the CCU in 1969 (fig. 67) in association with medical intensive care and the renal unit, the 3d Field Hospital provided the best in intensive medical therapeutics in Southeast Asia. Patients with any variety of renal, cardiac, or other medical illness could be stabilized there until transfer was safe and practical. In the first 6 months of operation, the CCU achieved 18 successful cardiac resuscitations and provided extensive monitoring support to critically ill patients undergoing hemodialysis (Paletta 1969).

Of particular concern to the internist and the cardiologist alike was the presence of individuals with prior myocardial infarction. Those on anticoagulation therapy for any reason were difficult, if not impossible, to maintain in-country. Under combat conditions, such patients were of little value to their organization and presented a burden to the medical command. Attempts to exclude from military service those people who were incapable of worldwide service precluded some of these difficulties, but errors continued to occur as exemplified by the following description of a patient at the 3d Field Hospital (Davis 1971).

A 39-year-old enlisted man with a P4 profile (unfitting) and a waiver to re-

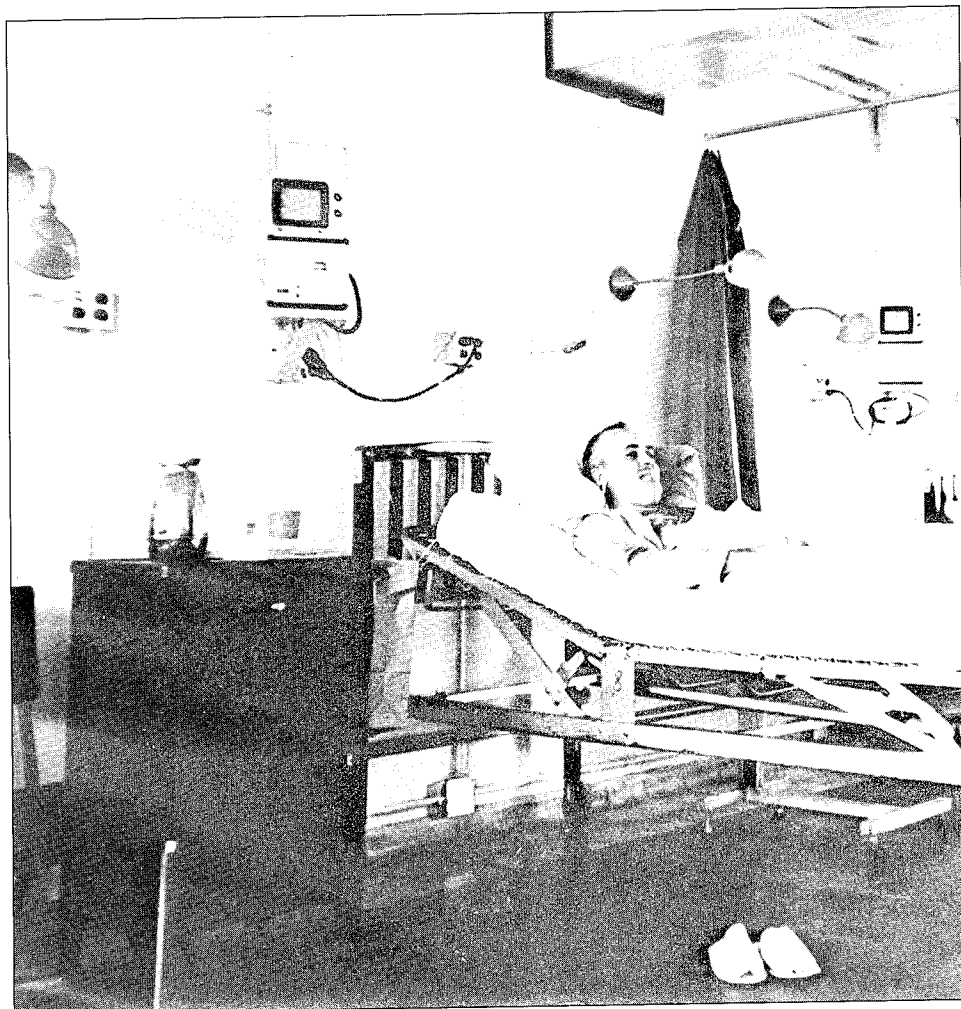


FIGURE 67.—Cardiac monitoring equipment in 3d Field Hospital coronary care unit, Saigon, 1969.

main on active duty had suffered two previous myocardial infarctions. He arrived in Vietnam in 1970 while on chronic anticoagulation. Some weeks after arrival, he suffered acute chest pain and was brought to the 3d Field Hospital. Despite efforts at resuscitation, the patient died.

The establishment of coronary care facilities at the 3d Field Hospital and the continued presence of patients with coronary disease on USARV hospital wards prompted a study of the incidence of coronary artery disease in combat casualties. The presence of a significant degree of coronary artery disease in the troop population in Vietnam was established by postmortem studies. Coronary angiography and cardiac dissection were performed on 105 U.S. soldiers killed in action, ranging in age from 18 to 37 years. Some evidence of atherosclerosis was

found in 45 percent, and 5 percent had gross evidence of severe coronary atherosclerosis (McNamara et al. 1971). According to these data, the incidence of coronary artery disease in this young age group in Vietnam was somewhat less than that reported in a similar series in the Korean war (Enos, Holmes, and Beyer 1953); nevertheless, it was significant. Older individuals in staff positions and advisory capacities added to the population in which clinical coronary artery disease surfaced. A significant incidence was noted at all hospitals, not just those supporting headquarters areas.

The need for resuscitation equipment and facilities for patients with cardiac arrhythmias (both postoperative surgical patients and intensive care medical patients) was realized early in the conflict. Such specialized equipment for support of fixed hospital installations must be standardized in future TOE (table of organization and equipment) or TD (table of distribution) units.

Although it was an immense burden in World War II, duodenal ulcer disease never became of medical significance in the Vietnam war. In Palmer's summary (1970) of military experience with ulcer disease, he notes that in 1941, 31 percent of all medical patients in the British Army had peptic ulcer and between 1942 and 1945, 53,450 men were separated from the U.S. Army because of gastroduodenal ulcer. Review of the USARV medical consultant's records of 1969, when there were approximately 500,000 troops in Vietnam, reveals only 10 patients per month requiring evacuation out of country because of ulcer disease (Ognibene 1969a). Selective Service data for 1942-43 indicate that 5.8 per 1,000 individuals, 17 to 37 years old, had ulcer disease (Palmer 1970). If this rate remained valid, approximately 3,000 ulcer patients were on duty in Vietnam in 1969.

Rounds at USARV hospitals rarely revealed a patient occupying a bed because of ulcer disease. This sharp contrast with previous conflicts was a result of the medical era's relaxation of rigid therapy for ulcer patients. Special diets were not prescribed in Vietnam; the medical policy encouraged selection of standard messhall foods and even more strongly recommended the use of combat rations. Profile limitations applied in the United States were, in general, removed on arrival in Vietnam. If antacids were considered necessary by the patient or physician, the chewable tablet could be carried in the standard combat uniform. The emphasis on effective performance without any limitation was rigidly adhered to. Thoughts similar to the following (Palmer 1970, p. 876) were kept in the minds of all physicians by constant official reminder.

Some patients seem unable to respond to treatment until they have been successful in manipulating a release from an unwanted job or from military service. But to emphasize the administrative trap that is involved, all will agree that, as soon as the presence of an ulcer is permitted to become either a handy medical excuse for getting rid of an unwanted employee or a personal excuse to get out of an unwanted job, a farce is created.

Hospitalization was not part of therapy unless a complication was documented. Hemorrhage, perforation, or obstruction resulted in early evacuation from country for followup therapy in the United States. The policy of management of routine therapy on an outpatient basis with no restrictions on any activity resulted in an incalculable manpower savings. Those patients who were

admitted for therapy found themselves at the 6th Convalescent Center doing calisthenics or filling sandbags and generally requested early return to their units.

The policy of encouragement, motivation, and removal of secondary gain, while successful in maintaining troop strength, was never formalized or carefully documented, nor were the results ever tabulated. Future endeavors in this area should begin with formal directives followed by documented study of results, favorable and unfavorable, in relation to both patients' and units' requirements. The dramatic difference between the impact of ulcer disease in Vietnam and that in World War II should be scientifically secured since application to civilian practice can have far-reaching economic impact.

The significant number of soldiers with allergies or asthma led to the clarification of treatment and evacuation policy. In general, it was believed that patients with allergic disorders were fit for duty in USARV. Individuals undergoing desensitization provided their serum and their supporting medical unit administered it. If an individual had received serum from an Army allergy clinic, his unit physician could simply request resupplies through military channels. However, primary allergy evaluations had to be deferred until the individual returned to CONUS (continental United States). Insect allergy did not preclude duty in South Vietnam. A vaccine for various stinging insects, prepared by the allergy clinic of Walter Reed General Hospital, was available through the medical consultant. Skin testing in this condition was not warranted before the institution of hyposensitization, which was based strictly on the history obtained from the patient. Specific instructions were published in the USARV Medical Bulletin in January 1969 and delivered to all unit physicians. Under these policies, there was significantly less difficulty in managing patients with allergic disorders in Vietnam than in previous conflicts.

Despite recommendations following World War II that "irrespective of the cause or causes, tropical service appears to be contraindicated for individuals giving a history or presenting symptoms of asthma" (MD-IM3, p. 185), no absolute restriction applied to the Vietnam conflict. Patients with asthma generally were fit for duty in Vietnam; however, if repeated hospitalization was required or if the patient failed to respond to conventional therapy, medical evacuation was considered. The consulting internist's findings and documentation provided by the unit physician were the basis for the decision. In the absence of this documentation, it was often difficult for a consulting internist to decide on the appropriate disposition of the case. With the establishment of communication under the MEDCON (Operation Medical Consultant) concept, asthmatic attacks were better documented in health records in unit-level medical services.

A major portion of the evacuations from Vietnam in the chest disease category were for asthma; at the peak of troop concentration, at least 15 patients monthly were removed from duty there because of it (Ognibene 1969a). If induction rates of 1 per 1,000 for asthma in World War II (Gold and Basemore 1944) remained valid, approximately 500 asthmatics were on duty in Vietnam during 1969 and approximately 320 completed their tour. Whether the 320 addi-

tions to troop strength justified the medical effort expended on the 180 evacuees is difficult to ascertain, but the Vietnam experience may provide a basis for further decisions about asthma and the combat soldier.

Patients with urolithiasis were not included in evacuation breakdowns for the medical consultants since most of them were evacuated from urology services. Studies of the actual incidence of urolithiasis and associated diseases are not available. However, an analysis of admissions to the 568th Medical Company, which supported 15,000 American soldiers, is available (Scott, Ardison, and Wells 1967). Of the 2,050 admissions during the 1-year period, 54 were for urolithiasis; 51 patients were white, 2 were black, and 1 was Vietnamese. During the period of study, blacks represented approximately 18 percent of total hospital admissions, although their incidence of admission for renal stone was low. No significant seasonal variation was noted in the Cam Ranh Bay area, and there seemed to be no relation of the disease to time served in Vietnam. Three individuals were in their first month in Vietnam. Of the 54 patients, 10 gave a previous history of urolithiasis, and in 5 a positive family history of the disease was obtained.

The clinical picture was remarkably similar in the majority of patients. Most presented a classical picture of sudden onset of severe unilateral costovertebral angle pain with radiation along the ureteral pathways. Attempts to correlate the incidence of urolithiasis with an acute diarrheal state were unsuccessful, and there were not sufficient data to document a state of dehydration. Unrecognized systemic illness manifesting as urolithiasis has been demonstrated in other studies, but in the evaluation of the 568th Medical Company patients, no primary diagnosis of gout, hyperparathyroidism, or other systemic illness could be found. Forty-four of the patients were returned directly to duty after a short period, while 10 were hospitalized in urology services of various supporting hospitals.

SNAKES AND LEECHES

A discussion of problems in general medicine in Vietnam could not be considered complete without reference to snakes and leeches. Although they posed only a minor medical problem, the psychological impact of unwarranted fear made a significant number of troops ineffective in tropical terrain. Leeches were, on the whole, less likely to promote noneffectiveness, although infestation with the nasal leech *Dinobdella ferox* (Blanchard) produced nosebleeds and hemoptysis (Keegan, Radke, and Murphy (1970). Snakes, on the other hand, were capable of inducing fear out of proportion to reality. Maj. Herschel H. Flowers, VC (fig. 68), and Capt. Frederick G. Berlinger, MC (1973), summarized the problem:

The authors found, upon interviewing troops in Vietnam, that the majority believed that poisonous snakes were to be found in abundance there and that few persons survived a bite. Soldiers from rattlesnake infested areas in the United States harbored little fear of these reptiles but were deathly afraid of the "bamboo vipers" of Vietnam. In actuality, the "bamboo viper" is a small snake which



FIGURE 68.—Maj. Herschel Flowers, VC, presenting to the 3d Field Hospital staff the lecture on snakes and snakebites which he gave at many other times and places during his Vietnam tour.

seldom injects sufficient venom to inflict a serious bite, whereas rattlesnakes are capable of producing death or permanent injury in victims. Almost all of the persons questioned had heard of the "cigarette snakes" (when you are bitten you only have time for one cigarette); or the "two-step snake" (no explanation necessary), but were not cognizant that only one snakebite death had occurred in US forces since United States involvement there.

Other misconceptions were that no antiserum existed for some of the snakes, and snakebites were very common. Studies indicated only 25-50 snakebite incidents occurred annually in US forces. Of these, only a few necessitated intensive therapy. Capitalizing on the average American's fear, the Viet Cong frequently left snakes in caves and bunkers to harass our troops and to impede their progress. In each case, great publicity was given the incident and fears were perpetuated. As a result, some soldiers refused to search tunnels, and some incidents of refusal to stand perimeter guard in a dark bunker were recorded. Incidents also occurred where positions were given away at night when a snake entered a foxhole.

There are three large categories of medically important snakes in Vietnam. The Elapidae family are the neurotoxic snakes, including cobras, kraits, and coral snakes; of these the Asian cobra and banded krait were significant. The sea snakes, of which there are 15 species, have a highly lethal myotoxic venom but were of little or no medical significance to U.S. troops. Of the pit vipers, which have a hemotoxic venom, the white-lipped bamboo viper and Malayan pit viper were most important. The most common venomous bite was from the arboreal white-lipped bamboo viper, but such a bite was never lethal for an American soldier (Berlinger and Flowers 1973) (fig. 69).

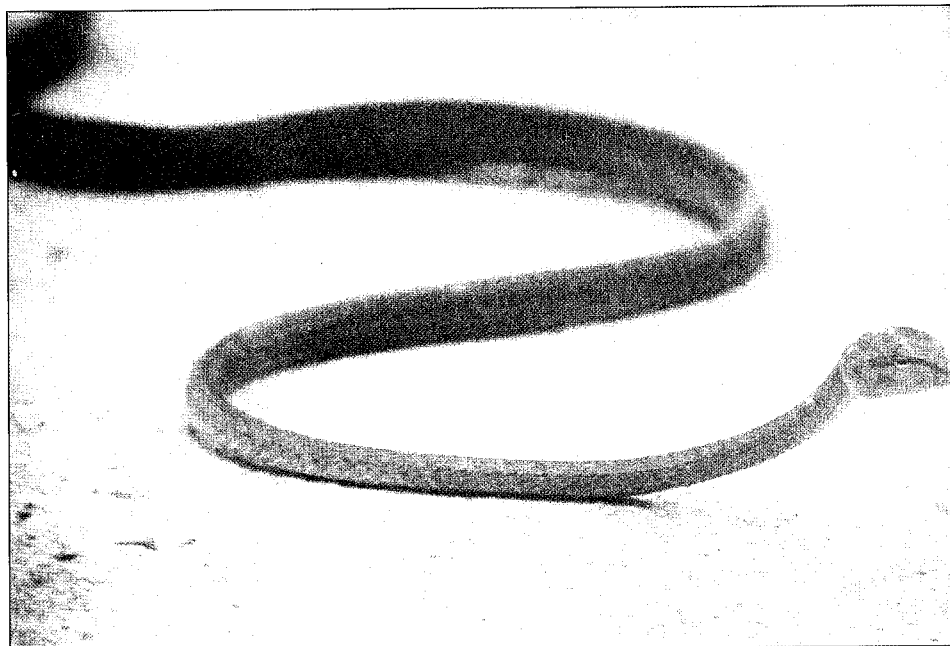


FIGURE 69.—Green coloring of the bamboo viper was excellent camouflage for its arboreal existence.

The commonest symptom of snakebite is fear, which can be easily overcome by authoritative reassurance and education programs. Treatment in the field or at an aid station was discouraged in favor of evacuation. General treatment measures included tetanus toxoid and analgesics, plus sedation and antibiotics when indicated.

Systemic treatment depends upon the type of snake involved; in all cases, specific antivenin should be used. For cobra bites, Cobra-Krait Polyvalent Antivenin (made by the Haffkine Institute, Bombay, India) was used immediately. For krait bites, the same antivenin was used, but treatment usually could be delayed until the patient was evacuated to a snakebite treatment center or until neurotoxicity became apparent. For viper bites, serial clotting times were followed but treatment did not begin until hemorrhagic signs became manifest. With bamboo vipers, the drug of choice was Polyvalent Crotaline Antivenin (Wyeth), while with Malayan pit vipers it was Thai Red Cross Anti-Malayan Pit Viper Antivenin.

Most bites were not by venomous snakes, however, and few of those which were caused systemic envenomation. Even fewer required any systemic therapy.

STAFFING REQUIREMENTS

Medical consultants maintained a deep and abiding interest in the flow of medical patients to hospitals and through the evacuation system. The records

they compiled are testimony to the magnitude of the medical effort. Although the actual practice of general internal medicine fell to those 40 to 50 internists in USARV hospitals, the need for medical expertise spread beyond the confines of the combat area. There were those whose abilities were exercised in hospitals in Japan and those who were required to provide additional staff support to medical services in CONUS. Just how many more physicians with a basic 3139 (internist) or medical subspecialty designation were actually required to render specialty care to an Army of one-half million in the field is difficult to estimate. For direct support only, 50 to 70 were appropriate estimates for Vietnam with up to 20 additional internists in Japan. However, another 50 to 70 individuals would be required in CONUS hospitals, bringing the total additional requirement, conservatively, to 120 to 160 internists. The conservatism of this estimate can be verified by a review of the medical admissions in Vietnam, tabulated by the USARV medical consultant (Edgett) for the calendar year 1970 from feeder reports sent him by the chiefs of medicine in USARV hospitals. That year there were 41,328 medical admissions. The peak year, 1969, produced even more, as was shown in chapter 3. The following is a partial breakdown of the categories of medical admissions in 1970:

Malaria, total.....	8,216	Typhoid and paratyphoid.....	38
Falciparum.....	4,635	Encephalitis.....	61
Vivax and mixed.....	3,581	Drug-related disorders.....	397
Amebiasis.....	246	Shigellosis.....	401
Hepatitis.....	1,666	Agranulocytosis.....	9

In addition, 556 hemodialyses were performed and 11 malaria deaths occurred. In December 1970, the medical consultant's final monthly tally was carefully recorded (table 36), a practice ultimately discontinued with the wind-down of troop strength. Admissions had fallen to one-half the 1969 monthly peak but still constituted a significant volume of patients.

TABLE 36.—Admissions for medical causes to USARV hospitals, December 1970

Hospital	Number of admissions	Deaths	
		Number	Cause
8th Field	60	0	
27th Surgical	111	1	Drowning.
85th Evacuation	218	0	
91st Evacuation	282	2	Drug overdose; acute myocarditis.
95th Evacuation	246	0	
18th Surgical	134	0	
67th Evacuation	289	0	
3d Field	274	3	Cerebral malaria; malaria with renal failure; ulcerative colitis.
3d Surgical	124	0	
24th Evacuation	339	0	
93d Evacuation	298	1	Guillain-Barré syndrome.
Total	2,375	7	

Source: Lt. Col. Joseph W. Edgett, Jr., MC, USARV Medical Consultant. 1970 yearly admissions tabulations. Report, undated.

The documentation of the effort in internal medicine, except for the continuation of the drug abuse program, ended in the ensuing months. A broad, sustained, and productive era in Army medicine had closed.

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Part III

CLINICAL DISORDERS: MALARIA

Malaria: Introduction and Background

*Brigadier General Andre J. Ognibene, MC, USA, and
Colonel O'Neill Barrett, Jr., MC, USA (Ret.)*

The battle between man and the pathogenic organisms with which he shares this planet has been a seesaw affair. Finding himself for years essentially defenceless against a disease, man has sometimes, by dint of hard work and a bit of luck, slowly turned the tide. With apparent victory in his grasp, his complacency has more often than not been abruptly interrupted by a vicious counter-thrust from the enemy and he has found himself in battle newly joined. This has been the story of man and penicillin against the staphylococcus, man and sulfadiazine against meningococcus and, more recently, man and the synthetic antimalarials against the *Plasmodium falciparum* [McCabe 1966].

Although American involvement in the war in Vietnam has ended, the battle against malaria throughout the world continues. The success of military campaigns since history has been recorded has often hinged on the presence of this disease rather than on tactics or military strength. The influence of malaria on military expeditions requires reemphasis early in any future operation to avoid those catastrophes of history so indelibly recorded on the pages of reports from ill-advised campaigns.

In the American Civil War, the armies of the North recorded 1,163,814 cases of "pure malarial fevers" among whites, of which 8,140 were fatal (Smart 1888, p. 79). C. H. Melville (1910) chronicled the disastrous French Campaign in Madagascar in 1895 in which there were only 13 deaths in action and more than 4,000 deaths directly attributable to malaria.

The Macedonian campaign in World War I was immobilized for 3 years by malaria. Among an average of 124,000 British troops per year in Macedonia, malaria accounted for 162,152 hospital admissions from 1916 to 1918 and an estimated 2 million man-days lost in 1918. The French Army fared no better; once, when ordered to attack, the French commanding general replied, "Regret that my Army is in hospital with malaria" (MacDonald 1923; Russell, West, and Manwell 1946).

After World War I, as soldiers returned to their homelands, serious epidemics developed throughout Europe. The Russian epidemic of 1922 was the largest in modern times in Europe, reaching as far north as Archangel within the Arctic Circle and causing millions of deaths among a population greatly weakened by famine and war (Boyd 1949, pp. 725, 731).

Successful therapy for malaria dates back to the first half of the 17th century. It was first recorded in a chronicle of the Order of St. Augustine, written by a monk of that order named Calancha and published in 1639. In this book appeared a paragraph describing the "fever tree" (arbol de calenturas) found in the country of Loxa (now the province of Loja, Ecuador), whose cinnamon-colored bark, when made into a powdered beverage, cured the fevers and "tertianas." Reference was made to miraculous results in Lima, Peru. Brother Calancha had announced a cure for the most widespread disease in the world. The tree was subsequently referred to as the Chincona tree, after the Countess of Chincon, who according to legend was cured of the "tertian fever" by its bark and then distributed it to the people of Lima, so that they might also be cured (Duran-Reynals 1946, pp. 20-32).

In 1776, the American Continental Congress purchased Peruvian bark for use by the Continental Army, probably representing the first involvement of the U.S. Army in treatment of this disease (Hume 1943, p. 160). Two centuries after its discovery, the active principle, quinine, was isolated and, in 1945, its chemical structure was defined.

The search for synthetic antimalarials began actively after the First World War when quinine was denied to the Germans by Dutch and British control of the East Indies. When the supply was once more cut off by the Japanese conquest of these islands in World War II, research was intensified, largely by investigators in the United Kingdom and the United States (Bruce-Chwatt 1964; Powell 1966; Duran-Reynals 1946, pp. 210-49).

World War II proved no exception to the established patterns of history. About 500,000 cases of malaria were reported in the U.S. Army alone (MD-PM6, pp. 116, 513). The experience of American troops in the Southwest Pacific in late 1942 and 1943 was particularly tragic. The impact of malaria on military operations there was vividly expressed in MacArthur's famous comment, "This will be a long war, if for every division I have facing the enemy, I must count on a second division in the hospital with malaria, and a third division convalescing from this debilitating disease" (Russell, West, and Manwell 1946). Both medical and line officers lacked adequate training and education about malaria control. For instance, despite the fact that anopheline mosquitos are night biters, large concentrations of troops were allowed to attend open-air night movies. Not until malaria discipline became a command interest was control achieved. Sir Neil Cantlie, Director General of British Medical Services, called it "Health Discipline" and stated, "When for the first time in history a combatant officer was considered unfit to command a unit on the grounds that he had allowed his men to become ineffective through disease, a new day in military medicine dawned" (MD-PM6, pp. 5-6).

Interest in antimalarials had been focused on the 8-aminoquinolines before World War II. German scientists made the first breakthrough in 1926 when they synthesized pamaquine, an 8-aminoquinoline which proved effective although too toxic for clinical use. Five years later, they synthesized quinacrine (Atabrine), a 9-aminoacridine. The secrets of its manufacture were soon discovered by the Allies, and it became the most important malaria suppressant used

during World War II. At that time it was repeatedly observed that quinacrine cured falciparum malaria. In early to mid-1943, with attention to prevention and the initiation of daily doses of this drug, the admission rates for malaria in the U.S Army in the Pacific diminished greatly (Bruce-Chwatt 1964; Powell 1966; MD-PM6, pp. 513, 568).

The intensive research carried out in the United States from 1941 to 1945 led to the screening of some 16,000 compounds, of which about 80 were selected for testing on human malaria. The advent of quinacrine as both a suppressant and a schizonticidal agent against erythrocytic forms of malaria was followed by the development of a less toxic drug, chloroquine. Field trials with chloroquine late in the war demonstrated its effectiveness as a suppressant against the New Guinea strains of *Plasmodium vivax* and *P. falciparum* and other strains from the South Pacific associated with a high incidence of relapse or recurrence. Chloroquine in a dose of 1.5 g over a 3-day period emerged as an effective regimen capable of clinically curing several strains of vivax and falciparum malaria (Bruce-Chwatt 1964; Powell 1966; MD-IM2, pp. 572-74).

Other drugs that emerged from this period were amodiaquine, a 4-aminoquinoline; sontoquine, which had been used successfully by the French in North Africa; chlorguanide (proguanil), a biguanide discovered by British investigators; and pentaquine, another 8-aminoquinoline. Subsequently, pyrimethamine, a diaminopyrimidine and antifolate structurally related to the active metabolite of chlorguanide, was discovered by a joint British and American effort in 1950. However, resistance to pyrimethamine occurred readily when it was used against falciparum strains in tropical Africa and later in the United States against *P. vivax* and *P. malariae* strains in neurosyphilis patients (Bruce-Chwatt 1964).

The development of these new drugs, as Tigertt (1966) observed, fostered complacency about malaria control. The development of eradication programs by epidemiologists, sanitarians, and health technicians under the auspices of the World Health Organization, the Rockefeller Foundation, and the national health agencies of many countries increased the sense of security.

With the opening of hostilities in Korea in 1950, malaria again became a focus of interest. Chloroquine had been field tested in nonimmune volunteers in Panama with excellent results (Elmendorf 1947; Boldt and Goodwine 1949). However, malaria relapse (predominantly in vivax strains) had been established as due to an exoerythrocytic stage, primarily in liver parenchymal cells (Shortt and Garnham 1948); the parasite in this stage is not vulnerable to schizonticidal drugs, such as chloroquine and quinacrine. Fortunately, investigators during World War II had been developing safe, effective drugs to prevent vivax (benign tertian) malaria. Primaquine, a 6-methoxy-8-aminoquinoline, the least toxic and most effective 8-aminoquinoline, was recognized for its value in preventing relapses and curing vivax malaria (Powell 1966; Alving, Arnold, and Robinson 1952; Edgcomb et al. 1950).

At the time of the Korean conflict, volunteer studies established the superiority of primaquine against the early and late tissue phase of the Chesson strain of *P. vivax*. The efficacy of this drug was further demonstrated by Alving

and associates (1953) in large-scale clinical trials. These researchers studied 975 U.S. soldiers with Korean vivax malaria who were treated at the station hospitals in Fort Knox, Ky., and Fort Benning, Ga. One group received the standard 3-day chloroquine regimen (total dose of 1.5 g); a second group received, in addition, 27 mg of pamaquine base daily for 14 days; and the third group received chloroquine plus 15 mg primaquine base daily for 14 days. The results are shown in table 37 and indicate the relapse rate after 2 years.

TABLE 37.—*Comparative incidence of relapse in treatment of Korean vivax malaria, 1951-52*

Treatment	Number of patients	Relapses	
		Number	Percent
1.5 g chloroquine base, 3 days	355	137	39.0
1.5 g chloroquine base, plus 27 mg pamaquine base daily, 14 days	272	2	0.8
1.5 g chloroquine base, plus 15 mg primaquine base daily, 14 days	348	0	0

Source: Alving, A. S.; Hankey, D. D.; Coatney, G. R.; Jones, R., Jr.; Coker, W. G.; Garrison, P. L.; and Donovan, W. N. 1953. Korean vivax malaria. II. Curative treatment with pamaquine and primaquine. *Am. J. Trop. Med.* 2: 970-76.

Based on preliminary results of this study, The Surgeon General of the Army approved the use of primaquine as terminal prophylaxis for 14 days in all U.S. troops returning from Korea. A team headed by Dr. Alf Alving was dispatched to the Far East Command in August 1951 to determine the practicability of this program and on 16 December 1951 it was initiated (FEC-AR).

Archambeault (1954) reviewed the incidence of malaria, based upon the number of troops transported by sea from the Far East between January 1951 and June 1953, and demonstrated a considerable reduction in the attack rate of vivax malaria as reported in the United States. Despite the availability of drugs and the medical effort, the U.S. Army suffered over 30,000 cases of malaria during the Korean conflict (McCabe 1966, p. 314).

In the ensuing years, a 3-day chloroquine, 14-day primaquine base regimen became the standard treatment for malaria throughout the world. Alving and his group were aware of the toxicity of a dose of 30 mg primaquine base daily (twice the amount needed to effect a radical cure of vivax malaria) (Arnold et al. 1954); they noted that approximately 10 to 15 percent of healthy American blacks developed a severe but self-limited hemolytic anemia when given a daily dose of primaquine. On the basis of additional clinical trials, Alving et al. (1960) predicted and then demonstrated that a single 45-mg dose of primaquine base per week plus the standard 300 mg of chloroquine would be an effective radical cure for naturally acquired vivax infection. Clinically demonstrable hemolysis was not produced by this dose of primaquine in adult males with glucose-6-phosphate dehydrogenase deficiency who were sensitive to the drug. This regimen was considered superior to the 14-day primaquine course.

In 1960, U.S. military and civilian personnel stationed in Korea were placed on weekly C-P (chloroquine-primaquine) tablets in a large-scale field trial involving more than 50,000 adults (Vivona et al. 1961). The results were so successful that the C-P tablet became the standard Army regimen by 1962 (DA-Circ).

Malariologists became complacent; some even believed significant drug resistance was unlikely to occur.

The basis for this contentment was a true sense of pride in the accomplishments of the preceding decade. This was the period of "smug satisfaction," characterized by comments such as one which appeared in the 1961 World Health Organization Bulletin indicating that the clinician had at his disposal a complete series of effective drugs for the treatment of all stages of the disease (Tigertt 1972). The efficacy of chloroquine and the 8-aminoquinolines essentially erased malaria from consciousness in the minds of military planners. Concomitant developments in insecticides led in 1955 to the World Health Organization global eradication effort (WHO), which was aimed at interrupting the transmission cycle by spraying infected areas twice yearly for several years, with a followup case-finding period.

At the dawning of the Vietnam war, progress in malaria control and therapy had apparently relegated the disease to historical interest and eliminated it as a threat to the modern field army (chart 12). The following chapters will attest to the error of this judgment. The ability of the malarial parasite to repeatedly meet the challenge of manmade chemical assault demands continued skepticism toward any claim to the development of a "final chapter" in the history of malaria.

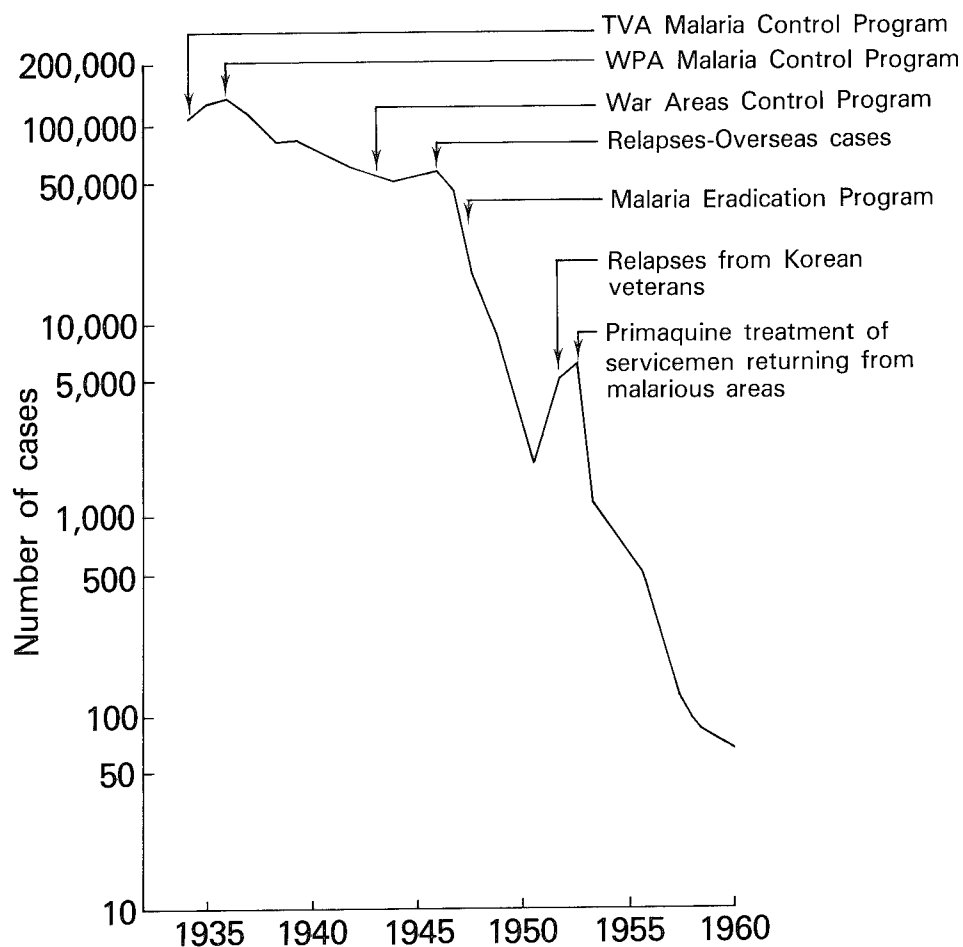
The story of malaria in Vietnam before American involvement has been briefly summarized by Kiel (1968). The disease had apparently been known for thousands of years and was ascribed to evil spirits in the mountainous regions, which lived near the water and attacked men during sleep. Persons with malaria were described by the popular phrase *mat bung, da chi* or "pallor of the face with slate-like tint."

One of the earliest stories describing the importance of what was probably malaria in Vietnamese history concerns the Mongolian ruler, Kublai Khan. To secure trade routes to India and Persia, he sent his son Togan in 1285 to conquer the Red River Valley in what is now Vietnam. After several months of success, many of the invaders fell ill from "the climate" and Togan was driven from the country (Kiel 1968, p. 2).

The French experience began in 1858, and malaria was soon the most serious medical problem. Laveran reported that between 1890 and 1896, 25 percent of the European troops stationed in Vietnam died of malaria. During the period 1945 to 1954, a total of 293,814 cases were recorded, though only 620 deaths occurred. The incidence of the disease showed a progressive decline during that period, however. In 1946, the incidence was 40 per 1,000 troops per year; it had dropped to 9 per 1,000 per year by 1954 (Kiel 1968, pp. 2-5).

Although precise statistical data are difficult to obtain, malaria had always been a serious problem for the Vietnamese. Data concerning deaths from infectious diseases in the period 1955-65 confirm its importance (table 38). The disease is hyperendemic in the Central Highlands. A study by Pham Trong indicated that in this area, at less than 1,000 meter altitudes, the splenic index is 50 to 80 percent and malaria parasites are found in 49 to 100 percent of groups studied. Above 1,000 meters, the splenic index falls to 3 percent or less, and

CHART 12.—Cases of malaria reported in the United States, 1935-60



Source: Neva, F. A. 1967. Malaria—recent progress and problems. *New England J. M.* 277: 1241-52. Reprinted by permission of The New England Journal of Medicine.

parasites are found in zero to 6 percent. The disease is common among the Montagnards and North Vietnamese refugees, especially the former. Pham Trong found that 473 of 1,834 Montagnard slides examined were positive, while only 13 of 512 refugee slides were positive (Kiel 1968, p. 3).

Along the littoral and in Saigon, the disease is far less common. Le Van Long studied malaria in children in the Saigon area and found that positive smears varied from 0.43 to 3.47 percent in different precincts. *P. vivax* was the predominant species, while in the highlands there was a higher incidence of *P. falciparum* (Kiel 1968, p. 4).

Data concerning malaria in Vietcong troops have been difficult to obtain, but 80 to 100 percent were reported to have contracted malaria despite the use

TABLE 38.—Deaths from infectious diseases in South Vietnam, 1955-65

Disease	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965
Malaria	508	683	1,116	681	332	211	153	44	40	24	21
Tuberculosis	436	645	1,123	327	508	441	427	470	289	204	214
Bronchopneumonia ..	337	397	243	192	290	223	230	280	276	193	167
Typhoid	61	47	84	53	66	83	77	69	70	67	66
Paratyphoid	18	3	1	12	16	10	8	13	9	2	4
Smallpox	218	56	1	11	3						

Source: Kiel, F. W. 1968. Malaria in Vietnam. In *Pathology Annual*, ed. S. C. Sommers, pp. 1-27. New York: Appleton-Century-Crofts.

of Paludrine prophylaxis (Kiel 1968, p. 9). Joseph Alsop (1967) reported that malaria rates of 50 to 75 percent were common. In his column he quoted a captured Vietcong battalion report: "General health in 10 days from Aug. 8 to 18—Malaria 60 percent, beri beri 10 percent, other diseases 20 percent."

Malaria was to have an impressive impact on American troops in Vietnam as well. The average annual rate of admission to hospital and assignment to quarters for this disease (26.7 per 1,000 per year) was low compared to those of the Southwest Pacific Area (70.3 per 1,000 per year) and the China-Burma-India theater (101 per 1,000 per year) during World War II. However, the debilitating impact of malaria on American troop strength was not reflected in overall rates. In December 1965, the overall rate in Vietnam reached a peak of 98.4 per 1,000 per year, while certain units operating in the Ia Drang valley experienced rates up to 600 per 1,000 per year and at least two maneuver battalions were rendered ineffective by malaria (Neel 1973, pp. 37-38).

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Malaria: Epidemiology

Colonel O'Neill Barrett, Jr., MC, USA (Ret.)

SPECIES AND VECTORS IN VIETNAM

Of the four species of malarial parasites affecting humans, three have been found in Vietnam: *Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium malariae*. While *P. falciparum* and *P. vivax* are endemic throughout the country, *P. falciparum* is hyperendemic in the Central Highlands. *P. vivax* and *P. malariae* occur in greater proportions along the coast and in the delta (Nowosiwsky 1966).

At least 11 species of anopheles mosquitoes have been identified as vectors in the transmission of human malaria (table 39). *Anopheles minimus*, *A. jeyporiensis*, and *A. balabacensis* are important in the mountains and forests while *A. sundaicus* and, to a lesser degree, *A. minimus* are important along the coast and in the Mekong Delta. *A. maculatus* is found only in the high plateau areas (map 6) (Kiel 1968; Stojanovich and Scott 1966).

When the rainy season begins in the highlands, the density of *A. minimus* increases. The breeding environment becomes unfavorable for this species as the rain increases in amount and force and the vector's density then decreases. *A. jeyporiensis*, which breeds effectively during the period of heavier rainfall, appears next. As the rainy season ends, this vector's density drops, in conjunction with increasing levels of *A. balabacensis*. The latter species seems to be the most important vector for the mountain-plateau regions, according to epidemiological observations (Nowosiwsky 1966, p. 32).

INCIDENCE IN AMERICAN TROOPS IN VIETNAM

During the early buildup of the American forces in Vietnam, between March 1962 and February 1963, 20 cases of malaria were treated at the 8th Field Hospital in Nha Trang. Nineteen of these were caused by *P. falciparum* and 1 by *P. vivax*.* During 1963 and 1964, 59 patients were hospitalized and treated. In 1965, as the buildup increased and units became engaged in inland tactical operations, 1,972 cases were recorded (Kiel 1968, pp. 6-7). The largest number of cases was seen during 1967 and 1968 (table 40), although the rate—expressed as

*Maj. O'Neill Barrett, Jr., USARV Medical Consultant, Mar. 1962-Feb. 1963: Unpublished data.

TABLE 39.—*Distribution and relative importance¹ of Anopheles species as malaria vectors in Vietnam*

Species	Coast and delta	Highlands
<i>Anopheles minimus</i>	+++	+++
<i>Anopheles sundaicus</i>	+++	—
<i>Anopheles sinensis</i>	++	—
<i>Anopheles vagus</i>	++	—
<i>Anopheles barbirostris</i>	+	—
<i>Anopheles tessellatus</i>	+	—
<i>Anopheles umbrosus</i>	+	—
<i>Anopheles jeyporiensis</i>	—	+++
<i>Anopheles balabacensis</i>	—	+++
<i>Anopheles aconitus</i>	—	+
<i>Anopheles maculatus</i>	—	+

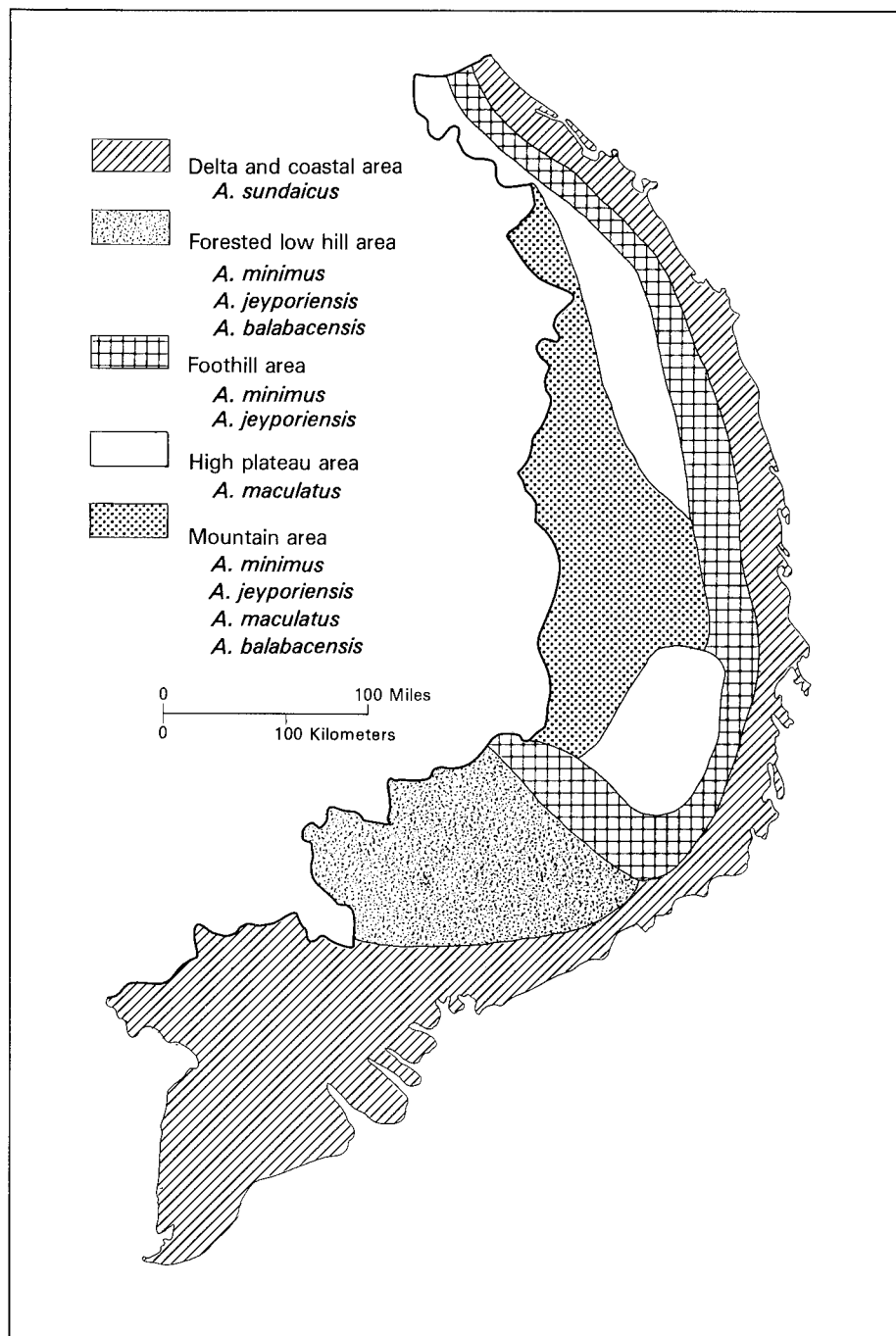
¹(+) and (—) indicate degree of importance, as interpreted by the author of this chapter.

Sources: (1) Stojanovich, C. J., and Scott, H. G. 1966. *Illustrated key to mosquitoes of Vietnam*. Atlanta: National Communicable Disease Center, U.S. Department of Health, Education, and Welfare, pp. 139-45. (2) Kiel, F. W. 1968. Malaria in Vietnam. In *Pathology Annual*, ed. S. C. Sommers, pp. 1-27. New York: Appleton-Century-Crofts.

number of admissions per 1,000 average strength per annum—showed a progressive decline from 98.4 per 1,000 per year in December 1965 to an average of 30 per year in 1969 (chart 13). From 1965 to 1970, a total of 78 deaths from malaria were recorded, an average of 13 per year (Neel 1973, p. 39).

Malaria rates have been shown to correlate with region of operation, climatic conditions, degree of contact with the enemy, proper use of malaria prophylaxis, and effectiveness of malaria discipline at the command level (Neel 1973, pp. 37-40). That region of operation is important is verified by the observation that, in Vietnam, very little transmission of malaria occurred in Army base camps or around cities and large towns, most of which had active insect control programs (Nowosiwsky 1966, p. 33), while large numbers of cases were reported from mountain and forest areas and from the Central Highlands (USARV-CHR 1967). The geographic distribution for the 8-month period of July 1967 to February 1968 is shown in map 7. This distribution generally is applicable to 1966 as well (map 8). Using such general epidemiological data along with local and regional malaria surveys, unit medical officers were able to compile experience maps of their sectors which helped them to estimate the number of malaria cases to be expected. A typical example is the map compiled by the division surgeon, 1st Cavalry Division, for the period of September 1965 to December 1966 (fig. 70).

Degree of contact with the enemy also had a marked effect on the incidence of new cases of malaria. In March and April 1966, the 1st Cavalry Division conducted field operations in hyperendemic areas, including Operations JIM BOWIE (13-21 March, in the Bong Son valley), LINCOLN (25 March-8 April, in the Ia Drang valley), and MOSBY (beginning 11 April in the southwest Kontum Province). The 1st and 3d Brigades of the division were involved in these operations while the 2d Brigade patrolled highway 19 and held the perimeter at An Khe. Following the first two operations, the 1st Brigade sustained 204 new cases



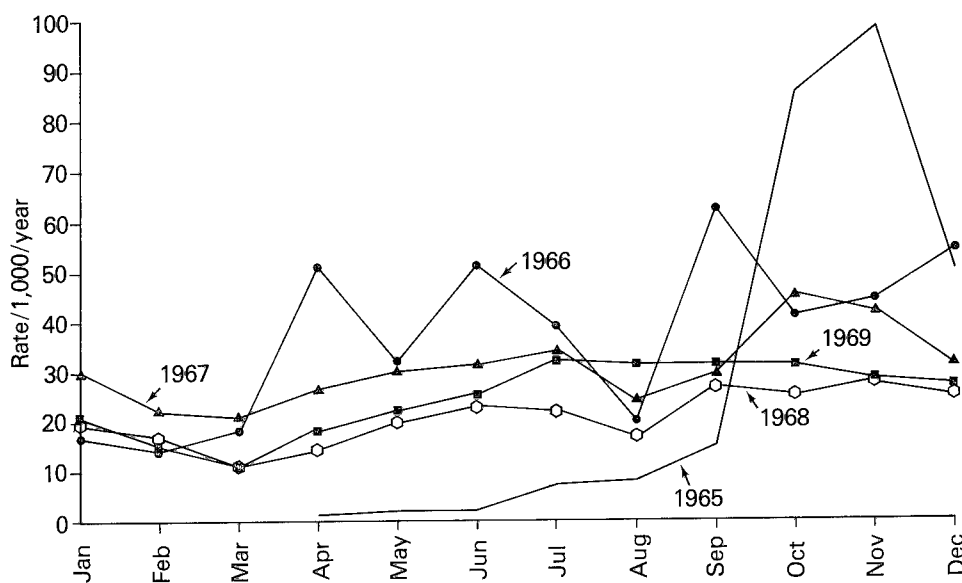
MAP 6.—Distribution of proven and suspected malaria vectors in Vietnam. (Kiel, F. W. 1968. Malaria in Vietnam. In *Pathology Annual*, ed. S. C. Sommers, pp. 1-27. New York: Appleton-Century-Crofts.)

TABLE 40.—Total cases and deaths caused by malaria, U.S. Army, 1965-70

Year	Number of cases	Number of deaths
1965	1,972	16
1966	6,662	14
1967	9,124	11
1968	8,616	15
1969	7,322	10
1970	6,718	12

Source: Neel, S. 1973. *Medical support of the U.S. Army in Vietnam, 1965-1970*. Vietnam Studies. Washington: Government Printing Office, p. 39.

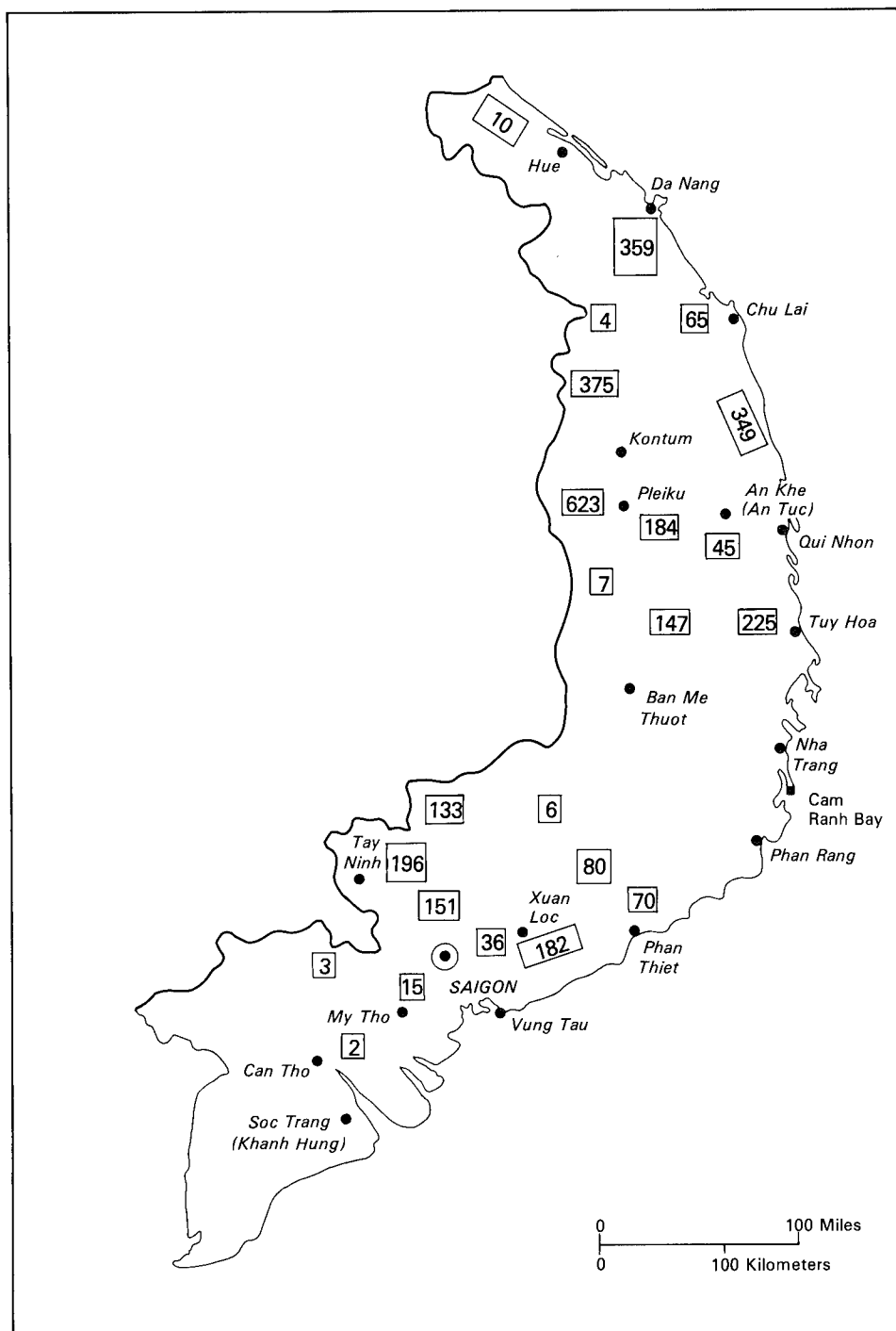
CHART 13.—Admissions to hospital and quarters for malaria among U.S. Army personnel in Vietnam, 1965-69



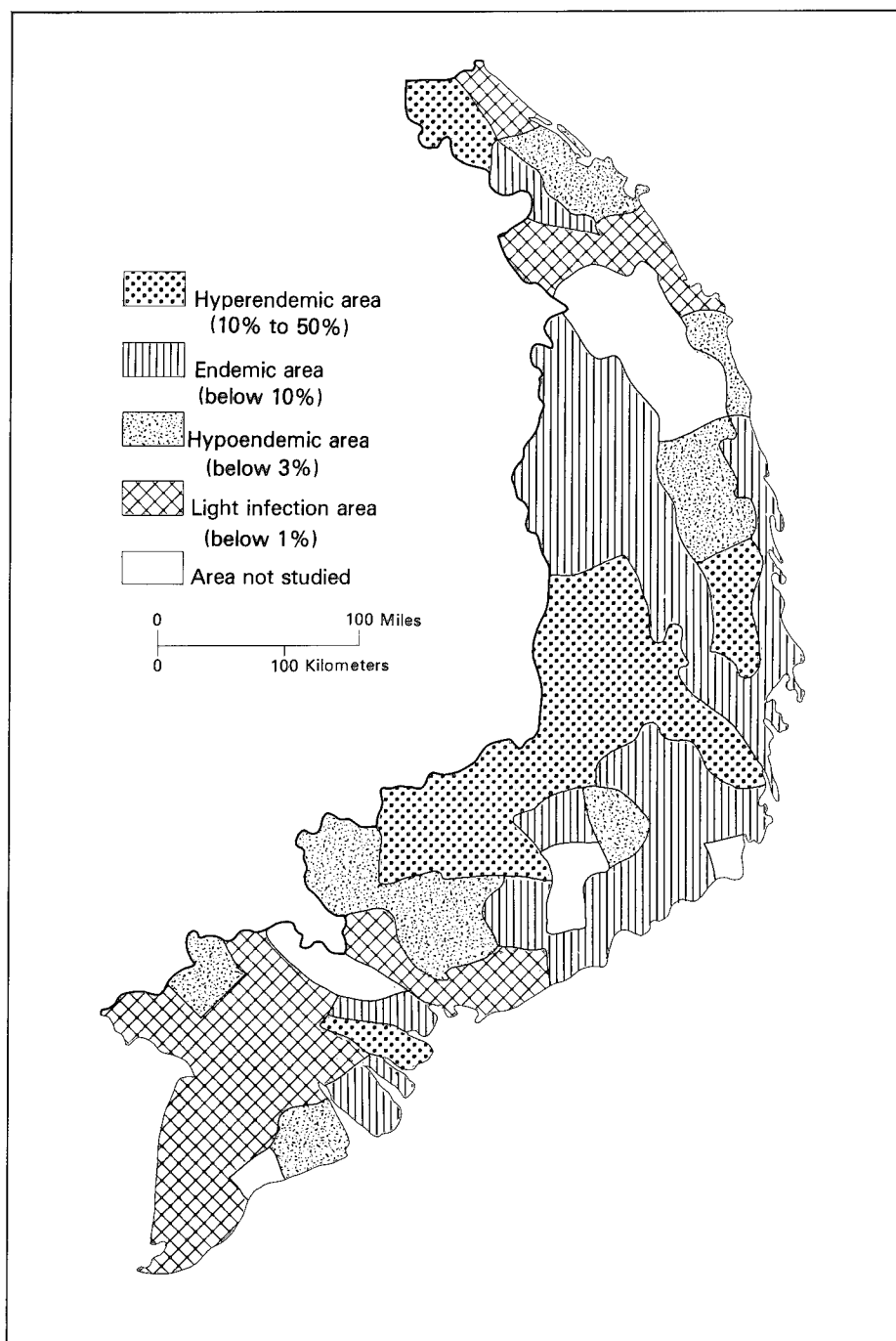
Source: Office of the Surgeon General, Department of the Army. Health of the Army, May 1965, May 1966, May 1967, May 1968, May 1969, and May 1970.

of malaria and the 3d Brigade had 104. Onset of the increase in incidence was shown in each instance to occur 14 days after the midpoint of an operation, corresponding to the usual 10- to 14-day incubation period for falciparum malaria. The 2d Brigade recorded only 12 new cases during the same period (USARV-MC).

Another example is the experience of a Special Forces Mobile Strike Force company, during Operation PAUL REVERE IV, November-December 1966. Chart 14 shows that five cases occurred early in the operation, whose date of onset precluded acquisition in the operational area. Subsequently, however, 43 cases were diagnosed. The first of these cases occurred 12 days after first exposure to the area and the last case 15 days after last exposure. The majority of



MAP 7.—Geographical occurrence of malaria, 29 February 1968. (USARV surgeon. 1968. Monthly Command Health Report to USARV commander, Feb. 1968.)



MAP 8.—Relative malaria endemicity in Vietnam, 1966. (Kiel, F. W. 1968. *Malaria in Vietnam*. In *Pathology Annual*, ed. S. C. Sommers, pp. 1-27. New York: Appleton-Century-Crofts.)

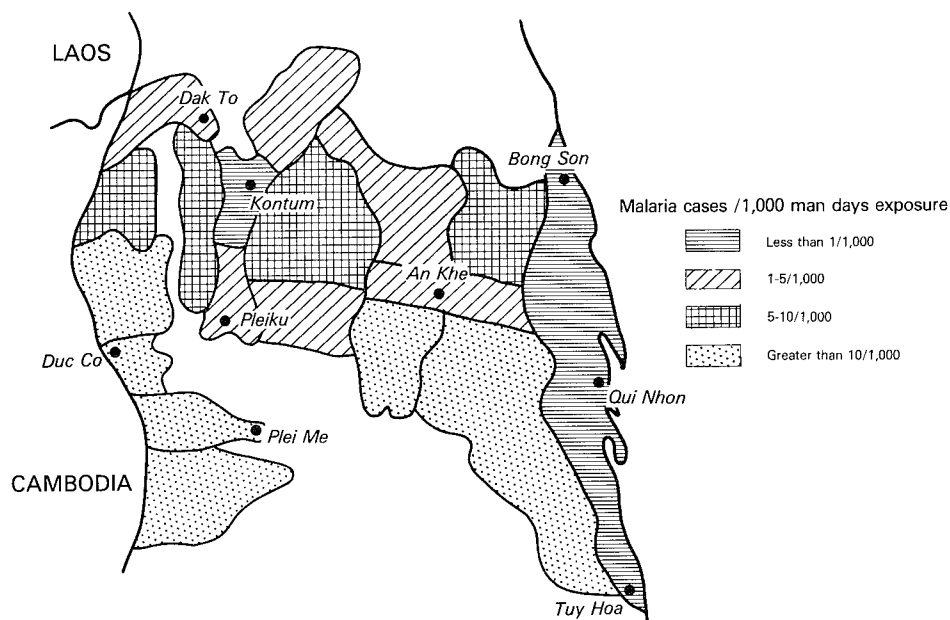


FIGURE 70.—Malaria experience, 1st Cavalry Division, September 1965-December 1966. (Kiel, F.W. 1968. Malaria in Vietnam. In *Pathology Annual*, ed. S. C. Sommers, pp. 1-27. New York: Appleton-Century-Crofts.)

cases occurred between 10 and 14 days after midpoint of exposure (Cottingham, Boone, and Legters).

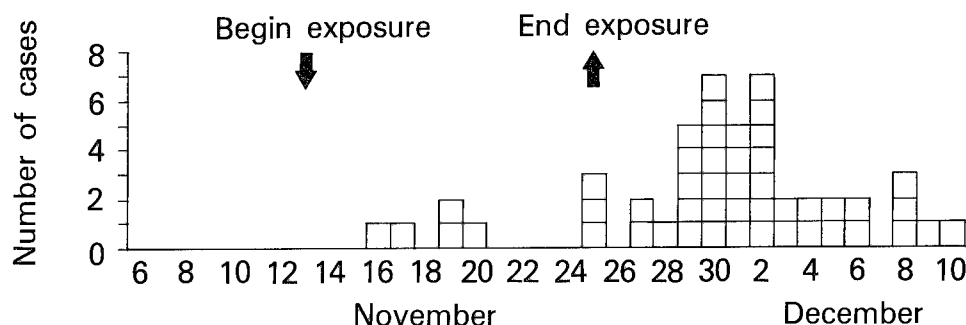
The role of enemy contact is further emphasized by the distribution of cases by MOS (military occupational specialty). Of all cases of malaria reported in 1967 in the U.S. Army, Vietnam, 58.5 percent occurred in individuals with the 11B (light weapons infantryman) MOS, although persons with this specialty represented only 15.3 percent of the total strength (USARV-CHR 1967, table 2).

Malaria discipline and the proper use of malaria chemoprophylaxis are discussed in chapter 14.

MALARIA IN ENEMY TROOPS

Scant data are available concerning malaria in enemy troops. A U.S. Army Medical Intelligence report compiled during 1965 suggested that it was a significant cause of noneffectiveness in some units (Killenberg 1965). One NVA (North Vietnamese Army) officer told interrogators that between February and June 1965 his company of 113 men had lost 34; 11 were killed in action and 23 died from malaria. This unit had traveled along the Laotian border into the Central Highlands and engaged in operations in Darlac, Phu Bon, Pleiku, and Binh Dinh Provinces. In November 1965, 12 captured NVA soldiers were examined and 8 were found to have blood smears positive for *P. falciparum*. They had been in combat near Pleiku and had been in the Republic of Vietnam for 2½ months. On

CHART 14.—Morbidity from malaria by date of onset, related to activities of one indigenous company in conjunction with Operation PAUL REVERE IV, Vietnam, November-December 1966



Source: Cottingham, A. J.; Boone, S. C.; and Legters, L. J. In Annual Progress Report, U.S. Army Medical Research Team (WRAIR) Vietnam and Institute Pasteur of Vietnam, 1 Sept. 1966-31 Aug. 1967, pp. 2-23.

the other hand, only 3 of 113 VC (Vietcong) prisoners captured in Binh Tuy Province had positive smears. These captives were local VC popular force personnel, most of whom were not normally engaged in field operations.

Information about the prophylaxis used by enemy forces is even less complete. A container removed from the body of an NVA soldier near Pleiku in November 1965 contained 20 tablets of quinacrine. A captured main force soldier described taking "two pills of quinine a day for 24 days a month." Another captured infantry private indicated that each soldier received 100 antimalarial pills as part of his basic issue. These data suggest that VC field elements did attempt to suppress malaria with oral medication. Lack of uniformity may have been the result of differences in the availability of drugs as well as variations in medical policy (Killenberg 1965).

MALARIA IN THE UNITED STATES

Anopheline infestation without malaria probably existed before the exploration and settling of North America. It is likely that the disease was brought to the East Coast by early settlers from certain swampy counties in England and to the Gulf Coast by French and Spanish settlers. An increase in incidence occurred with the importation of slaves from Africa. Malaria was at a peak in the United States by 1855, when it had become endemic throughout the country and hyperendemic in the southeastern states (Duffy 1953, pp. 204-14; Lisansky 1958).

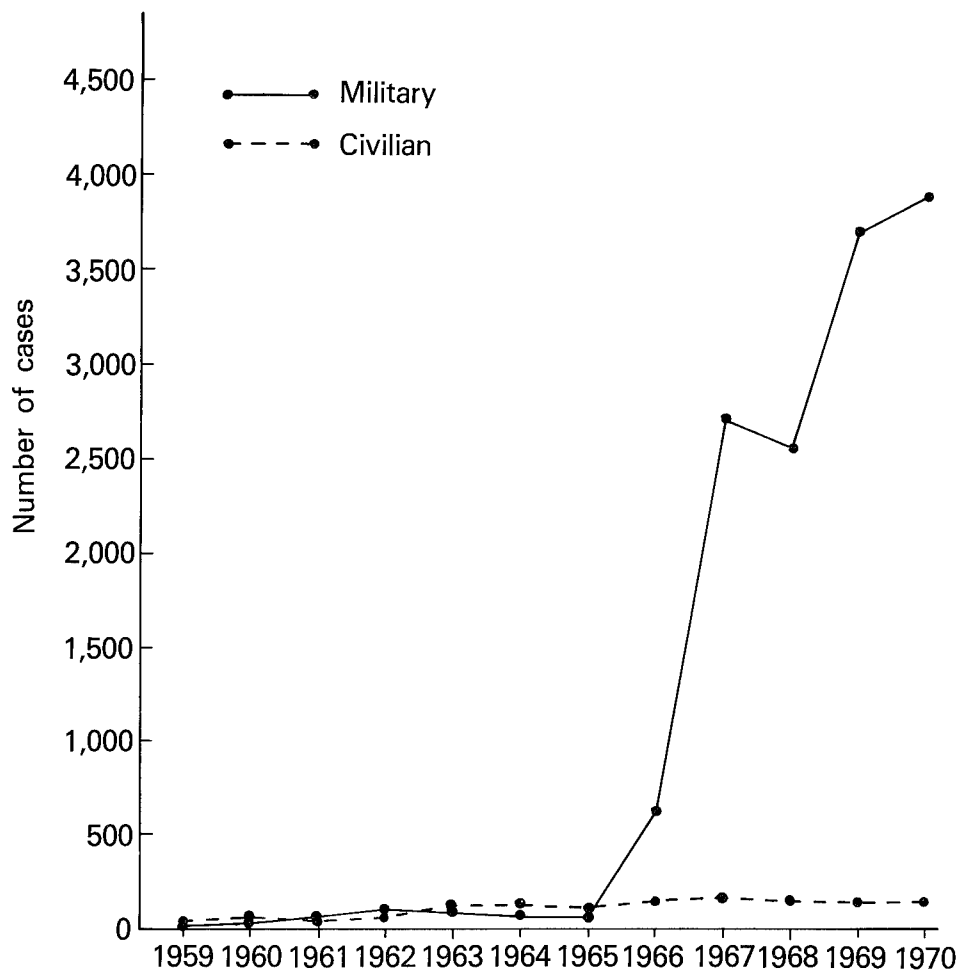
During the next century, the incidence of malaria gradually declined as a consequence of social and economic changes and organized malaria eradication programs. By 1956, endemic malaria had virtually disappeared in the United States (Lisansky 1958, pp. 437-38). The decline of the disease was temporarily reversed when infected troops returned from overseas, most notably during and immediately following World War II and the Korean war (Fisher et al. 1970).

United States involvement in Vietnam led to a predictable rise in imported cases of malaria in this country (NCDC-MS68; Barrett 1968), because of the increased number of troops assigned there, failure of prescribed prophylaxis pro-

grams, and drug resistance in some cases (Barrett and Reiley 1971). In 1965, 156 cases were reported in the United States and Puerto Rico (NCDC-MS65); in 1970 the number had risen to 3,997 (Walzer, Dover, and Schultz 1972). The progressive increase during this period is shown in chart 15. Military personnel, including recently discharged veterans, accounted for almost all of the upsurge; incidence in civilians remained constant. Most of the military cases occurred in Army personnel (table 41).

Although both troops in Vietnam and returnees to the United States experienced an increase in cases, a striking difference between the two groups was noted. Of those cases which developed in Vietnam during the early years of the war, 98 percent were caused by *P. falciparum* infection (Sheehy 1967). However,

CHART 15.—Cases of malaria in the military and civilian populations, United States, 1959-70



Source: Walzer, P. D.; Dover, A. S.; and Schultz, M. G. 1972. Malaria surveillance in the United States and Puerto Rico—1970. *J. Infect. Dis.* 125: 194-96. Reprinted by permission of The University of Chicago Press. © 1972 by the University of Chicago. All rights reserved.

TABLE 41.—*Malaria in military personnel returning from Vietnam to the United States, 1970*

Service	Cases		Variation (percent) from 1969 to 1970
	Number	Percent	
Army	3,182	82.9	+13.8
Marines	418	10.9	−39.9
Navy	18	0.4	+ 5.9
Air Force	8	0.2	−11.0
Unknown	214	5.6	+98.1
Total	3,840	100.0	+ 5.9

Source: Walzer, P. D.; Dover, A. S.; and Shultz, M. G. 1972. Malaria surveillance in the United States and Puerto Rico—1970. *J. Infect. Dis.* 125: 194-96. Reprinted by permission of The University of Chicago Press. © 1972 by the University of Chicago. All rights reserved.

P. vivax infection was responsible for 83 to 93 percent of the cases which occurred in the United States (Waterhouse and Riggenbach 1967; Martelo, Smoller, and Saladin 1969).

In Vietnam, all individuals were supposed to receive weekly C-P (chloroquine-primaquine) prophylaxis, which is highly effective in suppressing vivax malaria (JAMA) but less effective against *P. falciparum* (Blount 1969). Each individual was also instructed to take one C-P tablet weekly for 8 weeks following return to the United States. This program should have resulted in radical cure of *P. vivax* infection, thus virtually eliminating vivax cases in the United States (Barrett and Reiley 1971). The high incidence of vivax malaria observed suggested that either the drug program itself or the enforcement of it was ineffective. There was no evidence to support the first possibility (USMED). On the other hand, Barrett (1968) found that, of 29 patients with vivax malaria treated at Letterman Army Hospital in San Francisco, none had completed the prescribed 8-week treatment regimen or maintained treatment until onset of symptoms.

This observation led to a study of 671 asymptomatic Vietnam veterans to determine the degree of participation in the prophylactic program (Barrett et al. 1969). Overall results are shown in table 42. The most striking finding was that 70 percent of all individuals had failed to complete the prescribed course of malaria prophylaxis upon return to the United States. A variety of reasons were given (table 43). Although 20 percent noted side effects from the therapy, only 11 percent gave this as the reason for discontinuing it. Rank was not a factor, as the failure rate was similar for officers and enlisted personnel. Persons stationed in "high risk" areas were more likely to comply with therapy than were those in locations where the disease was not a significant epidemiological problem. On the other hand, previous experience with malaria provided little stimulus to comply, as 76 percent of those who had clinical disease in Vietnam failed to complete treatment when they returned to this country.

The practical impact of imported malaria on a military unit in the United States was demonstrated by Di Napoli and Dicey (1969). During the winter and spring of 1966-67, there was a sharp increase in the incidence of malaria at Fort Bragg, N.C., and during 1967, 353 cases occurred, 274 (77.6 percent) of them in personnel of the 82d Airborne Division. With an average stay of 14 days per pa-

TABLE 42.—*Results of malaria chemoprophylaxis survey in 671 U.S. servicemen returned from Vietnam*

Item	Individuals interviewed	
	Number	Percent
Total in study	671	100.0
Officers	73	10.9
Enlisted men	598	89.1
Failed to complete full course of therapy	470/671	70.0
Took no medication	175	
Stopped taking medication	295	
Failure rate by military rank:		
Officers	44/73	60.3
Enlisted men	425/598	71.1
Failure rate by area of assignment in Vietnam	470	100.0
High-risk areas	167	35.5
Low-risk areas	303	64.5
Had malaria in Vietnam	59/671	8.8
Failed to complete prophylaxis despite previous infection	45/59	76.3
Had malaria after return to United States	16/671	2.4
Had malaria after return despite completion of chemoprophylaxis	7/16	43.8

Source: Barrett, O., Jr.; Skrzypek, G.; Datel, W.; and Goldstein, J. D. 1969. Malaria imported to the United States from Vietnam. *Am. J. Trop. Med.* 18: 495-99. (Corrected).

TABLE 43.—*Reasons given by 470 U.S. servicemen returned from Vietnam for failure to complete therapy in malaria chemoprophylaxis survey*

Reason	Individuals interviewed	
	Number	Percent
Side effects from medication	52	11.1
Given insufficient number of pills	148	31.5
Forgot to take medication	103	21.9
Lost medication	78	16.6
Believed treatment not important	51	10.8
Refused to take medication	26	5.5
Miscellaneous reasons	12	2.6
Total	470	100.0

Source: Barrett, O., Jr.; Skrzypek, G.; Datel, W.; and Goldstein, J. D. 1969. Malaria imported to the United States from Vietnam. *Am. J. Trop. Med.* 18: 495-99. (Corrected).

tient at Womack Army Hospital, these cases represented a total of 3,836 man-days lost and an estimated monetary cost of \$204,600 to the division. Extrapolating these data to the overall incidence of malaria in the U.S. Army in 1967, the authors estimated fiscal loss from the disease to be \$1.8 million.

The return of large numbers of troops from malarious areas also raised the question of introduced malaria (malaria acquired by mosquito transmission from an imported case in an area where the disease is not a regular occurrence). For successful mosquito transmission of malaria, three ingredients are necessary: a susceptible population, a parasite reservoir, and an effective anopheline vector; all three exist in the United States. The reservoir is provided by infected individuals who return from malarious areas. *Anopheles freeborni* is an efficient

vector in the western half of the country and *Anopheles quadrimaculatus* in the eastern half. Introduced malaria has, however, been uncommon in the United States, apparently because of improvements in standards of land use and housing, together with increased urbanization and a concomitant decline in the rural population, all factors which tend to separate man from mosquitoes and, in many instances, promote an adverse environment for the anopheline vector (Barrett 1968, p. 431).

Nonetheless, introduced malaria has been documented in this country. In 1952, 35 cases occurred among a group of Camp Fire Girls in California. The probable source was a recently returned Korean veteran (Brunetti, Fritz, and Hollister 1954). At Fort Benning, Ga., two cases of introduced vivax malaria were observed in 1964 and 1965, the probable source again being a serviceman who had been stationed in Korea (Luby et al. 1967). There is evidence of at least one instance of introduced vivax malaria resulting from exposure to a person returned from Vietnam (ABNEWS). In 1970, two introduced cases were reported from rural, south-central Texas where a migrant Mexican agricultural worker was the probable index case (Walzer, Dover, and Schultz 1972, p. 195). Between 1952 and 1974, a total of 11 outbreaks of introduced malaria in the United States were reported to the Center for Disease Control. *P. vivax* was the species identified in all of the cases (CDC 1974).

Of perhaps greater significance than introduced malaria in the United States is induced malaria (malaria acquired through artificial means, especially via blood transfusion or the use of common syringes and needles).

Gubb (1919) reported what was probably the first case of transfusion-induced falciparum malaria 8 years after the danger of transmission of malaria by transfusion was first recognized (Belding 1965, p. 313). The first case of transfusion-induced falciparum malaria from a Vietnam returnee in the United States was reported by Chojnacki, Brazinsky, and Barrett (1968). This case was of interest for two reasons. First, investigation established that the source of infection was a soldier who had returned from Vietnam 7 months previously and had never had symptoms of malaria. Equally significant was the fact that routine evaluation of this individual, during the attempt to establish the source of the infection, was unrewarding. Twenty-four thick and thin smears done at least 1 day apart were negative for malaria. Diagnosis was based on parasite identification in a sternal bone marrow aspirate. Belding (1965, p. 307) had previously commented on the value of marrow aspirate evaluation in confirming clinically suspected cases with negative peripheral smears.

Forty cases of transfusion-induced malaria were reported in the United States from 1963 to 1974. *P. vivax* was the cause of 16 (40 percent) of these, *P. falciparum* of 13 (32 percent), *P. malariae* of 10 (25 percent), and a mixed infection of 1 (3 percent). Only one case of transfusion-induced disease was noted in the United States in 1975; this was a fatal case caused by *P. malariae*. Because only 1.4 percent of all malaria cases in the United States were caused by *P. malariae* while 25 percent of transfusion-related cases involve this strain, it is proportionately the most important cause of transfusion-induced malaria in this country (CDC 1976).

Theoretically, current routine blood banking restrictions prevent most cases of transfusion-induced disease by precluding donation of blood for 2 years after termination of treatment for, or known exposure to, malaria (AABB, pp. 9-10). However, some donors, particularly paid ones, do not provide honest information concerning previous exposure. Furthermore, there are well-documented cases with unusually long incubation periods, so that the 2-year restriction does not exclude all infected donors (NCDC-MS68). A practical indirect fluorescent antibody technique for detecting previous exposure to malaria is available. It is especially valuable for investigating febrile transfusion reactions but has not as yet been used routinely as a screening technique by blood banks (Leibovitz et al. 1969).

While whole blood is the greatest source of transmission of induced malaria, component therapy is also a potential hazard. There is one case report of transmission of *P. vivax* by leukocyte concentrate component therapy (Dover and Guinee 1971). The patient, who had leukemia, received leukocyte infusions from a Vietnam veteran. The component product was probably contaminated with parasitized erythrocytes.

Another documented cause of induced malaria is illicit parenteral drug use. Several isolated cases were reported from various parts of the country in 1970 and 1971 (Dover 1971). An epidemic of induced malaria involving 48 people occurred between December 1970 and March 1971, in Kern County, Calif. All patients were heroin users who frequently shared syringes and needles. The probable index case was a 22-year-old veteran who had returned from Vietnam in March 1970 and had taken none of the chemoprophylaxis tablets. He experienced a clinical attack of malaria in December. During the time between the onset of symptoms and diagnosis, he had injected heroin at least once daily and shared his injection equipment with at least seven persons, three of whom subsequently developed malaria. An epidemiological investigation was initiated and a special clinic was established by the Kern County Health Department to interview all contacts and suspected cases. Parasites of *P. vivax* were seen on the peripheral blood smears of 42 patients, and all had recent or current symptoms typical of vivax malaria (CDC 1971). The possibility of malaria should always be considered in the evaluation of fever in persons using illicit drugs parenterally.

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Malaria: The Clinical Disease

Colonel O'Neill Barrett, Jr., MC, USA (Ret.), and Colonel Raymond W. Blohm, Jr., MC, USA

CLINICAL MANIFESTATIONS

In Vietnam, the typical symptoms of malaria did not differ greatly from classic descriptions of them. The incubation period—the interval from mosquito bite to first symptoms—averages approximately 2 weeks for vivax and ovale infections and can be as short as 9 days for falciparum and as long as 5 weeks for malariae (Belding 1965, pp. 291-96). In American troops taking the combined C-P (chloroquine-primaquine) tablet once weekly the onset of symptoms, as determined by observations from "search and destroy operations," was often delayed as long as 19 days (Blount 1966). Table 44 is a composite of the symptoms and physical findings in 621 cases of malaria acquired in Vietnam. Species differentiation has not been attempted since there are no accurate data providing for a distinction in uncomplicated malaria.

One of the most characteristic features of malaria is periodicity, with fever and chills occurring every second or third day. However, this "typical" picture is not usually present early in the course of disease, when most military patients were seen. Synchronization of parasitic cycles is often established late or not at all during the primary attack (Heineman 1972), especially in the nonimmune subject. Synchronization of fever spikes at the onset of symptoms usually implies relapse (Barrett and Reiley 1971). The typical fever pattern may also be obscured by previous prophylaxis. The nondiagnostic fever curve is especially characteristic of falciparum malaria (Heineman 1972).

The initial fever characteristics of acute malaria may offer some diagnostic clues, however. The temperature nearly always spikes from normal to 103°F or higher and returns to normal within 24 hours; it is rarely sustained at a high level (Barrett and Reiley 1971, p. 29). Fever and chills are noted in almost all initial attacks. In second, third, or further attacks, the spiking temperature and shaking chills—and other symptoms in general—become less marked and even less typical; some patients may experience no fever and complain only of malaise.

Headache is present in 75 to 100 percent of the cases but is usually not severe. Persistent or worsening headache may be an early manifestation of cerebral malaria (Daroff et al. 1967). Gastrointestinal symptoms, especially

TABLE 44.—*Summary of symptoms, signs, and laboratory data in 621 cases (five studies) of malaria acquired in Vietnam*

Finding	Percent of cases				
	Study 1	Study 2	Study 3	Study 4	Study 5
Fever	100	100	100	100	100
Chills	92	89	89	100	100
Headache	88	89	83	75	100
Vomiting	40		40	29	81
Myalgia	32	57	31		62
Arthralgia	22		19		31
Abdominal pain			18	79	58
Nausea		41		29	85
Diarrhea			36	11	38
Splenomegaly	39	49	35	29	65
Hepatomegaly	22	31	16		38
Hypotension	16		11		100
Jaundice	12		13	7	
Mental disturbance			8	7	
Delirium				7	
Anemia	42	25	58	18	
Elevated SGOT	40	31	44	68	
Albuminuria	40				
Elevated bilirubin	34	30	33		
Elevated BUN	14	18	14	29	
Thrombocytopenia		30			

Sources: Study 1 (*falciparum*; 100 patients): McCabe, M. E. 1966. *M. Serv. J. Canada* 22: 313-32. Study 2 (*species unspecified*; 357 patients): Heineman, H. S. 1972. *Arch. Int. Med.* 129: 607-16. Study 3 (*falciparum*; 110 patients): Bartelloni, P. J.; Sheehy, T. W.; and Tigertt, W. D. 1967. *J.A.M.A.* 199: 173-77. Study 4 (*species unspecified*; 28 patients): Deller, J. J., Jr., and Russell, P. K. 1967. *Ann. Int. Med.* 66: 1129-43. Study 5 (*falciparum*; 26 patients): Brooks, M. H.; Malloy, J. P.; Bartelloni, P. J.; Tigertt, W. D.; Sheehy, T. W.; and Barry, K. G. 1967. *Am. J. Med.* 43: 735-44.

nausea and vomiting, occur in about half of malaria cases but are not usually serious; however, they may prevent effective oral therapy. When diarrhea occurs concomitantly, as it did in 35 to 38 percent of cases in two studies, the disease may be mistaken for "gastroenteritis" (Bartelloni, Sheehy, and Tigertt 1967; Quint 1966). Arthralgia and myalgia, especially in the lumbar area, may also be prominent symptoms. Radiologists at the 12th Station Hospital in the Pacific in World War II recognized that the combination of severe back pain and a negative X-ray of the lumbar spine was a frequent manifestation of the disease (MD-R, p. 669).

The absence of certain symptoms of common febrile diseases may also facilitate the diagnosis of malaria. Rhinorrhea and nasal congestion are not features of the disease. Cough, if present, occurs only during the febrile period and is rarely productive (Barrett and Reiley 1971).

The physical examination in uncomplicated malaria is not generally helpful. The spleen is palpable in 30 to 40 percent of cases but is not greatly enlarged (Barrett and Reiley 1971; Bartelloni, Sheehy, and Tigertt 1967; McCabe 1966; Deller and Russell 1967). This is in contrast to findings in Vietnamese patients with chronic malaria, among whom the incidence of splenomegaly is 70 to 90 percent (in children and adolescents) and spleens are frequently massively enlarged

(Colwell, Legters, and Fife 1970). Hepatomegaly occurs in approximately 25 percent of the cases (see table 44) but is usually minimal. The liver is almost universally involved (Deller et al. 1967). Glasser (1967) was the first to call attention to the relative bradycardia which occurs during temperature spikes, especially in cases of *P. falciparum* infection. Others have subsequently confirmed this observation (Fisher et al. 1970).

An evaluation of routine blood counts reveals that patients may have anemia, thrombocytopenia, leukopenia, or any combination of these findings, as a consequence of either malaria or malaria chemotherapy, or of both (Heineman 1972; Sheehy and Reba 1967).

Widely varying rates have been reported for the occurrence of anemia, depending on the definition, the length of illness, and the percentage of falciparum infections in the group (Heineman 1972). In one study of 50 patients, 10 of whom had falciparum malaria, 46 percent (23 patients) had hemoglobin concentrations of less than 12 g per 100 ml (Khan, Zinneman, and Hall 1970). In another study involving only falciparum infections, 29 of 50 patients (58 percent) had hematocrit values of less than 38 percent (Glor 1969). The cause of anemia in these cases is not always clear.

Hemolysis is an integral feature of all malarias and is always present with clinical disease (Conrad 1969). Fulminant hemolysis can be produced by falciparum infections, which attack erythrocytes of all ages. Other forms of human malaria are less virulent because they parasitize red cells of specific ages. The parasites of *P. vivax* infect reticulocytes while the parasites of *P. malariae* invade only mature erythrocytes; in these infections, therefore, hemolysis is self-limited (Young 1966, p. 322).

Relatively few recent studies have been done on red cell abnormalities in malaria, despite the apparent importance of hemolysis in this disease. An immune response has been implicated as the cause of the hemolysis by most investigators, who support this hypothesis with the fact that specific malarial antibodies can be found in convalescent plasma (Zuckerman 1964; McGregor, Carington, and Cohen 1963). Yet there is little evidence that such antibodies attach to erythrocytes and bring about their premature destruction. Very few malaria patients exhibit a positive antiglobulin (Coombs') test, and animal studies have not demonstrated either that antibodies adsorb to red cell surfaces or that they affect the lifespan of circulating erythrocytes (Adner, Altstatt, and Conrad 1968; George et al. 1966).

Furthermore, a greater degree of hemolysis occurs than might be expected from the number of parasitized cells in the circulating blood (Zuckerman 1960). Conrad and Dennis (1968) found that the spleen removes parasites from infected erythrocytes and returns to the circulation these injured cells whose survival is shortened. Based on their observations on the increased severity of disease in splenectomized animals and on the potential activation of latent malaria in humans, The Surgeon General in May 1968 directed that no individual whose spleen had been surgically removed or was congenitally absent would be assigned to Vietnam or Thailand (OTSG-MS).

Conrad (1969) postulated that hemolysis is caused by loss of negative charge

from the surface of red blood cells because the parasite usurps essential metabolic functions of the infected cells.

Intrinsic enzyme abnormalities of the red blood cells found in certain ethnic groups also contributed to hemolysis in some anemic malaria patients on drug therapy. The most common deficiency, involving the enzyme G6PD (glucose-6-phosphate dehydrogenase) is commonly found in blacks and people of Mediterranean origin and is genetically transmitted as a sex-linked trait. It is fully expressed in males carrying a single dose of the abnormal gene (hemizygote) and in females carrying a double dose of the gene (homozygote) and has intermediate expression in heterozygote females (Tarlov et al. 1962). In the Mediterranean type, the enzyme is almost completely absent; in blacks, sufficient enzyme is present in younger red cells so that only older cells are destroyed, usually resulting in mild, self-limited hemolysis and anemia (Motulsky and Stamatoyannopoulos 1966).

Both primaquine and dapsone produce hemolysis in the G6PD-deficient individual (Tarlov et al. 1962; Ognibene 1970). Theoretically, at least, all soldiers in Vietnam received primaquine on a weekly basis in the combined C-P tablet. Dapsone prophylaxis was authorized for use by commanders, upon advice of the command surgeon, in hyperendemic areas (USARV Reg); there are no data on the number of troops who received this drug.

There was a small but continuous evacuation of G6PD-deficient troops from Vietnam because of severe hemolysis secondary to primaquine sensitivity, averaging 17 per month.* Most of these patients were black, although hemolysis supposedly took a mild form in this ethnic group. Despite a recommendation by the USARV (U.S. Army, Vietnam) medical consultant that all individuals, especially blacks, scheduled for Vietnam duty be challenged with C-P before departure from the continental United States,** no official screening policy was adopted.

Another recognized, though uncommon, and preventable cause of anemia in malaria patients was treatment with pyrimethamine, which became a standard component of therapy for falciparum disease in 1967 (OTSG-G). Pyrimethamine acts as a dihydrofolic acid reductase inhibitor, preventing conversion of folic to folinic acid, thus inhibiting nucleic acid synthesis (Kaufman and Geisler 1960). Sheehy and Reba (1967) observed three cases of megaloblastic anemia among 135 patients who received pyrimethamine-quinine treatment for chloroquine-resistant falciparum infection. Tong et al. (1970) demonstrated that the incidence of anemia secondary to pyrimethamine treatment, which was 24 percent in their group, could be reduced to 4 percent by the concurrent administration of folic acid, without loss of therapeutic efficacy.

Canfield (1969), in ferrokinetic studies of patients treated with quinine, pyrimethamine, and sulforthodimethoxine (Fanasil), demonstrated delayed red blood cell incorporation of iron until the malaria infection was brought under control.

*Lt. Col. Andre J. Ognibene, MC, USARV Medical Consultant, 1969: Unpublished data.

**Lt. Col. Andre J. Ognibene, MC, USARV Medical Consultant, 1969: Personal communication.

Another interesting abnormality of erythrocyte function was reported by Cohen et al. (1968), who studied six soldiers evacuated from Vietnam because of cyanosis which developed while taking antimalarial drugs. The red blood cells of these patients and two other subjects were found to have a markedly decreased concentration of NAD (nicotinamide-adenine dinucleotide) methemoglobin reductase and a decreased capacity to reduce methemoglobin to hemoglobin in vitro. It was demonstrated that chloroquine, primaquine, and dapsone, in doses that have no effect on normal persons, each provoke methemoglobinemia in enzyme-deficient subjects. With greater use of these drugs in combination and with increased troop strength, the problem of cyanosis became more common.

Despite the availability of reasonably detailed data about red blood cells in malaria patients, the leukocyte response in acute malaria received only casual mention in the literature. Clyde (1964) discussed the leukocyte response in an East African population, but his results were obscured by the fact that his studies were performed on individuals partially immune to malaria and among whom there was a high incidence of associated disease. Martelo, Smoller, and Saladin (1969) found leukopenia in 12 percent of 176 individuals who developed malaria following return from Vietnam and leukocytosis in 5 percent. The disease was caused by *P. vivax* in 93 percent of the group. Goldstein (1968) reported data in a similar group; 30 percent of his 64 patients with falciparum disease and 24 percent of 17 with vivax manifested leukopenia. Fisher et al. (1970) noted these trends but also observed a significant difference in the leukocyte count between races: they found leukopenia in 22 percent of white subjects but in only 12 percent of blacks.

Reiley and Barrett (1971) reported the only detailed study of the leukocyte response in acute malaria. Their series included a total of 404 cases from three separate sources. In one group, 43 cases from the Panama Canal Zone were all caused by *P. vivax*. The second group, 81 cases treated at the 8th Field Hospital in Nha Trang, was caused by *P. falciparum*. The third group, 280 cases treated at Tripler General Hospital in Hawaii, occurred in individuals recently returned from Vietnam: 110 were caused by *P. falciparum*, 159 by *P. vivax*, and 11 by mixed infection. The data from these three groups were especially valuable since they came from a large number of cases of acute disease in otherwise healthy, nonimmune individuals. Of greatest importance, perhaps, was that they provided additional comparison between vivax and falciparum disease and that the Panama Canal group, which had not received chemoprophylaxis, served as a control in terms of drug effect. Without this control group, the data from Vietnam could have been clouded by the fact that most individuals received weekly C-P tablets and many also received dapsone.

Leukopenia was the most consistent feature of the leukocyte response in this study, occurring in approximately one-third of the cases. There was no difference in the total white count based on patient source. These data are shown in table 45. Chart 16 shows a distribution of leukocyte count in 404 cases by infecting species and, again, no difference is noted. Furthermore, using the Panama Canal cases as a control group, it was shown that leukopenia was not aggravated by the chemoprophylaxis program in Vietnam since white counts were similar in

TABLE 45.—*Distribution of leukocyte count, by patient source, in 404 cases of malaria*

Patient source	Number of patients	Leukocyte count, mm ³		
		< 5,000	5,000-10,000	> 10,000
		Percent	Percent	Percent
Hawaii ¹	280	31.0	62.0	6.0
Vietnam ²	81	33.0	62.0	5.0
Panama ³	43	37.0	60.5	2.5
All cases	404	31.2	63.5	5.3

¹Tripler General Hospital.²8th Field Hospital at Nha Trang.³Canal Zone.Source: Reiley, C. G., and Barrett, O., Jr. 1971. Leukocyte response in acute malaria. *Am. J. M. Sc.* 262: 153-58.

both groups. In addition to the decrease in the total leukocyte count, a "left shift" or increase in immature neutrophilic leukocytes was also observed. This finding, present in one-third of the cases, was not uncommon even in patients with leukopenia. Severity of disease, duration of symptoms, and response to therapy were apparently not related to the changes in the neutrophilic leukocyte count.

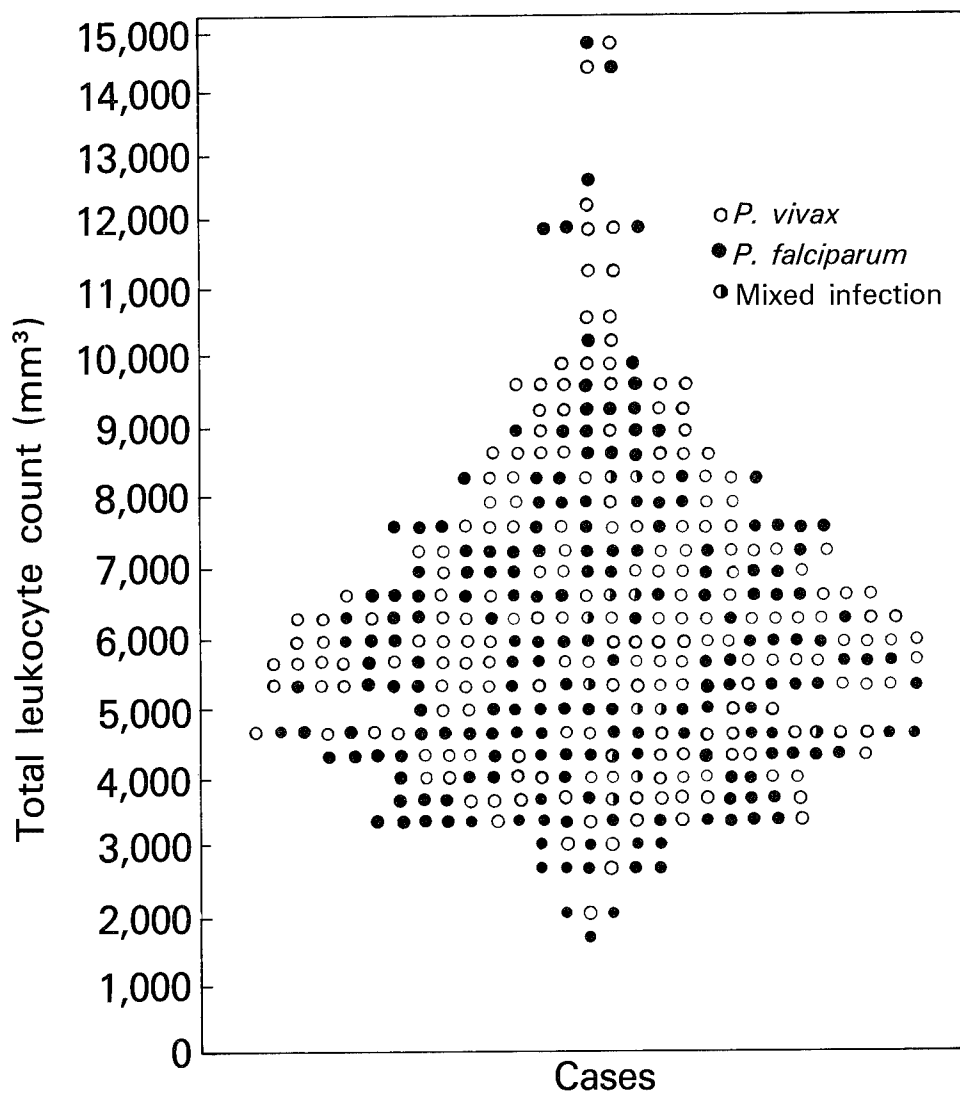
Eosinophilia was not part of the leukocyte picture in untreated malaria but developed in 30 percent of the patients following treatment with antimalarial drugs. Contrary to older reports in the literature, the monocyte count did not show a significant elevation in most cases although occasionally a striking elevation of the absolute monocyte count was observed.

Despite the potential for the development of the leukopenia secondary to drug treatment, only a few serious problems were reported from medical facilities in Vietnam. In one study at the 6th Convalescent Center, Rogoway (1967) reported severe neutropenia with an absolute granulocyte count less than 400 per mm³ in 10 of 2,200 patients treated between 1 December 1966 and 15 April 1967. Results of bone marrow examination in these patients were compatible with maturation arrest of the myeloid elements. All patients had received a combination of quinine, pyrimethamine, and dapsone, any or all of which can produce leukopenia. Specific drug cause was not established since none of the patients was rechallenged with the drugs.

Dapsone seemed least likely to have been the offending agent in this group since all patients had been on dapsone prophylaxis before the development of malaria. On the other hand, Ognibene (1970) reported the development of agranulocytosis in 16 soldiers in Vietnam who had received daily dapsone prophylaxis against falciparum malaria for 3 weeks to 3 months. There were eight deaths in this group, and this evidence of serious though uncommon toxicity resulted in a limitation in the use of dapsone in U.S. troops.

Thrombocytopenia was reported in 30 percent of the 357 cases summarized by Heineman (1972). Again the mechanism is unclear, although Neva and associates (1970) made a thorough study and drew tentative conclusions. They considered a number of possible mechanisms but rejected them because of lack of evidence in both animal models and human studies. These included the decreased production of platelets by marrow megakaryocytes, hypertrophy of the

CHART 16.—Distribution of total leukocyte count in 404 cases of malaria



Source: Reiley, C. G., and Barrett, O., Jr. 1971. Leukocyte response in acute malaria. *Am. J. M. Sc.* 262: 153-58.

reticuloendothelial system, action of cross-reacting antibodies, and endotoxin mediated reactions. They also excluded consumption coagulopathy or intravascular coagulation since there was no evidence of abnormality or fluctuation of clotting factors or of fibrinolysis. Because of the temporal relationship to the decrease in platelet count, the development of antimalarial antibodies, and a drop in serum complement levels, they proposed that an antigen-antibody complex produces an immunologically mediated thrombocytopenia.

Convincing evidence for DIC (disseminated intravascular coagulation) as a serious complication of malaria in Vietnam is not available, largely because even

screening studies for this disorder could not be performed due to lack of facilities. In an evaluation of 42 patients with acute renal insufficiency secondary to falciparum malaria, 7 of 11 patients tested were judged to have evidence of DIC. The only coagulation studies performed, however, were platelet count, PT (prothrombin time), PTT (partial thromboplastin time), and plasma fibrinogen levels (Stone, Hanchett, and Knepshield 1972). Fletcher et al. (1972), studying 26 patients admitted to the Naval Support Activity Station Hospital in Da Nang, measured the PT, PTT, fibrinogen level, platelets, and fibrin split products. Only one patient in this group showed evidence of probable DIC.

Dennis et al. (1967) did coagulation studies of 31 American soldiers evacuated from Vietnam with relapsed chloroquine-resistant falciparum malaria. They found multiple coagulation defects in these patients, including platelet counts below 150,000 per mm³ in two-thirds, and either prolonged prothrombin time or prolonged partial thromboplastin time, or both, in all patients. Depletion of factors V, VII, VIII, and X was shown in specific factor assays. Ten patients had fibrinogen concentrations of less than 200 mg per 100 ml. Heparin therapy, administered to several patients, was followed by an increase in the platelet count and improvement in first and second stage coagulation defects. Recurrence of thrombocytopenia and depression of coagulation factors were noted when the therapy was stopped. In animal studies evaluating the usefulness of heparin therapy in the treatment of malaria, Dennis and Conrad (1968) found that the drug has an antimalarial as well as an anticoagulant effect. This finding has not yet been confirmed in man, however.

Cerebral malaria was recognized as a complication of falciparum infection in Vietnam. The diagnosis, often an imprecise one, was made on the basis of confirmed parasitemia and neurologic manifestations which could not be explained on the basis of hyperpyrexia or associated metabolic abnormalities. The incidence in Vietnam was estimated to be 1.6 percent (of 2,600 total malaria cases). This figure is remarkably similar to that reported in World War II, which was 2.3 percent (of 6,059 total cases) for U.S. and Allied troops (Daroff et al. 1967; Carr 1967).

The symptoms of cerebral malaria are frequently nonspecific, especially since the functional versatility of the brain permits expression of a number of syndromes. The best data for Vietnam are from Daroff et al. (1967) and Carr (1967). Based on 19 cases studied, Carr tabulated the following symptoms of cerebral malaria:

Headache.....	17	Convulsions.....	9
Disorientation.....	16	Restless agitation.....	7
Recent memory loss.....	16	Abnormal plantar reflex.....	6
Hyperreflexia.....	13	Pseudobulbar affect.....	6
Ankle clonus.....	12	Papilledema.....	4
Coma.....	11	Decerebrate rigidity.....	1
Ataxia.....	10		

Daroff and associates classified the 19 cases by five syndromes which characterize cerebral malaria, as follows:

Disturbed consciousness.....	8	Chorea or myoclonus.....	3
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Organic mental syndrome.....	4	Focal disorders.....	1
Personality changes.....	3		

In the classic form, coma develops, usually insidiously but at times with alarming rapidity. The comatose state is unusual in that the patient may appear to be awake with eyes open but roving, simulating the postictal state or pseudobulbar palsy.

The pathophysiology of cerebral malaria is not well understood but has been attributed to stickiness of parasitized erythrocytes with distention and plugging of small cerebral capillaries (Spitz 1946). Pathologic correlation with cases of cerebral malaria in Vietnam is difficult to obtain. None of the 19 patients studied by Daroff et al. and Carr died. In autopsy data from the case cited by Kiel (1968), there was gross evidence of cerebral edema and infarction of the pituitary gland. No microscopic material was described.

Renal involvement is common, especially in falciparum malaria. The term "blackwater fever" has sometimes been confused with renal failure but, in fact, simply represents a urinary manifestation of rapid or severe intravascular hemolysis. It does not imply a renal function abnormality; rather, it indicates that the plasma hemoglobin-binding concentration of haptoglobin has been exceeded and that the kidney is excreting hemoglobin or its breakdown products (Neva et al. 1970). Renal failure may occur during infection with *P. falciparum*, however, associated sometimes with hemoglobinuria and frequently with fluid and electrolyte abnormalities, hypotension, and DIC (Canfield 1969).

Sheehy and Reba (1967) reported on 14 patients in Vietnam who developed acute renal insufficiency secondary to falciparum disease in 1965. They were evacuated to Clark Air Force Base in the Philippines because there were no facilities for hemodialysis in Vietnam at that time. The mortality rate was 50 percent in this group: four patients died before definitive treatment could be started, and three died of coexistent complications. This prompted the decision to establish a renal team in Vietnam capable of dealing with the problems of acute renal insufficiency. The history of the team and the results obtained in the treatment of this disorder are described in detail in chapters 20 and 21 of this text.

The frequency and extent of renal lesions in patients not manifesting overt renal failure have not been determined. However, proteinuria has been noted in about one-half of patients with falciparum disease, and azotemia is seen in approximately 7.8 percent (Heineman 1972). Ward and Kibukamusoke (1969) have presented evidence indicating that the glomerular lesion is an immunologic disorder characterized by deposits of soluble immune complexes.

Respiratory symptoms and signs occur in 3 to 10 percent of patients with acute falciparum malaria (Applebaum and Shrager 1944; Bergin 1967; Neva et al. 1970, p. 304), ranging from mild upper respiratory complaints to fatal pulmonary edema. Applebaum and Shrager described the occurrence of clinical pneumonia in 3.7 percent of their group of 87 military patients in Panama. Based on the therapeutic response, they classified the disease as bacterial pneumonia with a satisfactory response to sulfonamides, atypical (viral) pneumonia with inadequate response to therapy, or malarial involvement with response to an-

timalarial drugs. Spitz (1946) studied 50 cases of fatal falciparum malaria at the Armed Forces Institute of Pathology and found evidence of bronchial pneumonia in 28 percent and interstitial pneumonia in 12 percent.

Clinical pneumonia was not a prominent feature of malaria in Vietnam (Heineman 1972). Fletcher et al. (1972) performed pulmonary function studies and arterial blood gas determinations in 26 randomly selected patients with acute falciparum malaria in Da Nang. All had previously been in good health and had undergone no known treatment for malaria. One patient had an initial arterial oxygen tension of 57 mm of mercury. He had recently recovered from an upper respiratory infection but was asymptomatic from a pulmonary standpoint. There was no clinical or radiographic evidence of pulmonary disease. All values in this patient returned to normal within 24 hours and remained so throughout hospitalization. Pulmonary studies on the other 25 patients were normal on admission and remained so during the study.

Acute pulmonary edema is an uncommon but serious complication of falciparum malaria, occurring in less than 1 percent of all cases (Fletcher et al. 1972). Newman and Hale (1969) reported six cases of this complication in a series of 1,200 patients treated for malaria at the 71st Evacuation Hospital in Vietnam. There were two deaths in this group. Of six patients who died in Hagan's (1970) series of 1,146 cases in Vietnam in 1969, three had significant pulmonary involvement.

Although acute pulmonary edema was first described as a complication of malaria in 1905 and has often been observed at autopsy, its pathogenesis has not been completely examined (Brooks et al. 1968). In some cases, it may result from fluid overload and coexisting renal failure. Sheehy and Reba (1967), for example, described progressive weight gain, dyspnea, tachycardia, rales, and pitting edema in some cases. Stone, Hanchett, and Knepshield (1972) described pulmonary edema in 8 of 12 deaths in their series of 42 patients with malaria and acute renal insufficiency.

Brooks et al. (1968) performed detailed clinical and pathological studies on five patients with falciparum disease who died of acute pulmonary edema and found that development of the complication could not be related to fluid retention, cardiac decompensation, or peripheral circulatory collapse. Central venous pressure remained normal throughout the course of the edema in the three patients in which it was monitored. None of these patients had roentgenographic evidence of cardiac enlargement. On the other hand, all patients had signs of central nervous system dysfunction, and the onset of the edema correlated closely with the degree of cerebral depression. On the basis of the pathologic and physiologic studies, Brooks and associates proposed the following explanation of the pathogenesis. Generalized vasodilatation, with clinical manifestations of a decreased effective circulating volume, occurs during the acute phase of falciparum malaria, accompanied by a decrease in organ perfusion. Further aggravation is produced by local changes in the microcirculation, aggregation of erythrocytes, diminished flow, increased capillary permeability, and interstitial edema. This hypothesis is supported by the autopsy results. Severe congestion of pulmonary capillaries, thickened alveolar septums, diffuse pulmonary edema,

focal hyaline membrane formation, and scattered areas of intra-alveolar hemorrhage were among the major microscopic findings. No significant cardiac abnormalities were observed.

This picture, therefore, closely resembles "shock lung" or the "adult respiratory distress syndrome" and is probably caused primarily by abnormalities of the pulmonary microcirculation (Heineman 1972, p. 612; Brooks et al. 1968). Treatment for this complication involves the usual modalities for pulmonary edema, including meticulous attention to maintaining pO_2 (Neva et al. 1970, p. 304). In addition, there is evidence that large doses of adrenal corticosteroids may help bring about reversal of the process. Newman and Hale (1969) thought that methylprednisolone sodium succinate enhanced recovery in the four survivors among their six patients, and Bergin (1967) reported a similar observation.

There have been few clinical studies concerning liver involvement in malaria in Vietnam, although the liver appears to be almost universally involved; most observations have dealt with events that occurred during the early and late exoerythrocytic phase in experimental malaria. Generally malarial hepatitis is of no clinical significance (Heineman 1972, p. 613). Deller et al. (1967) reported one of the few extensive clinical evaluations of it, in a study of 38 patients admitted to the 93d Evacuation Hospital with acute falciparum malaria during a 2-month period in 1966. Liver function studies were performed daily for 3 days. Enzyme abnormalities were detected in approximately two-thirds of the group and some histologic abnormality was discovered by liver biopsy in all. Histologic changes included Kupffer's cell hyperplasia, increased pigmentation, periportal mononuclear cell infiltration, and increased hepatocyte activity. De Brito, Barone, and Faria (1969) had similar findings.

DIAGNOSIS

The diagnosis of malaria depends primarily upon identifying the parasite in a peripheral blood smear (Neva et al. 1970, p. 296). As noted earlier, the symptoms and signs lack the specificity required for diagnosis except perhaps in the unusual case in which a true periodic fever is present. Once malaria is suspected on the basis of history, including travel through an endemic area and a compatible clinical syndrome, laboratory confirmation is necessary (Heineman 1972, p. 613). Standard peripheral blood smears stained with Wright's stain were used to diagnose the early cases of malaria among troops in Vietnam. Diagnosis was made by identification of a characteristic trophozoite or schizont within erythrocytes. This technique was quite effective but time-consuming, and evaluation of several slides was frequently necessary; most clinicians required three negative malaria preps before discarding the diagnosis in a patient with an unexplained febrile illness (Kiel 1968, pp. 13-14).

Blohm* made an interesting observation which reflected the inexperience of most American physicians with the disease. He noted that the transient ap-

*Col. Raymond W. Blohm, MC: Personal communication.

pearance of gametocytes in the peripheral blood 6 to 12 days after treatment for falciparum malaria was not recognized as part of the natural history of the disease. Thus, patients were unnecessarily retreated for incorrectly diagnosed recurrence until this information was disseminated to treatment facilities.

Because of the increasing volume of work, the thin smear became impractical for routine use in most laboratories in Vietnam, and the thick smear, from which the diagnosis in malaria is most easily made, was "rediscovered." It was used primarily as a screening technique; if it was negative, the thin smear was not examined; if it was positive, the thin smear was studied to determine specific species and parasite index. The parasite index was categorized as mild, moderate, marked, or severe. Mild infection meant less than 9 trophozoites per oil immersion field on thick smear and moderate infection meant 10 to 99. If more than 30 were counted, the thin smear was examined to exclude marked infection, defined as 1- to 9-percent infestation with trophozoites on thin smear. Severe infection was defined as greater than 10-percent trophozoite parasitemia on thin smear (Kiel 1968, p. 14).

The diagnosis of vivax infection was made when large ragged trophozoites were found in enlarged red cells. For falciparum malaria, diagnostic criteria included: small trophozoites in normal-sized erythrocytes, double chromatin dots, multiple trophozoites in the same cell, appliqué forms, and characteristic gametocytes (Kiel 1968, p. 15; Erickson 1967). Price, at the Armed Forces Institute of Pathology, called attention to several other characteristics of falciparum infection (Kiel 1968, pp. 15-16). "Teardrop" forms are small trophozoites which lack a prominent vacuole, common in patients who have had recurrent attacks of malaria with long remissions in between. "Flag" forms are parasites having large rings of thickened cytoplasm at one point, resembling a "flag on its string." "Tenue" forms show very fine ameboid cytoplasm with small and often multiple chromatin dots. Patients in whom this form persists may be seriously ill yet show a relatively low parasitemia. "Bird's-eye" forms show cytoplasm completely surrounding the nucleus, which appears as a free-standing strip or a dot.

In addition to the standard thick smear concentration technique, several other diagnostic techniques have been used, with varying degrees of success. Keffer (1966) described concentration with saponin hemolysis of erythrocytes. Cranmore, at the 406th Mobile Medical Laboratory in Saigon, devised a venous blood formaldehyde concentration technique (Kiel 1968, p. 16), and Van den Berghe and Chardome (1951) employed scarification of skin in the scapula area to increase the ratio of parasites to red blood cells.

The diagnosis of malaria in American troops in Vietnam was not always easy. Erickson (1967) reviewed the problem, emphasizing the frequency and sources of errors, and made recommendations to laboratory officers and technicians. His study included an examination of the first 300 slides from patients referred to the 6th Convalescent Center at Cam Ranh Bay. Very few of the patients had had thick smears made and even when they had, they were of little value because cells had not been properly lysed. Most of the slides had been prepared with Wright's stain. They were generally overstained and contained

numerous artifacts. Use of improperly washed slides resulted in clumping of red blood cells on thin smeared preparations. Improperly prepared buffer contained free-living protozoa which led to erroneous diagnoses because of their resemblance to malaria parasites. False positive diagnoses were made from 42 (14 percent) of the 300 slides. Incorrect species identification was made from 14 (4.7 percent) and infections by more than one species in the same patient were missed in 15 other cases; a frequent error was failure to recognize falciparum infection on a slide known to contain vivax organisms. The results of this study led to development of the standardized diagnostic techniques subsequently used in Vietnam.

Fulkerson (1970) performed an interesting but unrewarding study attempting to hasten the appearance of trophozoites in the treated patient liable to relapse. He developed an "Exercise Provocative Test," based on the clinical observation that relapse of falciparum disease tended to occur shortly after strenuous physical activity. In essence, 22 patients who had recently been treated for falciparum malaria exercised by jogging 1 mile in 12 minutes. Malaria smears were obtained immediately before and after jogging, and 1, 3, 12, and 24 hours afterward. Any smear in which trophozoites appeared within 24 hours was considered positive. None of the patients in the study had a positive response, however. Only one had to terminate the study early because of fatigue.

The occurrence of immunity in malaria is well known. The progressive mildness of relapses, eventual spontaneous cure, and survival of indigenous populations in endemic areas are attributed to this phenomenon (Heineman 1972, p. 6). As early as 1956, a constant relationship between the rising concentration of serum gamma globulin and the acquisition of clinical immunity to plasmodial infection was demonstrated, in field studies in Africa (McGregor et al. 1956). While a humoral component for such immunity was suspected, there was no practical method by which antibody could be specifically measured and related to alterations in gamma globulin levels. Furthermore, alterations in gamma globulin levels were difficult to interpret in subjects living in hyperendemic areas since preinfection levels were not known (Tobie et al. 1966).

However, the study of the primary malaria attack in human volunteers and the use of specific immunologic techniques has produced data concerning preinfection levels of immunoglobulins and alterations following infection. In a study from the National Institutes of Health (Tobie et al. 1966), immunoglobulins IgM, IgG, and IgA were quantitated in 12 volunteers infected with *P. vivax* and 5 with *P. cynomolgi*. Each subject's serum levels were measured before, during, and after the primary malarial attack and in one case after relapse. All subjects synthesized large amounts of IgM globulin. The volunteer with vivax who relapsed produced essentially as much IgM during the secondary response as he did initially. All volunteers showed large increases in absolute values for IgG, but the percentages of increase were less striking in IgG and IgA than in the macroglobulins. Similar data on persons infected with *P. falciparum* are not yet available. These immunologic techniques have also allowed more precise epidemiological data to be collected, and current evidence indicates that circulating antibody is of both protective and diagnostic value (Heineman 1972; Kagan, Matthews, and Sulzer 1969).

Two basic immunologic techniques have been developed, each with subsequent modifications (Kagan, Matthews, and Sulzer 1969). Desowitz and Stein (1962; Stein and Desowitz 1964) developed an IHA (indirect hemagglutination) test utilizing formalin and sheep red cells treated with tannic acid and sensitized with antigens from *P. cynomolgi* and *P. coatneyi*. Mahoney, Redington, and Schoenbechler (1966) developed a more sensitive and specific test by systematically extracting antigens from crude *P. knowlesi* and *P. falciparum* suspensions. Subsequently, Rogers, Fried, and Kagan (1968) described a microhemagglutination test with antigen from *P. knowlesi* using methods similar to Mahoney's. Antigen preparations used in the IHA test had been prepared by lysis of parasitized cells followed by extraction of antigens from the "freed" parasites, the initial lysate from the infected cells being discarded. Wellde et al. (1969) developed a micromethod using lysates of parasitized erythrocytes as antigen. This technique has proved to be highly sensitive and requires only small amounts of both antigen and serums, making it a practical tool for seroepidemiological studies. D'Antonio, Von Doenhoff, and Fife (1966) also described a technique of antigen purification using the principle of preferential fragmentation by controlled pressure in a French press which was free of erythrocyte contaminants.

Several uses of the IHA techniques have been suggested, including delineation of the extent of malarial transmission, detection of focal outbreaks in an endemic area, monitoring seasonal changes in malaria transmission, and assessing the efficacy of chemoprophylaxis and eradication programs (Kagan, Matthews, and Sulzer 1969, pp. 1033-36). Recent outbreaks of malaria can be detected only by testing young people or by noting a rise in the geometric mean titer over a given period of time because of the long duration of the antibody in infected persons (Collins, Skinner, and Jeffery 1968).

The IFA (indirect fluorescent antibody) test for malaria was introduced initially by Tobie and Coatney (1961) and later modified by Kagan, Matthews, and Sulzer (1969). It is now the most widely used serologic technique for the diagnosis of malaria, although it is not practical for mass screening because of technical difficulties. The sensitivity and specificity of the tests are very high, specificity being greater than 99 percent (Sulzer, Wilson, and Hall 1969). The IFA test is especially valuable in determining the plasmodium species when a determination cannot be made with stained slides. Etiologic diagnosis may be difficult because of distortion of parasites by drugs, improper preparation of slides, or scanty parasitemia. The method may also be used to detect responsible donors in transfusion-induced malaria or to screen high-risk potential donors (Kagan, Matthews, and Sulzer 1969, p. 1039).

The rise and fall of antibody titer in returning military personnel may be useful diagnostically in that high antibody titer may indicate recent or current infection, especially if there is no history of recent treatment (Wilson, Sulzer, and Runcik 1970). Leibovitz et al. (1969) reported significant titers in 49 (26 percent) of 183 returning Vietnam servicemen, none of whom had past or present symptoms of clinical malaria.

Sadun et al. (1969) performed studies on human volunteers infected with

either *P. falciparum* or *P. vivax* to determine and compare the time course of development of fluorescent and hemagglutinating antibodies. Both tests were equally sensitive and specific for following the course of antibody development in either falciparum or vivax malaria. While *P. falciparum* antibody titers were usually higher and more persistent than *P. vivax* titers, the antibody curves followed almost parallel lines in the two tests.

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Malaria: Chemotherapy

Brigadier General Andre J. Ognibene, MC, USA, and Colonel Nicholas F. Conte, MC, USA (Ret.)

INITIAL EXPERIENCES, 1960-65

As the 1960's commenced, the relaxed satisfaction of malaria researchers was shattered by rapidly increasing reports from various parts of the world of the emergence of chloroquine-resistant strains of *Plasmodium falciparum*. Moore and Lanier (1961) reported the first cases of chloroquine-resistant falciparum malaria in two American geophysicists working in Colombia, South America. Both received several courses of chloroquine and were finally cured with a 10-day course of quinine therapy. The strain from one patient, who had acquired his infection in the Magdalena Valley, was used in a study of volunteers with neurosyphilis which demonstrated unequivocally that it was indeed chloroquine-resistant (Young and Moore 1961). Similar reports followed about strains from Thailand (Young et al. 1963), Cambodia and Malaya (now West Malaysia) (Contacos, Lunn, and Coatney 1963; Montgomery and Eyles 1963), and Brazil (Box, Box, and Young 1963). Sandosham, Eyles, and Montgomery (1964) reported on an outbreak of drug-resistant malaria in north Malaya near the Thai border among Australian troops on daily proguanil prophylaxis. Contacos, Lunn, and Coatney (1963) compared the sensitivity of two Cambodian, three Malayan, one Colombian, and one Thai strain of *P. falciparum* (table 46). The susceptibility of all strains to quinine was striking.

The first documented case of chloroquine-resistant falciparum malaria in U.S. military personnel was that of a 34-year-old marine who acquired the disease while stationed in Vietnam (Powell et al. 1964). Captain Sn. experienced his first acute clinical attack in late August 1962, and on 27 August asexual erythrocytic forms of *P. falciparum* were found in his blood smears. He was then given three courses of chloroquine base, in the standard regimen (1,500 mg over a period of 3 days) or in larger doses (2,700 mg over 7 days). These courses were administered three times: during the last week of August, the third week of September, and the first week of October. Each resulted in a temporary abatement of symptoms and overt parasitemia, but recrudescence (fever and positive smears) occurred 2 to 3 weeks after both of the first two courses. During the second and third weeks of November 1962, after transfer to the U.S. Naval Hospital, Great Lakes, Ill., the patient received 1,935 mg of quinine sulfate daily

TABLE 46.—Comparison of the responses of five strains of *Plasmodium falciparum* to antimalarial drugs administered at normally curative doses

Strain of parasite	Antimalarial drugs				
	Chloroquine	Proguanil	Mepacrine	Pyrimethamine	Quinine sulfate
Cambodian I ----	Susceptible	-----	-----	-----	-----
Cambodian II --	Resistant	Resistant	Resistant	Resistant	Susceptible.
Malayan I -----	Resistant	Resistant	-----	Susceptible	Susceptible.
Malayan II -----	Resistant	Resistant	Resistant	Resistant	Susceptible.
Malayan III ----	Resistant	Resistant	Susceptible	Resistant	Susceptible.
Colombian -----	Resistant	Susceptible	Resistant	Susceptible	Susceptible.
Thailand -----	Resistant	Resistant	Resistant	Resistant	Susceptible.

Source: Contacos, P. G.; Lunn, J. S.; and Coatney, G. R. 1963. Drug-resistant falciparum malaria from Cambodia and Malaya. *Tr. Roy. Soc. Trop. Med. & Hyg.* 57: 417-24.

for 10 days and a concurrent course of 50 mg of pyrimethamine daily for 3 days, resulting in radical cure. A summary of the patient's clinical record* follows:

The patient is a 34-year-old white male Marine Captain who was first admitted to the 8th Field Hospital on 27 August 1962. For approximately 5 days prior to admission he had noted fever, myalgia, arthralgia and recurrent, shaking chills recurring at about 48-hour intervals. System review was negative otherwise except for severe retro-orbital headaches.

Past History: Was significant in that the patient had a previous episode of malaria eight years previously while in Korea.

Physical Examination: Well developed, thin white male who appeared acutely and seriously ill—perspiring profusely. BP 108/60. P 100/min. T 102F. R 16/m. Skin negative. Lymph nodes negative. ENT normal. Lungs clear to P&A. Heart sinus tachycardia, no murmurs, no cardiomegaly. Abdomen normal except for spleen, palpable 2 cm on deep inspiration, firm and nontender.

Course in Hospital: Blood smear on admission was positive for malaria, judged to be falciparum on the basis of double ring forms in the erythrocytes; no more mature forms were seen (this Dx was confirmed by the Malaria Control Commission Nha Trang, Vietnam). Routine blood count showed wbc 6100 with normal differential, hematocrit 44; urinalysis and chest X-ray normal. Patient treated with chloroquine 0.6 gm (base) stat followed by 0.3 gm in 6 hours then 0.3 gm daily x 3 and primaquine 15 mg per day for 14 days. He was afebrile in 96 hours, remained asymptomatic and was discharged on 6 Sept. to convalescent leave then duty.

Second Admission: Patient was readmitted to the hospital on 20 September. Several days prior to admission he had watery diarrhea lasting 1 day then had recurrence of myalgia and fever but without shaking chills until the day before admission.

Physical Examination: Was unchanged except that the patient was quite pale; spleen was palpable 5 cm below the costal margin and was tender. Temperature 105F. Smear was again positive for *P. falciparum*. Because of the anemia which was felt to be hemolytic in nature, a direct Heinz body preparation was made but was negative (patient had been given a course of primaquine on first admission). The anemia was judged secondary to the hemolytic effect of the disease. No facilities were available to further characterize the anemia. He was given a repeat course of chloroquine with maintenance for 6 days. On admission the hematocrit was 29 and gradually rose to 35 while in the hospital. He has had a leukopenia or low normal wbc throughout. Liver battery showed bilirubin 0.3 mg % total; SGPT 6 units; BSP retention 3% in 45 min. Patient was afebrile for 11 days then had temperature to 101F. This was felt due to an acute prostatitis for which Rx was begun. 48 hours later he had temperature of 104F, a shaking chill and again had a positive smear. A third course of chloroquine was given.

This patient has had three separate episodes of *P. falciparum* within a 6-week period. The course suggests that this is chloroquine-resistant *P. falciparum*. In keeping with the suggestion of

*Maj. O'Neill Barrett, Jr., MC: Narrative summary, clinical record of Captain Sn., 8th Field Hospital, Nha Trang, 1962.

Col. William Tigertt, Office of the Surgeon General, Research and Development Command, this patient is to be transferred to Great Lakes Naval Hospital for further study and treatment by Dr. Alving and his group.

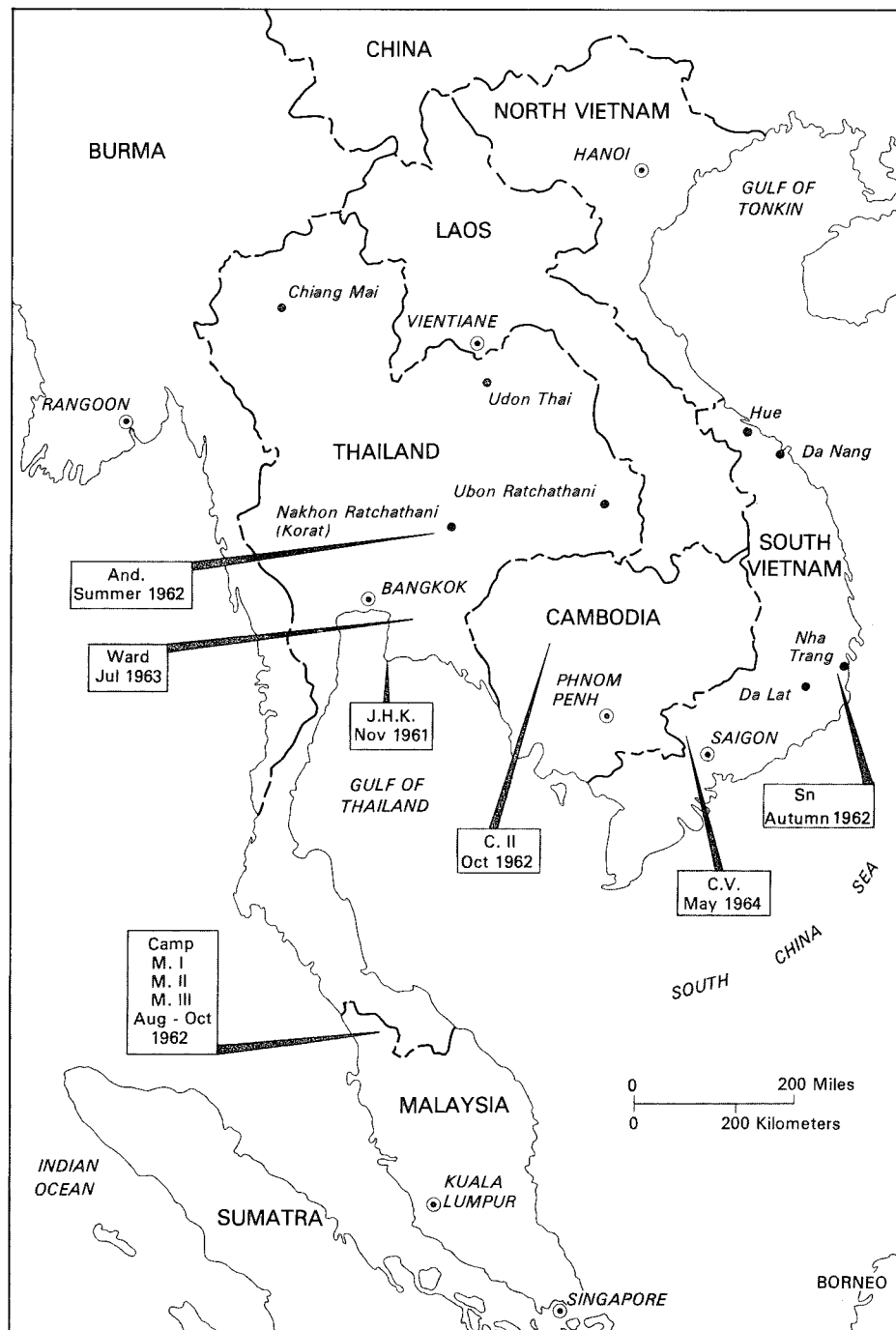
The therapeutic pendulum had swung from quinine to chloroquine and now back to quinine. Infected blood inoculated into volunteers was used to establish refractoriness to several synthetic antimalarials and support the efficacy of the quinine and pyrimethamine combination. The strain was designated Vietnam (Sn.) (Powell et al. 1964).

Legters et al. (1965) presented a detailed report of three soldiers who acquired falciparum malaria in Vietnam and required several courses of chloroquine and quinine before a radical cure was achieved. One of these patients provided the resistant strain designated Vietnam (CV). Later, this strain was used in volunteer clinical studies which demonstrated the ineffectiveness of chloroquine and pyrimethamine against it and provided additional evidence of variability among different strains of chloroquine-resistant *P. falciparum* in their response to pyrimethamine (Eppes et al. 1966). Map 9 shows the locations in Southeast Asia where drug-resistant malaria was contracted.

Thus, it was quite clear, particularly to those in research positions, that the research and development problem which would require the highest priority was drug-resistant malaria. At U.S. Army Medical Research and Development Command Headquarters on 6 August 1965, members of The Surgeon General's staff convened to assess the problem. They recommended that the Army Vice Chief of Staff, Gen. Creighton W. Abrams, Jr., and the MACV (Military Assistance Command, Vietnam) surgeon, Col. (later Maj. Gen.) Spurgeon H. Neel, Jr., MC, be advised of the seriousness of the situation. The consensus at that time was to retain the standard 3-day chloroquine treatment during the acute attack of malaria while research progressed. Furthermore, it was believed that the weekly C-P (chloroquine-primaquine) tablet should be the routine method of chemoprophylaxis and should also be given following therapy for clinical malaria in preference to the 14-day primaquine regimen. The potential problem with G6PD (glucose-6-phosphate dehydrogenase) deficiency was recognized, but the efficacy of primaquine in eradicating the tissue phase was considered overriding. The Surgeon General, Lt. Gen. Leonard D. Heaton (1965) dispatched a memorandum to General Abrams following the meeting, emphasizing the impact of malaria on the effectiveness of troops in Southeast Asia, the essential elements of good malaria discipline, drug prophylaxis, and the necessity for indoctrination of all officers. Medical officers attending the Medical Field Service School were to receive additional instruction about malaria.

The malaria attack rate was low before June 1965 when there were few military personnel in Vietnam. Only 800 U.S. Army personnel were present in 1960, principally military advisers and Special Forces personnel; the number had risen to slightly less than 15,000 in 1964. By the end of 1965, however, the United States had fielded a significant military force in South Vietnam, numbering 184,300, of which almost 117,000 were U.S. Army troops (MACV-MP).

As contact with the opposing forces increased, the malaria attack rate rose precipitously. Early data grossly understated the problem because of the dif-



MAP 9.—Locations where United States and allied military personnel contracted drug-resistant falciparum malaria in Southeast Asia, 1965. (Office of the Surgeon General. 1965. Status of SEASIA Plan. Report to Chief, Research and Development, 31 Jan. 65.)

difficulties of reporting cases and the large number of patients evacuated out of country. By the end of 1965, 1,972 cases of malaria were recorded, most of which occurred during the last 3 months of the year; 16 cases were fatal (Neel 1973, pp. 38-39). The incidence in some combat units, such as the 1st Cavalry Division (Airmobile [AM]), approached 350 per 1,000 per year, in contrast to 22 per 1,000 per year in combat support units.* This high incidence in combat units was directly related to military operations in the Central Highlands where malaria was known to be highly endemic and troops were in close contact with Vietcong and North Vietnamese elements.

It was difficult to assess the early clinical experience because of the multiplicity of drug regimens, incomplete medical records, and hasty evacuation of patients from Vietnam. Sheehy and Reba (1967) reviewed the initial experience in several Army hospitals in the country. They noted that up to 50 percent of personnel participating in operations in the Ia Drang and Vinh Thanh valleys of central Vietnam developed clinical malaria, and about 5 percent developed an asymptomatic parasitemia which was ultimately cleared by chemoprophylaxis with chloroquine and quinine. Vivax infections continued to be effectively suppressed with chloroquine-quinine treatment. However, virtually all the clinical infections were caused by *P. falciparum* and most were resistant to chloroquine therapy. Seventy percent of the *P. falciparum* infections in nonimmune patients were only partially responsive to chloroquine therapy, with early recrudescences 1 to 4 weeks later; 10 to 20 percent of these cases were refractory to a second course of treatment. Quinine was more reliable in terminating the acute attack, although a dosage of 650 mg every 8 hours for 14 days proved inadequate to effect a radical cure, and there was a 70 to 90 percent rate of recrudescence within a month. Pyrimethamine used alone was no better; in small groups treated with a dose of about 25 mg every 8 hours for 3 days, early recrudescences ranged from 15 to 40 percent. With this background, five drug regimens were systematically evaluated in late 1965, as outlined in table 47. Regimen III, quinine 14 days with 3-day pyrimethamine, was the best of the group with a radical cure effected in 93 percent (125 of 135 patients). Nine patients had recrudescences and only one was refractory to subsequent therapy. Three of the 135 patients treated with quinine and pyrimethamine, an antifolic acid compound, developed megaloblastic anemia (which was later responsive to folic acid administration).

Orbison (1966) reported a similar experience with drug-refractory falciparum malaria at Tripler General Hospital in Honolulu when many patients were being evacuated to Hawaii from Vietnam. Within 2 months, October to December 1965, 286 patients were admitted. Altogether they had received 11 individual or combined drug treatment schedules in Vietnam. The early arrivals at Tripler were placed on the standard 3-day chloroquine regimen followed by the weekly C-P tablet, since it was uncertain whether they had acquired malaria because they failed to take the prescribed medication while under treatment

*Brig. Gen. Frederic J. Hughes, Jr., Director, Professional Services Division: Disposition form to the Deputy Surgeon General, 23 Nov. 1965.

TABLE 47.—Evaluation of five drug regimens for *Plasmodium falciparum* in U.S. Army troops in Vietnam, 1965

Regimen ¹	Days given on	Total dose (g)	Number of patients				Mean duration time (days)
			Treated	Refractory	Radical cure	Recrudescence within 4 weeks	
I. Chloroquine hydrochloride	1-3	1.4	14	6	1	7	12
Quinacrine	1-7	2.6					
II. Chloroquine diphosphate	1-3	1.5	160	2	31	87	14.5
Quinine sulfate	1-14	27.3					
III. Pyrimethamine	1-3	0.23	135	1	125	9	16
Quinine sulfate	1-14	27.3					
IV. Pyrimethamine	1-3	0.23	60	0	57	3	15
Quinine sulfate	1-14	27.3					
Sulfadiazine	1-5	10.0					
V. Chloroquine diphosphate	1-3	1.5	40	0	0	0	
Quinine sulfate	1-14	27.3					
Pyrimethamine	15-17	0.23					
Sulfadiazine	15-19	10.0					

¹Regimen I: Chloroquine hydrochloride (intramuscularly), 200 mg base every 8 h for a total of 7 doses. Quinacrine 200 mg every 6 h on day 1 followed by 100 mg every 8 h for 6 days. Regimen II: Chloroquine base (600 mg) given orally followed in 6 h by 300 mg of chloroquine base. Chloroquine base (300 mg) given on days 2 and 3. Quinine sulfate (oral) 650 mg thrice daily. Regimen III: Pyrimethamine (oral) 25 mg thrice daily. Quinine sulfate (oral) 650 mg thrice daily. Regimen IV: Pyrimethamine, 25 mg thrice daily. Quinine sulfate, 650 mg thrice daily. Sulfadiazine, 0.5 g every 6 h. Regimen V: Chloroquine base, administered as in regimen II. Quinine sulfate, administered as in regimen II. Pyrimethamine, 25 mg every 8 h. Sulfadiazine, 0.5 g every 6 h.

Source: Sheehy, T. W., and Reba, R. C. 1967. Treatment of chloroquine-resistant *Plasmodium falciparum* infections in Vietnam. *Ann. Int. Med.* 66: 616-22. (Modified).

(secondary gain), or whether there was indeed a drug-resistant strain involved. The treatment failure rate was 43 percent: 70 of 163 patients had relapses, most of them within 3 weeks, although several relapses occurred as late as 69 days after completion of treatment, attesting to the resistance of *P. falciparum* in this group. Three regimens were then evaluated, using pyrimethamine, quinine sulfate, and a combination of both. The results appear in table 48. The superiority of combined quinine sulfate-pyrimethamine therapy was again clearly demonstrated in a 12-day schedule with a low recrudescence rate (1.3 percent).

Reed, Feinstein, and Steiger (1968) analyzed the results of treatment in malaria patients at the U.S. Army Hospital, Camp Zama, Japan, between August and December 1965. Of 462 patients admitted with a diagnosis of *falciparum* malaria, 426 were selected for study because they satisfied the criteria for diagnosis and their records were adequate. The recrudescence rate with 3-day chloroquine was 89 percent a month after treatment and was not improved with repeated courses. Quinine alone effected a radical cure in 50 percent, but this was because of the inclusion of a group receiving the drug for periods up to 30 days. In another small group on pyrimethamine alone, the cure rate was 91 percent, but dose range was not indicated. The best regimen was quinine-pyrimethamine, with which a 95-percent cure was obtained; the total dosage range of pyrimethamine was usually 75 to 150 mg, reaching 400 mg in

TABLE 48.—*Relapses occurring in three different malaria treatments, Tripler General Hospital, October-December 1965*

Schedule ¹	Number of patients	Relapse ²	
		Number	Percent
I _____	60	5	8.3
II _____	31	9	29.0
III _____	78	1	1.3

¹Schedule I: Pyrimethamine 25 mg thrice daily, 3 days. Schedule II: Quinine sulfate 975 mg thrice daily, 2 days; then 650 mg thrice daily, 10 days. Schedule III: Quinine sulfate and pyrimethamine given concurrently in same dosage as schedules I and II.

²30-day posttreatment follow-up.

Source: Orbison, Col. James A., MC, Chief, Department of Medicine, U.S. Army Tripler General Hospital. 1966. Malaria experience. Memorandum to Col. Philip J. Noel, Jr., MC, Deputy Commander, Tripler Army Medical Center, 25 Jan. 66.

some patients, while quinine was given for 3 to 12 days and in several instances as long as 30 days.

Despite the apparent effectiveness of 14-day quinine and 3-day pyrimethamine therapy, investigation continued into available drugs which might increase the effectiveness of the therapeutic regimens and of C-P prophylaxis. In Sheehy and Reba's original study (1967), dapsone (4,4'-diaminodiphenylsulfone) as a supplement to a chloroquine-quinine regimen had given promising results; only 1 of 105 patients had a recrudescence during the 30-day supplemental dapsone treatment. Interest began to focus on this compound.

The antimalarial properties of the sulfones had been recognized by the Italians in World War II (Tarabini-Castellani and Secreto 1945). Dapsone had been used in the treatment of leprosy since 1949; in a daily dose of 100 mg or less, it was considered relatively nontoxic. However, Lowe and Smith (1949) described a "mononucleosis syndrome" and a peripheral dermatitis caused by sulfones in patients with glandular fever, and McKenna and Chalmers (1958) established a relationship between agranulocytosis and dapsone administration.

Among lepers treated with the drug in certain areas of Africa, it was observed that the incidence of clinical malaria was lower than among the indigenous population. In the early 1960's, investigators in India and Nigeria demonstrated that a single 200 to 250 mg dose of dapsone produced a clinical cure in semi-immune patients with falciparum malaria. Although the initial response was favorable in some patients, treatment failures were frequent. Dapsone was less effective in clearing parasitemia caused by vivax infections (Basu, Mondal, and Chakrabarti 1962). Subsequent volunteer studies conducted under the Army Malaria Research Program demonstrated that dapsone, 25-50 mg daily, decreased severity of infections with two strains of chloroquine-resistant *P. falciparum* from Southeast Asia (DeGowin et al. 1966; Eppes et al. 1967). When the 25-mg daily dose of dapsone was used with the weekly C-P tablet before the infection was introduced, and continued for 4 to 6 weeks afterwards, suppression of infection and a radical cure were attained.

These results prompted field trials in American troops stationed in Vietnam. In November 1965, Maj. (later Col.) Robert J. T. Joy, MC, then chief of the U.S. Army Medical Research Team, Vietnam, a unit detached from Walter Reed Army Institute of Research, was encouraged to evaluate dapsone as

chemoprophylaxis by Brig. Gen. (later Maj. Gen.) Robert E. Blount and Col. (later Brig. Gen.) William D. Tigertt, MC, during their visit to the country. A pilot study was conducted in January and February 1966 among personnel of the 1st Cavalry Division (AM); it suggested that dapsone was effective, without evidence of toxicity, and justified a more extensive evaluation. This was carried out—amid the difficulties of jungle combat conditions—in March and April 1966 with 12 companies of the 1st Brigade of the division, deployed to the west of Pleiku in the Central Highlands. The dose regimen for the study group was 25 mg dapsone daily plus the weekly C-P tablet. Six companies served as a control group. There was 50 percent less malaria in units taking dapsone than in units taking a placebo (Joy, McCarty, and Tigertt 1969).

The second part of the study was conducted in units of the 3d Brigade Task Force, consisting of the 3d Brigade, 25th Infantry Division, and elements of the 1st Cavalry Division (AM). The study took place during Operation PAUL REVERE I in the Ia Drang and Ya Lop River valleys along the Cambodian border where malaria was endemic. The entire task force, except for the two battalions from the 1st Cavalry Division, was placed on daily dapsone prophylaxis, 25 mg, in addition to the weekly C-P tablet. Records of all patients admitted to the 85th Evacuation Hospital at Qui Nhon and the 8th Field Hospital in Nha Trang during the subsequent 2-month period were reviewed. The malaria incidence among troops taking dapsone was one-tenth of that observed in units not taking it. Other factors related to malaria discipline, such as use of repellants and wearing of long sleeves, were not controlled. This, and the fact that comparison was made between two divisions rather than within a single divisional force jeopardized definitive conclusions; nevertheless, the difference was striking (Joy, Gardner, and Tigertt 1969).

The next step was to acquire adequate stocks of dapsone and put to use the findings of these field trials. By the end of July 1966, The Surgeon General had instructed all commands of the changes in malaria treatment and in the chemoprophylaxis regimen (OTSG-MT). Dapsone, in addition to the weekly C-P prophylactic tablet, was to be used by troops at high risk of exposure to drug-resistant *P. falciparum* as determined by the USARV (U.S. Army, Vietnam) preventive medicine officer. The recommended treatment of clinical cases consisted of quinine sulfate, 975 mg thrice daily for 2 days, then 650 mg thrice daily for 12 additional days; pyrimethamine, 25 mg every 8 hours for the first 3 days; and dapsone, 25 mg daily from day 7 to day 28. Personnel taking dapsone prophylaxis in Vietnam were required to remain on the drug for 28 days following departure from the country.

Another study was conducted in late 1965 and early 1966 by Sheehy et al. (1967) at the 85th Evacuation Hospital in Qui Nhon. This study involved 155 nonimmune American soldiers. The controls and the dapsone-treated patients received similar treatment regimens: both groups had the standard 3-day course of chloroquine (1.5 g), and both received quinine sulfate (650 mg thrice daily), the controls for 14 days and those on dapsone for 7 to 10 days. The experimental group received dapsone for 30 days. Only 3 percent (3 of 105) of the dapsone-treated patients had a recrudescence within 3 weeks, as opposed to

41 percent (20 of 48) of the control group. Although 45 of the soldiers studied were black, only one hemolytic complication due to G6PD deficiency was observed. Dapsone as a supplement to basic treatment schedules was clearly shown to be effective.

EXPERIENCES WITH QUININE-PYRIMETHAMINE-DAPSONE THERAPY, 1966-68

Implementation of the treatment regimen for chloroquine-resistant falciparum malaria which resulted from Joy's field studies actually began in Vietnam in 1966. Dapsone, in addition to the daily C-P tablet, was authorized for use in major combat units of the I Field Force area, which extended from the Chu Lai region to the Laotian border and as far south as Da Lat. It was emphasized that any soldier on dapsone prophylaxis who acquired clinical malaria was to continue on the drug without interruption in daily dosage. This was important since it was learned very early that breakthroughs occurred when prophylaxis was interrupted for even a few days while soldiers were on rest and recuperation leave (Blohm 1966b).

Thus, the early recommended treatment for falciparum malaria was a 14-day quinine, 3-day pyrimethamine regimen in the following schedule (USARV Msg):

Quinine sulfate, 975 mg thrice daily, days 1 and 2, then 650 mg thrice daily, days 3 through 14.

Pyrimethamine, 25 mg thrice daily, days 1 through 3.

Personnel on daily dapsone were to continue daily dosage of 25 mg without interruption. Table 49 shows the reduction in major complications which occurred after standardization of therapy.

The weekly C-P tablet was discontinued during therapy for falciparum malaria and resumed immediately afterwards. The combination of primaquine and dapsone had the potential for causing marked hemolysis and methemoglobinemia in susceptible individuals. A convalescent period of 10 to 14 days was recommended and extended if a significant anemia persisted (hematocrit less than 36). With the opening of the 6th Convalescent Center, at Cam Ranh Bay, patients with malaria could complete treatment and convalescence and then engage in a graduated physical fitness program that would

TABLE 49.—*Reduction in major complications from Plasmodium falciparum by standardized therapy, October 1965-July 1966*

Item	October-December 1965	January-July 1966
Number of cases	1,300	2,000
Acute renal insufficiency	11	8
Cerebral malaria	9	7
Pulmonary complications	2	1
Deaths	19	0

¹0.4 percent.

Source: Sheehy, T. W., and Reba, R. C. 1967. Complications of falciparum malaria and their treatment. *Ann. Int. Med.* 66: 807-9.

insure their return to duty in a combat-ready condition. Original peripheral blood smears accompanied the patient through the chain of evacuation, so that the diagnosis could be confirmed or, in recrudescences, errors could be uncovered or mixed infection diagnosed (Blohm 1966b).

The standardization of therapy permitted studies evaluating drug efficacy, toxicity, and detection of signs of drug resistance. Consequently, after only a few weeks, it became apparent that the increased dosage of quinine during the first 2 weeks of therapy was not well tolerated; nausea and vomiting occurred frequently. Furthermore, high doses actually contributed little to the prompt lysis of fever and further recovery. A three-times-daily dosage of 650 mg of quinine sulfate through the entire treatment course was adopted (Cooper 1966).

Blount (1969) reviewed the first year's experience at the 85th Evacuation Hospital at Qui Nhon. The only modification in therapy after the reduced total quinine dosage was adopted was to further decrease the pyrimethamine dosage from 225 mg to 150 mg over the 3-day period. This reduction was prompted by the increased development of megaloblastic anemia in patients treated with the higher dosage and, in the later years of the war, was officially adopted in preference to the 225 mg total dose. Early studies had demonstrated that continued administration of 25 mg of pyrimethamine daily resulted in megaloblastic anemia, leukopenia, and maturation arrest of the bone marrow (Myatt, Hernandez, and Coatney 1953; Kaufman and Geisler 1960). At the 85th Evacuation Hospital, a sulfonamide was substituted in the occasional patient with megaloblastic anemia without documented difference in response. When parenteral quinine therapy was indicated, 650 mg of the hydrochloride was diluted in 1,000 cc 5-percent dextrose/water or isotonic saline and infused intravenously over an 8-hour period and repeated every 8 hours until oral medication was tolerated. The oral dose regimen was as follows:

Quinine sulfate, 650 mg every 8 hours, days 1 through 14.

Pyrimethamine, 25 mg every 12 hours, days 1 through 3.

Dapsone, 25 mg daily, when the patient was taking the drug as prophylaxis.

Table 50 gives the total number of admissions to the hospital from September 1966 until the end of August 1967; 35 percent of all medical admissions were for malaria, of which 75 percent were falciparum, 22 percent vivax,

TABLE 50.—*Malaria admissions, 85th Evacuation Hospital, September 1966-August 1967*

Malaria species	Attacks	
	Number	Percent
Falciparum	2,003	75.0
Vivax	579	21.7
Malariae	11	0.4
Vivax-falciparum	76	2.9
Vivax-malariae	1	
Total	2,670	100.0
Total medical admissions	7,603	

Source: Blount, R. E., Jr. 1969. Acute falciparum malaria. Field experience with quinine/pyrimethamine combined therapy. *Ann. Int. Med.* 70: 142-47.

and 3 percent mixed. Malariae malaria was diagnosed in 12 patients, one of whom had a mixed infection with *Plasmodium vivax*. *P. vivax* and *Plasmodium malariae* infections were treated in the conventional manner with no difficulty. Mixed falciparum-vivax infections were treated with chloroquine and primaquine in addition to the basic regimen for falciparum malaria. The recrudescence rate for falciparum malaria was less than 1 percent during the 4-week followup period. There were no deaths in this series. The complications of falciparum malaria that were observed are listed in table 51. Hemoglobinuria, an indication of the density of parasitemia and extent of hemolysis, was present in eight patients. Acute renal failure was not seen in this series. Twenty-four patients had neurological abnormalities indicative of cerebral malaria; an adrenal corticosteroid, either dexamethasone or hydrocortisone, was used with parenteral quinine in these patients, sometimes with dramatic response. The role of parenteral steroids in the reduction of cerebral edema was unclear; however, clinical use of them was widespread in Vietnam and anecdotal evidence was strong that they hastened the response to quinine. Anemia severe enough to require transfusion was another hematologic complication in 18 patients. Eleven had pancytopenia when admitted or at the start of multiple drug therapy, with recovery beginning during the first week of therapy in most. Methemoglobinemia was observed only once, and acute hemolysis secondary to G6PD deficiency was an occasional finding.

Because of the concern that quinine might have been responsible for some of the more severe hematologic complications, it was desirable to learn whether the amount needed to effect a clinical cure could be reduced. There was also a need to reduce the number of days lost from duty, which at this time was estimated by the medical consultants* to be 30 to 35 days for falciparum malaria. Longer patient observation periods had been required during the latter half of 1966 to assess drug efficacy.

TABLE 51.—*Complications of falciparum malaria and therapy, in 2,003 cases, 85th Evacuation Hospital, September 1966-August 1967*

Complication	Number of cases	Percent of 2,003 admissions
Malaria with hemoglobinuria	8	0.4
Acute renal failure	0	0
Cerebral malaria	24	1.2
Pancytopenia	11	0.6
Anemia requiring transfusion	7	0.4
Petechiae	3	0.1
Total	53	2.7

Source: Modified from Blount, R. E., Jr. 1969. Acute falciparum malaria. Field experience with quinine/pyrimethamine combined therapy. *Ann. Int. Med.* 70: 142-47.

*Lt. Col. Thomas W. Sheehy, MC, Nov. 1965-May 1966; Lt. Col. Raymond W. Blohm, Jr., MC, Apr. 1966-June 1967; Lt. Col. Nicholas F. Conte, MC, June 1967-June 1968.

Further contributions to standardization of therapy for falciparum malaria were made in January 1967, at the 6th Convalescent Center. Rogoway and Bailey (1967) conducted a study to determine whether the duration of quinine therapy could be reduced from 14 to 10 days, consequently reducing the total dosage, without risking an increased relapse rate. Two groups, comparable in age and race, were evaluated, totaling 141 patients (table 52). The same drugs were used in both groups; quinine 650 mg thrice daily for 10 or 14 days, pyrimethamine 25 mg thrice daily for 3 days, and dapsone 25 mg daily. Only the duration of quinine therapy was varied. All patients were followed up 21 days after completion of quinine treatment. There were no treatment failures in either group. Three patients on the 14-day regimen had complications: one developed a drug reaction with high fever, headache, maculopapular eruption, and arthralgias; a second had megaloblastic anemia; a third had vivax infection breakthrough. No complications were observed with the shorter regimen and length of hospital stay was shortened by 3 days. The USARV surgeon adopted this shorter regimen in July 1967 for use in all treatment facilities in Vietnam.

The early field trials with sulfonamides were restricted because of the limited availability of these drugs in field hospital pharmacies and even in larger military medical centers in the United States. They were never used alone because of their low activity against falciparum strains. Used in various combinations, they failed to influence the recrudescence rate. There was a certain rationale in using them in combination with antifolate drugs such as pyrimethamine, however. Sulfonamides were known to compete with para-aminobenzoic acid in folic acid synthesis, and pyrimethamine to interfere with the action of dihydrofolic acid reductase; thus there was a two-pronged attack on folic acid synthesis, which is essential to the formation of plasmodial nucleotides. It had been recognized for some time that the action of pyrimethamine could be potentiated by sulfonamides and even prevent the emergence of resistance (Hurley 1959).

Laing (1965) reported that a long-acting sulfonamide, sulforthodimethoxine (Fanasil), when administered to semi-immune Africans with falciparum malaria

TABLE 52.—A comparison of 10- and 14-day quinine in multidrug therapy for acute falciparum malaria

Item	Total		10 days		14 days	
	Number	Percent	Number	Percent	Number	Percent
Patients	141	100.0	71	50.4	70	49.6
Race:						
White	126	89.4	64	90.0	62	89.0
Black	15	10.6	7	10.0	8	11.0
Mean age (years)	21.8		23.3		21.3	
Mean length of stay (days)	27.2		25.7		28.8	
Relapses	0		0		10	
Patients with previous malaria	24	17.0	14	19.7	10	14.3

¹Three complications observed.

Source: Rogoway, W. M., and Bailey, W. H. 1967. Comparison of 10-day and 14-day quinine therapy with falciparum malaria. *USARV M. Bull.* (USARV Pam 40-5), Sept.-Oct., p. 25.

as a single dose in a range of 250 to 1,000 mg, produced a rapid clinical and radical cure. The compound is an isomer of sulfadimethoxine (Madribon) with a biologic half-life of 100 to 200 hours. This is 25 times the half-life of sulfisoxazole and is attributable to its slow excretion in the urine (Bartelloni, Sheehy, and Tigertt 1967). Theoretically, a 1-g dose of Fanasil is equivalent to a 1-g daily dose of another long-acting compound, sulfamethoxypyridazine (Kynex). Peak blood levels of Fanasil are reached 4 hours after ingestion and the compound is excreted in the urine slowly.

Bartelloni, Sheehy, and Tigertt (1967) conducted preliminary trials with these compounds at the 3d Field Hospital in Saigon in 1966. The posttreatment observation period ranged from 28 to 63 days. Ten patients with recrudescence of falciparum malaria had a clinical cure with a single 1-g dose of Fanasil plus 50 mg pyrimethamine. Five patients with an initial infection also had a rapid clinical cure with this regimen. Triple-drug therapy in 55 patients with initial infection, using the same single dose combination of Fanasil and pyrimethamine, plus quinine 650 mg every 8 hours for 14 days, was also highly effective with only one clinical relapse 3 days after treatment was completed.

Several other studies were conducted at the 3d Field Hospital and the 93d Evacuation Hospital during this period. Eighty-four patients were treated with quinine for 14 days, pyrimethamine for 3 days, and Fanasil 500 mg on day 1. Only one recrudescence was observed. Fifty-nine patients were treated with quinine for 14 days, pyrimethamine for 3 days, and sulfisoxazole (Gantrisin) 50 mg thrice daily for 5 days, with no recrudescences. However, the posttreatment observation period did not exceed 16 days (Blohm 1966a). A few trials with sulfadiazine were carried out in late 1965 in combinations with chloroquine or quinine.

Berman (1969) reported his experiences with triple-drug therapy in a study of 99 marines. Chloroquine was given in the standard dosage of 1.5 g base over 3 days. Pyrimethamine was administered in a 50-mg initial dose, followed by 25 mg every 8 hours for 10 doses, for a total dosage of 300 mg. Sulfisoxazole was also given concurrently, 4 g daily in divided doses for 6 days, for a total of 24 g. There were no treatment failures among the 76 patients whose cases could be followed up.

Because of the recognized problem of drug resistance and the relatively slow activity of sulfonamides, large-scale clinical field trials with these drugs were discouraged; it was preferable to await the development and testing of new compounds in this class under controlled conditions. A USARV regulation (USARV Reg) on the treatment of malaria permitted the use of sulfonamides for treatment failures but only in combination with quinine and pyrimethamine.

Sheehy and Reba (1967) reviewed the early experience with sulfadiazine in multiple drug therapy and devised a 14-day quinine, 3-day pyrimethamine regimen combined with sulfadiazine 0.5 g every 6 hours for 5 days concurrently. Radical cure was effected in 57 of 60 nonimmune soldiers. All 40 patients treated with another regimen, chloroquine-quinine-pyrimethamine-sulfadiazine, also had radical cures (see table 47). Chin and coworkers (1966) evaluated the effectiveness of sulfonamides used alone or in combination with pyrimethamine. Volunteers were infected with drug-resistant strains and sulfadiazine, Fanasil,

and sulfamethoxypyridazine were employed. Again, these drugs were slow in reducing parasitemia and in terminating the acute attack, even when used with pyrimethamine. The combination of pyrimethamine and sulfadiazine was inferior to the other two combinations. The most effective was 50 mg pyrimethamine and 1 g Fanasil given as a single dose. Powell, DeGowin, and McNamara (1967) evaluated the efficacy of sulfadiazine and pyrimethamine in volunteers infected with the chloroquine-resistant Malayan Camp strain, Thailand (JHK) strain, and Vietnam (CV) strain of *P. falciparum*. They confirmed previous observations that combinations of a sulfonamide and pyrimethamine are ineffective in potentiating the blood gametocidal effect. They also found that sulfadiazine alone does not satisfactorily treat acute drug-resistant strains of *falciparum* malaria; however, under certain conditions, when combined with pyrimethamine, its therapeutic efficacy is enhanced and it may be useful in treating individuals infected with chloroquine-resistant strains of *P. falciparum*.

VIVAX MALARIA

Although vivax malaria was prevalent throughout South Vietnam, and there were indications that the attack rate among the Vietcong was high, few cases were reported in U.S. troops during the early period, indicating good malaria discipline, especially in terms of chemoprophylaxis. There were no reported cases of vivax malaria in the last half of 1965 (AMEDS/AMEDD-AR65, pp. 20-21). *P. vivax* and *P. malariae* infections were less likely to be acquired during the dry season or cool months of the year. This was the experience with vivax infections acquired in Korea; recrudescences were usually observed in the late spring and summer when the mean ambient temperature exceeded 70°F (Neel 1973, p. 13).

Later in the war some concern was expressed that drug-resistant strains of *P. vivax* were emerging, particularly when the attack rate rose in 1967. The clearly increasing attack rate among personnel returning to the continental United States, however, could be traced to unsupervised, inadequate terminal chemoprophylaxis.* Approximately 1 in every 100 Vietnam returnees was infected with malaria in 1967, a fact that prompted The Surgeon General (Heaton 1967) to inform all medical commanders of the situation.

Many explanations were offered for the failure of troops to take the C-P tablet regularly. First, it required discipline to take the tablet once a week voluntarily, particularly under conditions of jungle fighting, although some units employed a malaria roster and a system to insure that each soldier swallowed a tablet as he approached the mess line each Monday. Second, the pill was believed to have various side effects. The incidence of gastrointestinal symptoms was reportedly high and diarrhea 24 hours after ingestion was not uncommon, an undesirable situation in a combat operation. Some who took the pill complained

*On 4 Apr. 1966, a circular (DA Cir 40-24) was published, requiring all cases of malaria diagnosed at a U.S. Army medical facility to be reported to local or state health authorities, to The Surgeon General, and to the National Communicable Disease Center in Atlanta. Imported malaria was now a matter for strict surveillance.

of insomnia, but this symptom was especially difficult to evaluate (Conte 1968).

"Folklore" aside, some serious side effects were reported. In 1968, the 3d Surgical Hospital reported a death from anaphylaxis after ingestion of a C-P tablet (SH-3), and unconfirmed reports of anaphylaxis and death following ingestion of a C-P tablet reached the medical consultant in 1969.* In 1970, the medical consultant documented a case of bronchospasm on challenge with a C-P tablet (Edgett 1970). The offending agent was probably the chloroquine component. Fortunately the incidence of such reactions remained inconsequential. Physicians were continually aware of significant hemolytic reactions in both whites and blacks. A number of patients were evacuated each month because of self-limited but severe hemolytic episodes (AMEDS/AMEDD-AR69, p. 14). This was not unexpected on the basis of the conclusions of George, Sears, and Conrad (1966). In studying three whites and one black with G6PD deficiency, they found that assay of G6PD or measurement of pentose shunt activity did not directly provide a basis for the prediction of primaquine sensitivity. Chart 17 demonstrates the response of a primaquine-sensitive patient to a single C-P tablet.

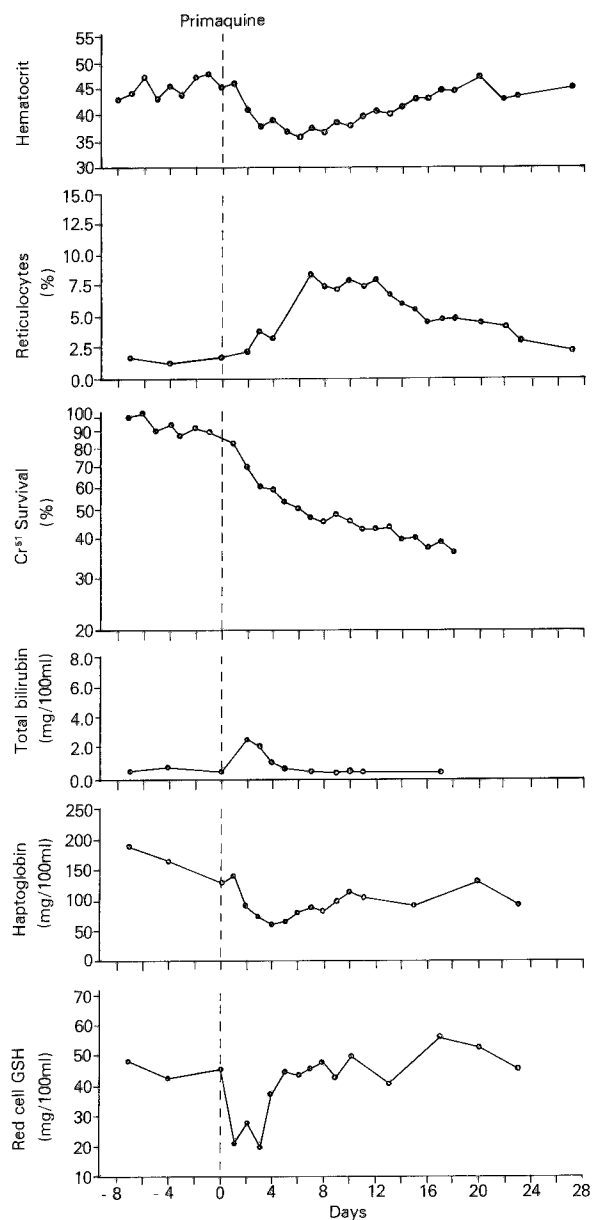
In addition to possible allergic reactions to chloroquine and hemolysis related to primaquine, cyanosis during malaria chemoprophylaxis was a cause of evacuation of U.S. soldiers. Study of the effects of both dapsone and primaquine demonstrated that significant methemoglobinemia could occur in NAD (nicotinamide-adenine dinucleotide) methemoglobin reductase-deficient subjects. Because of the cyanosis produced by these drugs, clinical recognition of a usually undetected enzymatic defect of the erythrocyte became possible. At levels above 20 percent methemoglobinemia, Cohen et al. (1968) noted headache, dizziness, anorexia, nausea, and vomiting. Whether a lesser degree of methemoglobinemia produced impaired function in the combat soldier was unclear. Aviators were not affected because they did not generally participate in malaria prophylaxis.

Between 1 September and 1 December 1966, 1,309 cases of malaria were treated at the 85th Evacuation Hospital in Qui Nhon, of which 13 percent (165) were vivax infections. The vivax response to chloroquine was always prompt, giving added support to the belief that poor malaria discipline was the decisive factor in the development of clinical vivax malaria.** At the 6th Convalescent Center, Carbon (1967) reviewed the experience with vivax malaria from 1 June 1966 to 30 April 1967, because it had been observed that the recrudescence rate had risen significantly when the treatment schedule was changed in December 1966, resuming the weekly C-P tablet in lieu of 14-day primaquine therapy. Whereas, at the end of December 1966, 6 percent of the total malaria cases at the 6th Convalescent Center were caused by *P. vivax*, by the end of April 1967 this figure had increased to 17 percent. The recrudescence rate had also changed

*Lt. Col. Andre J. Ognibene, MC, USARV Medical Consultant, 1969.

**Maj. Robert E. Blount, Jr., MC. Note to Brig. Gen. Robert E. Blount, Commander, U.S. Army Fitzsimons General Hospital, forwarded to Col. Marshall E. McCabe, MC, 16 Dec. 1966.

CHART 17.—Response of primaquine-sensitive patient to a single C-P tablet



Source: George, J. N.; Sears, D. A.; and Conrad, M. E. 1966. Primaquine sensitivity in Caucasians. Contribution No. 133, Army Research Program on Malaria.

from slightly more than 12 percent to 18 percent, and a majority of the patients who experienced a relapse did so in the hospital, where they presumably had not

been taking the C-P tablet.* As a result of this and other experiences, the USARV surgeon changed the policy for the treatment of vivax malaria to include the concurrent administration of 15 mg primaquine base daily for 14 days, in lieu of the weekly C-P tablet, in treatment schedules and on departure from Vietnam. No change was prescribed for field chemoprophylaxis (USARV-CG).

One other aspect of weekly C-P chemoprophylaxis deserves mention. In and around base camps, it was not uncommon for personnel to avoid the side effects attributable to primaquine by substituting a chloroquine tablet (300 mg base). To what extent this was practiced in the field is not known, although the consensus was that most personnel took the C-P tablet, if only erratically (Conte 1968). Powell (1966) had shown that primaquine, like pamaquine, exhibited sporonticidal and gametocidal activity against drug-resistant falciparum strains. In the standard 45-mg primaquine dose, it not only eliminated the gametocytes that would ordinarily circulate in the peripheral blood but also inhibited parasite development in the mosquito vector (Rieckmann et al. 1968). Thus, the use of chloroquine alone was unwise since primaquine prevented troops from becoming a source of falciparum infection in areas where they were based.

Throughout 1968, it was evident that the inclusion of 14 days of primaquine in the treatment regimen for vivax infections had virtually eliminated the problem of early relapse observed in late 1966 and early 1967 (Conte). However, this was of little comfort in the face of the persisting primary incidence rate, which reached 31.5 per 1,000 by October of 1968 (USARV-CHR Oct. 68).

A consequence of this problem was the increasing number of malaria cases reported in the United States each year from 1965 through 1971. Canfield (1972), using Center for Disease Control malaria surveillance reports, determined that during this 6-year period more than 14,000 cases of vivax malaria were reported in the United States, accounting for over 80 percent of the country's total malaria cases. The data provided by Barrett et al. (1969) in their survey of 671 Vietnam returnees indicated that this was largely the result of failure to complete the prescribed terminal chemoprophylaxis regimen, as was the case in 70 percent of their group. This was a serious indictment of the method of administration, for the C-P tablet, though highly effective in itself, had to be taken faithfully for 8 weeks by individuals who were apparently in good health.

TREATMENT OF MALARIA, 1968-72

In January 1968, an analysis of 1,000 consecutive cases of falciparum malaria admitted to the 6th Convalescent Center during the months of November and early December 1967 — when the attack rate was at its peak — indicated that the treatment failure rate approximated 1 to 2 percent with the 10-day triple-drug regimen, quinine-pyrimethamine-dapsone. Most patients at the center were returned to duty within 5 days after completion of therapy. The average time lost from duty for falciparum malaria was now 24 days; for vivax

*Figures modified by Brig. Gen. Andre J. Ognibene.

malaria, it was 12 days (Conte 1967). Some units, such as the 173d Airborne Brigade, were experiencing very high attack rates; approximately half of the infections were vivax, indicating a breakdown in malaria discipline. The evidence notwithstanding, there was still some lingering concern that strains of *P. vivax* present in Vietnam were not responsive to the weekly C-P tablet as a suppressant.

In 1969, Hiser et al. (1971) conducted a study of the 71st Evacuation Hospital, Pleiku, where a group of 30 patients with acute vivax malaria was evaluated. A second group of 12 vivax patients was studied at Walter Reed General Hospital, Washington, D.C. The group in Vietnam was treated with a single C-P tablet weekly for 2 weeks and returned to duty at the end of the second week. Urine chloroquine determinations were made before and 1 week after the first C-P tablet. No patients had evidence of urine chloroquine before treatment; two-thirds had a positive urine test a week after receiving a single C-P tablet. Plasma chloroquine levels were not measured. The Walter Reed group was treated with a single C-P tablet, observed for 3 weeks, and then given the standard treatment to effect a radical cure (3 days of chloroquine plus 14 days of primaquine). All patients in both groups responded to treatment promptly with no relapses. This fact, and the absence of residual chloroquine from the urine of all patients in the Vietnam group on admission, gave added support to what many had suspected all along: the most important factor in the high incidence of vivax infections in selected U.S. troops in Vietnam was failure to take the chemoprophylactic tablet regularly.

The remarkable success of the 10-day quinine-pyrimethamine regimen against falciparum malaria prompted some to wonder whether treatment could be shortened again, thereby reducing drug-related morbidity and days lost from duty even further. Reback, Theus, and Freebern (1968) conducted a study at the 6th Convalescent Center at the end of 1967 to evaluate a 7-day course of therapy with the daily dosage of quinine and pyrimethamine remaining the same; the total amount of quinine administered was thus reduced from 4.6 to 3.2 g. The treatment failure rate in 135 cases was about 6 percent, indicating the inferiority of this shortened regimen.

Meanwhile, the search for more effective sulfonamides continued, because induced resistance was a real danger and drug combinations with pyrimethamine had certain limitations. One promising compound was sulfamethoxypyrazine (2-sulfanilamide-3-methoxypyrazine), or sulfalene, which also acts as an antifolate through its competitive inhibition of para-aminobenzoic acid. Its half-life is approximately 63 hours (Martin and Arnold 1968a). Early clinical trials of sulfonamides against acute falciparum infections in Africans were encouraging, although some workers reported disappointing results. However, success with Fansil and pyrimethamine against chloroquine-resistant falciparum malaria had been reported by Bartelloni, Sheehy, and Tigertt (1967) at the 3d Field Hospital. Martin and Arnold (1968a) evaluated the sulfalene compound in volunteers, using the drug-sensitive East African Uganda I strain and the drug-resistant Malayan Camp strain. Curiously, the drug, given as a single dose, was more effective against the drug-resistant Camp strain. Furthermore, with

relative resistance to pyrimethamine, the Uganda I strain's sensitivity to sulfalene was enhanced. As the authors point out, this suggests that there are qualitative differences in the actions of sulfonamide drugs.

Martin and Arnold (1968b) also evaluated the efficacy of sulfalene in combination with trimethoprim [2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine], a dihydrofolate reductase inhibitor which was developed out of a survey of pyrimidine antibacterial compounds and was demonstrated to have less toxicity than pyrimethamine, with a relatively short half-life of 16 hours. Volunteers in this study were infected with the same strains, Uganda I and Camp. A single dose of 0.75 g sulfalene plus 0.5 g trimethoprim was used to treat infections with Camp strain, while the Uganda I strain was treated with smaller single doses of both drugs. All eight patients with the nonresistant Uganda I strain of *P. falciparum* were cured more rapidly than with quinine; 10 of 11 patients with the multiresistant Camp strain were cured.

Late in 1969, Canfield et al. (1971) conducted field trials with this drug combination among soldiers at the 71st Evacuation Hospital with naturally acquired falciparum malaria. This group was compared with a group of patients at Walter Reed General Hospital who had documented recrudescences from previous therapy. The patients in Vietnam received one oral dose of trimethoprim 1.5 g and sulfalene 1.0 g and were followed up for at least 35 days. The patients at Walter Reed were divided into two subgroups: one received trimethoprim 250 mg twice a day and sulfalene 250 mg four times a day on days 1, 3 and 5, while the other received trimethoprim 500 mg three times a day and sulfalene 250 mg four times a day for 3 days. All patients were followed up for 5 to 10 weeks. The results are shown in table 53. In group 1, only one patient failed to respond to treatment. In group 2, there were four treatment failures after a satisfactory initial response. The overall cure rate of 72 percent compared unfavorably with

TABLE 53.—Results of treatment of *Plasmodium falciparum* malaria from Vietnam with trimethoprim and sulfalene

Item	Group 1	Group 2(a)	Group 2(b)
Number of patients	26	5	5
Classification	Nonimmune	Semi-immune	Semi-immune
Dosage			
Trimethoprim	1.5 g	0.5 g	1.5 g
Sulfalene	1.0 g	1.0 g	1.0 g
Treatment time	Single dose	Every other day, for 3 doses	Daily, for 3 doses
Results:			
Type A ¹	20	4	2
Type B ²	5	1	3
Type C ³	1	0	0

¹Clinical and parasitological response without recrudescence during the period of observation.

²Clinical and parasitological response, but recrudescence during period of observation.

³Continued clinical manifestations and parasitemia.

Source: Canfield, C. J.; Whiting, E. G.; Hall, W. H.; and MacDonald, B. S. 1971. Treatment of acute falciparum malaria from Vietnam with trimethoprim and sulfalene. *Am. J. Trop. Med.* 20: 524-26.

that obtained with the 10-day quinine-pyrimethamine regimen, demonstrating the necessity of carefully performed field trials of new compounds whose initial success in a controlled environment often results in premature or optimistic claims.

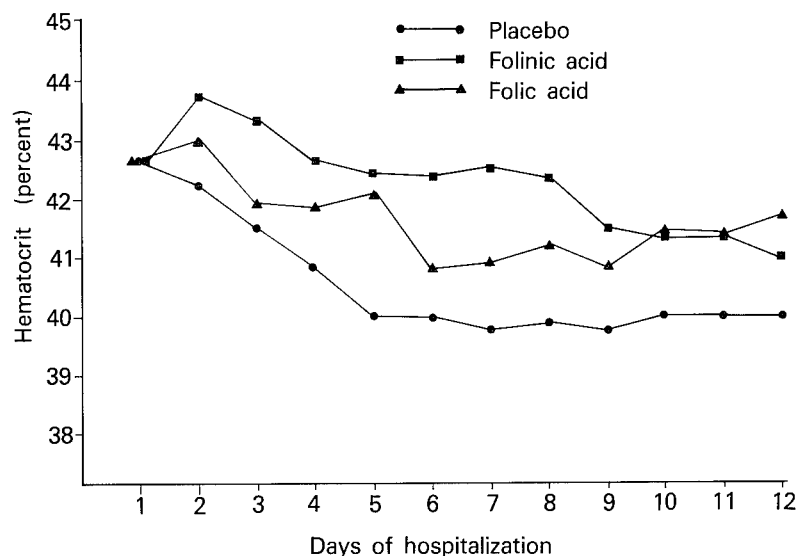
During the early part of 1969, uneasiness developed about the toxicity of dapsone, particularly since sentiment was growing to institute dapsone prophylaxis Army-wide in Vietnam. Previously, a large number of soldiers had been taking the drug without untoward effect although it was known to cause hemolysis and methemoglobinemia. By the end of the year, Ognibene (1970) reported 16 patients who had developed agranulocytosis while on dapsone prophylaxis and were admitted to Army hospitals in Vietnam; 50 percent of them died from overwhelming sepsis. None of these patients had been on dapsone for less than 4 weeks or more than 12 weeks; thus, the 28-day treatment schedule in combination with quinine and pyrimethamine appeared not to be in jeopardy. Agranulocytosis was not recorded in any U.S. personnel who were on C-P prophylaxis alone during this period. There was some suspicion that storage of dapsone for extended periods under high temperatures had resulted in deterioration, but subsequent studies carried out at WRAIR (Walter Reed Army Institute of Research) failed to substantiate it.

Consequently, the policy concerning dapsone prophylaxis was modified (USARV Reg). Dapsone was not required as prophylaxis against falciparum malaria except when combat operations occurred in known or suspected hyperendemic falciparum malaria areas. In such cases, commanders of divisions, separate brigades, and similar elements were granted authority, upon the advice of the command surgeon, to begin or continue dapsone chemoprophylaxis. Dapsone was considered necessary when exposure of U.S. military personnel to malaria might result in unacceptable manpower losses (more than 20 cases per 1,000 per year).

Because of its ability to induce methemoglobinemia, dapsone also produced cyanosis; this effect was potentiated by the concurrent use of primaquine. Studies demonstrated that about one in three troops receiving dapsone and the C-P tablet had a methemoglobin level in excess of 2.5 percent (MRP-Rev, p. 3). The Australian forces abandoned the use of dapsone in 1970. Thus, the treatment regimen for falciparum malaria became a short course of a sulfonamide, such as sulfisoxazole, in combination with other drugs, rather than dapsone for 28 days. Experimental data suggested that a diformyl derivative, DFD (4,4'-diformaminodiphenylsulfone) was more effective than dapsone. The antimalarial activity of DFD in rodent and *P. berghei* malaria had been demonstrated before World War II (Aviado 1967). Since it could be administered once a week, the serious complications experienced with dapsone could be reduced, although methemoglobinemia remained a serious drawback. However, U.S. troops were withdrawing and field trials were not carried out in Vietnam (Clyde et al. 1970).

Reports from the Naval Medical Research Unit No. 2 in Da Nang (Tong et al. 1970) suggested that the anemia, leukopenia, and thrombocytopenia in patients with malaria which became more severe during treatment with drugs

CHART 18.—Mean hematocrit values of falciparum malaria patients treated with supplemental folates or placebo



Source: Tong, M. J.; Strickland, G. T.; Votteri, B. A.; and Gunning, J. J. 1970. Supplemental folates in the therapy of *Plasmodium falciparum* malaria. *J.A.M.A.* 214: 2330-33. © 1970, American Medical Association.

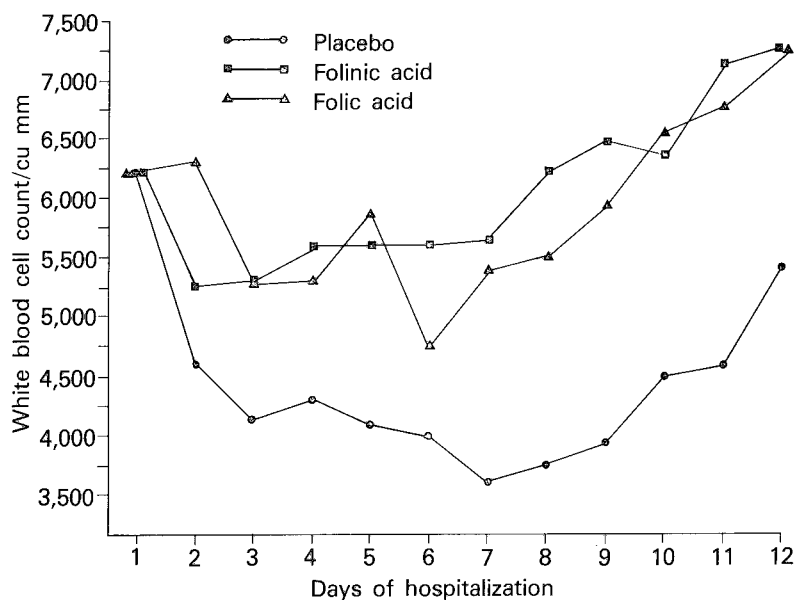
such as sulfonamides and pyrimethamine could be reversed by administration of 5 mg of folic acid daily. In 75 patients studied, no interference with antimalarial therapy was noted. Hematocrit, white count, and platelet count showed striking improvement in the folate-treated groups (charts 18, 19, and 20).

By 1970, there were indications that the "quinine regimen" which had served since 1966 was losing efficacy. Hall (1970; 1971) analyzed the experience with the standard 10-day quinine-pyrimethamine regimen at the 6th Convalescent Center in 792 patients admitted from 20 November 1969 to 23 February 1970. The recrudescence rate was 9.6 percent. The trend since 1965 is depicted in table 54.

Several reasons were offered in explanation of this trend, including differences in drug resistance with respect to geographic areas, poor or irregular absorption of quinine tablets, poor tolerance to ingestion of the drug, and deliberate avoidance (Hall 1970; 1971). It was recognized that drug-resistant malaria was most prevalent in troops engaged near the Cambodian border northwest of Saigon. Geographical differences are reflected in relapse rates with respect to referring hospital, as shown in table 55. Hospitals supporting III CTZ (Corps Tactical Zone) operations all had relapse rates over 10%.

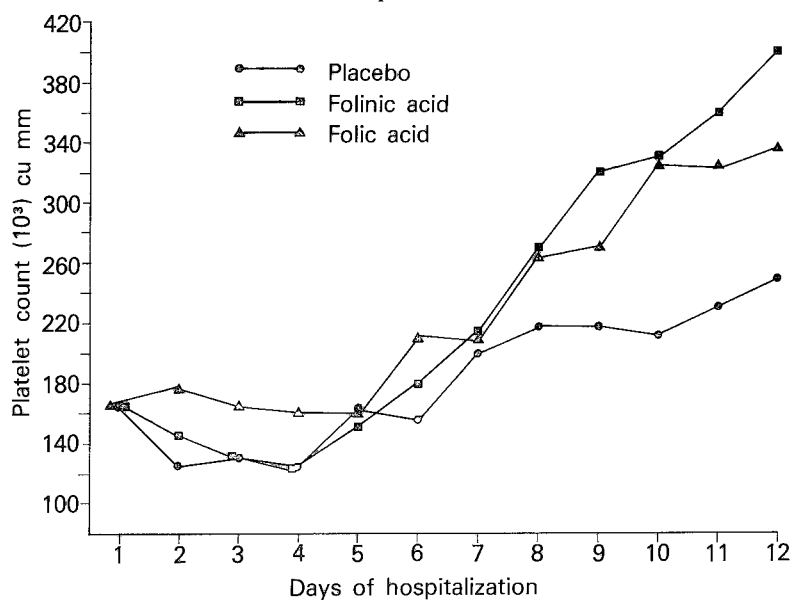
Jolson et al. (1970) conducted a study in healthy volunteers comparing quinine blood levels produced by tablets and by capsules. Capsules produced much higher blood levels after the first dose, although the sustained blood levels over the next 10 days were only slightly higher.

CHART 19.—Mean white blood cell counts of falciparum malaria patients treated with supplemental folates or placebo



Source: Tong, M. J.; Strickland, G. T.; Votteri, B. A.; and Gunning, J.-J. 1970. Supplemental folates in the therapy of *Plasmodium falciparum* malaria. *J.A.M.A.* 214: 2330-33. © 1970, American Medical Association.

CHART 20.—Mean platelet counts of falciparum malaria patients treated with supplemental folates or placebo



Source: Tong, M. J.; Strickland, G. T.; Votteri, B. A.; and Gunning, J.-J. 1970. Supplemental folates in the therapy of *Plasmodium falciparum* malaria. *J.A.M.A.* 214: 2330-33. © 1970, American Medical Association.

TABLE 54.—*Recrudescence rates in quinine, pyrimethamine, dapsone and/or sulfonamide treatment of Plasmodium falciparum infections in U.S. military personnel, Vietnam, 1965-70*

Year(s)	Recrudescence rate (percent)	Author
1965-66	2.0 (1/55)	Bartelloni. ¹
1966-67	3.0 (14/474)	Blohm. ²
1967	0 (0/141)	Rogoway. ³
1968	1.6 (5/319)	Reback. ⁴
1969-70	9.6 (76/792)	Hall. ⁵

¹Bartelloni, P. J.; Sheehy, T. W.; and Tigertt, W. D. 1967. Combined therapy for chloroquine-resistant *Plasmodium falciparum* infection. *J.A.M.A.* 199: 173-77.

²Blohm, R. W., Jr. 1968. Malaria: Present concepts of treatment. *M. Ann. District of Columbia* 37: 20-22 ff.

³Rogoway, W. M., and Bailey, W. H., Jr. 1967. Comparison of 10 day and 14-day quinine therapy with falciparum malaria. *USARV M. Bull.* (USARV Pam 40-5), Sept.-Oct., p. 25.

⁴Reback, H.; Theus, T. L.; and Freebern, R. K. 1968. Further observation in the therapy of falciparum malaria (seven day course of quinine). *USARV M. Bull.* (USARV Pam 40-8), Mar.-Apr., pp. 15-16.

⁵Hall, A. P. 1971. Clinical research, malaria, 6th Convalescent Center, Vietnam, May 1969-May 1970. Paper, dated 7 Jan. 71. Unpublished.

Source: Hall, A. P. 1971. Clinical research, malaria, 6th Convalescent Center, Vietnam, May 1969-May 1970. Paper, dated 7 Jan. 71. Unpublished.

TABLE 55.—*Relapse rates in malaria patients, by hospital and geographic area of troop deployment, Vietnam*

Hospital (location)	Number of patients	Relapses	
		Number	Percent
93d Evacuation (Long Binh)	125	21	17
24th Evacuation (Long Binh)	64	9	14
3d Field (Saigon)	59	9	15
12th Evacuation (Cu Chi)	44	5	11
67th Evacuation (Qui Nhon)	24	1	4
17th Field (An Khe)	20	1	5
71st Evacuation (Pleiku)	28	0	0
Total	364	46	12.6 (mean)

Source: Hall, A. P. 1971. Clinical research, malaria, 6th Convalescent Center, Vietnam, May 1969-May 1970. Paper, dated 7 Jan. 71. Unpublished.

Hall (1970) conducted clinical trials comparing oral and intravenous quinine regimens over a 10-day period. Dapsone 25 mg daily for 28 days was initiated when the sulfonamide therapy was completed. Intravenous quinine was given as the hydrochloride salt 1,300 mg per 1,000 ml isotonic saline over an 8-hour period for 10 days (total 19.5 g). Preliminary studies had suggested that quinine given by continuous intravenous infusion effected a radical cure in a greater number of patients. Final results, which demonstrated the superiority of parenteral quinine therapy, are indicated in table 56. Retreatment of failures with the standard oral program resulted in cure in only 33 percent of the patients as compared with 89 percent when the quinine was given intravenously. The only side effects of parenteral therapy were transient tinnitus and deafness in a few patients, while

TABLE 56.—*Therapy of patients who had one relapse after treatment of falciparum malaria*

Mode of therapy	Number of patients	Number relapsing	Percent relapsing
Oral ¹	42	28	67
Intravenous ²	36	4	11

¹The oral regimen consisted of quinine sulfate 650 mg thrice daily for 10 days, pyrimethamine (Daraprim) 25 mg twice daily for 3 days, sulfisoxazole (Gantrisin) 0.5 g four times daily for 6 days, and daily dapsone for 28 days after the Gantrisin was finished. All drugs were given concurrently.

²The intravenous method provided quinine intravenously with pyrimethamine and sulfisoxazole orally.

Source: Hall, A. P. 1970. The value of intravenous quinine in clinical relapses of falciparum malaria (a controlled study). *USARV M. Bull.* (USARV Pam 40-22), Jul.-Aug., pp. 1-4.

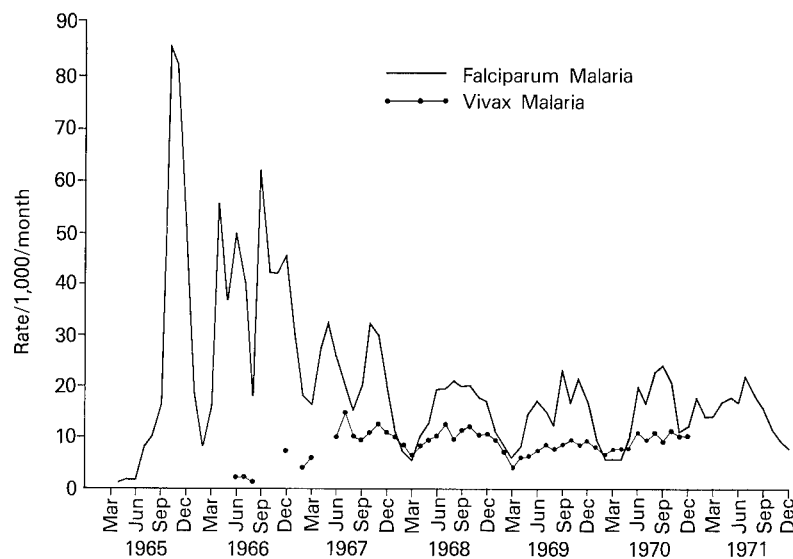
anorexia, nausea, and vomiting occurred more frequently in patients taking oral medication. Any patient who failed to respond to intravenous therapy was considered to have a severe drug-resistant infection. The conclusions of this study were not to be construed as a recommendation for routine intravenous therapy but to emphasize that drug resistance can be relative and variable.

The routine use of a specific drug over a period of time allows evolution of resistant mutations of the parasite. In this study, a small number of patients with repeated recrudescences in spite of a rigorous therapeutic program had to be evacuated to Walter Reed Army Medical Center and treated with investigational drugs from the Army Malaria Research Program (Hall 1971). The strains isolated from these patients were made available for study of new compounds in the clinical centers.

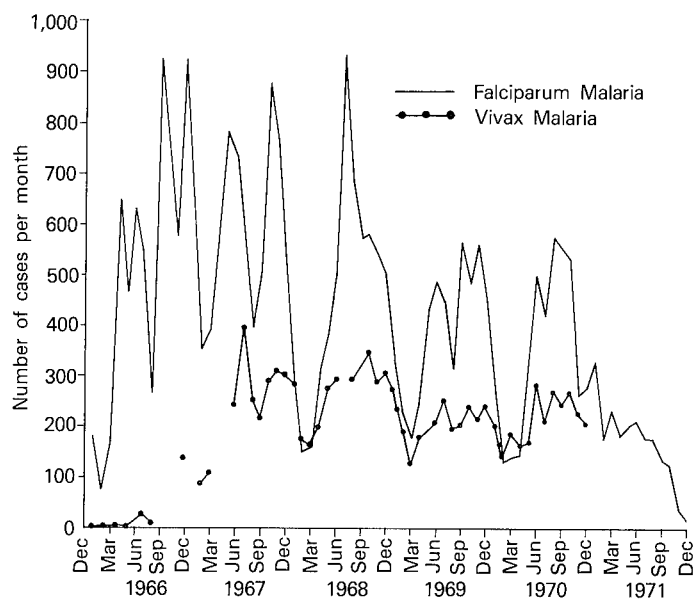
In 1970 and 1971, two other classes of drugs received limited clinical trials because of the intensified effort in the Army Malaria Research Program. One group was the arylaminoalcohols, of which the phenanthrene methanols received the most attention. The prototype was designated WR 33063 (6-bromo- α -[diheptylaminoethyl]-9-phenanthrenemethanol). In controlled studies with *P. falciparum*-infected nonimmune volunteers, Arnold et al. (1973) reported excellent results with a dosage of 0.4 g four times a day for 6 days. A radical cure was obtained in 18 of 22 volunteers infected with the Vietnam (Smith) strain, all 6 with the Vietnam (Marks) strain, 2 of 3 with the Vietnam (Brai) strain, all 5 with the Malayan Camp strain, and all 6 with the Uganda I strain.

Canfield et al. (1973) conducted a field study to test the efficacy of these drugs in the treatment of primary falciparum infections acquired in Vietnam, as well as a study of patient response with multidrug-resistant malaria. A radical cure was effected with the phenanthrene methanol WR 33063 in 23 of 25 patients admitted to the 93d or 24th Evacuation Hospitals in Vietnam with an acute attack of falciparum malaria.

Another compound of interest was quinoline methanol WR 30090 (6,8-dichloro-2-[3',4'-dichlorophenyl]- α -[di-*n*-butylaminoethyl]-4-quinolinemethanol hydrochloride). Volunteer studies using a dosage of 230 mg every 8 hours for 6 days demonstrated its efficacy against several *P. falciparum* strains. Cure was achieved in all 6 of the Uganda I strain, all 6 of the Malaya (Taylor) strain, all 6 cases with the Malayan Camp strain, all 5 with the Vietnam (Marks) strain, 2 of 3 with the Vietnam (Crocker) strain, and 17 of 20 with the Vietnam (Smith) strain.

CHART 21.—Incidence rate per month of falciparum and vivax malaria, USARV, 1965-71¹¹ Gaps indicate data not available.

Source: USARV surgeons. Monthly Command Health Reports to USARV commander, 1965-1971.

CHART 22.—Number of cases per month of falciparum and vivax malaria, USARV, 1965-71¹¹ Gaps indicate data not available.

Source: USARV surgeons. Monthly Command Health Reports to USARV commander, 1965-1971.

(Martin et al. 1973). In the study of Canfield et al., quinoline methanol WR 30090 cured 23 of 26 patients with falciparum malaria in Vietnam as well as 8 patients with multiple recrudescences admitted to hospitals in the United States. Adverse reactions to the drugs were not reported.

The final tabulations of incidence rate and total cases of malaria in Vietnam are reflected in charts 21 and 22. It is probable that a final chapter on malaria chemotherapy will not be written; rather, a continuing chronicle of effort, discovery, and drug-resistant mutation will occur. The presence of drug-resistant *P. falciparum* strains in many areas of the world will pose a formidable threat and challenge in all future malaria eradication programs. The experiences with malaria in Vietnam emphasize that there is no room for complacency in the chemotherapy of this disease. The discovery of and encouraging results with several classes of new compounds such as the aminoalcohols, and more recently the quinazolines, attest to the value of a continuous Army Malaria Research Program. Only through the acquisition of new knowledge concerning the pharmacologic and biologic aspects of drug resistance in the malarial parasite can we hope for more rational and effective treatments against this important scourge of mankind and formidable foe of all field armies.

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Part IV

CLINICAL DISORDERS: GASTROINTESTINAL
DISEASES

Gastrointestinal Diseases: Background and Buildup

Colonel Ralph F. Wells, MC, USA (Ret.)

* * * comfort may be derived from a knowledge that some of the best work of the profession has come from men whose clinical field was limited but well-tilled. The important thing is to make the lesson of each case tell on your education. The value of experience is not in seeing much, but in seeing wisely. [Osler (1894)].

Perhaps the ultimate medical irony of the Vietnam conflict is the paucity of substantial new information generated in the field of gastrointestinal disease. Areas which might have been, but were not, studied include the natural history of peptic ulcer in combat troops and the effect of new drugs, such as metronidazole, on the clinical course of the common enteric pathogens as well as on tropical sprue and amebiasis. The effect of antimalarial chemoprophylaxis on gut flora, though often the subject of speculation, was not investigated. Radioisotope capability was not available in Vietnam and was only belatedly available in offshore hospitals; thus, it remained for physicians in USAMCJ (U.S. Army Medical Command, Japan) or in CONUS (continental United States) to delineate the resolution time of amebic hepatic abscess. While the indirect hemagglutination test for amebiasis became available in 1965, neither this method nor other contemporary serologic methods were systematically investigated.

Several reasons for this lack of investigative accomplishment are apparent. The rapid buildup of troops and medical facilities meant that adequate laboratory support and diagnostic tools were not initially available. The short tour of duty militated against longitudinal study. Therefore, meaningful data were best collected by specifically designated teams. Although one might legitimately observe that the Vietnam conflict was not a vehicle for gastroenterologic research, the fact is that studies of gastrointestinal problems are mission-oriented, and the solution of these problems could contribute substantially to combat effectiveness in future conflicts. This is exemplified by the reduction in man-days lost from hepatitis resulting from classical clinical research conducted at the 6th Convalescent Center.

HISTORY AND MILITARY SIGNIFICANCE

Enteric diseases, including salmonellosis, shigellosis, and amebiasis, had a profound impact on the U.S. effort in World War II. It is estimated that over a

million man-days were lost because of the latter disease alone (MD-MS, p. 408). Merrill's Marauders in the CBI (China-Burma-India) theater sustained 424 battle casualties and 1,970 casualties from disease; amebic dysentery, of which there were 503 cases, led the list of serious illnesses (War D-MM, p. 114). In Korea, days lost from duty because of diarrhea and dysentery totaled 78,970, of which 15,795 were for amebiasis (AR-TSG). Dysentery showed a distinct seasonal pattern, reaching a peak in August 1950 with morbidity rates of 120 per 1,000 per year and ranking second only to neuropsychiatric casualties (HOA, pp. 16, 22).

In 1958, American troops were sent to Lebanon to help stabilize a deteriorating political situation. Task Force 201 was formed, and the first troops landed in late July. Enteric disease became a problem early, and diarrhea, although of short duration, caused significant morbidity. Specific morbidity rates per 1,000 troops per year are shown in table 57. In separate papers, Moore (1959) and Hurewitz (1960) analyzed the factors related to enteric disease incidence and assessed the sequelae as troops (particularly the 187th Airborne Battle Group) returned to Europe. They noted a breakdown of sanitation measures, improper food handling, a failure to load necessary preventive medicine equipment, and a critical shortage of preventive medicine personnel. An alarming shigella carrier rate approaching 5 percent was noted in troops returning to Germany. *Shigella boydii* (Type IV) was a common offender.

In May 1962, the 1st Battle Group, 27th Infantry Division, and marine units were airlifted to Thailand to meet a political crisis and experienced similar high diarrheal disease rates. The 1st Battle Group, 35th Infantry Division, relieved the 27th Division unit in September, and a further serious outbreak of diarrhea was prevented by rigid sanitation measures (Giffin and Gaines 1964).

GASTROINTESTINAL DISEASES IN VIETNAM

Some indications of the problems to be expected in Vietnam could be found in the French publication, *Revue Internationale des Services de Santé des Armées de Terre, de Mer et de l'Air* (Black). Between November 1945 and June 1954, there were 1,609,989 troops in Indochina: 614,981 European, 187,703 North African (Arab or Berber), 101,744 Black African, 704,131 Indochinese, and 1,400 from French India. A total of 193,380 cases of amebiasis were reported, most of which were diagnosed clinically; 88,568 amebiasis patients were hospitalized, 4,900 were repatriated, and 192 died. Other diseases of importance included shigellosis and viral hepatitis.

When the buildup of American forces in Southeast Asia began in 1965, the picture had changed little in the decade since the French experience ended. The magnitude of the diarrhea problem among U.S. personnel was evidenced by the rate of hospital admissions for diarrheal diseases in the first 7 months of 1965 (table 58). Accordingly, The Surgeon General dispatched a team from the AFEB (Armed Forces Epidemiological Board) Commission on Enteric Infections, composed of Doctors Horace M. Gezon, Franz J. Inglefinger, and Albert V. Hardy, to do an onsite survey in September 1965. The team was briefed by Col. (later Maj. Gen.) Spurgeon Neel, MC, Col. Samuel Gallup, MC, and Dr. Hugh Randel. Areas

TABLE 57.—*Weekly disease admissions, Army Task Force 201, Lebanon, 1958*

[Rates per 1,000 average strength per year]

Week ending	Disease admission rates		
	Total	Diarrheal	Percent of total
13 August	936	489	52
20 August	897	481	54
27 August	?	?	?
3 September	333	188	56
10 September	342	124	36
17 September	400	89	22
24 September	293	100	34

Source: Col. Arthur P. Long, MC, Chief, Preventive Medicine Division, Office of the Surgeon General, 1960. Preventive medicine lessons learned in Lebanon. Disposition Form to Director, Historical Unit, 26 Jan. 60.

TABLE 58.—*Diarrheal disease admissions, U.S. military personnel in Vietnam, January-July 1965*

[Rates per 1,000 per annum]

Month	U.S. Military Assistance Command, Vietnam	U.S. Army, Vietnam
January	44.5	97
February	52.7	84
March	28.8	53
April	29.4	75
May	60.7	70
June	89.6	99
July	142.0	101

Source: Gezon, H. M. 1966. Special report on the visit to Cairo and S.E. Asia in August and September, 1965. Report, Armed Forces Epidemiological Board, Commission on Enteric Infections, 22 Apr. 66.

of major military activity, including Saigon, Bien Hoa, Da Nang, Nha Trang, and Cam Ranh Bay, were visited. Doctor Hardy studied patients in the hospitals and outpatient facilities in the Saigon area; Doctors Inglefinger and Gezon, accompanied by Maj. (later Col.) Robert Joy, MC, and members of the WRAIR (Walter Reed Army Institute of Research) Medical Research Team, examined patients, cultured specimens, and interviewed medical officers at the other four bases. Doctor Gezon wrote the final report (1966), an extensive summary of which follows.

Although diarrheal disease was present throughout the country, severe debilitating disease was seen in only three places: Saigon, Nha Trang, and Cam Ranh Bay. The team questioned troops in the Bien Hoa area about their experience with diarrheal episodes since arriving in Vietnam. Nearly half of those who had been in the country for as long as two months reported having had an attack of diarrhea; about one-third of those reporting disease had had multiple attacks within four months. Only one-fifth of those with diarrhea had felt ill enough to seek medical attention. Reported rates clearly did not reflect the magnitude of the problem although they probably did reflect accurately that of

the more severe disease.

According to dispensary records at Bien Hoa and Da Nang, enteric complaints accounted for roughly 10 to 20% of dispensary visits. Skin, respiratory, and venereal disease complaints were comparable in frequency. However, there were not sufficient data to calculate accurate diarrheal disease rates for an extended period of time. There was no evidence of an epidemic in units at these two locations; this observation was confirmed by the medical officers.

Two kinds of disease were recognized, one in which no bacterial pathogen was present and a more severe variety apparently caused by *Shigella*. Gezon described them as follows (pp. 9-10):

Typically those with the first variety complained of a sudden onset of mild abdominal discomfort soon followed by watery diarrhea, with perhaps three to five stools a day. Usually there was tenesmus, some cramps and occasionally mild vomiting, but without fever and with a total duration of perhaps two or three days. On examination these patients were not in great discomfort nor did they show dehydration. On proctoscopic examination the mucosa of the rectum appeared to be normal. The stool frequently was greenish liquid with no red or white cells present on microscopic examination. Culture revealed no pathogens. Fresh smears showed no *Entamoeba histolytica*.

Patients with the second type of disease also gave a history of sudden onset of symptoms but frequently with vomiting, fever as high as 105°F, chills, and numerous liquid stools per day. Stools usually were described as mucoid, liquid, and bloody. A maximum frequency of upwards of 20 stools per day was reported. These patients on examination appeared to be acutely ill, quite toxic, and sometimes moderately dehydrated. On proctoscopic examination the mucosa was found to be hyperemic, edematous, friable, but with no distinct ulcerations present. Mucus obtained at proctoscopy or direct stools obtained on these patients sometimes was grossly bloody. Microscopic examination frequently showed large amounts of cellular exudate with innumerable white cells. Frequently innumerable red cells were also seen. On culture approximately 60% of these patients were positive for *Shigella*.

The severe form was found particularly among patients from Cam Ranh Bay and Nha Trang, but only in a limited number of units. The patients in Nha Trang were mainly recent arrivals who were quartered in an area known as "Tent City." In Cam Ranh Bay they were largely from one company, the 611th Ordnance, also recently arrived. Nearly one-half of this unit developed diarrhea within a three or four day period; the outbreak was attributed to the mistaken use of untreated bay water for dishwashing.

The results of cultures from the 176 patients examined by the team are given in table 59. Nine serotypes of *Shigella* were isolated altogether, and as many as seven serotypes were found to be present simultaneously in a given area. *Sh. flexneri* 2A, which predominated, was isolated largely from one group in the Nha Trang area. All of the *Shigella* isolates were found to be resistant to sulfadiazine and most to tetracycline; only a few were resistant to chloramphenicol or kanamycin. The results of drug trials are shown in table 60.

Amebiasis was reported to be the principal etiologic agent of diarrhea in hospitalized patients. The incidence varied during different periods but the disease had been reported steadily during most of 1964 and 1965. The team was told that 600 amebiasis patients were diagnosed at the Navy Hospital alone in

TABLE 59.—*Enteric pathogens cultured from 176 U.S. military personnel with acute diarrheal disease in Vietnam, September 1965*

Site	Number cultured	<i>Aeromonas</i>	<i>Salmonella</i> <i>tennessee</i>	<i>Proteus</i>	Providencia	<i>Shigella</i>								
						<i>dysen-</i> <i>teriae</i>	<i>flexneri</i>			<i>boydii</i>				<i>sonnei</i>
						2	2a	3	6	2	4	11	12	1
Saigon:														
Navy Station Hospital --	31	8												2
16th Med. Dispensary (General) and 3d Field Hospital --	18	2								1	1			
Bien Hoa:														
173d Airborne Infantry --	9													
2d Battalion, 1st Infantry Division --	10													
145th Med. Dispensary	2													
Air Force Dispensary	6													
Da Nang:														
3d Med. Battalion -	14			2	3		1							
Air Force Dispensary	14		1		1									
Nha Trang:														
8th Field Hospital --	41			1	1	2	18	1	1			1	2	1
Cam Ranh Bay:														
161st Med. Detachment	31				1	1	3	1		1		4		
Total -----	176	10	1	3	6	3	22	2	1	1	6	2	-----	3

Source: Gezon, H. M. 1966. Special report on the visit to Cairo and S.E. Asia in August and September, 1965. Report, Armed Forces Epidemiological Board, Commission on Enteric Infections, 22 Apr. 66.

the first six months of 1964 and again in the first six months of 1965. Most of these, of course, were seen as outpatients. Amebiasis was treated with emetine, carbarsone, Diodoquin, Entero-Vioform, and tetracycline, singly or in combination; in some instances as many as four drugs were used on a given patient. Patients were said to respond promptly to the anti-amebic therapy.

Gezon, Inglefinger, and Hardy made a direct microscopic examination of freshly obtained stool or proctoscopic specimen, with and without iodine staining, from approximately 90% of the 176 patients they studied; no *E. histolytica* cysts or trophozoites were seen. A portion of the specimen was placed in

TABLE 60.—Antibiotic sensitivity of *Shigella* strains isolated in 176 U.S. military personnel in Vietnam, September 1965

Shigella strain	Shigella serotype	Number tested	Number resistant to antibiotics			
			Sulfa	Kanamycin	Tetracycline	Chloramphenicol
Dysenteriae	2	2	12	22	(2)	(3)
Flexneri	2a	19	19	3	16	
Flexneri	3	2	2	1		
Flexneri	6	1	1			1
Boydii	2	1	1			
Boydii	4	1	1			
Boydii	11	2	2			
Boydii	12	2	2	1	1	
Sonnei	1	3	3	1	2	1
Total		33	33	8	19	2

¹Resistant to 10 µg/ml.²Resistant to 5 µg/ml.³Resistant to 20 µg/ml.

Source: Gezon, H. M. 1966. Special report on visit to Cairo and S.E. Asia in August and September, 1965. Report, Armed Forces Epidemiological Board, Commission on Enteric Infections, 22 Apr. 66.

polyvinyl alcohol/Schaudinn's solution and sent to Dr. Elvio Sadun at WRAIR for a definitive parasitological diagnosis. Only 37 specimens were in satisfactory condition when received in his laboratory after a nearly 3 month delay in transit; none was positive for *E. histolytica*.

On several occasions the team was able to reexamine the stool and perform another proctoscopy on the patient on the same day that the clinical laboratory found *E. histolytica* cysts or trophozoites in his stool; in no instance could they confirm the diagnosis of amebiasis either clinically or parasitologically. In at least two of the laboratories, white cells and macrophages were being called cysts and trophozoites of *E. histolytica*, and in some instances both trophozoites and cysts were reported in the same specimen. It was evident that amebiasis was being grossly overdiagnosed. Undoubtedly many patients who had been treated for intestinal amebiasis had either nonspecific diarrhea or shigellosis.

Casual inspection of the several bases revealed numerous environmental problems caused largely by the rapid buildup of personnel and overuse of existing facilities. Dishwashing and handwashing facilities were inadequate in most activities. Frequently there were not enough latrines and those which were available were unsanitary. Water in the field was of questionable quality; much of it was surface water which was treated in an Erdlator. Thus it seemed that much of the diarrheal problem could be attributed to inadequate environmental control and only a small fraction of it to food obtained off base. The most obvious environmental difficulties were in areas where troops arrived in large numbers and facilities for receiving them were inadequate. This was true particularly in Nha Trang and Cam Ranh Bay and to some extent in Saigon.

The final recommendations made by the team were as follows (p. 12):

(1) That a competent parasitologist instruct the laboratory technicians in the correct diagnosis of amebiasis and that the diagnosis of acute amebic colitis be made only when multiple trophozoites

were found in the stool. These trophozoites should have a clear cytoplasm, definite directional motility and at least some with ingested red cells.

(2) That the acute diarrheal disease accompanied by fever and with WBC's in the direct stool smear be considered as probably due to a bacterial agent. When feasible the treatment instituted should be based on cultural studies. If cultural facilities are unavailable these should be treated as bacterial infections.

(3) That handwashing facilities, more adequate dishwashing facilities and screening of mess halls and kitchens be procured and tighter policing of kitchens be instituted.

(4) That the Commission on Enteric Infections prepare a proposal to continue this investigation, which began as a scouting visit, and attempt to carry out a definitive study on etiology, therapy and control of diarrheal disease in our troops in Vietnam.

The rate of admission to hospital or quarters in Vietnam for diarrheal disease in comparison to malaria and total disease admissions is given in table 61. Diarrheal disease rates were relatively constant, while the rates for malaria and other diseases seemed to fluctuate in relation to combat or geographic factors. Some indication of the difficulty encountered in identifying the specific causes of diarrheal disease is seen in table 62, which compares all reported diarrheal disease with amebiasis and bacillary dysentery. Amebiasis was diagnosed with decreased frequency in early 1966 as a direct consequence of the AFEB report's sharp criticism of diagnostic standards. In fact, diagnostic criteria became so stringent that amebic colitis was probably underdiagnosed, resulting in a disproportionate number of hepatic abscesses being encountered for the number of reported cases with intestinal involvement (Sheehy 1968). It remained for Col. Hinton Baker, MC, commander of the 9th Medical Laboratory, to carry out an intensive educational program for laboratory personnel to correct the situation.

TABLE 61.—Admissions to hospital or quarters, U.S. Army active-duty personnel in Vietnam, January 1965-March 1966

[Rates per 1,000 average strength per year]

Date	Admissions			
	All causes	Disease	Diarrheal diseases	Malaria
1965:				
January	507	429	97	0
February	385	331	84	0
March	394	327	53	0
April	444	353	75	1
May	437	344	70	2
June	461	354	100	2
July	315	228	101	8
August	407	315	53	10
September	528	399	84	15
October	642	492	102	86
November	602	404	62	81
December	517	377	35	46
Average	450	363	76	21
1966:				
January	409	287	29.2	18.5
February	520	317	43.1	8.4
March	518	334	62.4	15.5

Source: USARV surgeon. Monthly Command Health Reports to USARV commander, Jan. 1965-Apr. 1966.

TABLE 62.—*Number of diarrheal cases reported to USARV medical consultant, January-March 1966*

Week ending	Other diarrheal diseases	Amebiasis	Bacillary dysentery
5 January ¹			
12 January	44	0	0
19 January	57	5	3
26 January ¹			
2 February ¹			
9 February	156	1	1
16 February	107	3	0
23 February	121	7	1
2 March	135	8	7
9 March	112	3	0
16 March	131	1	4
23 March	169	5	3
30 March	108	0	5

¹Report not received.

Source: Personal records of Col. Ralph F. Wells, MC.

In 1967 and 1968, it was noted that diarrheal diseases among the troops increased significantly during the "dry season" (March through June). Studies were conducted in 1969 to further clarify the etiology of these disorders. A team under the direction of Lt. Col. John Kalas, MC, conducted an extensive study at hospital and troop level. Their report (Kalas and Bearden 1969) describes the first part of the study, which was conducted at the 3d Field Hospital in Saigon, the 8th Field Hospital in Nha Trang, and the 17th Field Hospital in An Khe, as follows (p. 2):

Two hundred and four hospitalized and/or dispensary cases were studied. All of the cases were sigmoidoscoped; a biopsy taken; mucosal scraping for wet mount preparation was performed; and cultured for bacteria. Fecal smears were also fixed in Schaudinn's solution, PVA, and 10% buffered formalin; all for later confirmation of parasites after exposure to appropriate staining. Many of the hospitalized patients were also intubated for duodenal drainage for parasites, and small intestinal biopsy.

Results were as follows:

(1) No etiologic agent could be identified in 80% of the cases.

(2) *Shigella* and *salmonella* organisms were isolated from the stool specimens of 29 (14%) of 204 cases; 23 patients had *shigella* organisms and 6 had *salmonella* organisms.

(3) Upon initial examination, 57 of 204 patients were believed to have a bacterial enterocolitis (history of elevated temperature, bloody diarrhea, sigmoidoscopic evidence of grossly involved colon, and a wet prep exam of stool revealing clumps of WBC's with no evidence of *E. histolytica*). However, a possible etiologic bacterial agent was found in only 29 cases.

(4) Parasites were found in 17 of 204 cases (8%). Amebiasis was identified in four patients and was considered responsible for the symptoms in all of them. Four cases of hookworm were found, only one of which was symptomatic. Two

patients (from Puerto Rico) had eggs of *Schistosoma mansoni* in their stools but their symptoms were not believed to be related to the intestinal parasites. Only one patient had pinworm infection, which was asymptomatic. Five patients had *Giardia lamblia* infections, four of which were symptomatic.

(5) "Pathogenic *E. coli*" was isolated from 16% of the patients. However, it was also isolated from the stool specimens of 19% of control patients (patients without diarrhea and not subjected to antibiotics within the past month).

The second part of the study was conducted at three battalion aid stations in Bong Son and in one clearing company of the 173d Airborne Brigade there; at the battalion aid station and the clearing company at Bao Loc (173d Airborne Brigade); in the 43d Medical Group; and at four battalion aid stations in Qui Nhon (55th Medical Group). The method of study used was inquiry, since the caseload at this level was not sufficient to make the results significant. The fact that diarrheal diseases were not a problem at this level explained the low rate of diarrheal disease reported in the Command Health Report.

Six platoons of the 173d Airborne Brigade in Bong Son were also studied, using an extensive questionnaire and cultures obtained by rectal swab. It was evident that diarrheal disease was a significant problem at the platoon level. About 60% of the 100 troops interviewed had diarrhea at the time of the questioning. A similar situation was believed to exist throughout the country, based on verbal reports from troops in units in other areas (III, and IV Corps).

One possible explanation for the high incidence of diarrhea was the failure of the combat troops to use their water purification tablets properly; 54% of those interviewed admitted they did not use them as directed while on patrol. The major objection to the halazone tablets was the taste they imparted to the water, although some individuals attempted to solve this problem by adding concentrated fruit flavoring. The second important objection was that troops really had no satisfactory method of carrying the tablets with them on combat missions. It is noteworthy that 94% of the same combat troops stated they faithfully used the weekly chloroquine-primaquine tablets as directed.

The authors of the report made the following recommendations (pp. 4-5):

(1) This is the second disease which has been investigated at the platoon level, the first being skin diseases in the delta [Allen et al. 1972]. Neither of these diseases has ever received the necessary attention, and neither appears significant in the Command Health Report. It appears that platoon level epidemiology is necessary for the adequate management of diseases at the combat troop level.

(2) A more complete search for bacterial and viral etiology in enteric disease in troops is necessary since 80% of the cases do not have a demonstrable etiology. * * *

(3) A more complete understanding of the altered physiology of diarrheal diseases is necessary for immediate treatment of the patient, regardless of etiology. At least for the foreseeable future many of the cases of gastroenteritis will not have a demonstrable etiologic agent. These diseases should be classified according to altered physiology and treatment adjusted accordingly.

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Bacterial Diarrheal Diseases

Layne O. Gentry, M.D., Colonel Kenneth W. Hedlund, MC, USA, Colonel Ralph F. Wells, MC, USA (Ret.), and Brigadier General Andre J. Ognibene, MC, USA

Diarrheal diseases have always been of major military importance because of their severe, albeit short-lived, debilitating effects and the speed with which epidemics may occur. Gordon (1965, p. 78) provides the following definition of acute diarrheal disease:

Acute diarrheal disease is a clinical syndrome of varied etiology, in large part infective, and having diarrhea and often fever as the common manifestations. It includes specific infectious diseases such as shigellosis, salmonellosis and amebiasis and also infections with enteropathogenic *Escherichia coli*, enteroviruses, protozoa and helminths. A variety of infectious agents of low pathogenicity, when present in large numbers, also may be etiologically associated. More often than not, no definable infectious agent can be identified. Looseness of the bowels is also due to other than microbial or parasitic causes.

The diarrheas may be classified on the basis of specific etiology or on the basis of their epidemiological pattern. Gordon suggested five epidemiological categories. The more stereotyped classification based on specific etiology will be the system used in this review.

Section I. Shigellosis

Layne O. Gentry, M.D.

HISTORY AND MILITARY SIGNIFICANCE

Historically, shigellosis has had a major impact on confined populations. Numerous epidemics have occurred in homes for the mentally ill, in orphanages, aboard ships, and in prisoner-of-war camps. Reports of severe dysentery among British prisoners of war arriving in Italy from North Africa in 1942 describe classical shigellosis which resulted in many deaths (Bloom 1944). Personnel on naval vessels during World War II suffered from repeated outbreaks of shigellosis. In one outbreak at Pearl Harbor, 9.3 percent of a ship's company of 905 men were infected, a morbidity rate which made the vessel unfit for sea duty (Philbrook et al. 1948). Reports from the United Nations prisoner-of-war camps in Korea revealed that shigellosis had infected 8 percent of 1,000 prisoners

despite specific preventive measures; ineffectiveness of these measures was caused in part by the high endemic level of infection at the time of capture (Garfinkel et al. 1953).

Shigellosis has become such a common problem in the United States that the CDC (Center for Disease Control) has added it to the list of infectious diseases currently under surveillance. The magnitude of the problem is indicated by the number of isolations of shigellae reported by the CDC, which totaled 13,752 in 1972. Of these, 68.3 percent were obtained from children under 10 years of age and 90.9 percent from patients under 30 years of age. Of all *Shigella* isolates in the United States, 13.2 percent were obtained from either Indian reservations or mental institutions, none of which was involved in an epidemic or outbreak during this period. There was no predominance by sex (CDC-73).

EPIDEMIOLOGY

Shigellosis proved to be the most common enteric infection identified among U.S. personnel in Vietnam. The peak incidence months for diarrhea were April, May, and June, reflecting seasonal increases in shigellosis (USARV-CHR). Shigellosis occurred more often and was more widespread than parasitic infestations, with the possible exception of amebiasis. A comparison of two epidemics substantiates this point. In March 1966, in a single outbreak from a 1st Cavalry Division unit (Vandeveld 1966), 39 men were admitted to the hospital because of severe hookworm gastroenteritis; symptoms included diarrhea in 91 percent, epigastric discomfort in 82 percent, frank abdominal tenderness in 17 percent, and vomiting in 22 percent. In contrast, in April 1968 (USARV-CHR Apr. 68, pp. 3-4), an outbreak of shigellosis occurred, also in the 1st Cavalry Division, involving an estimated 7,000 individuals, including personnel in units attached to the division. Most individuals improved with supportive therapy in 24 to 48 hours, and only 11 cases were hospitalized.

The shigellosis epidemic was described as follows. On 16 April a temporary breakdown had occurred in the chlorinating machines at the water point in the Quang Tri area. On 18 April, an outbreak of gastroenteritis occurred in the 1st Brigade, 1st Cavalry Division, which received its water from this source. Members of the 1st Brigade moved to an area southwest of Camp Evans between 20 and 22 April. Individuals from the unit swam and bathed upstream from the Camp Evans water point, which was not being operated as prescribed. Another outbreak of gastroenteritis began on 23 April, was full blown on the 24th, and peaked between the 24th and 26th, after which the epidemic abated. *Shigella flexneri* was cultured from stool samples and from the raw water in the stream. By the time cultures could be obtained, water was again being adequately chlorinated.

During 1972, in the United States, *S. sonnei* was responsible for 79.2 percent of all cases of shigellosis reported, and almost all of the remaining cases were caused by the subtypes of *S. flexneri* (CDC-73, p. 1). A regional epidemic of

shigellosis occurred in 1969 and 1970 in Central America and Mexico and was caused by *S. dysenteriae* subtype 1, which had essentially disappeared from the world by 1920. This epidemic was responsible for fatality rates of 7 to 8 percent and involved thousands of people (Mata et al. 1970; Gangarosa et al. 1970).

ETIOLOGY AND PATHOGENESIS

Shigellosis, or bacillary dysentery, as it was termed by the Japanese bacteriologist Shiga, was first described in the 4th century B.C. Table 63 outlines the *Shigella* classification by species, serological subgroup, and serological subtype.

Shigella was the first group of bacteria to demonstrate the extraordinary genetic instability of intestinal coliform bacteria; in Japan during the 1960's, the genus was shown to contain a plasmid which carries genes capable of transferring multiple antibiotic resistance to other intestinal coliform bacteria (Mitsuhashi 1969). This plasmid, termed "R factor," has had worldwide impact, the most recent complication being the emergence of a markedly drug-resistant shigella in the United States and Mexico (NCDC-ShS).

All known species of the genus *Shigella* are pathogenic for man. Investigations in Russia, Japan, and the United States have established essential features in the pathogenesis of *S. flexneri* shigellosis (Labrec et al. 1964; Ogawa et al. 1967; Voino-Iasenetskii and Khavkin 1964). Pathogenicity is caused by penetration of colonic mucosal epithelial cells with subsequent intracellular multiplication of bacteria. This gives rise to mucosal ulcerations and to the accumulation of polymorphonuclear leukocytes and fibrin accompanied by unformed stools containing blood and mucus.

More recently, it has been shown that *S. dysenteriae*, unique among members of the dysentery group because it produces potent neurotoxin and/or enterotoxin, must maintain the ability to penetrate and multiply in the colonic mucosa to produce disease (Gemski et al. 1972). Loss of the ability to penetrate and multiply within cells, despite the capability of producing toxin, resulted in failure to cause classic shigellosis in animals. In volunteer studies (Levine et al. 1973), virulent strains of *S. dysenteriae* produced disease in doses as low as 10^1 organisms. This capability undoubtedly influenced the rapid epidemic spread of shigellosis seen during the Central American outbreak.

CLINICAL FEATURES, COURSE, AND COMPLICATIONS

Shigella dysentery is characterized by the sudden onset of abdominal cramps, diarrhea, and fever after approximately 1 to 4 days of incubation. Stools are characterized by mucus containing inflammatory cells and blood. It is rare to see systemic spread of shigellosis; however, bacteremia, osteomyelitis, pneumonia, and meningitis have been described. Infrequently, a persistent colitis which mimics ulcerative colitis proctoscopically and radiographically may be

TABLE 63.—*Shigella* classification

Species	Serological subgroup	Serological subtype(s)
<i>S. dysenteriae</i>	A	1-10
<i>S. flexneri</i>	B	1-6
<i>S. boydii</i>	C	1-15
<i>S. sonnei</i>	D	1

seen. Three such cases studied sequentially in Vietnam showed complete resolution.* None of the patients had had prior inflammatory bowel disease. Fluid and electrolyte loss may cause metabolic disturbances, especially in young children and infants. Specific agglutinins may appear in serum during convalescence; local mucosal antibody of the IgA type is also produced but its role in recovery is not yet clearly defined.

Because persons residing in an area where shigellosis of a specific type is endemic rarely suffer from repeated bouts of disease, there appears to be naturally acquired immunity, although this immunity may be strain specific. Recent investigation attests to this fact; it also clearly demonstrates that reinfection with a known virulent strain, in large doses, produces dysentery. Investigators were able to effectively immunize volunteers against severe dysentery by giving a live attenuated strain of *S. flexneri* by mouth after neutralizing stomach acid with bicarbonate. Most of these volunteers who received the attenuated vaccine had elevated humoral antibody titers (DuPont et al. 1972a; 1972b). No local mucosal IgA antibody studies were done in this group. It is important to note that the attenuated strain used had lost its ability to penetrate intestinal mucosal epithelial cells.

Laboratory Diagnosis

Because *Shigella* species do not remain viable for long in excreted fecal material despite often being present in large numbers during active disease, it is mandatory to obtain specimens in appropriate holding media or to culture them properly as rapidly as possible (Thomas 1969). Preferably, specimens for culture are obtained either directly from mucosal lesion at proctoscopy or by a rectal swab. Methylene blue or Gram's stains of specimens under direct vision are most helpful because excessive inflammatory exudate and large numbers of gram-negative bacteria strongly suggest bacterial etiology rather than amebic dysentery, which is often mistaken for shigellosis.

Rising humoral antibody titers are often helpful, but the illness usually abates before laboratory test results become available. Another problem with the tests is that they require specific antigens of the *Shigella* subtypes which are often unavailable in hospital laboratories.

*Col. Ralph F. Wells, MC: Personal communication.

Treatment

Because many of the infections caused by *Shigella* species are acute but self-limiting, antibiotic therapy has not been standard or routine. However, severely ill patients obviously require drug therapy, as well as supportive fluid and electrolyte repletion. In general, *Shigella* species are sensitive to ampicillin, tetracycline, chloramphenicol, kanamycin, and gentamicin. Ampicillin has been considered the drug of choice.

Resistant strains may emerge during therapy; in the recent Central American and Mexican epidemic, the strain of *S. dysenteriae* was shown to be multiply drug-resistant but fortunately did respond to ampicillin (Mata et al. 1970, p. 175). As early as May 1967, Heggers and Smith (1967) detected a potential problem with tetracycline-resistant shigellae. This was confirmed in a study by Stone (1968) at the 3d Field Hospital, Saigon; he advocated the use of neomycin. Martin and associates (1970) later found widespread resistance to various antibiotics tested but recommended ampicillin, neomycin, or kanamycin therapy (table 64). A study from the 3d Medical Battalion, 3d Marine Division (Chow et al. 1971), recommended ampicillin as the antibiotic of choice, a selection in keeping with the author's experience.

Because of the ability of intestinal bacteria to transfer drug resistance upon exposure to antibiotics, there has been a trend toward more restrained use of these drugs unless the systemic toxicity suggesting severe shigellosis is present. The USARV (U.S. Army Vietnam) medical consultant in 1969, Lt. Col. (later Brig. Gen.) Andre J. Ognibene, MC, strongly favored only intravenous fluid therapy at division level, with evacuation of nonresponders to hospitals where culture and additional therapeutic effort could be coordinated.* Indiscriminate antibiotic use was believed to produce resistance or delay recover in some cases.

TABLE 64.—Antibiotic resistance of 505 *Shigella* strains, Vietnam, 1968-69

Drug	Microgram discs	Number of resistant isolates	Percent resistance
Streptomycin	2	308	61
Oxytetracycline	5	223	44
Tetracycline	5	193	38
Chloramphenicol	5	181	36
Kanamycin	5	25	5
Kanamycin	30	22	4
Cephalothin	30	42	8
Ampicillin	2	167	33
Ampicillin	10	34	7
Neomycin	5	39	8

Source: Martin, D. G.; Tong, M. J.; Ewald, P. E.; and Kelly, H. V. 1970. Antibiotic sensitivities of shigella isolates in Vietnam, 1968-1969. *Mil. Med.* 135: 560-62.

*Lt. Col. Andre J. Ognibene, MC, USARV Medical Consultant, 1969: Personal communication.

More recently, the use of drugs such as opiates and diphenoxylate hydrochloride with atropine (Lomotil), which retard intestinal motility, has been shown to effectively reduce the duration of the diarrhea but at the expense of prolonging the febrile response (DuPont and Hornick 1973a).

Prevention

Man-to-man spread is the primary source of transmission of shigellosis. Sanitation measures involving "food, feces, flies, and fingers" are most important. Inapparent carriers are common and complicate epidemiological control measures. Recently, the use of attenuated live oral vaccines has shown promise in protecting human volunteers (DuPont et al. 1972b). There is need for a vaccine which is multivalent against the activity of *S. sonnei* and several subtypes of *S. flexneri* in the United States.

SUMMARY

Shigellosis was recognized as the most common specific bacterial cause of acute diarrhea in Vietnam. While laboratory evidence of tetracycline resistance emerged, no major clinical problems arose. Ampicillin was the drug of choice when antibiotic therapy was indicated. Studies of the R factor were not accomplished in Vietnam, although it was postulated as a mechanism for the emergence of drug resistance.

Section II. Typhoid Fever and Other Salmonellosis

Colonel Kenneth W. Hedlund, MC, USA, and Brigadier General Andre J. Ognibene, MC, USA

TYPHOID FEVER

History

The genus *Salmonella* contains more than a thousand distinct serotypes, a large number of which are pathogenic for both animal and man. Frequently, these etiologic agents were not isolated and characterized until the clinical syndromes and associated pathologic lesions they produced were well delineated. The clinical manifestations of salmonella infection range from enteric fevers to septicemias and acute gastroenteritis.

Typhoid fever, the classic form of enteric fever, has a recorded history from the time of Hippocrates. The first complete description of the clinically recognizable syndrome is attributed to Thomas Willis, who, in 1659, described a fever which had an insidious onset and was marked by stepwise increases during the first week. The fever, he said, was maintained during the second and third

weeks and then resolved by gradual lysis. Willis also described the relapse in some patients who had recovered (Huckstep 1962, p. 4).

In 1826, Bretonneau delineated the pathological picture of typhoid fever by demonstrating the characteristic inflammatory involvement of both Peyer's patches and Brunner's glands. In 1829, Pierre Louis coined the term "Fievre Typhoide." In 1837, William Gerhard, a student of Louis, set down the clinical criteria to differentiate typhoid fever from typhus. At the time, this was a radical and generally unaccepted concept; both diseases were considered to be merely variants of the same disorder. Not until 1850, when Sir William Jenner confirmed and expanded upon Gerhard's work, did the distinction gain general acceptance (Huckstep 1962, p. 5).

Between 1856 and 1860, William Budd demonstrated that typhoid fever was transmitted from man to man through excreta, and that contaminated water and milk could cause typhoid. Eberth, in 1880, described "*B. typhosus*" in the tissue of patients. Four years later, Gaffky successfully isolated and cultured *Salmonella typhosa*, the typhoid bacillus, for the first time. After these breakthroughs, the subgroups of the *Salmonella* grew progressively larger as systematic investigations were made of patients with typhoidlike illnesses. The term "paratyphoid fever" was introduced in 1896 by Achard and Bensaude following their isolation of *S. paratyphi B* (Huckstep 1962, p. 6). In that same year, Gruber and Durham (1896) and Widal (1896) detected agglutinating antibodies in the serum of animals and patients previously infected with the typhoid bacillus.

The first immunizations of humans against typhoid fever were performed by Wright and Semple (1897) in 1896; they injected heat-killed typhoid bacilli subcutaneously in two volunteers. The first attempt at the immunization of U.S. Army troops against typhoid was by means of an oral vaccine in 1904; it proved unsuccessful because of the probable presence of viable bacilli in what was erroneously believed to be a heat-killed vaccine (Tigertt 1959). In 1909, subcutaneous injection of heat-killed typhoid bacilli was given to U.S. troops on a voluntary basis, and by 1911 it became compulsory. In 1915, the vaccine was fortified with *S. paratyphi A* and *B* (MD-WW9, pp. 21, 41).

In 1947, chloramphenicol was introduced (Erlach et al. 1947). One year later, Woodward and associates (1948) reported the beneficial effects of this drug in the treatment of typhoid fever. With the advent of an effective antibiotic, the mortality rate of typhoid fever in young men dropped from 10 percent to 1 percent (MD-WW9, p. 17).

Strains of *S. typhosa* which are resistant to chloramphenicol have been encountered since 1950 (Colquhoun and Weetch 1950). However, it was not until 1972 that reports of the first epidemic caused by a resistant *S. typhosa* were received (CDC-M&M; Vazquez, Calderon, and Rodriguez 1972; Gangarosa 1972). This epidemic, which began in Mexico in that year, persisted for months and affected thousands of people. In a report given at the Interscience Conference on Antimicrobial Agents and Chemotherapy, Gangarosa noted that the multiresistant organisms caused a clinically severe disease with a high mortality rate. In addition, epidemiologically, there appeared to be greater infectivity and

transmissibility. Although water was implicated as a vehicle in the spread of the disease, person-to-person contact has also been implicated. The latter method of transmission is not usually seen in widespread typhoid epidemics.

Anderson and Smith (1972) pointed out that the causative organism in the Mexican epidemic was resistant to chloramphenicol, tetracycline, streptomycin, and the sulfonamides and that the resistance to these drugs is attributable to an R factor. This extrachromosomal element can be transferred to a sensitive *S. typhosa* by an intestinal commensal such as *Escherichia coli* or a resistant strain of shigella organisms. These authors suggest that two conditions optimize the possibility for such a transfer of en bloc drug resistance. The first is the presence of endemic typhoid so that the organism is frequently present in the intestine. The second is the continuous, indiscriminate use of chloramphenicol so that its widespread selective pressure promotes the emergence of stable R factors coding for specific resistance. These conditions existed in Mexico and also in Southeast Asia.

Davis and Anandan (1970) have pointed out that in isolated "antibiotic virgin" areas R factors had evolved in nature before the manmade antibiotic era. The members of the enteropathogens that by chance have received R factors by conjugation possess a selective advantage only after the introduction of man-made antibiotics. These enteropathogens have emerged in some instances as the predominant members of their population.

Vivona and coworkers (1966) showed the presence of en bloc antibiotic resistance to sulfonamide drugs, streptomycin, tetracycline, and chloramphenicol in various strains of *Shigella flexneri*, *Sh. sonnei*, and *E. coli* cultured from Vietnamese patients with acute diarrhea. Gaines and Nhu-Tuan (1968), although not reporting directly on R factor resistance, demonstrated that, among a native Vietnamese population of 645 strains of *Shigella* sampled, 437 (67.7 percent) were resistant to chloramphenicol. Of 287 strains of *E. coli* tested, 196 (68.2 percent) were resistant to the drug, as were 60 (24.3 percent) of 246 strains of *Salmonella*.

Military Significance

Insight into the past military significance of typhoid fever can be obtained by reviewing both the American and British experiences in an era before controlled immunizations and antibiotics. Walter Reed (Reed, Vaughan, and Shakespeare 1900, pp. 190-92) noted that one-fifth of the soldiers in the national encampment in the United States in 1898 developed typhoid fever. Among the 107,973 officers and men in 92 regiments, the number of cases was 20,738 (an incidence rate of 19.21 percent). The death rate was 7.61 percent (1,580 cases). Deaths from typhoid fever accounted for 86.24 percent of the total deaths from all causes. The morbidity from the disease was 192.65 per 1,000 average strength, or a little less than one-fifth. Mortality per 1,000 average strength was 14.63.

Although a partial attempt at immunization was made by the British, the American experience correlates fairly well with that of the British Army during

the Boer War (1899-1901) (MD-WW9, p. 17). There 209,404 men developed 59,750 cases of typhoid fever, with 8,227 deaths, or a morbidity of 114.13 per 1,000 and a mortality of 14 per 1,000.

With improved field sanitation and compulsory antityphoid-paratyphoid immunizations, the incidence rates among the U.S. military fell remarkably during the First World War (table 65).

Vaughan's study (1920) suggests that the high mortality rate given for World War I (14.85 percent) is really somewhat inflated. If one accepts his conclusions, untreated typhoid fever carried then, as it does now, a mortality of approximately 10 percent.

The incidence rates for varying types of *Salmonella* infections during both World War II and the Korean war are shown in table 66. These reflect the fact that when good field sanitation and compulsory immunizations are maintained, *Salmonella* infections cease to be a significant threat to the Army's operations or activities.

In Vietnam, the environment beyond the confines of the base camp could not be controlled with any reliability. Protection against salmonella infections took the form of immunization for all incoming personnel and maintenance of "safe in-house" water and food supplies at the base camps. In the field, canned rations were supplied along with iodine or chlorine tablets to disinfect available "field water."

No one actually knows, with any certainty, the real incidence of typhoid fever which occurred among U.S. troops in Vietnam. For example, in 1968, during a brief 6-week inspection tour of several installations in Vietnam, Dr. Samuel B. Formal,* a WRAIR (Walter Reed Army Institute of Research) bacteriology consultant, was able to gain indirect evidence of at least three deaths following *S. typhosa* infections. However, only eight cases of typhoid fever among American personnel were reported that year for all of Vietnam (PAD 1968), which would imply a 37.5-percent mortality rate. No matter what the total number of cases or the true mortality rates were, the only reasonable statement that can be made about the incidence of typhoid fever among American troops in Vietnam is that it was underestimated.

TABLE 65.—Admissions and deaths from typhoid fever during the Spanish-American War and World War I

War	Average strength per year	Admissions		Deaths		
		Number	Rate per 1,000	Number	Case rate	Rate per 1,000
Spanish-American War ¹	147,795	20,926	141.59	2,192	10.47	14.83
World War I ²	1,501,265	1,529	0.37	227	14.85	0.05

¹1898.

²April 1917 to December 1919.

Source: Medical Department, U.S. Army. 1928. *Communicable and other diseases*. The Medical Department of the United States Army in the World War, vol. IX. Washington: Government Printing Office, p. 17.

*Dr. Samuel B. Formal: Personal communication.

TABLE 66.—*Salmonella infections, active-duty Army, 1942-45 and 1950-53*

[Incidence rate per 1,000 average annual strength]

Year and area	Typhoid fever		Paratyphoid fever		Food infection from <i>Salmonella</i>		Other salmonellosis ¹	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
<i>1942-45</i>								
Worldwide	491	0.02	812	0.03	2,655	0.10		
Continental United States	85	0.01	118	0.01	1,110	0.07		
Overseas areas	406	0.04	694	0.07	1,545	0.15		
Europe	64	0.02	84	0.02	370	0.09		
Mediterranean and Middle East	153	0.09	237	0.14	345	0.21		
China-Burma-India	80	0.18	104	0.23	85	0.19		
Southwest Pacific	79	0.05	164	0.10	305	0.19		
Other Pacific	19	0.01	32	0.02	410	0.28		
All other areas	11	0.01	73	0.06	30	0.02		
<i>1950-53</i>								
Worldwide	20	0	53	0.01	70	0.01	25	0
Continental United States	5	0	25	0.01	10	0		
Overseas areas	15	0.02	28	0.01	60	0.03	25	0.01
Europe					40	0.06		
Korea	5	0.01	15	0.02	10	0.02	15	0.02
Other Far East and Western Pacific	10	0.17					5	0
All other areas			13	0.02	10	0.01	5	0.01

¹Data not available for World War II.

Source: Office of the Surgeon General.

Incidence

Typhoid fever was endemic in Vietnam. In mid-1965, the indigenous population was 16.1 million with a projected growth rate of 2 percent per year (Smith et al. 1967). The number of cases of typhoid and paratyphoid fevers among the South Vietnamese for each year between 1965 and 1970 was as follows (NIS-VSY, p. 268):

1965	3,321	1968	3,420
1966	3,934	1969	3,805
1967	3,531	1970	3,305

These numbers represent only the number of reported cases and are best considered a reflection of the problem. During the same period of time, the average U.S. Army troop strength was 250,000 per year and the total number of cases of typhoid fever reported in American Army troops was 29 (table 67). There were also 425 cases of undefined salmonellosis.

The incidence of typhoid fever was 141.59 per 1,000 during the Spanish-American War, with a mortality rate of 10 percent. Following compulsory immunization procedures, the incidence rate dropped to 0.37 per 1,000; however, the mortality rate was no lower. Statistics from World War II, the Korean war, and the Vietnam war all show very low overall incidence rates. This is a testament not only to the efficacy of immunization but also to the advances of preventive medicine and public health in establishing the techniques of typhoid control in food handling, water supplies, and typhoid carrier surveillance.

Retrospectively, it appears that while control measures reduced the incidence, the introduction of chloramphenicol reduced the mortality rate. The potential threat of en bloc antibiotic-resistant strains of *S. typhosa*, such as those found in the Mexican typhoid epidemic, is one that should not go unnoticed, especially since person-to-person contact has been implicated in the establishment of the epidemic. New antibiotic combinations may not provide a long-lasting solution.

TABLE 67.—Incidence of typhoid fever and salmonellosis in U.S. Army troops in Vietnam, 1965-70

Year	Typhoid fever		Salmonellosis	
	Number of cases	Rate per 1,000	Number of cases	Rate per 1,000
1965	0		10	0.2
1966	1	0.01	17	0.1
1967	11	0.04	201	0.7
1968	8	0.02	70	0.2
1969	19	0.05	70	0.2
1970	23	0.08	30	0.1
Total	62		398	

Sources: Typhoid fever statistics from: Patient Administration Division, Health Services Command, Department of the Army. Individual Medical Records (IMR), 1965-1970. Salmonellosis statistics calculated from: (1) Office of the Surgeon General, Department of the Army. Health of the Army, May 1965, May 1966, May 1967, May 1968, May 1969, May 1970. (2) Military Assistance Command, Vietnam. 1973. U.S. military personnel in South Vietnam, by month, by service. Report, 7 Dec. 73.

Etiology

The *Salmonella* are gram-negative, nonspore-forming, motile bacilli. In classic form they do not ferment lactose or sucrose; however, variants have been found that do ferment lactose. Although the genus can be separated from many other varieties of enteric bacilli by differing metabolic reactions, the final identification of individual *Salmonella* species is based on differences in specific H, O, and Vi (virulence) surface antigens. More than a thousand subtypes have been distinguished on the basis of these specific antigens and identified by exhaustive cross-absorption and cross-reaction serological tests.

Previously, attempts were made to categorize *Salmonella* on the basis of infectivity. For practical purposes, one can say that *S. typhosa* produces a disease—typhoid fever—which is found only in man, while the bulk of other

Salmonella organisms can produce disease in both man and animals. The propensity spectrum ranges from those organisms more frequently found to cause human disease, such as *S. paratyphi A* and *B*, which produce typhoidlike disease, to those organisms which seem to be uniquely animal pathogens, such as *S. gallinarum*. The middle ground includes *S. typhimurium*, *S. choleraesuis*, and *S. enteritidis*, which produce disease primarily in animals but can also infect man.

Epidemiology

Salmonella typhosa organisms are spread primarily by human contamination of either water or food. In the more advanced countries, periodic modern outbreaks of typhoid have occurred when public water supply surveillance has lapsed or when unprotected and untreated water and food stores are used (Bernard 1965). In Vietnam, U.S. troops who were fed in carefully controlled mess halls could and would drink from and swim in polluted waterholes. Among the 17 patients treated by the author for typhoid fever at the 85th Evacuation Hospital during 1970, there were at least three distinct sources of infection: a polluted waterhole along the highway where troops swam, a food handler in Phu Bai, and a popsicle vendor in the city of Hue.

The nontyphoid salmonellae capable of causing human disease have a wide host distribution in nature. Domestic animals, poultry, and hen and duck eggs are potential sources of infection, as are human beings with clinical or inapparent disease.

Clinical Features, Course, and Therapy

Typhoid fever is one of the historically classic diseases that very few American physicians have seen or treated. The signs and symptoms which are present at the time of admission depend to a large degree on how long the patient has been ill; the classic onset is insidious. Early symptoms—frontal headache, dizziness, anorexia, and general malaise—are similar to those of many other febrile illnesses. The patient in Vietnam usually ignored these and a large variety of other nonspecific symptoms until the onset of fever, which was seen as a valid reason for seeking medical aid.

The classic "stepladder" increases in fever were rarely, if ever, seen. One reason was that symptoms usually began between 5 and 8 days before the patient came to a hospital. On admission, fevers ranged from 101° to 104°, and a relative bradycardia was common. Signs of meningismus were seen in 17 percent of the author's patients, suggesting meningitis, but examinations of the spinal fluid were negative.

One-third of the patients had an intermittent nonproductive cough and auscultatory signs of bronchitis. The abdomen was characteristically diffusely tender, with distention. While the spleen was not palpable, left upper quadrant tenderness was noted frequently. "Rose spots" were identified in only 1 of the author's 17 patients.

In the interval between hospitalization and laboratory confirmation of the diagnosis of typhoid fever, there was usually a progression of toxicity. In some of the more seriously ill patients, mental confusion replaced apathy, and the initial tenderness and cramping pain in the abdomen progressed to the ileus with overt distention. In some, the skin became sallow and doughy feeling.

Chloramphenicol therapy brought the temperature to normal within 3 to 4 days. Bronchitic signs and toxemia diminished with the fever, and abdominal distention resolved within 72 to 96 hours. Chart 23 shows the course of a previously immunized American patient who contracted typhoid fever in Vietnam. It illustrates the characteristically low white count, which is unfortunately shared with several other febrile illnesses endemic to Southeast Asia, such as dengue and malaria. The response to chloramphenicol therapy is reflected in the temperature chart after 72 hours. Also shown is the unpredictability of the Widal reaction, perhaps influenced in this case by prompt treatment with chloramphenicol.

Chloramphenicol is the drug of choice against sensitive typhoid strains. It is usually given 50 mg per kg per day, either orally or intravenously, until the patient is afebrile. At that point, the daily dosage is reduced by half until a total of 2 weeks of chloramphenicol therapy has been given. An effective alternative drug, when chloramphenicol is contraindicated, is amoxicillin, 1 g every 6 hours for 14 days (Afifi, Adnan, and El Garf 1976).

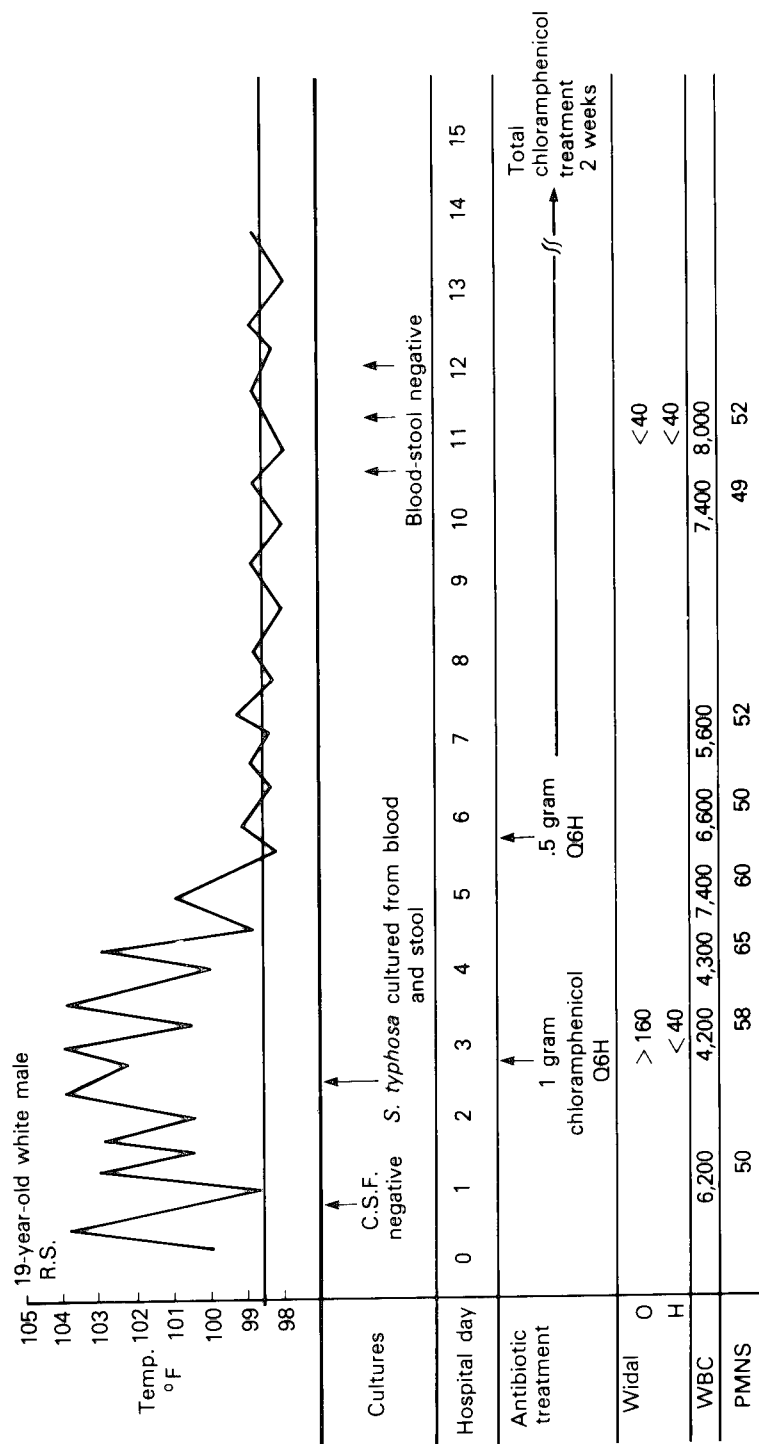
Stamps and Wicks (1972) treated 92 South African typhoid fever patients with a combination of trimethoprim and sulfamethoxazole. There were only three treatment failures and the side effects were minimal. The average time to bring the temperature to normal was 4.1 days, which compares favorably with that required by chloramphenicol. This drug combination and others like it will doubtlessly be useful in areas where antibiotic-resistant strains of *S. typhosa* are present.

The general supportive treatment of patients with typhoid fever, paratyphoid fever, or severe acute *Salmonella* gastroenteritis with suspected bacteremia is best undertaken in a hospital and in an area separated from the general patient population. Cooling blankets and antipyretics were used in Vietnam for temperatures above 103°F. Antiemetics were used to control nausea and vomiting. Diarrhea was not a major problem and, when present, was easily controlled.

Laboratory Diagnosis

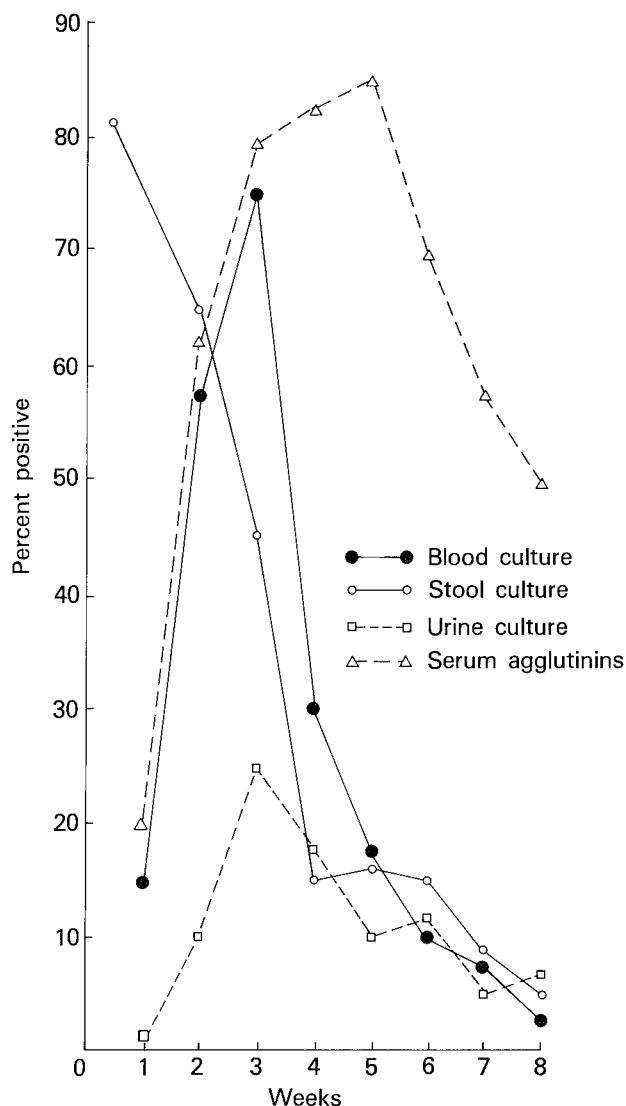
The cornerstone of the diagnosis of typhoid fever is isolation of *S. typhosa* from the blood, stool, or urine of the patient. As seen in chart 24, positive blood cultures are obtained in 80 to 90 percent of the cases during the first week. As many as 25 percent have positive urine cultures in the later stages of the disease. In acute *Salmonella* gastroenteritis while positive stool cultures are found in the early stages of the disease, blood cultures are usually negative. Specific agglutinins formed in response to the surface antigens of the *Salmonella* organism can usually be demonstrated in the serum of patients 1 to 2 weeks

CHART 23.—Course of typhoid fever of a previously immunized American patient in Vietnam



Source: Records of patients treated by Lt. Col. Kenneth W. Hedlund, MC, 85th Evacuation Hospital, Vietnam.

CHART 24.—Relative frequencies with which blood, urine, and stool cultures and serum agglutination tests are positive during the course of typhoid fever



Source: Morgan, H. R. 1965. The enteric bacteria. In *Bacterial and mycotic infections of man*, eds. R. J. Dubos and J. G. Hirsch, pp. 610-48. Philadelphia, J. B. Lippincott Company.

after the onset of typhoid fever, septicemia, or the more severe acute gastroenteritis cases.

Variations occur between the H and O titers of unimmunized persons and those of immunized persons. In the unimmunized individual, the O agglutinins appear before the H and are usually higher at first. (Their positions are reversed in the convalescent phase.) The presence of high O titers (1:160) with low H titers thus suggests typhoid fever in an unimmunized individual. Active immunization with typhoid-paratyphoid vaccine produces both H and O agglutinins; therefore,

high titers of H agglutinins (1:1280) can be invoked as an anamnestic response to typhoid bacilli in a previously immunized individual. However, it should be stressed that a generalized increase in H titers occurs in patients with certain non-*Salmonella* infections. Therefore, the only realistic way to follow possible typhoid infections in previously immunized individuals is by serial determinations of H and O titers at 3-day intervals. If the titers progressively increase, and especially if the O titers rise, then typhoid fever is a strong possibility.

Early treatment with chloramphenicol or any other effective antibiotic will cause the agglutinin titers to remain low or within normal limits (El-Rooby and Gohar 1956). In addition, nontyphoid *Salmonella* organisms may cause an increase in agglutinin levels but usually to a lesser degree than typhoid salmonellae. Serological determinations are therefore at best an indication of possible *Salmonella* infection.

Complications

Typhoid fever has a mortality rate of 10 to 14 percent in untreated cases, as mentioned earlier. If one substitutes the word "undiagnosed" for "untreated," the true dimensions of the problem become apparent. The following case illustrates the point.*

The patient, a 22-year-old male, was admitted to the 9th Surgical Hospital on 31 August 1968, with a 2-week history of fever. On 9 September he was transferred to the 2d Surgical Hospital with fever, tachycardia, and right upper quadrant tenderness. On 13 September he was transferred to the 67th Evacuation Hospital with a persistent temperature of 103°F. Four days later, blood cultures were reported as positive for *S. typhi*.

The patient was apparently then started on colistin and later on chloramphenicol. By 21 September, he had developed overt gastrointestinal hemorrhage and perforation. The hematocrit was 23%. After transfusion, an exploratory laparotomy was performed on 24 September and a portion of the ileum was resected. One day later, a subtotal colectomy was done. The patient died on 28 September 1968. At postmortem, the stomach showed no areas of ulceration. What remained of the small and large bowel showed focal areas of hyperemia over the serosal surfaces. The mucosal surface of the small intestine was described as discolored and hemorrhagic.

This case demonstrates that the longer diagnosis and treatment are delayed, the greater the possibility of perforation and hemorrhage. Once formed, these lesions are generally unaffected by antibiotics. Gastrointestinal hemorrhage and perforation account for 75 percent of all the deaths caused by typhoid fever (Boyd 1965, p. 416).

Hemorrhage, like perforation, is rare before the 10th day of illness and, more importantly, hemorrhage and perforation in the antibiotic era may occur in afebrile patients who clinically are doing well. Osler (1935, pp. 1-33) noted a 7-percent incidence of overt intestinal hemorrhage in the 23,721 cases he reported during the preantibiotic era. The incidence of overt hemorrhage has been

*Dr. Samuel B. Formal: Personal records.

relatively uninfluenced in the antibiotic era (Woodward and Smadel 1964; Rowland 1961). Stuart and Pullen (1946) reported chemically detectable blood in the stool in 52 percent of their 360 patients. Obviously, small hemorrhages may go unnoticed. The larger ones may be preceded by abdominal pain, vomiting, and dizziness, progressing to overt shock. Prompt diagnosis and blood replacement therapy are important in lowering mortality.

The incidence of perforation reported is about 1.3 to 5.1 percent (Woodward and Smadel 1964, p. 150; Rowland 1961, p. 107). Many investigators believe that the incidence is not appreciably affected by treatment with chloramphenicol (Woodward and Smadel 1964, p. 150; El Ramli 1950). The immediate cause of perforation, as of hemorrhage, is ulceration followed by necrosis. The onset of perforation may be either insidious or sudden. In sudden perforation, prodromal signs of increasing pain and hemorrhage are not invariably present. Abdominal pain, rigidity, vomiting, and rapidly progressive collapse occur. In the insidious type of perforation, there may be little pain and the signs and symptoms of generalized peritonitis may be absent or slow in appearing.

Typhoid fever patients are frequently apathetic and even obtunded. Abdomens are often mildly distended, white cell counts low, and temperatures elevated. A sudden drop in temperature may be seen following perforation, in some after a modest initial 1° to 2° rise. The white cell count may rise rapidly following perforation, going to $10,000/\text{mm}^3$ or $15,000/\text{mm}^3$ within a few hours. In patients who are being given high levels of antibiotics and steroids, the signs and symptoms may be markedly atypical or masked altogether.

The treatment of intestinal perforation in patients with typhoid fever has been debated for some time. There is classic disagreement between proponents of conservative medical management and aggressive surgical intervention. In the preantibiotic era, when perforation occurred, death was almost inevitable. However, Osler (1935, pp. 18, 32) suggested that early diagnosis and surgery could save about one-third of patients who developed this otherwise fatal complication.

Huckstep (1962, pp. 187-95) in a 23-patient series, points out that 27 percent of 15 patients with intestinal perforation alone died following aggressive surgical management, while 13 percent of eight patients with peritonitis and probable perforation died with medical management alone. Medical management in the series consisted of gastric aspiration, large doses of chloramphenicol, careful monitoring and maintenance of electrolyte balance, and mild sedation as well as a high level of nursing care. Huckstep notes two important exceptions to conservative medical management. The first is when sudden perforation is seen in the convalescent patient within 6 hours of onset. The second is when perforation has led to complications, such as adhesions causing obstruction. In both of these exceptions, he advocates surgical intervention.

Li (1963), in a 20-case series of proven typhoid perforation, reported only a 10-percent mortality following surgical intervention and chloramphenicol therapy. Archampong (1969), in a 121-case series, advocated early surgical intervention. His overall mortality rate following surgical intervention was 29.8 percent. However, 90 percent of the patients he operated on had perforation before their admission to the hospital and therefore had no prior antibiotic

therapy. More importantly, he points out that there is only a 13.3-percent mortality if surgery is performed in the first 24 hours. If a delay of 2 to 5 days occurs, the mortality rate rises to 26.2 percent; after the fifth day, it jumps to 76 percent.

Woodward and Smadel (1964, p. 152) emphasize that when it becomes obvious to the clinician and the attending surgeon that the infectious process is failing to localize under antibiotic therapy, as evidenced by the findings on examination and by the persistence of shock and leukocytosis, it may be surmised that the ulcer is not healing and that surgical intervention is indicated.

Early surgical intervention became the standard of practice in Vietnam for perforation.

The other complications of typhoid fever include cholecystitis, pneumonia, hemolytic anemia, nephritis, arthritis, psychosis, diffuse intravascular coagulation syndromes, hepatitis, thrombophlebitis, toxic myocardopathy, and metastatic abscesses throughout the body.

Pathogenesis

Whether or not one becomes ill following infection depends upon the interaction of a large number of variables. Among these are the virulence of the pathogen and the size of the inoculum. The "natural" and "acquired" resistance of the host also plays an important role. Using human volunteers immunized against typhoid fever, Hornick and coworkers (1970a) were able to establish an I.D.₅₀ (median infective dose) of 10^7 *S. typhosa* (Quailes strain) organisms. This strain contains the Vi antigen. In contrast, when a numerically equivalent inoculum of *S. typhosa* organisms lacking the Vi antigen was used, the disease rate was only 26 percent. Once induced, the disease in immunized volunteers is identical to the naturally acquired disease regardless of the size of the initial inoculum. Following ingestion, the bacilli multiply rapidly in the intestinal tract and stools are frequently, but not always, positive for *S. typhosa* within 24 hours. *S. typhosa* multiplication within the intestinal tract, however, is not an absolute indication that the volunteer will contract typhoid fever or even become ill. In addition to multiplication, there is rapid penetration. Sprinz (1969) points out that, in contrast to shigellae, salmonellae are readily transported through the intestinal epithelial lining without marked local inflammatory response.

Once through the intestinal wall, the bacilli migrate to the mesenteric lymph nodes where multiplication continues. From there, they gain access to the blood via the thoracic duct and are filtered by the reticuloendothelial system, primarily the spleen and liver. They subsequently reinvade the bloodstream.

Microscopically, the activated reticuloendothelial system responds to typhoid bacilli challenge by an active proliferation and accumulation of macrophages (mononuclear phagocytes) within the lymphoid tissue of the intestine. The packing of these lymphoid pockets by enormous numbers of macrophages disrupts the normal architecture. During the first week of illness, the pockets of lymphoid tissue become grossly swollen and project above the mucosal surfaces.

The macroscopic lymphoid swelling is caused by the large number of phagocytic cells and by the edema which results from local circulatory compromise. Vascular occlusion leads to ischemic necrosis and then the formation of a superficial slough. The necrosis may extend laterally into the mucosa or deeply into the tunica muscularis or the peritoneum. The areas most frequently involved are the lower portion of the ileum, the cecum, and the proximal portions of the colon. If the local processes leading to necrosis are slow, the vessels involved are usually obliterated; if the process is rapid, the blood vessel walls are frequently eroded.

As Boyd (1965, pp. 414-21) points out, the gravity of hemorrhage is appreciated when one considers the blood supply of the Peyer's patches. A large number of parallel vessels run into the patch from the plexus in the submucosa, so that even a superficial ulceration may cause a very severe hemorrhage.

The role of bacterial endotoxins is still being elucidated. These lipopolysaccharides form an integral part of the gram-negative cell wall and are released into the host circulation upon destruction of the bacterium. Hornick et al. (1970b) found that as little as 0.25 μ of purified endotoxin from *S. typhosa* given intravenously can produce chills, fever, and headaches as well as a depression of platelets and leukocytes. Neither the tolerance developed to increasing amounts of pure endotoxin nor the resultant high anti-O antibody titer affords protection in volunteers to the subsequent development of classic typhoid fever. Endotoxin, a potent inflammatory agent, also provides the endogenous release of pyrogens from polymorphonuclear cells and monocytes, and this explains in part the sustained temperature elevations. In addition, chemotactic factors are generated for both polymorphonuclear leukocytes (Snyderman, Gewurz, and Mergenhagen 1968) and monocytes (Ward 1968) by the interaction of complement components with endotoxin or other bacterial products. The characteristic mononuclear cell infiltrate in typhoid fever, in contrast to the polymorphonuclear leukocyte inflammatory response in other *Salmonella* infections remains incompletely explained.

Summary

In areas where typhoid fever is endemic, it is common for local physicians to miss the diagnosis on admission (Chalmers 1971). This was as true for American physicians in Vietnam as for physicians elsewhere. There were a number of reasons for this, but perhaps the most important was that the disease was simply not included in the differential diagnosis because of a misunderstanding of the effectiveness of typhoid immunizations. In addition, the classic textbook presentation of epidemic typhoid fever is the exception rather than the general rule in the endemic disease (Wicks, Holmes, and Davidson 1971; Paul 1952, pp. 291-315).

Typhoid fever can be controlled in large measure by immunizations and by the enforcement of common public health measures; however, immunizations per se do not give complete protection to a person if he receives a large enough inoculum (Hornick et al. 1970a, pp. 687-88). Typhoid fever now (Chalmers 1971), as in the past, remains a great imitator of other febrile illnesses. It always must

be considered in the differential diagnosis of febrile illnesses in areas where the disease is endemic. Early antibiotic treatment and fluid replacement are the basis of therapy.

OTHER SALMONELLOSES

The approximately 1,500 serotypes which comprise the genus *Salmonella* make taxonomy unwieldy. They may more easily be classified into three ecological groups according to host preference—those specifically adapted to man, those adapted to animals, and those with no specific host preference. Table 68 clarifies the relationship of *Salmonella* species and representative serotypes to human disease.

Although *Salmonella* infections other than typhoid cause relatively mild and self-limited disease, they are of military significance because of their abrupt onset and the frequent epidemic clustering of cases.

Kuhns and Learnard reviewed the subject of typhoid and paratyphoid fevers from the beginning of the Army's reporting system in 1818 through World War II (MD-PM4, pp. 463-82). (Kuhns reviewed *Salmonella* food poisoning separately [MD-PM4, pp. 417-31].) Table 69 reflects the experience of the U.S. Army in that conflict with "paratyphoid fevers."

Precise data on the occurrence of salmonella infection in Vietnam are not available, although USARV Command Health Reports (USARV-CHR) from 1969 to 1970 indicate a monthly incidence of one or two confirmed cases.

In the United States, the number of salmonella infections other than typhoid increased from 504 in 1942 to 19,723 bacteriologically confirmed cases in 1967 (NCDC-SS). This number is believed to reflect only a fraction of actual cases. This increase represents increased surveillance and changing patterns of mass food processing and distribution. The major reservoirs of human salmonellosis are livestock and poultry. Outbreaks have occurred as a result of contamination of dried milk, poultry, pork, shellfish, eggs, water, and carmine dye (DuPont and Hornick 1969; Bauer 1973).

The disease varies with the infecting species of *Salmonella* and the number of organisms ingested. While salmonella infection does involve intestinal epithelial invasion, it does not result in extensive destruction of the intestinal mucosa. The epithelial lining is left intact, and an inflammatory response is elicited when the organisms reach the lamina propria. The nature of the inflammatory response seems to be important in determining the pathogenesis of the disease and the resultant symptomatology. *S. typhosa* organisms, for reasons that are not understood, produce a predominantly mononuclear inflammatory response in which the organisms are carried into the circulation, resulting in enteric fever with systemic symptoms and bacteremia. In contrast, nontyphoid salmonellae produce a predominantly polymorphonuclear reaction in which the organisms are phagocytized and contained in the lamina propria, the clinical expression being a gastroenteritis. Although suitable pathologic studies have not been conducted on human salmonella gastroenteritis, it is probable that in most cases invasion of the distal small bowel as well as the colonic mucosa occurs (DuPont and Hornick 1973).

TABLE 68.—*Relation of Salmonella species and representative serotypes to human disease*

Species	Representative serotype(s)	Natural host	Human disease
<i>S. choleraesuis</i>		Animal (swine)	Septicemia and arteritis.
<i>S. typhi</i>		Man	Enteric (typhoid) fever.
<i>S. enteritidis</i>	Paratyphi A	Man	Enteric fever or gastroenteritis.
	Schottmuelleri ¹		
	Pullorum	Animal (fowl)	None.
	Dublin	Animal (cattle)	Gastroenteritis.
	Typhimurium	Man and many animals	Gastroenteritis, septicemia or focal infection.
	Derby	Man and many animals	Gastroenteritis.
	Enteritidis		
	Heidelberg and hundreds of related serotypes.		

¹Current name for paratyphi B.Source: Grady, G. F., and Keusch, G. T. 1971. Pathogenesis of bacterial diarrheas. Part I. *New England J. Med.* 285: 831-41. Reprinted by permission of The New England Journal of Medicine.TABLE 69.—*Incidence of paratyphoid fever in the U.S. Army, by area and year, 1942-45¹*

[Rate expressed as number of cases per annum per 1,000 average strength]

Area	1942-45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States	125	0.01	19	0.01	35	0.01	41	0.01	30	0.01
Overseas:										
Europe	84	0.02	2	0.02	2	0.01	20	0.01	60	0.03
Mediterranean ²	212	0.14	1	0.04	141	0.31	45	0.07	25	0.07
Middle East	34	0.23	2	0.33	13	0.25	9	0.19	10	0.24
China-Burma-India	96	0.22	1	0.11	8	0.20	37	0.22	50	0.23
Southwest Pacific	183	0.10	1	0.01	18	0.09	24	0.04	140	0.14
Central and South Pacific	33	0.03	3	0.02	4	0.01	6	0.01	20	0.05
North America ³	1	0	1	0.01	0	0	0	0	0	0
Latin America	70	0.18	7	0.07	49	0.41	9	0.10	5	0.07
Total overseas ⁴	714	0.07	18	0.03	236	0.14	150	0.04	310	0.07
Total Army	839	0.03	37	0.01	271	0.04	191	0.02	340	0.04

¹Preliminary data based on individual medical record sample tabulations of primary and secondary diagnoses.²Includes North Africa.³Includes Alaska and Iceland.⁴Includes admission on transport in 1943.Source: Medical Department, United States Army. 1958. *Communicable diseases transmitted chiefly through respiratory and alimentary tracts*. Preventive Medicine in World War II, vol. IV. Washington: Government Printing Office, p. 473.

While the O or somatic antigen relates to production of an exotoxin which is toxic to man when injected under experimental conditions, it is likely that endotoxins from senescent bacteria are continuously present in the gut and that few or none of them are absorbed under normal circumstances. Other factors that may influence the pathogenicity of salmonella are intestinal immune factors, bowel motility, gastric acidity, and the bacterial flora of the gut. Short chain fatty acids, such as acetic and butyric acid, are produced by many intestinal bacteria in sufficient concentrations to inhibit the growth of virulent enteric pathogens (DuPont and Hornick 1973b).

Salmonella gastroenteritis is the most common clinical manifestation of salmonella infections in man. Symptoms begin 12 to 24 hours after ingestion of the organism. There is sudden onset of abdominal pain, nausea, diarrhea, and vomiting. Fever nearly always occurs. Dehydration in infants may be severe. Anorexia and loose stools may continue for several days. The process is self-limited, and recovery occurs in 2 to 5 days (Bauer 1973, p. 324).

The enteric fever pattern of salmonellosis is less common than salmonella gastroenteritis but may occur with any of the species of *Salmonella* infecting man. Clinically, the illness is less severe than typhoid, but on occasion it may be serious and, rarely, fatal. The onset is characterized by malaise, anorexia, and diarrhea. Shortly, the temperature begins to rise and will persist for 1 to 3 weeks if untreated; initially, it may reach 102° to 104°. During the first week, blood cultures will be positive and stool cultures often negative. *S. enteritidis* serotypes, *S. paratyphi A*, and *S. schottmülleri* tend to be more common causes of enteric fever but also may cause gastroenteritis.

Septicemia is the most serious form of salmonella infection. When septicemia occurs, the patient manifests high fever and prostration while gastrointestinal symptoms are often minimal. Focal abscess formation may occur with endocarditis, septic arthritis, osteomyelitis, meningitis, cholecystitis, or abscess of the lungs or kidneys. While any of the species of *Salmonella* can cause widespread sepsis, it is most common with *S. choleraesuis*.

The mortality rate is highest among patients over 50 years of age. Saphra (1950) reported 174 fatalities (5.3 percent) in 3,279 human infections, with a fatality rate of 15 percent in patients over age 50, 5.8 percent in infants, and 2 percent in patients between ages 1 and 50. *S. choleraesuis* had the highest fatality rate, 21.3 percent, while *S. typhimurium* and *S. oranienburg* had fatality rates of 5.5 percent.

Following acute infections, 40 to 60 percent of patients continue to shed salmonella when tested at 1 month, with a rapid decrease thereafter (Rubenstein, Feemster, and Smith 1944). The carrier state is usually temporary in untreated patients. Permanent carriers are primarily typhoid and paratyphoid patients. The carrier rate in the general population is estimated at 0.2 percent (Saphra and Winter 1957).

There is often a leukocytosis, although patients with septicemia may have a leukopenia. In salmonella gastroenteritis, the white count may be normal or only slightly elevated. Definitive diagnosis depends on isolation and identification of the offending salmonella from blood, feces, or urine. Blood cultures obtained dur-

ing the first week of illness are often the most productive source of material, although a rectal swab or fresh stool specimen plated promptly may also be positive.

While indirect serologic means of diagnosis are available, there has recently been some concern about their validity. If serologic tests are used, the only meaningful value is the titer for O antigen. However, even this may be suppressed by early antibiotic treatment or elevated by immunization (Bauer 1973; Schroeder 1968).

Proper processing, preparation, and handling of food are fundamental to the prevention of salmonellosis. As mentioned earlier, mass production and distribution of food for both humans and animals are conducive to wide dissemination of salmonellosis. This implies appropriate education of food processors and handlers and adequate bacteriological checks on production items. There is no salmonella vaccine for man except that for *S. typhosa* and *S. paratyphi A* and *B* (Hornick et al. 1970a, b).

The appropriate therapy for salmonella gastroenteritis is strictly supportive, with fluid and electrolyte replacement. Continued emphasis of this point is required in a combat theater. Antimicrobial therapy is indicated only in patients with positive blood cultures or with septicemia and focal abscesses. The latter cases require adequate local management as well. The antibiotics of choice are chloramphenicol in doses of 1 to 2 g per day, or ampicillin in doses of 2 to 4 g per day, each in four divided doses. There is growing evidence, however, that the price paid for early control of toxicity is prolonged shedding of bacteria in the stool (Aserkoff and Bennett 1969). Therapy of the chronic carrier is frustrating unless an accessible focal lesion, such as cholelithiasis, is present.

There was a continuing awareness of the problem of salmonellosis throughout the Vietnam conflict, although no concerted effort was made to determine the incidence of carriers or to culture all patients with diarrheal illness. In 1969, a complete study of 204 patients yielded only 6 with salmonellosis (Kalas and Bearden 1969). This information paralleled clinical impressions; the reported incidence remained low and was overshadowed by acute nonspecific diarrhea and shigellosis. Antibiotic resistance was not recognized as a major management problem in salmonellosis and was not studied. The impact of widespread unnecessary antibiotic usage in diarrheal disease was not delineated.

Section III. Cholera and *Vibrio parahemolyticus* Gastroenteritis

Colonel Ralph F. Wells, MC, USA (Ret.)

CHOLERA

History and Military Significance

The U.S. military experience with cholera through World War II has been well summarized by Mosley (MD-PM4, pp. 451-62). The disease has had remark-

ably little impact on U.S. forces during any major conflict. In World War II, only 13 cases and two deaths were reported among American military personnel. These cases stemmed from two epidemics of limited extent, both occurring in China during the summer of 1945. One epidemic involved six men and the other, seven; each involved one death. In both instances, breaches of sanitary discipline were directly responsible. The only other case cited by Mosley was that of a Red Cross worker who apparently acquired a mild but bacteriologically confirmed infection while serving in Calcutta. Despite deployment of large numbers of military personnel to the India-Burma theater, the disease was not reported in American troops there, in contrast to British and Indian military experience and experience in the civilian populace. The two factors believed to be responsible for the remarkably low incidence of cholera among U.S. forces were an aggressive immunization program and rigid sanitary policies directed primarily toward the more common diarrheal diseases.

Calcutta was a major endemic focus throughout World War II and, in the early 1960's, became one of two sites on the Indian subcontinent for major clinical investigation (Carpenter, Mitra, and Sack 1966). Studies in Calcutta were conducted jointly by the Calcutta School of Tropical Medicine, the Calcutta Infectious Disease Hospital, and the Johns Hopkins University Center for Medical Research and Training, Calcutta. The other major investigative program had been launched in the late 1950's with the establishment of the Pakistan-SEATO (South East Asia Treaty Organization) Cholera Research Laboratory in Dacca, East Pakistan (now Bangladesh) (Gordon et al. 1966). These two programs are mentioned because of their fundamental contribution to the pathophysiology and therapy of cholera and, perhaps more importantly, for their pioneering work in the study of diarrheal disease in general.

Endemic cholera remained a continuing problem in India from the end of World War II throughout the Vietnam conflict.

When the buildup began in Vietnam, the disease, particularly the El Tor type, occurred in epidemic form in the Philippines. In 1964, the Republic of Vietnam had its first epidemic in 20 years; 20,000 cases were reported from areas under governmental control, concentrated in major urban centers such as Saigon, Hue, Da Nang, and Nha Trang. The continuing nature of the problem became apparent when more than 2,800 cases were reported in the first 3 months of 1966 (Sheehy 1968). Precise data on the incidence of cholera in North Vietnam are not available, although the existence of rigid immunization requirements for foreign visitors entering the country suggested the possibility of a significant problem (HD-25, p. 19).

Incidence and Epidemiology

The period beginning in 1961 has been classified as the "Seventh Cholera Pandemic." Although epidemic cholera occurred among the Vietnamese civilian populace during the peak years of the U.S. commitment in Vietnam, no cases were reported among American military personnel under U.S. military control. This generalization apparently also applies to military advisers. The incidence of

cholera among American prisoners of war is unknown. One possible explanation for this rather remarkable record is the aggressive policy of immunization before entry into the country with a booster immunization at approximately 6 months. A second consideration is the generally good nutritional state our personnel enjoyed, and a third is that the diagnosis may simply have been missed and the disease treated supportively as nonspecific diarrhea because of a lack of refined laboratory methodology.

Etiology and Pathogenesis

If an apology need be presented for discussing an uncommon disease at length, it is that the knowledge gained from the study of cholera not only promises to be of value in its prevention and treatment but also has led to isolation of an enterotoxin responsible for the massive fluid loss it causes. This, in turn, has resulted in a better understanding of the pathogenesis of other infectious diarrheas and added to our knowledge of normal mechanisms of fluid and electrolyte movement across the gut and other mucosal membranes.

Vibrio cholerae is a gram-negative, nonsporeforming, usually slightly curved (comma shaped) rod that is motile by means of a single polar flagellum. The two classic serotypes are the Ogawa and Inaba. Another biotype is the El Tor. A schema for its distinction from classic cholera will be presented when laboratory diagnosis is discussed. The El Tor vibrios are so named because they were first isolated from pilgrims at the El Tor quarantine station in the Sinai Peninsula in 1905.

Vibrio cholerae organisms neither invade the host nor cause morphologic damage to the intestinal epithelium. However, they proliferate rapidly, reaching tremendous numbers (10^4 to 10^8 organisms per ml) in the luminal content of the small bowel and the colon (Elliott et al. 1970; Gorbach et al. 1970). The pathologic effects of the organism are attributed entirely to the action of the exotoxin (enterotoxin or cholera toxin) produced in the intestinal lumen. This exotoxin has been purified and described as a heat- and acid-labile protein having a molecular weight of about 90,000 (Finkelstein and Lo Spalluto 1969).

The rapid loss of water and electrolytes in the stool, which may reach 20 liters or more in a 24-hour period, explains the clinical signs and metabolic derangements characteristic of cholera. As the colon is relatively normal, the small bowel has been incriminated as the site of this fluid loss. Four mechanisms of fluid loss have been proposed: exudation, increased transudation or filtration, inhibition of absorption, and increased intestinal secretion (Hendrix 1972). Several recent reviews have summed up the evidence, dismissing the first three mechanisms and implicating the fourth (Field 1971; Carpenter 1971b; Sladen 1973; Banwell and Sherr 1973).

John Snow, in 1855, had suggested that "cholera poison" played a key role, a viewpoint further spelled out in 1882 by Cohnheim, who concluded that under the influence of cholera organisms "there takes place an extra-ordinary profuse secretion from the glands of the small intestine" (Hendrix 1972). Further delineation of the mechanism was contingent on the definition of the functional anatomy

of the small bowel, the development of appropriate laboratory methods such as the rabbit ileal loop and the Ussing chamber, and some knowledge of the role of cyclic AMP (adenosine 3',5'-monophosphate).

Sutherland and Rall (1958) found that the glycogenolytic effect of epinephrine and glucagon was associated with an increase in cellular cyclic AMP. This observation led to extensive investigations which have clarified the subcellular biochemical changes responsible for mediating the physiological effect of catecholamines as well as many other hormones. Cyclic AMP serves as the intracellular mediator for hormonal action as follows (Field 1971, p. 1142). The hormone, or other stimulating substance, binds on the cell membrane with its specific receptor. The hormone receptor binding stimulates adenyl cyclase activity. An increase in adenyl cyclase activity catalyzes the conversion of ATP (adenosine triphosphate) to cyclic AMP, initiating a series of intermediate steps which ultimately result in the physiological response or responses characteristic of a cell or an organ. Cyclic AMP is degraded to 5'-AMP by the enzyme phosphodiesterase. Thus, increased cyclic AMP activity may result either when adenyl cyclase is stimulated or when the breakdown via phosphodiesterase is inhibited. Apparently all nucleated mammalian cells may contain a cyclic AMP mechanism. ACTH (adrenocorticotrophic hormone), TSH (thyroid-stimulating hormone), and thyroxine, among other hormones, seem to act through a cyclic AMP intermediate.

Both cyclic AMP and cholera toxin produce active secretion of chloride by ileal mucosa in an Ussing chamber; they also cause similar changes in transmucosal potential difference. These in vitro effects parallel the events in naturally occurring and experimentally induced cholera, which can be produced by cyclic AMP itself, by inhibition of phosphodiesterase and by at least one group of hormones, the prostaglandins, which increase the levels of cyclic AMP in the mucosa by activating intestinal adenyl cyclase (Field 1971).

In summary, the enterotoxin or cholera toxin released by *Vibrio cholerae* binds firmly and rapidly to the mucosa, fixing to the tips and crypts of the villi. Either directly or by means of an undefined mediator, the interaction between cholera toxin and the epithelium activates adenyl cyclase in cell walls of the secretory epithelium, resulting in an increase in the concentration of cyclic AMP. Binding appears to occur near the villus tip but does not involve the brush border. The effect of even brief contact of the cholera toxin with the intestinal mucosa persists for some hours. It has been suggested that exposure of new cells in the crypts to a substance such as cycloheximide, which inhibits the secretory process, may apparently take 2 to 3 hours and, not uncommonly, 12 hours to reverse the secretory process (Hendrix 1972; Sladen 1973).

Cholera toxin completely inhibits the absorption of sodium through the brush border; however, sodium transport via glucose or amino acid carrier is not affected. Since the glucose-mediated mechanism for sodium transport remains intact, patients with cholera can be given a balanced glucose-electrolyte solution for oral repletion. The active chloride pump moving chloride into the cell is likewise inhibited or even reversed by cholera toxin with a resultant flux of chloride into the gut lumen. The net effect is that the enterocyte becomes a

secretory cell with a large efflux of sodium and chloride associated with corresponding fluid loss accounting for the 10- to 20-liter fluid loss per day in the cholera patient. The bicarbonate loss remains unexplained (Field 1971; Carpenter 1971b; Sladen 1973; Banwell and Sherr 1973).

The mechanisms described above are applicable not only to *Vibrio cholerae* but also to *Escherichia coli*, *Clostridium perfringens*, *Shigella dysenteriae*, and staphylococci as well as a number of noninfectious but humorally mediated diarrheas (Field 1971; Carpenter 1971b; Sladen 1973; Banwell and Sherr 1973).

Clinical Features, Course, and Complications

Cholera usually occurs in an epidemic pattern, isolated cases being extremely rare. However, documented cases among American travelers in endemic areas have been infrequent, paralleling the American military experience. This may reflect travel at times when the vibriocidal effect of recent immunization is at its peak (Gangarosa 1971).

The incubation period varies from 1 to 3 days or longer. The prodrome may range from mild malaise and mild diarrhea to depression and prostration. The onset of clinical illness is usually explosive with profuse watery diarrhea. The stools may initially be normal colored or yellow but rapidly become colorless and odorless, the "rice water" stool that is the hallmark of cholera. Vomiting may occur; fever is uncommon. While colic and tenesmus are not often seen, severe muscle cramps of the extremities and abdominal wall are noted, reflecting fluid and electrolyte losses. The character of stool electrolyte losses is shown in table 70. Stool volumes, as noted earlier, may be as high as 20 liters per day. Oliguria and anuria may follow. In endemic areas, the cholera cot is widely used; this is a canvas cot with a "porthole" for the perineum, under which a large receptacle is placed allowing constant monitoring of fecal fluid losses. Volume for volume replacement is critical. Untreated severe cases may result in shock and death in 4 hours or less. Before the advent of current therapeutic measures, epidemic mortality rates varied from 30 to 80 percent (Carpenter, Mitra, and Sack 1966, p. 165; Phillips 1966). Milder cases and asymptomatic carriers constitute the bulk of the cases in most epidemics and are a major public health hazard.

TABLE 70.—Composition of intestinal fluid (mEq/l)

Item	Na	K	Cl	HCO ₃
Jejunum (cholera and normal)	148	5.6	138	15
Ileum (cholera and normal)	146	5.7	121	42
Cholera stool	140	10.0	110	48
Normal stool	30	100.0	15	32

¹In normal stool, organic anions account for the discrepancy between cations (Na + K) and anions (Cl + HCO₃). The great volume of choleraic stool purges the colon of organic anions which are normally derived from unabsorbed foodstuffs and shed cells.

Source: Hendrix, T. R. 1972. Cholera: New lessons from an old disease. *Viewpoints Digest. Dis.* 4 (May).

Laboratory Diagnosis

As Feeley pointed out (Gordon et al. 1966), laboratory diagnosis is of no significance to immediate treatment in the critically ill patient. To confirm the diagnosis, cultures should be obtained from rectal swabs or fluid stool. Conventional media used for "enteric pathogens," such as MacConkey's agar, eosin-methylene blue, or Salmonella-Shigella agar, are suboptimal and even inhibitory. The simplest and most effective media are gelatin agar plates, tellurite taurocholate gelatin agar plates, and enrichment-transport media. Typical colonies are recognized by a turbid or cloudy zone caused by gelatinase production. Alkaline peptone water is a suitable enrichment medium and may be substituted for the tellurite medium. In the field, the transport medium is used for both transmission and enrichment of the vibrios during shipment. Suspicious colonies are then confirmed by appropriate agglutination and biochemical tests. Other diagnostic modalities include dark field microscopy, fluorescent antibody methods, and serologic diagnosis. A schema for the distinction of El Tor from classic biotypes is given in table 71.

Prevention and Treatment

Appropriate sanitary measures and immunization are the cornerstone of prevention. The actual efficacy of cholera immunization has been under scrutiny, as has typhoid immunization. There is considerable variation from manufacturer to manufacturer, and the duration of effectiveness is unknown. The U.S. military policy of recommending booster injections at 6-month intervals while in endemic areas undoubtedly contributed to the degree of success in Vietnam. A summary of control measures in the 1970's as outlined by Benenson (1970, p. 1207), follows.

1. Effective treatment of cholera as a diarrheal case.
2. Bacteriological surveillance of diarrheal diseases.
3. Chemoprophylaxis for members of the patient's hearth-group.
4. Sanitary improvements:
 - Water supply.
 - Disposal of excreta.
5. Health education.
6. Immunizations on a voluntary basis.
7. Elimination of quarantine measures.

While intravenous fluids of appropriate volume and composition may be lifesaving, the logistical problems of this approach are insurmountable in underdeveloped countries (Carpenter 1971a; Phillips 1966). Fortunately, tetracycline therapy has been shown to rapidly eliminate the vibrio from the stool and significantly reduce the amount of fecal fluid loss (table 72).

Of equal importance has been the demonstration that cholera enterotoxin does not inhibit glucose transport and that it is thus feasible to administer a balanced glucose and electrolyte solution orally, which further reduces the requirement for intravenous fluids. The composition of this oral glucose-electrolyte solution is as follows (Carpenter 1971a, p. 1201):

Sodium.....	100 mEq/l	Bicarbonate.....	40 mEq/l
Potassium.....	10 mEq/l	Glucose.....	120 mM/l
Chloride.....	70 mEq/l	Osmolarity.....	327 mOsm/l

This solution may temporarily increase fecal fluid loss but when it is used in conjunction with tetracycline therapy, this untoward effect is short-lived.

New Advances

It is paradoxical that study of a disease infrequently encountered among U.S. military personnel provided a major breakthrough in the understanding of all enterotoxin-related diarrheal diseases. Because cholera was endemic among the civilian populace in the entire area of operation, there was ample opportunity for clinical study. Both NAMRU (Naval Medical Research Unit)-2 and the SEATO laboratories were intimately involved in fieldwork in conjunction with civilian activities in Bangkok, the Philippines, and Vietnam. Additional work was performed by other agencies, particularly in Calcutta and Dacca. Much of the fundamental laboratory work on the pathogenic mechanism of diarrhea, both in cholera and *E. coli*, was subsequently accomplished in the laboratory at WRAIR (Walter Reed Army Institute of Research).

TABLE 71.—Laboratory tests used to distinguish classical from El Tor biotypes of *Vibrio cholerae*

Test	Classical cholera vibrios	El Tor vibrios
Hemolysis (sheep or goat cells)	Negative	Positive
Hemagglutination (chicken cells)	Negative	Positive
Phage susceptibility (Mukerjee's phage IV)	Susceptible	Resistant
Voges-Proskauer (Barritt method)	Negative or weakly positive	Positive

Source: Gordon, R. S., Jr.; Feeley, J. C.; Greenough, W. B., III; Sprinz, H.; and Oseasohn, R. 1966. Cholera. *Ann. Int. Med.* 64: 1328-51.

TABLE 72.—Effect of tetracycline on stool volume in cholera patients, 1963 study

Stool volume (liters)	Mean value \pm standard deviation		p value by "T" test
	Tetracycline (10 patients)	No tetracycline (10 patients)	
Day 1	6.6 \pm 2.1	8.3 \pm 3.3	p > 0.3
Day 2	2.2 \pm 1.6	4.3 \pm 3.1	p > 0.05
Day 3	0.9 \pm 1.0	5.0 \pm 4.1	p < 0.01
Day 4	0.4 \pm 1.1	3.8 \pm 3.4	p < 0.01
Total	10.6 \pm 4.9	24.0 \pm 17.8	p < 0.05

Source: Carpenter, C. C. J. 1971a. Cholera: Diagnosis and treatment. In Symposium on cholera. *Bull. New York Acad. Med.* 47: 1192-1203.

VIBRIO PARAHEMOLYTICUS GASTROENTERITIS

History and Military Significance

Vibrio parahaemolyticus, a halophilic, noncholera vibrio, is a relative newcomer on the military scene. First isolated by Japanese workers in the 1950's, it was not recognized as a foodborne pathogen until the early 1960's. It is of some importance in that, in the few years since its recognition as a pathogen, a near global distribution has been identified. Barker (1974) cites reports of *V. parahaemolyticus* from India, Thailand, Malaysia, the Philippines, South Vietnam, Australia, Togo, Mexico, Panama, England, and the United States in a recent review from the Bureau of Epidemiology, Center for Disease Control, in Atlanta, Ga. The organism is discussed here because of the contributions of the WRAIR Medical Research Team, Vietnam, to the study of it (Neumann et al. 1972).

Incidence and Epidemiology

As part of their continuing effort to identify specific etiologic factors in patients with acute "nonspecific" gastroenteritis, the WRAIR team conducted an investigation of *V. parahaemolyticus* infection from 12 October 1970 to 3 April 1971. Rectal swabs were obtained from 965 Vietnamese gastroenteritis patients at Saigon's Cho Quan Infectious Disease Hospital and Nhi Dong Pediatric Hospital. Hospitalized U.S. servicemen were studied at the 3d Field Hospital, Saigon, and ambulatory patients, at the 299th Medical Dispensary, Tan Son Nhut. During preemployment physicals at the 218th Medical Dispensary, Saigon, 237 swabs were obtained from Vietnamese controls. In addition, cultures of seawater, sand, river water, and seafood purchased at local markets were collected from the Saigon and Cam Ranh Bay areas. *V. parahaemolyticus* was isolated from 59 of 702 Vietnamese adults with diarrhea, 1 of 263 Vietnamese children, and none of the Vietnamese control populations. Vibrios were isolated from 2 of 82 U.S. servicemen with gastroenteritis. Isolates of *V. parahaemolyticus* were obtained from fish, crabs, clams, shrimps, seawater, and sand but not from the fish or fresh water samples from the Saigon area. These results conform with the evidence accumulated in other epidemiological surveys and emphasize the halophilic nature of the organism.

Etiology and Pathogenesis

Crab, shrimp, lobster, and oysters have been incriminated in one or more outbreaks; these foods were eaten raw or cooked. In the former instance, poor refrigeration between preparation and serving allowed significant proliferation of organisms in shellfish naturally contaminated with small numbers of vibrios. When cooked foods have been implicated, either poor refrigeration or cross contamination of cooked seafood by uncooked appears to have been the cause. Crowded kitchens, the use of a common table for initial handling and subsequent

processing, and inadequate handwashing facilities for food handlers all played a role (Hooper, Barrow, and McNab 1974).

Observations suggest both bacterial invasion of the intestinal mucosa and enterotoxin production (Barker 1974, p. 553). The role of these and other mechanisms in pathogenesis is not yet resolved. While there may be serious morbidity, the mortality to date is exceedingly low.

Clinical Features, Course, and Complications

The common feature in all *V. parahemolyticus* infection is the history of recent seafood ingestion. The incubation time is typically 12 to 24 hours, though it may be as short as 2 to 4 hours or as long as 96. Inoculum size and host factors, such as gastric acidity, appear to modify the incubation time. Commonly, a cluster of cases may occur; the preparation of food for a large group predisposes to inadequate refrigeration or cross contamination (Barker 1974; Peffers et al. 1973).

The illness involves abdominal cramps, profuse watery diarrhea, nausea, vomiting, headache, fever, and chills, in decreasing order of frequency. Diarrhea, cramps, and nausea are almost universally present. The illness usually subsides spontaneously in 48 to 72 hours, though isolated cases lasting as long as 10 days have been reported (Barker 1974).

The case fatality ratio is low. In some, however, significant morbidity may occur. In a single epidemic of 12 patients who acquired their infection while aboard a chartered aircraft, 3 developed such severe dehydration and shock that *Vibrio cholerae* was initially suspected (Peffers et al. 1973).

Laboratory Diagnosis

When the organism is suspected, the most effective means of identification is direct culture on TCBS (thiosulfate, citrate, bile salts, sucrose) media. One may also use BTBST (bromothymol-blue, salt, "Teepol"). An alternate method, the technique used in Vietnam (Neumann et al. 1972), is to place the rectal swabs in Cary-Blair transport media for shipment to the laboratory. The specimen is then streaked on MacConkey's agar and Salmonella-Shigella agar as well as selenite F broth and alkaline peptone water. To this routine should be added culture on TCBS. Overnight growth produces a characteristic green, domed colony. Other biochemical tests such as fermentation provide positive identification. The Kanagawa hemolysin test has also proved extremely useful. Most human isolates are Kanagawa positive. Thus far, more than 100 serotypes have been identified.

The organism proliferates rapidly. Generation time is 12 to 15 minutes at 37°C (Peffers et al. 1973). This rate may result in profuse stool passage of the organism, but as the infection is short-lived, stool studies must be done early.

Prevention and Treatment

The best prevention is good sanitation in the kitchen or food processing area. Adequate hand washing facilities properly used are mandatory.

Specific therapy is supportive, consisting of fluid and electrolytes. Rarely, tetracycline may be necessary in an extremely severe case.

New Advances

This is the first conflict in which *V. parahemolyticus* has been recognized as a definitive enteric pathogen. Its occurrence in epidemic fashion and in strategic areas of the globe implies a potential for major military importance.

Section IV. Pathogenic *Escherichia coli* Diarrhea

Brigadier General Andre J. Ognibene, MC, USA, and Colonel Ralph F. Wells, MC, USA (Ret.)

HISTORY AND MILITARY SIGNIFICANCE

Acute nonspecific or "traveler's" diarrhea is accepted as an inherent risk in foreign travel. The syndrome is characterized by the abrupt onset of diarrhea, usually within a few weeks of arrival in an underdeveloped area, and corresponds with the less severe of the two syndromes described in the report of the AFEB (Armed Forces Epidemiological Board) Commission on Enteric Diseases discussed in chapter 15 (Gezon 1966). It is dismissed by the casual traveler with a euphemistic descriptive term—for example, "Delhi belly" or "Montezuma's revenge"—and quelled with a bit of paregoric.

The problem is far more significant in the military where the question of personal inconvenience is overshadowed by that of reduced operational effectiveness. A review of military history quickly spells out the magnitude of the problem. During World War II, the Allied experience in the Middle East implicated acute diarrheal disease as an important cause of loss of effectiveness among newly arrived troops (Hone, Keogh, and Andrew 1942; Bulmer 1944; Wirts and Tallant 1944), as did the American experience in the China-Burma-India theater. In North Africa the tide may well have been turned by the diarrheal disease which afflicted Rommel's troops (MD-PM4, pp. 319, 376). Several excellent British surveys done in recent years have defined diarrheal disease as a continuous problem in Arabia and to a lesser extent in British Guiana (now Guyana) and the Far East (Barnes and Moylan-Jones 1966).

Rowe, Taylor, and Bettelheim (1970), in a study of acute diarrhea among 540 British soldiers airlifted to Aden, were able to identify recognized enteric pathogens, such as salmonellae, in only 5.7 percent of 35 cases. In 33 cases,

pathogenic *Escherichia coli* was implicated, with positive cultures for serotype O148k?H28 in 19 of these. This corresponds with the early experience in Vietnam, where approximately 80 percent of reported diarrheal disease was short-lived and of undetermined etiology (Kalas and Bearden 1969).

INCIDENCE AND EPIDEMIOLOGY

Diarrheal disease rates for Vietnam, abstracted from Command Health Reports from January 1966 through December 1970, are shown in table 73 and in chart 25. Only rarely did the monthly rate fall below 30 cases per 1,000 strength per annum. As specific pathogens were identified infrequently, it is safe to deduce that these rates basically reflect diarrhea induced by pathogenic strains of *E. coli* or by viruses. Serotyping of *E. coli* was not available in Vietnam during these years. Cultures obtained by a WRAIR research team were subsequently studied in depth at WRAIR and the University of Maryland, providing some useful retrospective data (DuPont et al. 1971). The problem of viral enteritis had not been addressed at the time of this writing.

Despite the fact that command responsibility was spelled out in several military publications (DA-FM, pp. 5-8; AR 40-5, p. 5-2; USARV Reg, par. 4), a large number of cases of diarrheal disease were assumed to stem from breaches of sanitary discipline in base camp or support areas. The possibility of troops consuming food, drink, or ice from indigenous sources remained throughout the conflict a risk which was hard to assess.

TABLE 73.—*Monthly diarrheal disease rates, U.S. Army, Vietnam, January 1966-December 1970*
[Rate expressed as number of cases per annum per 1,000 average strength]

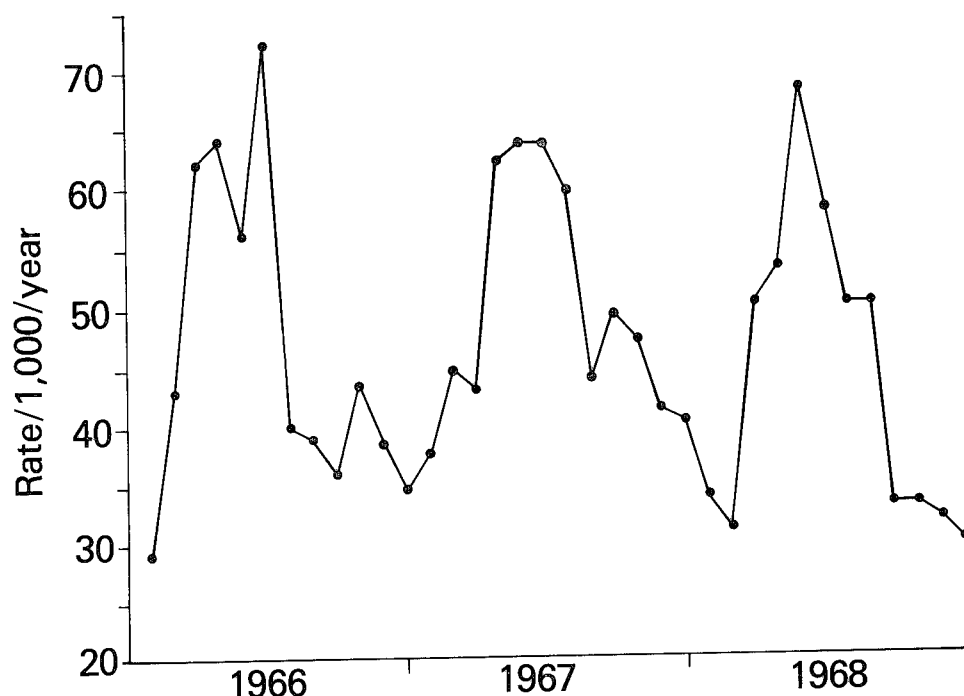
Month	1966	1967	1968	1969	1970
January	29.2	¹ 37.5	34.4	33.9	27.3
February	43.1	¹ 44.3	30.6	35.0	33.0
March	62.4	¹ 43.0	49.8	36.5	35.0
April	64.3	¹ 62.0	52.6	38.2	36.8
May	55.5	¹ 63.5	67.5	46.5	45.5
June	71.9	63.4	¹ 57.7	46.3	54.4
July	39.7	59.3	49.7	43.8	57.2
August	38.5	43.6	49.9	41.5	41.5
September	35.7	49.0	33.1	¹ 34.7	37.2
October	43.3	47.0	32.7	28.1	34.5
November	38.2	¹ 40.8	31.7	26.7	17.0
December	² 34.7	40.3	¹ 29.5	32.4	41.2

¹Figures from: Commander, U.S. Army Medical Command, Vietnam. 1969. Army Medical Department Activities Report to The Surgeon General, p. 57.

²Figure from: Office of the Surgeon General. 1967. Health of the Army, May 67, p. 11.

Source: USARV surgeons. Monthly Command Health Reports to USARV commander, 1966-1970.

CHART 25.—Monthly diarrheal disease rates, U.S. Army in Vietnam, January 1966-December 1968



Source: USARV surgeons. Monthly Command Health Reports to USARV commander, 1966-1968.

ETIOLOGY AND PATHOGENESIS

Escherichia coli strains B2C and B7A were isolated from diarrheal stools of two American soldiers in Vietnam by the WRAIR team (DuPont et al. 1971). Both men had the sigmoidoscopic appearance of acute colitis at the time of culture. The CDC (Center for Disease Control) determined strain B2C to be serotype O6:H16. The B7A strain typed by WRAIR was found to be antigenically identical to the O148:H28 strain reported by Rowe, Taylor, and Bettelheim (1970) as a cause of "traveler's diarrhea" in British troops in the Middle East.

The two strains from Vietnam produced an enterotoxin in a rabbit ileal loop; in volunteers, they caused a diarrheal syndrome resembling that of cholera. Studies to date suggest two types of enterotoxin, a heat-labile and a heat-stable toxin. An organism may produce both toxins or the stable toxin alone. Thus far, the strains pathogenic for man have been combined toxin producers (Donta et al. 1974; Gorbach 1974).

Two nontoxicogenic *E. coli* strains studied by DuPont et al. (1971) appeared to penetrate epithelial cells in laboratory models and produced a shigella-like illness in man which was characterized by dysentery, tenesmus, urgency, hyperpyrexia, and hypotension, with systemic toxemia. The organisms capable of producing a colitis-like syndrome include OK types O144:K?B, O143:K?B, O136:K78,

O124:K72, and O28a,c:K73. It is interesting that all of these types except one (O136) were found to possess somatic antigens related to one shigella serotype or another. Recently, an outbreak of invasive enteropathic *E. coli* dysentery caused by O124 serotype was reported in 28 adults (Tulloch et al. 1973).

CLINICAL FEATURES, COURSE, AND COMPLICATIONS

The clinical picture produced by the invasive *E. coli* varies with the host. In its most severe form, it includes dysentery with blood, mucus, and inflammatory cells in the diarrheal stool, tenesmus, and severe systemic toxicity. The colon appears to be the predominant site of multiplication of the organism, and the proctoscopic appearance may be indistinguishable from that of shigellosis. The disease has been studied primarily in volunteers, and in severe cases the natural course has been interrupted by therapy with ampicillin; therefore, few data are available on complications.

The effects of infection with toxigenic strains of *E. coli* also reflect significant host variability. In the Vietnam era, few documented cases of diarrhea caused by toxigenic strains were described. The spectrum of symptoms may range from a mild diarrhea lasting 2 to 5 days to a fulminant cholera-like illness with 5 to 10 watery stools per day for up to 19 days. The incubation period appears to be somewhat longer (24 to 30 hours) than for acute diarrheal syndromes (10 to 12 hours).

LABORATORY DIAGNOSIS

Because of limited laboratory capability, some selection of patients to be studied was necessary. In general, any patient with a bloody diarrhea, a temperature over 101°F, or diarrhea persisting more than 48 to 72 hours warranted study by proctoscopy, microscopic examination, and culture. A useful but underused technique was simple examination of a rectal swab stained with methylene blue for the presence of leukocytes. Details of the technique have recently been reviewed by Harris, DuPont, and Hornick (1972). The fecal leukocyte study could be prepared at the same time as rectal scrapings were screened for the trophozoites of *E. histolytica*.

Thomas (1969), at the 9th Medical Laboratory, reviewed the types of media used for the identification of enteric pathogens. These fell into three categories: differential media (such as eosin-methylene blue), differential-selective media (such as Salmonella-Shigella agar), and enrichment media. Unfortunately, toxigenic *E. coli* are indistinguishable from "normal flora" by such conventional tests. Demonstration of pathogenicity relies on a highly complex serotyping procedure; on the production of diarrhea or toxicity in a laboratory animal or model such as the guinea pig eye model (Sereny test) or rabbit ileal loop (DuPont et al. 1971); or on the demonstration of toxin effect on adrenal cell culture, as described by Donta et al. (1974). Most of these techniques were too complex for use even by the 9th Medical Laboratory and were clearly beyond the capability of other laboratories in-country, thus rendering the diagnosis one of exclusion.

PREVENTION AND TREATMENT

Prevention rests on the exercise of good sanitary discipline, an often unattainable goal under field conditions. Nevertheless, since the most significant outbreaks in Vietnam occurred in base camp situations, a responsible attitude by both command and medical staff is essential. There is an urgent need for the development of a vaccine, but in the interim proper sanitation and adequate nutrition are the key preventive measures.

Rehydration and symptomatic relief remain the basis of rational therapy. The use of balanced electrolyte solutions and glucose orally, as in cholera, may reduce or eliminate the requirement for parenteral fluids. Although antibiotics have been used to terminate apparently severe infection with invasive strains of *E. coli* in volunteers experimentally infected, there is little evidence for their efficacy and they should not be used routinely. There is no role for mass oral antibiotic prophylaxis or for the use of furazolidone or sulfonamide preparations.

NEW ADVANCES AND LESSONS LEARNED

Perhaps the key lesson learned was the definition and distinction of the two clinical syndromes related to pathogenic *E. coli*. The studies with the toxigenic strains of *E. coli* and cholera did much to clarify the mechanism for transport of fluid, glucose, and electrolytes across the small bowel mucosa and have provided a rational basis for symptomatic therapy. The recognition of a dysenteric phase places an even greater responsibility on the physician to correctly identify the patient with massive fluid loss.

In a study of the clinical records of 2,050 admissions to the 3d Platoon, 568th Medical Company (Clearing) between November 1966 and October 1967, Scott, Ardison, and Wells (1967) demonstrated a lack of correlation between acute diarrheal disease and urolithiasis, in contrast to the situation in the diarrhea of chronic inflammatory bowel disease.

McCloy and Hofmann (1970) investigated the possibility that tropical diarrhea might be bile-salt induced. In a clinical trial conducted at the 8th Field Hospital, Nha Trang, 31 patients were studied, who were receiving either 4 g of cholestyramine, a bile sequestering resin, four times a day for 4 consecutive days, or a placebo on a similar schedule. A majority of the patients still had diarrhea at the end of the 4-day study period. There was no significant difference of any sort between the treated and placebo groups.

Much remains to be learned about diarrhea in troops. From what little is known, less than half the cases can be attributed to a specific agent. To fully comprehend the problem, it is crucial to determine the days lost from duty in cases of known and unknown etiology. Attention should be focused on controlling and treating those disorders of most significance. Statistical reporting methods must be modified to accept this new information and methodology established to provide it. The reporting of various types of "diarrheal disease" as a single entity is imprecise; further definition is required for future reporting systems.

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Amebiasis and Other Parasitic Diseases

Brigadier General Andre J. Ognibene, MC, USA, Colonel Ralph F. Wells, MC, USA (Ret.), and Colonel O'Neill Barrett, Jr., MC, USA (Ret.)

Section I. Amebiasis

Brigadier General Andre J. Ognibene, MC, USA, and Colonel Ralph F. Wells, MC, USA (Ret.)

HISTORY AND MILITARY SIGNIFICANCE

Amebiasis was unrecognized as a clinical entity among U.S. forces until the Philippine Insurrection. Although the British experienced significant amebic disease in the Gallipoli campaign (MD-PM4, p. 485), reporting in U.S. troops during World War I was limited: in a laboratory survey of 934 cases of dysentery, only 38 specimens were positive for amebas (MD-WW6, p. 1101). With increased awareness, reporting of amebic diseases changed radically during World War II.

Official estimates are that approximately 1,261,000 man-days were lost because of diagnosed cases of amebiasis in the United States Armed Forces during World War II (TB MED). Amebic dysentery admission rates per 1,000 per annum for 1944-45 were 22.39 in the China-Burma-India theater (8,734 admissions), 5.63 in the Southwest Pacific (8,865 admissions), and 2.94 in the Central and South Pacific (2,393 admissions) (MD-PM4, p. 488). The admission rate of persons who were incidentally discovered to be asymptomatic carriers roughly paralleled that of persons with overt colitis in each of the above theaters. The crucial questions of actual carrier rate and prevalence of amebiasis in the indigenous populations were never answered.

Initial awareness of the disease in the United States was prompted by Giffin's report (1913) which noted a 4.6-percent incidence of carriers in a series of studies at the Mayo Clinic. More recent estimates also indicate an average carrier rate of 5 percent (Brooke 1964).

The Chicago epidemic of 1933 demonstrated the importance of contaminated water as a source of infection (NIH Bull). Subsequent studies of water purification showed that cysts of *Entamoeba histolytica* are more resistant to chlorination than are fecal bacteria (Chang and Fair 1941).

The adverse environmental conditions under which military operations are conducted can reasonably be expected to increase the incidence of amebiasis.

Large numbers of servicemen were exposed to infection abroad during World War I, World War II, and the Korean war. Public health authorities feared that returning infected troops would cause an increase in the incidence of disease in the United States (Juniper 1971). Studies on persons returning from combat theaters, however, failed to substantiate such fears (Brooke, Donaldson, and Brown 1954).

Precise data on the incidence of extra-intestinal manifestations of amebiasis were not generated during World War II, although concern about amebic abscess led to the definitive work of Klatskin and Friedman (1948) on abscess and specific emetine therapy. Conan (1948) and Murgatroyd and Kent (1948) independently reported on the effectiveness of chloroquine in the treatment of extra-intestinal amebiasis. The next major breakthrough in the treatment of hepatic abscess was use of metronidazole, introduced by Powell and coworkers (1966). While this drug was not approved by the Food and Drug Administration until the 1970's, its effectiveness against both the intraluminal and tissue phases of the disease resulted in its use by many U.S. military physicians during the peak years of the Vietnam conflict (Everett 1974).

INCIDENCE AND EPIDEMIOLOGY

It is almost axiomatic that amebiasis is a worldwide problem with its most frequent clinical expression in the Tropics and decreasing frequency of occurrence in more temperate climates. In the Tropics, *E. histolytica* vies with shigellosis as the major cause of diagnosed dysentery while in temperate climates shigellosis is more prevalent. A report by Elsdon-Dew (1968) delineates global trends from 1946 to 1956 and will be of interest to readers desiring more specific epidemiological information.

All epidemiological data concerning the incidence of amebic disease must be relatively suspect since the data reported to any central agency, such as the World Health Organization, are no more accurate than the observations of the physician or parasitologist involved with the individual patient. The Armed Forces Epidemiological Board report (Gezon 1966) focuses specifically on this problem as it applied to experience in Vietnam. The problem is further complicated by the detection of quadrinucleate cysts of nonpathogenic amebas in the stool which may be erroneously reported as *E. histolytica*.

ETIOLOGY AND PATHOGENESIS

"Amebiasis" generally refers to a whole spectrum of diseases in which an ameba with tissue-invading capability, usually *E. histolytica*, colonizes a tissue, producing necrosis and abscess formation. In its most benign form, the infection may be clinically inapparent and will be recognized only because the patient is shedding cysts in his stool. Clinically apparent amebiasis is usually manifested by diarrhea with or without gross bleeding. Less commonly, the ameba may produce a variety of clinical syndromes including single or multiple hepatic abscesses, ameboma of the colon, acute appendicitis, and fistulas to the biliary

tract, lung or pericardium, or even to the skin. Rarely, central nervous system involvement may occur. Dietschy (1974) reviewed the subject of amebiasis in depth, and this section draws extensively on his review.

All amebas belong to the phylum Protozoa, the class Rhizopoda, and the order Amoebida. Characteristically these organisms do not contain a cell wall and generally form pseudopodia by alternately shifting the cytosol from a gel to a sol phase. The order Amoebida may be divided further into those organisms which are principally free-living and those which are strictly parasitic.

The various genera of the family Endamoebidae generally are differentiated in terms of their morphologic characteristics, in particular the morphology of the nucleus on stained specimens. Several species of Endamoebidae occur in man, including *Entamoeba histolytica*, *Entamoeba coli*, *Entamoeba gingivalis*, *Entamoeba polecki*, *Endolimax nana*, *Iodamoeba buetschlii*, and *Dientamoeba fragilis*. All are lumen dwellers except *E. gingivalis*, and almost all except *E. histolytica* lack the ability to invade tissue.

All of the parasitic amebas have a similar life cycle, which begins for the host with the ingestion of the cyst. Little happens to the ingested cyst in the acid milieu of the stomach, but on entering the alkaline environment of the duodenum, dissolution of the cell wall and excystation follow. As a rule, the cytosol fragments into as many pieces as there are nuclei. The resulting structure is a metacystic trophozoite, which does not colonize the small intestine but passes rapidly to the colon. In the nonpathological strains, trophozoites phagocytize bacteria and other nutrients from the colonic contents. Under special circumstances, probably related to the bacterial flora of the gut, the trophozoite of *E. histolytica* is also capable of tissue invasion and active phagocytosis of cell components after dissolution of the cell membrane. In all species, the trophozoites reproduce within the luminal contents or colonic crypts by binary fission. The mature trophozoites are excreted in the stool only when a liquid or diarrheal stool is passed. During the process of solid stool formation, encystation occurs. As this occurs, the trophozoite undergoes loss of cytoplasmic vacuoles and condensation of the cytosol and cell membrane. In some species the nucleus reduplicates, so that cysts of *E. histolytica* in the precyst phase may form one, two, or four nuclei. The mature cyst is then excreted in the feces and enters the environment where it may persist for extended periods until ingested by another host (Hunter, Frye, and Swartzwelder 1966, pp. 269-308).

E. coli has a large trophozoite form, 20 to 30 μ in diameter, but its unique feature is a mature cyst usually containing eight nuclei. It may coexist with *E. histolytica*. It is a nonpathogen, and its chief importance is as an indicator of ingestion of fecally contaminated food. *E. gingivalis* is a parasite of the human mouth and is transmitted by direct oral contact or by droplet dissemination. *E. polecki* inhabits the colon of the monkey and the pig. One case of human disease, in a Peace Corps worker, has been reported (Levin and Armstrong 1970).

E. moshkovskii has been found in sewage containing human feces. Its pathogenicity is unknown. *End. nana* is a nonpathogen, although it may be occasionally detected in diarrheal stools. *I. buetschlii* may rarely cause tissue invasion with colitis or dissemination to the lung or brain while *D. fragilis* may cause

nonspecific mucosal irritation, hypermotility, abdominal pain, and diarrhea.

While the pathogenicity of the above organisms is still undecided, there is little doubt that in man the vast majority of clinical disease is produced by *E. histolytica* because of its capacity for aggressive tissue invasion (fig. 71). However, it has become apparent in recent years that the conventional morphologic criteria for the identification of *E. histolytica* cysts are totally inadequate. Variation in cyst size is recognized; a large race and a small race have been identified (Hunter, Frye, and Swartzwelder 1966, p. 276). The small race is now classified as *E. hartmanni* and is of questionable pathogenicity.

Recent work (Goldman 1969) has demonstrated that even the group of amebas designated as large race *E. histolytica* are not homogenous. The Laredo type (Laredo, Huff, 403, Nelson's, AG, and JA strains) has vastly different physical, cultural, and biochemical characteristics from pathogenic *E. histolytica*. The Laredo type can survive temperatures of 0° to 41° C, will grow in culture at temperatures as low as 10° C, and will survive in hypotonic media at a dilution of 1:64, as opposed to *E. histolytica*, which has a survival range of 20° to 43° C, a minimum temperature for growth in culture of approximately 30° C, and can survive only a 1:2 media dilution. The Laredo type will infect man but produces no disease; this is fortunate as it is consistently quite resistant to most antiamebic drugs. *E. moshkovskii* is another large strain nonpathogen which has the capacity to survive in low temperatures and in markedly hypotonic incubation media. These strains—the Laredo type and *E. moshkovskii*—are mentioned only because of the possibility that asymptomatic carriers may not in fact be infected with *E. histolytica* but rather with one of these morphologically indistinguishable quadrinucleate strains analogous to the carrier state for *E. coli*.

The precise mechanism by which trophozoites attack and invade tissues is unknown (fig. 72). The notion that a toxic substance produced by the amebas lyses normal cells, thus initiating invasion, might well be challenged on the basis of research on the pathogenesis of the disease. In cell cultures, the amebas are surrounded by lysed cells while more distant cells remain healthy. Phase microscopy and electron microscopy have been employed to study what happens. In all cultures when a cell comes in contact with the plasmalemma of the amebas, there is an immediate change in the characteristics of the cell membrane. Cell organelles become more prominent, the cell shrinks, and soon blebs of cytosol extrude from the portion of the cell in contact with the amebas. The amebas then begin to engulf the damaged cell either piecemeal or entirely. The mechanism of the contact lysis has been studied by electron microscopy. The amebas have a "fuzzy layer" representing surface lysosomes. This fuzzy layer has numerous shallow depressions, in the center of which is found a tubular projection or "trigger." This trigger comes in contact with the cell under attack. When contact is made, the trigger ruptures, emitting a toxin (hydrolytic enzymes?) capable of dissolving the limiting membrane of the target cell. Phagocytosis then progresses by an unknown mechanism. To date, there are no comparative data on the presence or absence of the surface lysosomes in pathogenic versus non-pathogenic organisms. Clarification of this process remains a major challenge.

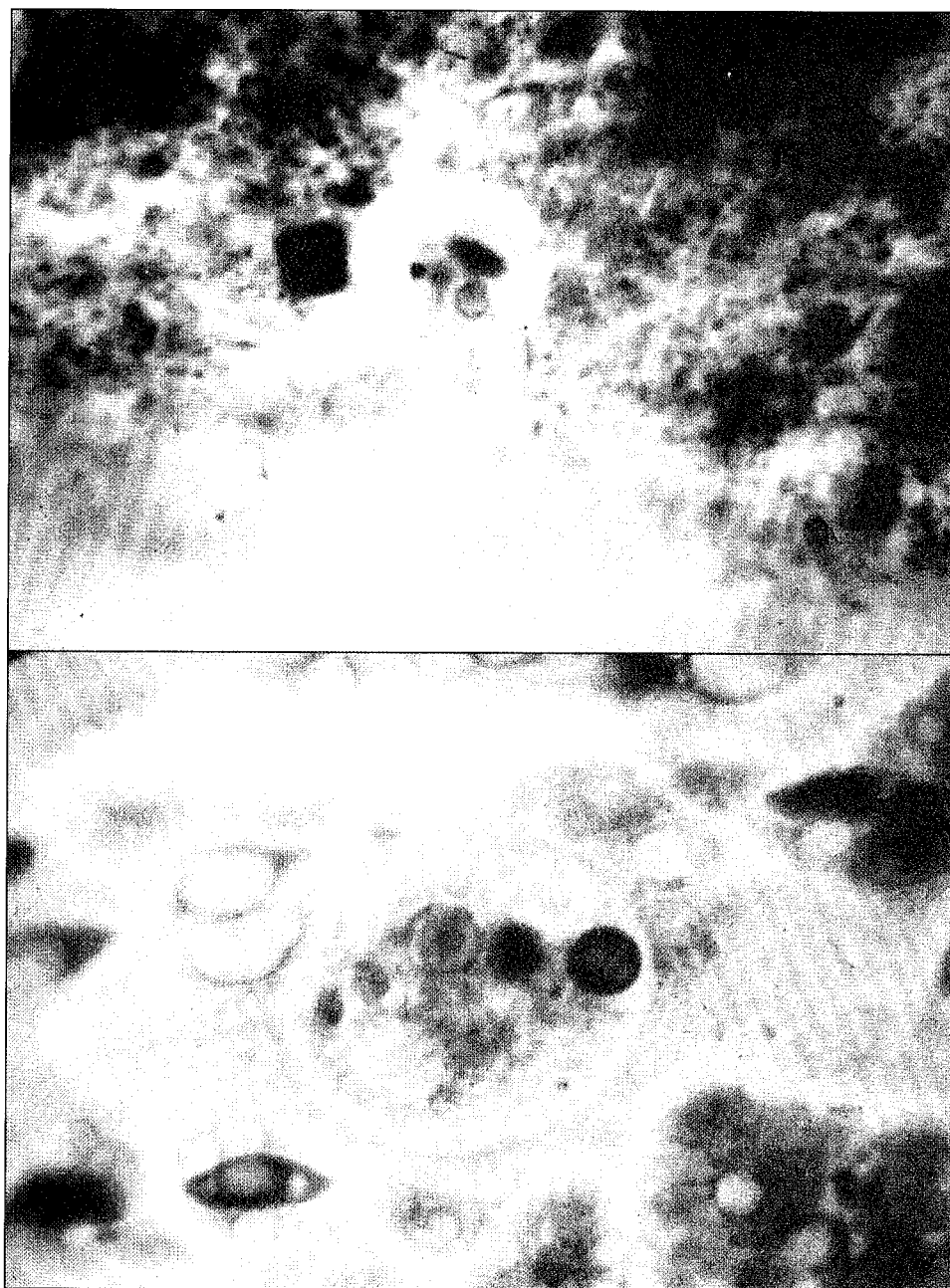


FIGURE 71.—*Entamoeba histolytica* (top) in stool sample, low power magnification, and (bottom) with ingested red cell, high power magnification.

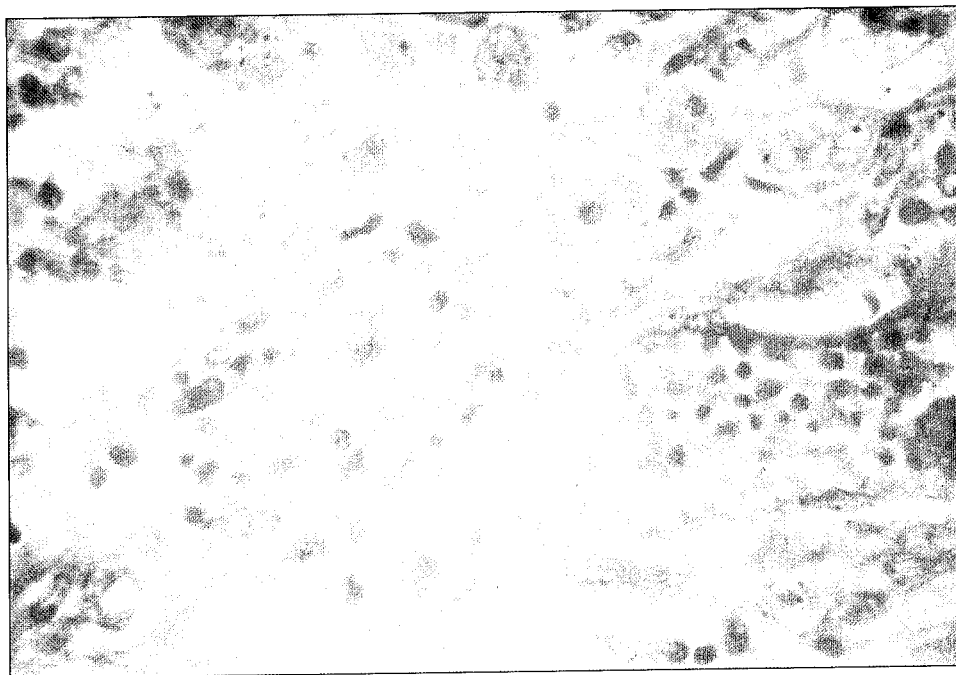


FIGURE 72.—Trophozoites of *Entamoeba histolytica* invading intestinal wall.

CLINICAL FEATURES, COURSE, AND COMPLICATIONS

The colon is the primary target organ for infection with *E. histolytica*. The subsequent clinical course is contingent upon the degree of invasiveness of the parasite in that organ. While clinical amebiasis is usually characterized by a diarrheal syndrome, the spectrum of severity ranges from the asymptomatic cyst passer to the patient with extra-colonic invasion either by contiguous spread or hematogenous dissemination. Hepatic involvement with abscess formation is most common in the latter situation. For example, direct spread by fistula formation may occur from the liver to the pleural or peritoneal cavities, the tracheobronchial tree, the pericardium, the biliary tract, or the skin, while hematogenous spread may lead to amebic abscesses in the lung parenchyma, brain, spleen, or kidneys.

The Asymptomatic Cyst Passer

Many asymptomatic individuals have cysts of *E. histolytica* in their stools. It is not known whether this is a function of the host or a characteristic of the parasite itself. The roles of gut flora and diet have been studied extensively without achieving a definitive explanation. The majority of persons in this category are detected by population surveys or during the course of epidemiological studies. Some authors would classify patients with "irritable

colon" symptoms and cysts in their stools as asymptomatic cyst passers if proctoscopy proved normal and trophozoites were absent (Curtis and Sleisenger 1973, pp. 1388-89; Hunter, Frye, and Swartzwelder 1966, p. 295).

Amebic Colitis

Clinical presentation of patients with amebic dysentery may run the gamut from a mild diarrheal disease to a fulminant process with severe systemic toxicity. Whatever the mechanism triggering tissue invasion, the process precedes the onset of clinical symptoms. The initial lesion seen at proctoscopy consists of a pinhead-size ulcer with hyperemic margins reaching only the muscularis mucosa. In some patients a more extensive superficial erosion is seen. This is followed by enlargement and penetration with an "inverted tack" appearance and overhanging edges. Aspirates, scrapings, or biopsy of these lesions will show numerous trophozoites. In many cases, the mucosa may be diffusely involved, mimicking nonspecific ulcerative colitis. The P.M.N. (polymorphonuclear neutrophil leukocyte) response is relatively less than one would expect and there is a corresponding reduction of P.M.N.'s on the fecal leukocyte smear.

Most primary intestinal lesions occur in the colon except for approximately 5 percent which occur in the lower ileum near the ileocecal valve. The ulcerations seem to be most common in the cecum, ascending colon, and the sigmoidorectal region. Sixty-one percent of patients will have multiple lesions scattered throughout the colon (Belding 1965, p. 65).

The process may be acute with severe bloody diarrhea, volume depletion, and occasional local complications such as amebic appendicitis, perforation with pericolic abscess, or "toxic megacolon" clinically indistinguishable from ulcerative colitis. Other complications include ameboma or granuloma formation and strictures. It is particularly important that ameboma be distinguished from carcinoma to avoid unnecessary radical surgery. Colitis must be distinguished from idiopathic ulcerative colitis to preclude steroid therapy; this can be done by demonstration of invasive trophozoites. Some patients may experience a chronic colitis in which a persistent nonbloody diarrhea may occur.

The therapy of acute amebic colitis was a source of confusion for the U.S. physician in Vietnam because of misleading claims about the efficacy of various regimens and because the need to address all possible sites (bowel lumen, intestinal wall, and liver) was overlooked. Powell (1971) summarized the action of available amebicides (table 74). Emetine was 30 to 50 percent effective, tetracycline 97 percent, and chloroquine 10 percent. At the beginning of the Vietnam war, most physicians were using a combination of all three drugs to achieve a complete therapeutic success, especially in severe cases. Soon after arriving in Vietnam, however, physicians questioned this therapeutic approach.

Carlin and Martin (1970) addressed the lack of uniformity in therapy and the question of whether chloroquine and/or emetine were needed in all cases. They were prompted by the report of Powell and coworkers (1966) on the efficacy of metronidazole to study its use in U.S. troops. Of 25 soldiers with amebic dysentery, almost all showed improvement within hours after their first dose of

TABLE 74.—*Site of action of amebicides used for acute amebic colitis in Vietnam*

Amebicide	Lumen	Bowel wall	Liver
Emetine HCl	—	+	+
Oral tetracycline	+	+	—
Chloroquine	—	—	+

Source: Powell, S. J. 1971. Therapy of amebiasis. *Bull. New York Acad. Med.* 47: 469-77.

the drug, given 750 mg three times daily. By the fifth day, 50 percent could be discharged as asymptomatic; by the tenth day this figure had increased to 92 percent. Temperatures normalized and pain in the right upper quadrant decreased promptly in eight patients with suspected liver abscess; all became ambulatory by the seventh day and were transferred to Japan for hepatic scanning. Followup on four of these patients confirmed abscess, with subsequent resolution in three. The patient with a negative scan had presented with a flank mass, positive stool examination, and abnormal SGOT (serum glutamic-oxaloacetic transaminase) and BSP (Bromsulphalein). He was scanned 2 weeks later and had no evidence of abscess.

This study further emphasized the importance of early sigmoidoscopy and direct examination of rectal mucus by the physician. Of the study patients, 75 percent were diagnosed on admission by meticulous and direct examination of sigmoidoscopically collected material.

In the patient with an active colitis, one of the most definitive diagnostic procedures is the demonstration of motile trophozoites with ingested red blood cells in the liquid or diarrheal stool. Even more productive is the examination of wet preparation obtained at proctosigmoidoscopy by aspiration or scraping of ulcers. Iron hematoxylin staining will increase the yield of positive findings (Curtis and Sleisenger 1973, pp. 1388-89). When immediate laboratory support is not available, use of PVA (polyvinyl alcohol) as a slide fixative or as a preservative mixed with equal parts of stool will facilitate the task of the diagnostic laboratory. Schaudinn's fixative is another useful vehicle allowing subsequent staining of a thin smear immersed in the solution. Rectal biopsy is a useful adjunct depending on available laboratory support.

Equipment and technical support to provide the necessary diagnostic capability were not available at the unit level in Vietnam; consequently, diagnosis of amebiasis was difficult in division-level medical service. Patients with diarrheal syndromes persisting beyond 48 hours, with accompanying fever or bloody diarrhea, required evacuation to a hospital facility for definitive study. Unsupervised antibiotic administration served only to hamper further diagnostic efforts and was discouraged.

Local Complications From Amebic Colitis

Acute perforation of the colon occurs in 1.5 percent of all cases, and in 4 to 19 percent of fatal cases. Autopsy incidence of perforation and peritonitis ranges from 29 to 74 percent (Belding 1965, p. 67). Perforation with pericolic abscess is

shown in figure 73. Perforations are most common in the cecum and rectosigmoid area, and multiple perforations are frequent. Abdominal distention, fever, and ascites are associated with perforation. Diagnostic paracentesis may demonstrate trophozoites.

Amebic appendicitis is indistinguishable from conventional appendicitis. The differential diagnosis in a young soldier in Vietnam often posed significant difficulty. The only clue may be a prior history of diarrheal disease. If appropriate chemotherapy is not initiated, a fecal fistula, cutaneous amebiasis, or intra-abdominal abscess may occur. Patients may go on to develop mixed amebic and pyogenic abscesses of the liver with a cutaneous-hepatic-biliary fistula.

There may also be primary cutaneous involvement or involvement of the female genital tract. These problems were rarely seen among U.S. personnel in Vietnam.

Amebic Abscess of the Liver

Amebic liver abscess is the most serious complication of amebiasis and, if unrecognized, causes considerable mortality (fig. 74). The diagnosis may be difficult because of the absence of a history of diarrhea and/or the inordinate delay between exposure and clinical presentation. Eighty to 85 percent of abscesses occur in the right lobe. Right upper quadrant pain, fever, chills, and weight loss are common features. Occasionally there may be point tenderness over the liver. Less commonly, the patient may present with a pleural effusion or cough or, in a left lobe abscess, with pericardial involvement. Jaundice is rarely seen. Stool studies are frequently negative, and the diagnosis is based on clinical assessment, liver scan, serologic testing, or, in some circumstances, diagnostic aspiration. Approximately 85 percent of patients will have radiographic abnormality on chest X-ray, including elevated right hemidiaphragm, loss of motility of the diaphragm, blunting of the costophrenic angle, atelectasis, and pleural effusion (Belding 1965, pp. 81-82).

Radioisotope capability was never established in Vietnam, although two significant studies of liver abscess were conducted on Vietnam returnees, one in Japan and one at Walter Reed Army Medical Center. The latter (Sheehy et al. 1968) documented the resolution time as determined by serial liver scans. A defect persisted an average of 4.3 months. Rarely a "cold spot" was demonstrable as long as 1 year after "definitive" treatment (fig. 75). In our opinion, persistent pain after abscess treatment was caused by either an incompletely resolved abscess or adhesions between Glisson's capsule and the parietal peritoneum analogous to the Fitz-Hugh—Curtis syndrome seen after gonorrhea infection.

The Japan study (Levin 1969) summarized experience, from 15 July 1968 to 3 April 1969, with 42 patients with hepatic abscess who were evacuated to Camp Zama. The presenting complaints of 31 of the patients were as follows:

Fever.....	13	Anorexia.....	2
Right upper quadrant abdominal pain.....	10	Right shoulder pain.....	1
Diarrhea.....	5		



FIGURE 73.—Anteroposterior (left) and lateral (right) films of the abdomen demonstrating a large pericolic abscess of the ascending colon resulting from invasive amebiasis with local perforation.

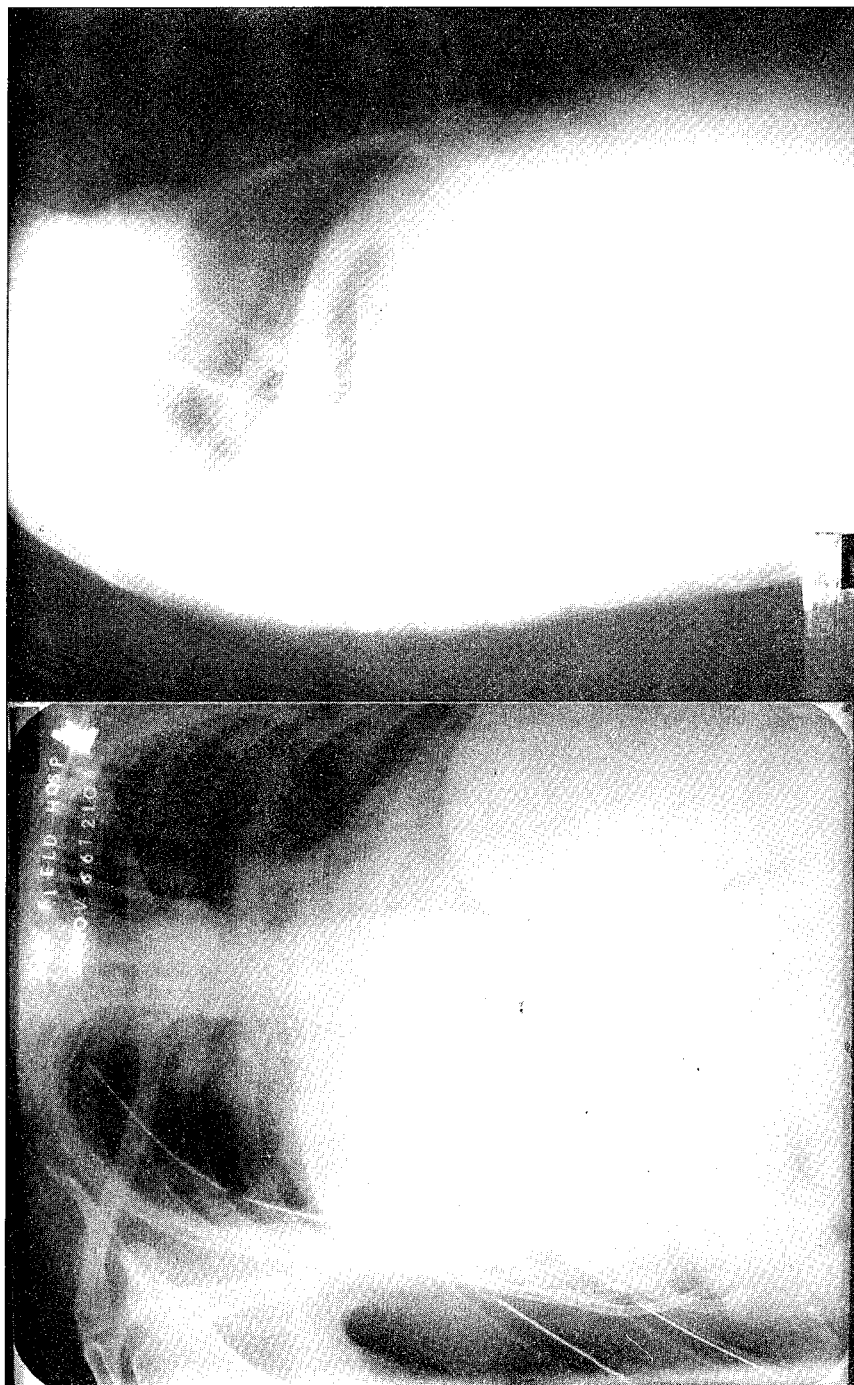


FIGURE 74.—Left: Anteroposterior film of chest and upper abdomen demonstrating elevated right hemidiaphragm with chest and subdiaphragmatic drainage tubes in place. Patient had perforation of diaphragm by amebic abscess. Right: Lateral view of the chest showing subdiaphragmatic abscesses with fluid levels.

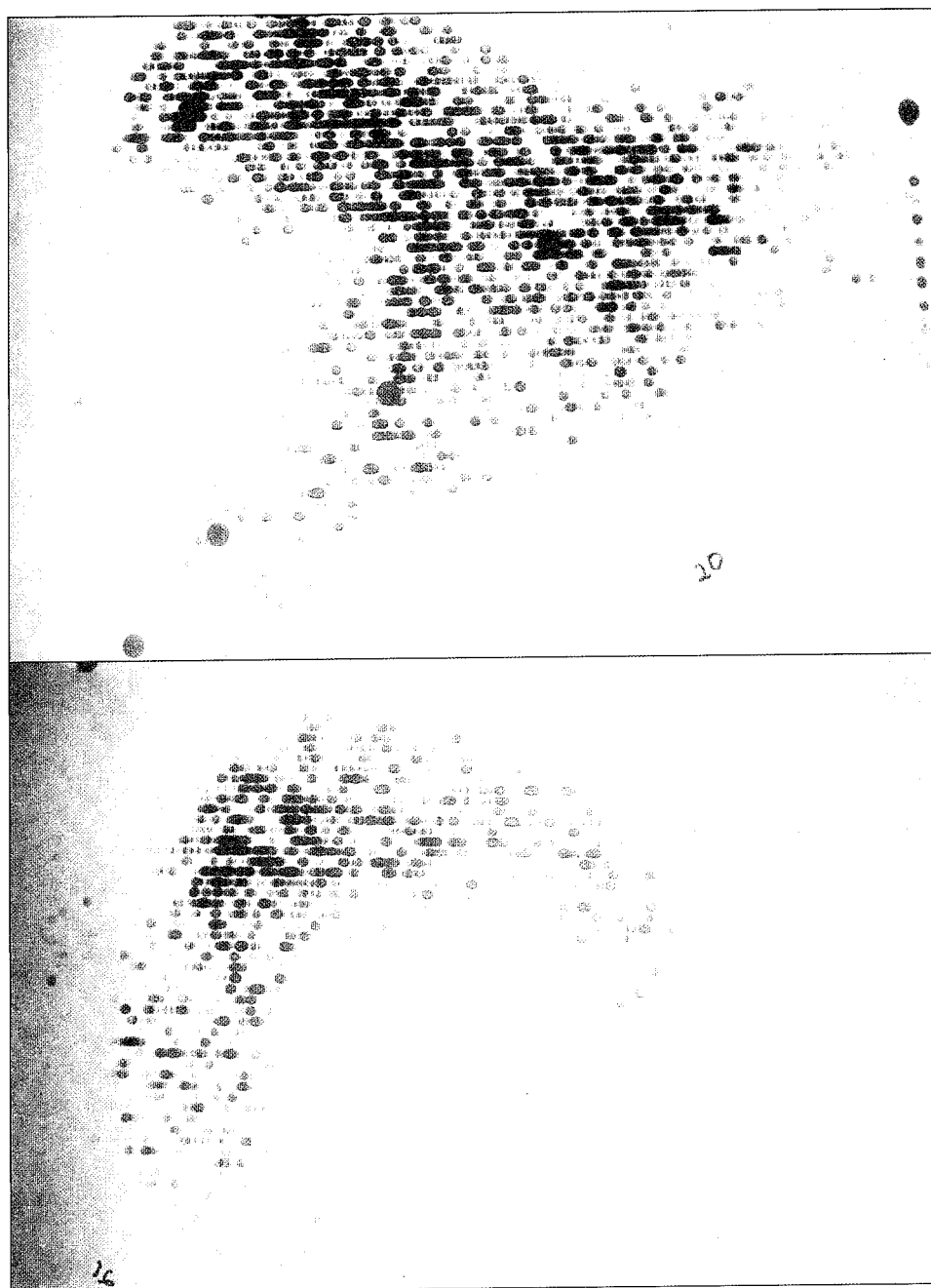


FIGURE 75.—Anterior (top) and right lateral (bottom) views of the liver using colloidal gold scanning at Camp Zama, Japan. Note the large defect in right lobe in both views.

The clinical findings are shown in table 75. The triad of fever, anorexia, and weight loss was almost universal, with right upper quadrant pain characteristically adding to the presentation. Laboratory findings are given in table 76. Leukocytosis and an abnormal prothrombin time were almost always present. Massive hepatomegaly was unusual (table 77). More than half the patients had minimal hepatic enlargement or normal size livers upon physical examination.

There were 52 abscesses identified in the 42 patients, located as follows (lobe was not determined in two cases; abscess was seen only on the lateral view):

Lobe (right).....	47	Inferior third of liver.....	16
Lobe (left).....	2	Anterior (lateral scan).....	20
Lobe (right and left).....	1	Central (lateral scan).....	10
Superior third of liver.....	27	Posterior (lateral scan).....	22
Mid third of liver.....	9		

The estimated sizes of the 52 abscesses were as follows:

17-150 cm ³	23	451-600 cm ³	3
151-300 cm ³	11	Over 601 cm ³	4
301-450 cm ³	6		

The four largest abscesses measured 746, 1,028, 1,540, and 1,690 cm³. Five abscesses were not visualized on the anterior view, and therefore were measured in cm².

Of the 42 patients, 6 required needle aspiration or surgical drainage because of failure to respond to drug therapy or because of increase in abscess size. All patients were treated with emetine, chloroquine, Diodoquin, and tetracycline. After April 1969, metronidazole was used extensively; however, definitive analysis of its effectiveness in hepatic abscess was incomplete at the time of cessation of hostilities.

Everett (1974) did review 12 patients with amebic liver abscesses acquired in Vietnam who were treated solely with metronidazole. Neither duration of illness nor size of the abscess had predictable correlation with response to therapy or healing rate. Metronidazole in doses of 750 mg three times a day for 10 days was effective in this series.

Serodiagnosis

A number of serologic techniques have been used in the past for diagnosis when stools were negative or other laboratory support questionable. During the

TABLE 75.—*Clinical findings in 42 patients with amebic liver abscess, Camp Zama, Japan, 15 July 1968-3 April 1969*

Finding	Total number reported ¹	Positive findings (percent)
Anorexia	32/32	100
Weight loss	37/37	100
Fever	40/41	97
Night sweats	18/24	75
Nausea and/or vomiting	11/15	73
Chills	24/34	70
Diarrhea	25/37	67
Diarrhea with blood	13/25	52
Pain: ²		
Abdomen, right upper quadrant	38/41	92
Right chest	21/41	51
Right shoulder	17/41	41
Back	12/41	29

¹Affirmative answers/patients questioned.²Pain also occurred in various combinations of the four sites noted.Source: Levin, R. M. 1969. Amebic liver abscesses. Preliminary report. *USARV M. Bull.* (USARV Pam 40-15), May-Jun, pp. 14-29.TABLE 76.—*Laboratory findings in 42 patients with amebic liver abscess, Camp Zama, Japan, 15 July 1968-3 April 1969*

Finding	Total number reported ¹	Abnormal (percent)
Leukocytosis (over 10,000 mm ³)	34/38	89
Prothrombin time elevated	12/15	80
Bromsulphalein retention elevated	9/12	75
Anemia (hematocrit under 40)	28/39	71
Alkaline phosphatase elevated	23/39	59
Serum glutamic-oxaloacetic transaminase elevated	14/39	36
Total bilirubin elevated	7/36	19
Stool (positive examination for <i>Entamoeba histolytica</i>)	8/30	26
X-ray:		
Elevated right hemidiaphragm	21/36	58
Right pleural effusion	12/35	34

¹Positive findings/patients studied.Source: Levin, R. M. 1969. Amebic liver abscesses. Preliminary report. *USARV M. Bull.* (USARV Pam 40-15), May-June, pp. 14-29.

Vietnam conflict, the Moan precipitin test became obsolete and was replaced by several new techniques. The IHA (indirect hemagglutination) test introduced by Lewis and Kessel (1961) and standardized by Milgram, Healy, and Kagan (1966) more closely approaches a definitive serologic test for amebiasis than any other previously available. A positive IHA response is seen in 85 to 96 percent of patients with hepatic amebiasis (100 percent positivity has been found in some small series) and in 82 to 95 percent of patients with invasive colonic disease (Juniper et al. 1972; Milgram, Healy, and Kagan 1966; Kessel et al. 1965). About 1 percent false positive reaction may be detected in the general population. The

TABLE 77.—*Estimated liver size on first hepatoscan in 42 patients with amebic liver abscess, Camp Zama, Japan, 15 July 1968-3 April 1969*

Liver size	Patients	
	Number	Percent
Normal	11	26
Mild hepatomegaly	16	38
Moderate hepatomegaly	13	31
Marked hepatomegaly	2	5

Source: Levin, R. M. 1969. Amebic liver abscesses. Preliminary report. *USARV M. Bull.* (USARV Pam 40-14), May-June, pp. 14-29.

two major drawbacks of the IHA are the lack of general availability and persistent positivity in treated patients. The test, however, was not available in Vietnam and was available in the continental United States only through the Center for Disease Control. As a result, it served only to confirm a diagnosis made by other means.

A combination of microimmunoelectrophoresis pattern analysis and IHA titer level used in a South African study (Krupp and Powell 1971) has helped to provide differentiation between active infection and persistent antibody positivity after treatment. There was little U.S. experience with this combination of techniques. The SAFA (soluble antigen fluorescent antibody) test devised by Sadun was readily available to military physicians, and recently a reliable latex fixation test kit yielding results similar to the IHA has become available. The CF (complement fixation) test at titers of 1:16 or above strongly suggests active disease and is useful in assessing the clinical significance of the positive IHA or latex fixation (Healy and Cahill 1971). In Vietnam, however, serological tests did not replace skilled clinical judgment and therapy could not await serological confirmation.

Treatment

Appropriate guidelines for the management of various types of *E. histolytica* infections were reported toward the close of the Vietnam conflict in *The Medical Letter* (table 78). Metronidazole was established as the drug of choice for both intraluminal and extraluminal amebiasis. As mentioned earlier, some controversy surrounded the treatment of amebiasis during the Vietnam war because many physicians wished to use this drug rather than conventional chemotherapeutic regimens although it was not yet FDA-approved for such therapy. The drug was used in Vietnam for amebiasis and giardiasis, but results of its efficacy were not extensively tabulated.

While a number of advances were made in the study of amebiasis, the only one to have a significant impact in Vietnam per se was the use of metronidazole. Neither nuclear medicine capability nor contemporary serodiagnostic methods were ever available there. In future conflicts in a tropical area, nuclear medicine capability and clinical laboratory support must be made readily available to preclude either unnecessary evacuation of personnel or delay in diagnosis.

TABLE 78.—Treatment schedule for amebic disorders caused by *Entamoeba histolytica*

Type of infection	Drug of choice	Adult dose	Alternative drugs	Adult dose
Asymptomatic cyst passer.	Diiodohydroxyquin	650 mg. t.i.d. for 20 days.	Metronidazole	750 mg t.i.d. for 5-10 days.
Mild to moderate intestinal disease.	Metronidazole	750 mg t.i.d. for 5-10 days.	A tetracycline <i>plus</i> diiodohydroxyquin.	250 mg q.i.d. for 5 days. 650 mg t.i.d. for 20 days.
Severe intestinal disease.	Metronidazole	750 mg t.i.d. for 5-10 days.	Dehydroemetine <i>or</i> emetine <i>plus</i> a tetracycline followed by diiodohydroxyquin.	1 to 1.5 mg/kg daily IM or subcutaneously for up to 5 days. 250 mg q.i.d. for 5 days. 650 mg t.i.d. for 20 days.
Hepatic abscess	Metronidazole	750 mg t.i.d. for 5-10 days.	Dehydroemetine <i>or</i> emetine <i>plus</i> chloroquine phosphate.	1 to 1.5 mg/kg daily IM or subcutaneously for up to 5 days. 1 g daily for 2 days, then 500 mg daily for 2 to 3 weeks.

Source: *The Medical Letter* 16: 5-12, Jan. 18, 1974.

Section II. Other Parasitic Diseases

Colonel O'Neill Barrett, Jr., MC, USA (Ret.)

INCIDENCE

Although a variety of parasites infested the Vietnamese civilian population, they were not a significant problem for American troops. Stool examinations of 235 civilians surveyed in Binh Duc village of Dinh Tuong Province in the Mekong Delta in 1968 showed 78 percent to be infested with roundworms (*Ascaris lumbricoides*); 35 of those infested also had hookworm (*Necator americanus*) (Poffenbarger 1972). In a prospective study of 500 American returnees from Vietnam, Sheehy and coworkers (1965) found that only 15 percent harbored intestinal parasites. Table 79 gives a breakdown of parasites found in 75 returnees.

HOOKWORM

Hookworm, the most common intestinal parasite seen in American troops in

TABLE 79.—Incidence of intestinal parasites in 75 American servicemen returning from Vietnam

Parasite	Cases	
	Number	Percent
<i>Necator americanus</i> or <i>Ancylostoma duodenale</i>	41	55
<i>Strongyloides stercoralis</i>	14	19
Mixed <i>Necator</i> and <i>Strongyloides</i>	11	14
<i>Ascaris lumbricoides</i>	9	12
Total	75	100

Source: Sheehy, T. W. 1968. Digestive disease as a national problem. VI. Enteric disease among United States troops in Vietnam. *Gastroenterology* 55: 105-12.

Vietnam, frequently caused troublesome symptoms and occasionally morbidity. Isolated outbreaks of infestation were documented; in one such outbreak, 39 men from a unit of the 1st Cavalry Division were hospitalized with severe hookworm gastroenteritis (Vandevelde 1966). It became clear that one need not go barefoot to become infested with hookworm in Vietnam; mud or muddy water seeping through the air vents or eyelets of boots, and other forms of earth contact, such as digging foxholes and leaning against parapets, were all sources of infestation (Sheehy 1968, p. 108).

A variety of symptoms can be produced by hookworm, especially in previously unexposed persons who acquire a heavy infestation with larvae. These include "ground itch" and "foxhole cough," as well as an acute duodenitis that clinically mimics peptic ulcer disease (Rogers and Dammin 1946).

The only detailed clinical study of hookworm infestation in American troops was performed by Levine and Sheehy (1966), who studied 11 patients admitted to the 3d Field Hospital, Saigon, with probable diagnoses of peptic ulcer. Gastrointestinal symptoms were always a prominent part of the clinical syndrome of these patients and apparently began 6 to 18 weeks after exposure. In some instances, the patients presented with an acute attack of abdominal pain, nausea, vomiting, and diarrhea, while in others, the symptoms were chronic and were associated with diarrhea and weight loss. Pain was the most prominent symptom and was usually epigastric. However, in contrast to the pain in peptic ulcer, it was aggravated rather than relieved by ingestion of food. Eosinophilia was an important laboratory finding; of the 11 patients, 9 had an absolute eosinophilia (greater than 500 per mm³), with eosinophils ranging from 7 to 38 percent of the total count. Roentgenologic changes in the gastrointestinal tract were common and included a "deficiency pattern" characterized by excessive peristaltic activity, segmental contractions of the small bowel, and distortion of the mucosal pattern. Improvement in the roentgen manifestations occurred promptly after therapy was begun.

The syndrome of abdominal pain simulating peptic ulcer but made worse by food, gastrointestinal roentgenograms which do not show an ulcer crater, and eosinophilia, especially in tropical areas, suggests hookworm infestation.

FILARIASIS

The problem of filariasis in U.S. troops has been recognized since World

War II. In the Central and South Pacific, there were large outbreaks of filariasis among military personnel. Wartman and King (1944) reported their experience with 268 Americans who developed acute filariasis with fever, lymphangitis, lymphedema, and scrotal inflammation, some of them as early as 3 months after arrival in the endemic areas. The average patient remained in the hospital for 16 days. When 25 of the patients were reevaluated in a followup study, it was found that most continued to have clinical attacks during the 16 years they had been out of the South Pacific (Trent 1963).

Filariasis was shown to be endemic in North Vietnam in 1954 (Mille 1954). Earlier suggestions of filariasis caused by *Wuchereria bancrofti* in South Vietnam, especially in the area around An Loc, northwest of Saigon, were confirmed by a U.S. Army survey team in 1967. Prevalence studies showed evidence of infection in up to 22 percent of Montagnard tribespeople, and 15.2 percent of 112 servicemen on field duty in the endemic area had filarial antibodies as determined by the soluble antigen fluorescent antibody test (Colwell et al. 1970). Microfilaremia, however, was rare (Beaver 1970). This, along with other data, supports the contention that the syndrome of "tropical eosinophilia" is caused by human or animal filariae, or both. The presence of antifilarial antibodies, marked eosinophilia, and dramatic response to diethylcarbamazine citrate, even in the absence of microfilaremia, lend credence to this hypothesis. Although only one clinically apparent case of filariasis in an American serviceman in Vietnam has been reported (Pittman 1972), cases of so-called tropical eosinophilia or otherwise unexplained eosinophilia in an individual who has been in an endemic area should raise the possibility of filariasis.

OTHER PARASITES

Strongyloides stercoralis parasites cause damage to the intestinal mucosa and, in cases of heavy infestation, produce malabsorption. Neither strongyloidosis nor ascariasis was an important cause of morbidity in American troops, but serious complications have been associated with both (Sheehy 1968, p. 108). While *Balantidium coli* infection is known to occur throughout Southeast Asia, there has been only one documented case in an American serviceman returning from Vietnam (Lerman, Hall, and Barrett 1970).

Human schistosomiasis was not demonstrated in Vietnam, a fortunate circumstance in view of extensive military operations in watery terrain. The liver fluke, *Clonorchis sinensis*, was a serious problem for Vietnamese troops but was never reported in Americans. Other tissue flukes were known to occur in Vietnam, including *Paragonimus westermani* and *Fasciolopsis buski*, but were never observed in U.S. troops.

TREATMENT

Because of the potential and real problem of parasitic infestations in American troops and the lack of previous experience among military physicians in treating them, once yearly the USARV (U.S. Army, Vietnam) medical consult-

ant published an internal medicine sourcebook outlining therapy for the wide variety of diseases seen in Vietnam. The treatment schedule for those parasitic infestations, published in 1971, is shown in table 80.

TABLE 80.—Treatment schedule for parasitic infestations in Vietnam, 1971

Organism	Drug (1) Drug of choice (2) Alternate drug	Dosage (adult)
Roundworms:		
<i>Ascaris lumbricoides</i>	{ (1) Piperazine citrate	2.4 g daily x 2 days.
	(2) Thiabendazole	25 mg/kg b.i.d. x 2 days.
<i>Trichuris trichiura</i>	{ (1) Thiabendazole	25 mg/kg b.i.d. x 2 days.
	(2) Hexylresorcinol (.01% solution)	500 ml by rectal retention for 1 hour.
<i>Necator americanus</i>	(1) Tetrachloroethylene	0.12 ml/kg single dose (max—5 ml).
	(2) Bephenium.....	5 g packet b.i.d. x 3 days.
	(3) Thiabendazole	25 mg/kg b.i.d. x 2 days.
<i>Ancylostoma duodenale</i>	{ (1) Same as for <i>Necator americanus</i> .	
	(2) Combined Rx (very good): Bephenium	$\frac{1}{2}$ packet } q.d. x 3 d. 3 ml }
	Tetrachloroethylene	
<i>Strongyloides stercoralis</i>	{ (1) Thiabendazole	25 mg/kg b.i.d. x 2 days.
	(2) Pyrvinium pamoate	Single dose, 5 mg/kg (max—250 mg); repeat after 2 weeks.
<i>Enterobius vermicularis</i>	{ (1) Piperazine citrate	65 mg/kg (max—2.5 g) q.d. x 8 days.
	(2) Thiabendazole	25 mg/kg b.i.d. x 2 days.
<i>Trichinella spiralis</i>	{ (1) No specific therapy	Adrenal corticosteroids for severe symptoms.
	(2) Thiabendazole	25 mg/kg b.i.d. until symptoms subside or toxic effects occur.
Cutaneous larva migrans (dog and cat hookworm).	(1) Thiabendazole	25 mg/kg b.i.d. x 2 days; repeat in 2 days if necessary.
Visceral larva migrans (dog and cat roundworm).	{ (1) No specific therapy; adrenal corticosteroids for severe symptoms.	20-40 mg prednisone daily for 3-5 days.
	(2) Thiabendazole	25 mg/kg b.i.d. until symptoms improve or toxicity develops.
Filaria:		
<i>Wuchereria bancrofti</i>	{ (1) Diethylcarbamazine citrate.	2 mg/kg t.i.d. for 14 days.
<i>W. (Brugia) malayi</i>		
<i>Loa loa</i>		
Flukes:		
<i>Clonorchis sinensis</i>	{ (1) Chloroquine phosphate	250 mg t.i.d. x 6 wks.
	(2) Bithionol	30-50 mg/kg q.o.d. x 15 doses.
<i>Paragonimus westermani</i>	{ (1) Bithionol	30-50 mg/kg q.o.d. x 15 doses.
	(2) Chloroquine phosphate	250 mg t.i.d. x 6 wks.

TABLE 80.—Treatment schedule for parasitic infestations in Vietnam, 1971—Continued

Organism	Drug (1) Drug of choice (2) Alternate drug	Dosage (adult)
Protozoa:		
<i>Entamoeba histolytica</i>	{ (1) Flagyl	750 mg t.i.d. x 10 days.
	(2) Emetine HCl plus	1 mg/kg (IM q.d. x 10 days.
	tetracycline followed	250 mg q.i.d. x 5 days.
	by diiodohydroxyquin.	650 mg t.i.d. x 20 days.
<i>Dientamoeba fragilis</i>	{ (1) Diiodohydroxyquin	650 mg t.i.d. x 10 days.
	(2) Tetracycline	250 mg q.i.d. x 7 days.
<i>Giardia lamblia</i>	{ (1) Quinacrine HCl	100 mg t.i.d. x 5-7 days.
	(2) Metronidazole	250 mg t.i.d. x 10 days.
<i>Trichomonas vaginalis</i>	(1) Metronidazole	250 mg t.i.d. x 10 days.
<i>Balantidium coli</i>	{ (1) Oxytetracycline	500 mg q.i.d. x 10 days.
	(2) Diiodohydroxyquin	650 mg t.i.d. x 20 days.

Source: Parasitic infestations. *USARV M. Bull.* (USARV Pam 40-25), Jan.-Feb. 1971, pp. 11-13.

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Hepatitis

Joe A. Dean, M.D., and Brigadier General Andre J. Ognibene, MC, USA

Viral hepatitis has been described as "an acute infectious illness in which hepatic cell necrosis is responsible for the most frequent, prominent, and characteristic symptoms" (Mosley and Galambos 1969). Certainly there are other causes of "infectious hepatitis," such as yellow fever, leptospirosis, louseborne relapsing fever, EBV (Epstein-Barr virus), rubella, and cytomegalovirus. This chapter will deal with the more classical "viral hepatitis" in the military setting.

HISTORY

Zuckerman (1976b) has written a fine review of the history of hepatitis, from which much of this historical background is drawn. Descriptions of liver diseases, jaundice in particular, can be found in Babylonian talmud of the 5th century B.C. During this early period, Hippocrates described "epidemic" jaundice as "the fourth kind of jaundice" (yellow bile) (Cockayne 1912). The first recorded reference to the contagious nature of jaundice appears to have been in the 8th century A.D., in a letter from Pope Zacharias to St. Boniface, Archbishop of Mainz.

That jaundice was a common disorder was especially evident in the Middle Ages when, during the many wars, "campaign jaundice" was described as following cholera and bubonic plague in importance as a cause of pandemics in Europe. An excellent historical account of campaign jaundice was given by Von Bormann et al. (1943), who described an outbreak occurring in Germany in 1629. The first definitive description of a jaundice epidemic in civilians was recorded in Germany in 1791 by Herlitz, who introduced the term "icterus epidemicus." Sydenham, in London, had already recorded some observations of epidemic jaundice (1624 to 1689).

The pathology of jaundice was described by Virchow (1865), after an examination of a single case in which mucus from the duodenum had blocked the terminal portion of the common bile duct. Fröhlich, in a review of jaundice outbreaks (1879), suggested that an infectious process might be responsible for only 1 of the 30 outbreaks studied.

Jaundice apparently afflicted Napoleon's army in Egypt, but whether this outbreak was caused by infectious hepatitis is questionable, especially because of the high mortality rate. During the American Civil War, the Union Army suf-

ferred a reported 71,691 cases of jaundice. Epidemic jaundice was also present in the Franco-Prussian War in 1870, the French referring to infectious hepatitis as "jaunisse des camps" and the Germans as "Soldatengelbsucht." In South Africa during the Boer War, 5,648 cases of jaundice were recorded with typically low mortality. The Japanese Navy experienced epidemics during Japan's war with Russia in 1904 and 1905, and huge epidemics occurred during World War I.

The epidemic of 1942 caused by use of batches of yellow fever vaccine contaminated with hepatitis virus, coupled with the eruption of 200,000 cases of viral hepatitis between 1942 and 1945, identified the disease as a matter of prime importance to our Armed Forces during World War II (MD-IM3, p. 332). It became evident during this conflict that effective methods to treat or prevent hepatitis in soldiers were urgently required.

ETIOLOGY

The clinical features and etiologies of viral hepatitis may be divided into Types A, B, and C. Type A hepatitis or "catarrhal jaundice" was described by Hirsch (1886, p. 418) as first occurring in epidemic form in 1745. More recently, the syndrome has been called "infectious hepatitis." Type B hepatitis refers to "serum" (posttransfusion) hepatitis, the earliest known epidemic of which, as described by Lürman (1885), occurred in 1883 after inoculation of shipyard workers with smallpox vaccine containing human serum. When Types A and B hepatitis have been excluded from the diagnosis, other viral types become apparent; these have been designated as Types C, D, etc. EBV, rubella, and cytomegalovirus are the three most commonly described Type C etiologic agents (Sherlock 1976).

Type A Hepatitis

Type A hepatitis may have been described in *De internis affectionibus* by Hippocrates (Mosley and Galambos 1969, p. 410):

This type of jaundice is called epidemic because it occurs in all seasons. It is caused above all else by over-indulgence, excesses of wine, and after a chill. From the first moment the body changes color and becomes yellow; the eyes become markedly jaundiced; the disease appears under the hair and under the nails. There are chills and low-grade fever. The patient is weak. The head aches; the urine is yellow and thick. This form of jaundice is less dangerous * * * and is cured if quickly treated.

Separation of Type A from Type B hepatitis did not occur until the 1940's, however, when volunteer studies demonstrated that the two were distinct entities (Yoshibumi and Shigemoto 1941; Voegt 1942; Havens 1946a & b; MacCallum and Bauer 1944; Neefe, Gellis, and Stokes 1946; MacCallum 1945; Neefe, Stokes, and Reinhold 1945; Paul et al. 1945). With the discovery of hepatitis B surface antigen (Australian antigen, HB_s Ag) in 1963 (Blumberg, Alter, and Visnich 1965) and the demonstration of hepatitis A antigen 10 years later (Feinstone, Kapikian, and Purcell 1973; Mascoli et al. 1973), the two major types of viral hepatitis could be differentiated.

The antigen of Type A hepatitis is a viruslike particle, 27 nm in diameter, which is present in the feces of patients in both the late incubation and early

acute phases of illness. The virus is resistant to heat, ether, and acid but sensitive to ultraviolet radiation, formalin, and chlorine. The antigen can be separated into "empty," "light," and "heavy" particles, but infectivity has not been associated with any one population of particles. The agent has been classified as an RNA virus (Purcell 1976; Provost et al. 1975; Dienstag and Purcell 1976; Sherlock 1976). Recovery of viruslike particles from the liver suggests that this organ is a site of viral replication. The fecal-oral transmission cycle of Type A hepatitis suggests that an intestinal phase of virus replication may also occur.

To date, only one serological type of hepatitis A virus has been identified. It is antigenically indistinguishable from the MS-1 strain which Krugman, Giles, and Hammond (1967) investigated at Willowbrook State School in New York. Infection with this virus has been demonstrated throughout the world (Dienstag 1976).

Serologic diagnosis of Type A hepatitis is presently confined to research laboratories because of the difficulty in obtaining hepatitis A virus for use as an antigen. Techniques include immune electron microscopy, immune adherence hemagglutination, complement fixation, and radioimmunoassay. Such serologic tests have confirmed that hepatitis A virus is the etiologic agent in almost all epidemics of hepatitis as well as in a significant number of sporadic cases (Purcell 1976). The prevalence of hepatitis A virus antibody in the population is directly proportional to age and inversely proportional to socioeconomic class. Approximately 45 percent of Americans studied have a positive antihepatitis A virus antibody (Szmuness et al. 1976).

Type B Hepatitis

As noted earlier, Type B hepatitis can be traced with certainty only from the late 1800's. The relatively late emergence of the illness seems to be compatible with the notion that its propagation depends primarily upon parenteral transmission. However, because barber venesection, scarification, and tattooing have been practiced throughout much of the world for centuries and are alternate routes of "parenteral" transmission, and because the virus is prevalent in culturally isolated populations (Mosley 1975), this theory of evolution must be viewed with skepticism.

The Type B hepatitis virus is an antigenically complex 42 nm ("Dane") particle (fig. 76). Its surface antigen (HB_s Ag), is, of course, the distinguishing characteristic of the infection. HB_s Ag has antigenic heterogeneity with approximately 12 different genotype variants (a, y, w, l, d, r, x, t, g, q, n, j). In combination, these genotypes form four principal phenotypic expressions (adw, adr, ayw, ayr) and a variety of less common phenotypes. There is no apparent clinical difference among the phenotypes, and they are of epidemiological interest only. At the center of the Dane particle is an antigenically distinct core which is synthesized in the hepatic parenchymal cell nucleus. Serum antibodies to the core antigen (HB_c Ag) can be detected in infected individuals, and DNA-dependent DNA polymerase activity has been described. A third antigen, the "e" antigen, may represent the DNA polymerase protein. The "e" antigen is found only with cir-

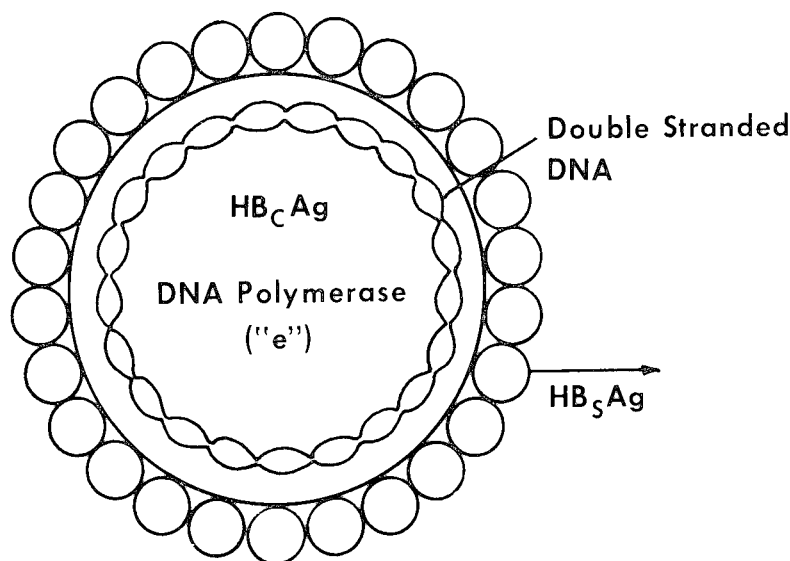


FIGURE 76.—The Dane particle. (Sherlock, S. 1976. Introduction: A bird's eye view. Paper, postgraduate course on viral hepatitis, American Association for the Study of Liver Disease, Nov. 76, pp. 1-1-1-10.)

culating HB_s Ag and is related to liver damage. Each antigen (HB_s Ag, HB_c Ag, "e" antigen) has corresponding antibodies, that is, anti-HB_s Ab, anti-HB_c Ab, and anti-"e" Ab (Zuckerman 1976a; Sherlock 1976).

EPIDEMIOLOGY

Type A hepatitis is endemic among school age children and young adults in the United States. There is no known reservoir for the virus, and propagation of the disease is by person-to-person transmission. Transmission is usually by the fecal-oral route since sufficiently large concentrations of the virus are present only in stool. The communicable period is short during the prodrome and diminishes with the onset of jaundice. Viremia is similarly short; therefore, only a few cases of instrument- or transfusion-related illness have been reported. Percutaneous introductions can occur (Mosley 1975; 1976).

Type B hepatitis is endemic among all age groups in the United States. A large reservoir of chronically infected humans can be established in any population in which it is introduced. Maintenance is, therefore, not dependent on chains of person-to-person infection as with Type A hepatitis. The major mode of transmission is parenteral, but other mechanisms are important, such as personal contact involving exchange of saliva, sexual contact, and vertical transmission (prepartal, intrapartum, and postpartum). By far the most common mode of transmission recently has been illicit self-injection of drugs using shared equipment (Mosley 1976, Szmunes 1975).

CLINICAL FEATURES

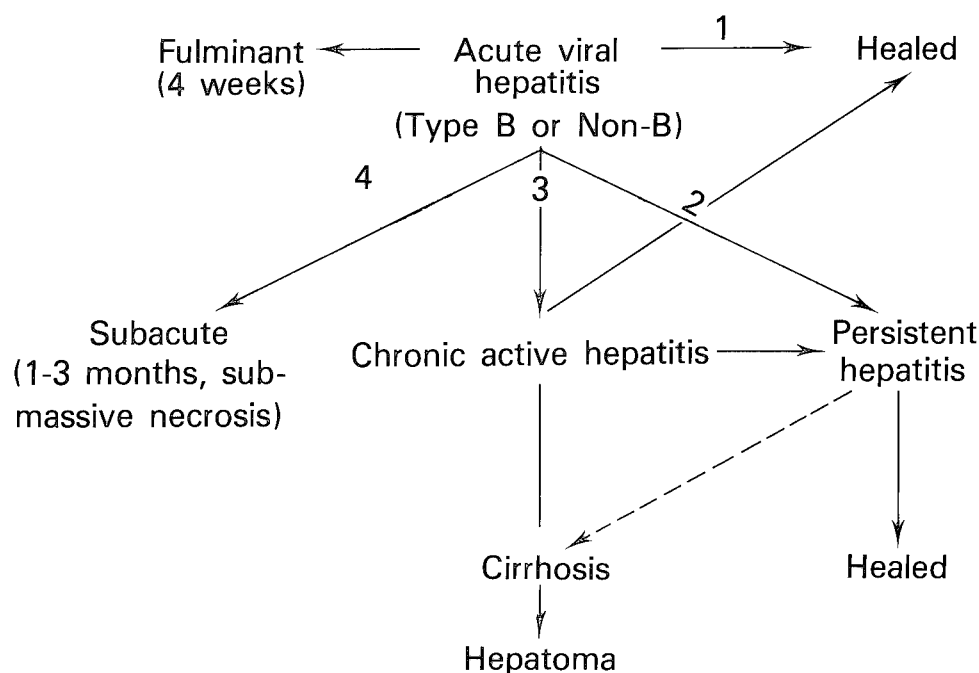
On 17 March 1975, the National Academy of Sciences convened a symposium on viral hepatitis, which represents the most complete single compilation of data on viral hepatitis to date. The opening remarks by Dr. Allan Redeker (1975) introduced the clinical aspects of viral hepatitis as follows:

Acute viral hepatitis is a relatively common illness caused by infection with one of two or more viral agents. Both the acute and the chronic phases may be either totally silent or clinically manifest. The acute infection can be abruptly fatal; chronic infection can result in the development of cirrhosis and is probably one of the leading causes of cirrhosis throughout the world. Fortunately, in the majority of instances, acute hepatitis resolves totally without sequelae. [See chart 26.]

Acute viral hepatitis is characterized by a prodromal phase of vague gastrointestinal and constitutional symptoms, including fatigue, malaise, lassitude, diarrhea, nausea, vomiting, and anorexia. Taste and olfactory disturbances may enhance the loss of appetite. Distaste for tobacco may occur but is an inconstant symptom. Especially in Type A hepatitis, fever (100° to 104°F), cough, coryza, myalgias, pharyngitis, and photophobia may be present. One to 4 days before the onset of jaundice, the urine darkens and the stool becomes lighter in color. Transient pruritus may occur.

The icteric phase of acute hepatitis usually lasts less than 6 to 8 weeks. There is no difference between types of viral agent in this phase. Mild weight loss (5 to 10 pounds) is common. The prodromal symptoms decrease in the first few days of jaundice. The jaundice usually peaks between 1 and 2 weeks after onset. Hepatic enlargement and tenderness occur initially but decrease after the first 2 weeks. A recovery phase of 2 to 6 weeks follows the icteric phase in which serum abnormalities may continue. The patient usually feels well (Koff and Isselbacher 1974).

Laboratory findings in acute viral hepatitis include a normal leukocyte count or mild leukopenia (transient), atypical lymphocytes (2 to 20 percent), and mild hemolysis with reticulocytosis (uncommon). The SGOT (serum glutamic-oxaloacetic transaminase) and SGPT (serum glutamic-pyruvic transaminase) may be abnormal 7 to 14 days before onset of jaundice, and peak typically between 400 and 3,000 units. The serum bilirubin is usually above 3 mg/100 ml at onset of icteric phase with a peak of 5 to 20 mg/100 ml. Patients with G6PD (glucose-6-phosphate dehydrogenase) deficiency or sickle-cell disease may have more significant hemolysis, and profound hyperbilirubinemia may occur. (In Vietnam, there was no apparent alteration of the clinical course of the disease in troops with G6PD deficiency.) The serum alkaline phosphatase is usually only mildly elevated (5 to 15 Bodansky units), although "cholestatic hepatitis" may occur with peak alkaline phosphatase levels greater than 15 Bodansky units. In these cases, infectious mononucleosis or other causes of obstructive jaundice require consideration. In uncomplicated acute viral hepatitis, the prothrombin time remains normal (Koff and Isselbacher 1974). An abnormal prothrombin time often heralds the onset of acute fulminant hepatitis; thus, in any combat theater where hepatitis is expected, this laboratory test must be made available.

CHART 26.—*Courses of acute viral hepatitis.*¹

¹ The decreasing frequency of each course is indicated by the numbers one to four.

Source: Redeker, A. G. 1975. Viral hepatitis: Clinical aspects. *Am. J. M. Sc.* 270: 9-16.

The characteristic pathologic changes in acute viral hepatitis involve the portal, periportal, and lobular areas of the liver (fig. 77). The portal tracts are enlarged by accumulation of inflammatory cells and edema. The inflammatory cells are predominantly mononuclear cells with some polymorphonuclear leukocytes. Ductular proliferation may be seen, as may necrosis of periportal hepatocytes and loss of a definite "limiting plate." The characteristic lesion is single cell injury and "spotty" necrosis. Affected areas are randomly scattered throughout the lobule but are most prominent around the efferent vein (Koff and Isselbacher 1974, pp. 1529-31; Boyer and Klatskin 1970).

COMPLICATIONS

Extrahepatic manifestations of viral hepatitis have been described as "Immune Complex Syndromes" (Alpert 1976; Gocke 1975). Usually these occur with hepatitis B virus infection, but non-B hepatitis viruses may also produce them. Three major syndromes are recognized. First and most commonly, a prodrome similar to serum sickness may occur, with rash, urticaria, polyarthralgia, and, in 10 to 20 percent of patients, acute arthritis. This syndrome usually occurs a few days to 6 weeks before the onset of hepatitis and is transient, lasting only 2 to 7

days. Circulating immune complexes (HB_s Ag-IgM, IgG) have been demonstrated. Components of serum complement ($\text{C}'\text{H}_{50}$, C'_3 , C'_4) are low in both serum and joint fluid.

The second syndrome is that of polyarteritis nodosa, which occurs with hepatitis B infection. The onset involves fever, myalgia, polyarthralgia, rash, and urticaria. Peripheral neuropathies, hypertension, eosinophilia, hematuria, and azotemia may ensue. Fibrinoid necrosis and perivascular inflammation in the walls of small arteries and arterioles can be demonstrated. HB_s Ag persists throughout the illness. In the early acute phase, serum $\text{C}'\text{H}_{50}$ is decreased and circulating complexes of HB_s Ag/anti- HB_s Ab are present. HB_s Ag, IgM, IgG, and C'_3 deposit in vessels (Gocke 1975).

The third syndrome is that of hepatitis B-associated glomerulonephritis, which usually presents in chronic form but may be acute. It is associated with chronic hepatitis in adults and may be responsible for over 30 percent of glomerulonephritis in children. Most often, it is membranous or membranoproliferative. Nodular deposits of HB_s Ag, IgG, IgM, and C'_3 occur on the glomerular basement membrane (Gocke 1975).

Fulminant hepatitis is an uncommon complication of acute viral hepatitis (fig. 78). Approximately 1.0 to 2.4 percent of patients hospitalized with acute viral hepatitis will develop this complication regardless of virus type. The term "fulminant" applies when abrupt hepatic failure occurs during the course of the illness. "Subacute (fatal) hepatitis" refers to a course of acute viral hepatitis with hepatic failure of more gradual onset. Fulminant hepatitis occurs infrequently in children and does not occur in anicteric hepatitis. The mortality rate increases with age, with the highest survival in the 0- to 14-year age group (37 to 47 percent) and the lowest in patients over 44 years (0.0 to 6.5 percent). In the active-duty military age group (15 to 44 years), the survival rate is 20 to 25 percent. These percentages are from two studies of patients with presumed fulminant viral hepatitis and stage IV portal-systemic encephalopathy ("hepatic coma") (Redeker 1975, pp. 9-11). It should be emphasized that the overall mortality for acute viral hepatitis is under 1 percent. It is theorized that the increased survival rate in younger individuals with fulminant hepatitis is related to their greater capacity for rapid hepatocyte regeneration. This concept derives support from the finding of high concentrations of serum alpha-fetoprotein, which indicates regeneration, in patients surviving fulminant viral hepatitis (Redeker 1975, p. 10; Karvountzis and Redeker 1974).

Preexistent cirrhosis or malignancy produces an unusually high mortality rate. Other than supportive measures, to date no mode of therapy is of established benefit. Exchange transfusion, extracorporeal hemoperfusion through heterologous liver, plasmapheresis, and corticosteroids are the most commonly considered therapies. Previous studies (Boyer and Klatskin 1970) have suggested that cirrhosis develops following severe necrosis; however, recent studies (Karvountzis, Redeker, and Peters 1974) demonstrate that patients recovering from fulminant hepatitis seldom develop cirrhosis, although liver biopsies that resemble chronic active hepatitis may persist. Following uncomplicated acute viral hepatitis, however, the majority of patients recover completely (Redeker 1975, p. 9).

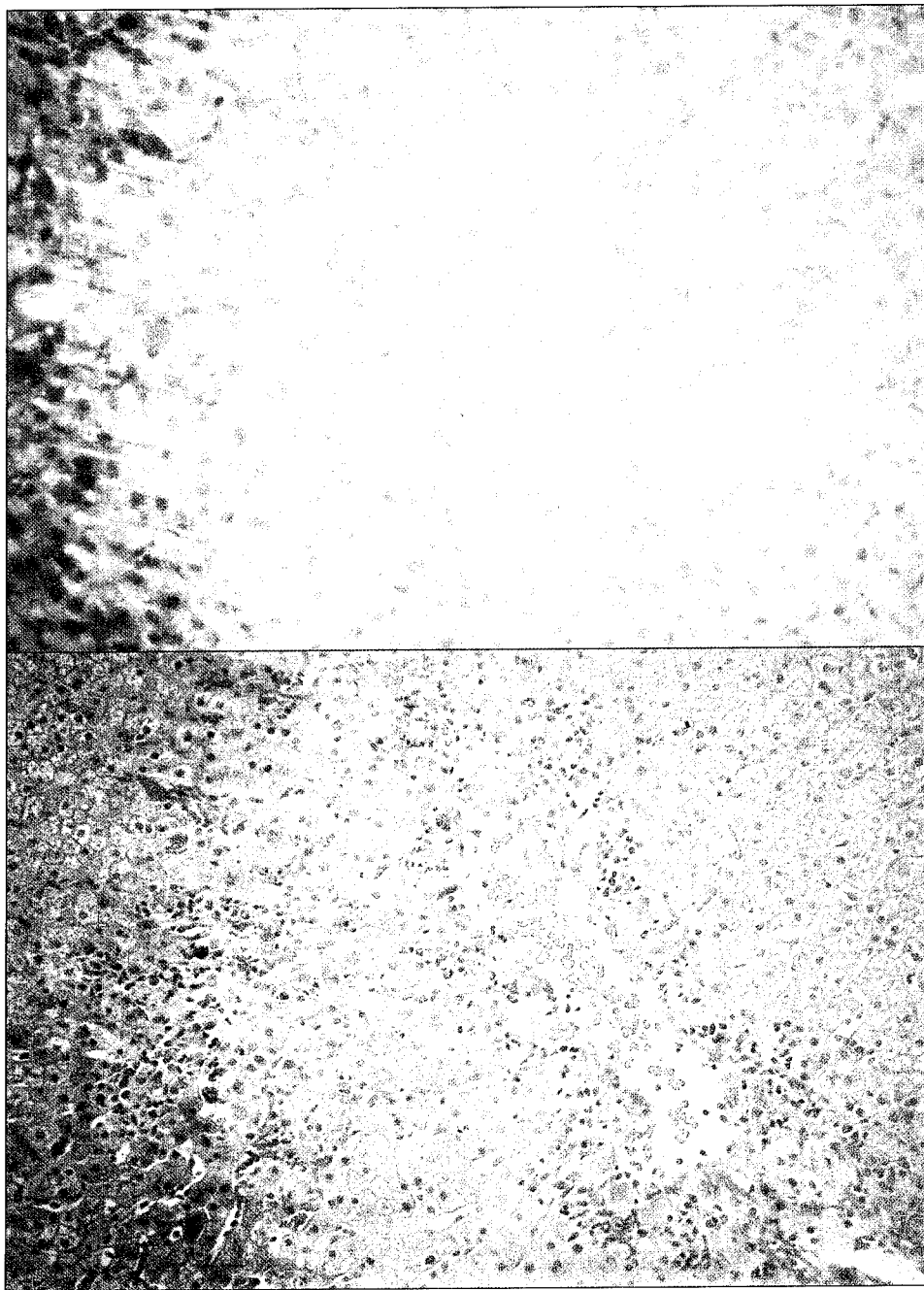


FIGURE 77.— High power microscopic views of hepatic parenchyma in acute viral hepatitis demonstrating (top) mononuclear leukocyte infiltration and edema (hematoxylin-eosin), and (bottom) prominent reaction about efferent vein (Masson).

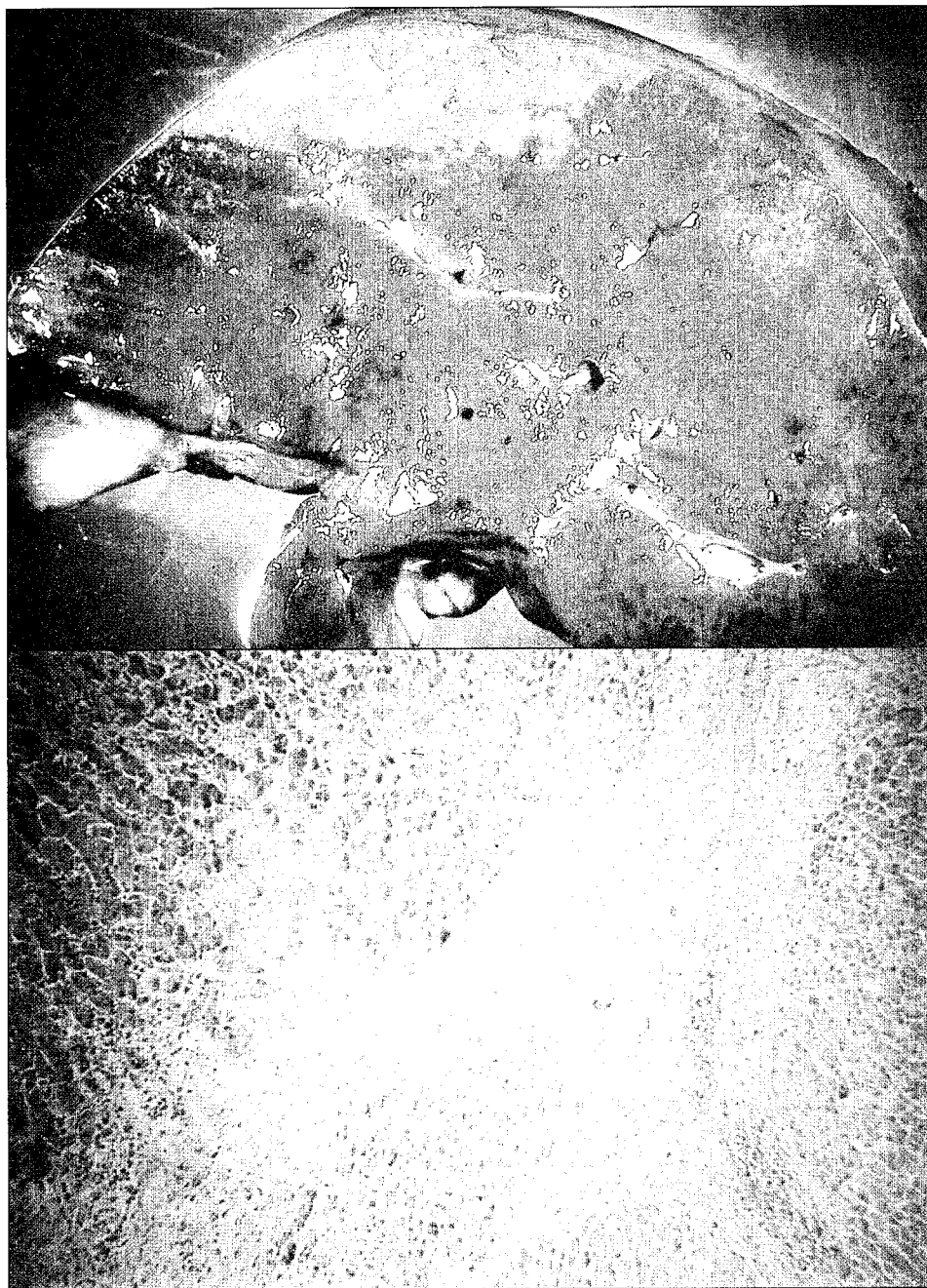


FIGURE 78.—Top: Liver of patient dying of fulminant viral hepatitis, showing massive hemorrhagic necrosis and fat deposition. Bottom: High power microscopic view (hematoxylin-eosin) of hepatic parenchyma in late fulminant hepatitis showing massive necrosis and fibrosis.

CHRONIC HEPATITIS

Approximately 10 percent of hepatitis B patients develop chronic hepatitis. Type A hepatitis rarely becomes chronic. The majority of patients found to have chronic hepatitis do not have a recognizable acute illness. The two basic types of chronic hepatitis are the chronic persistent and chronic active forms.

Chronic persistent hepatitis is the more common type, occurring 10 times more frequently than chronic active hepatitis. It is characterized by persistent elevations of the serum transaminase (100 to 300 unit range), with a gradual yearly decrease toward normal in an asymptomatic patient. Progression to cirrhosis is rare. HB_s Ag titers are normally high in Type B cases. Recurrent jaundice is not a feature of the illness. Some cases will resolve spontaneously, including disappearance of HB_s Ag (Redeker 1975, p. 12). The morphologic picture (fig. 79) is that of mild histopathologic changes with "cobblestone" hepatocyte architecture, minimal necrosis, and round cell reaction (Edmondson and Schiff 1975, pp. 256-57).

Chronic active hepatitis may be viral or nonviral. About 1 to 3 percent of patients with acute icteric viral hepatitis develop it (Redeker 1975, pp. 13-15). The range and pattern of hepatic distortion are broad. Many patients are totally asymptomatic. Recurrent or intermittent episodes of jaundice may occur, which are usually associated with impressive elevations of the serum transaminases. As Boyer and Klatskin (1970) have demonstrated, extensive necrosis ("submassive necrosis") during the initial acute hepatitis is a predisposing factor to development of chronic active hepatitis, as well as (questionably) to development of cirrhosis, and (unequivocally) to a poorer prognosis.

The pathologic changes which have been described as active juvenile cirrhosis, lupoid hepatitis, subacute hepatitis, autoimmune hepatitis, chronic viral hepatitis, plasma cell hepatitis, liver disease in young women with hyperglobulinemia, subacute hepatitis necrosis, chronic liver disease in young people, and numerous other synonyms are those of chronic active hepatitis. On biopsy (fig. 80), one observes cellular infiltration, including plasma cells, lymphocytes, and macrophages, a continuing type of hepatocyte injury indicated by ballooning (hydropic degeneration), active necrosis, eosinophilic degeneration, and dropout of liver cells. The periportal areas, particularly, are involved. The degree of collapse and fibrosis is variable. In early disease, collapse and necrosis may not be present, but "piecemeal" necrosis is. As the disease progresses, fibrous tissue entraps islands of parenchyma, frequently connecting the portal and centrilobular areas by the septa (bridges) which it forms. Lobular architecture is destroyed by these septa. Plasma cell infiltration is abundant. The end stage (fig. 81) is marked by regenerative pseudolobules with ongoing necrosis and chronic infiltration (postnecrotic or macronodular cirrhosis) (Edmondson and Schiff 1975, pp. 257-58).

Therapy of chronic active hepatitis usually consists of corticosteroids and possibly immunosuppressive agents (Sherlock 1974). A limited number of controlled studies have been done, and understanding of the natural history of

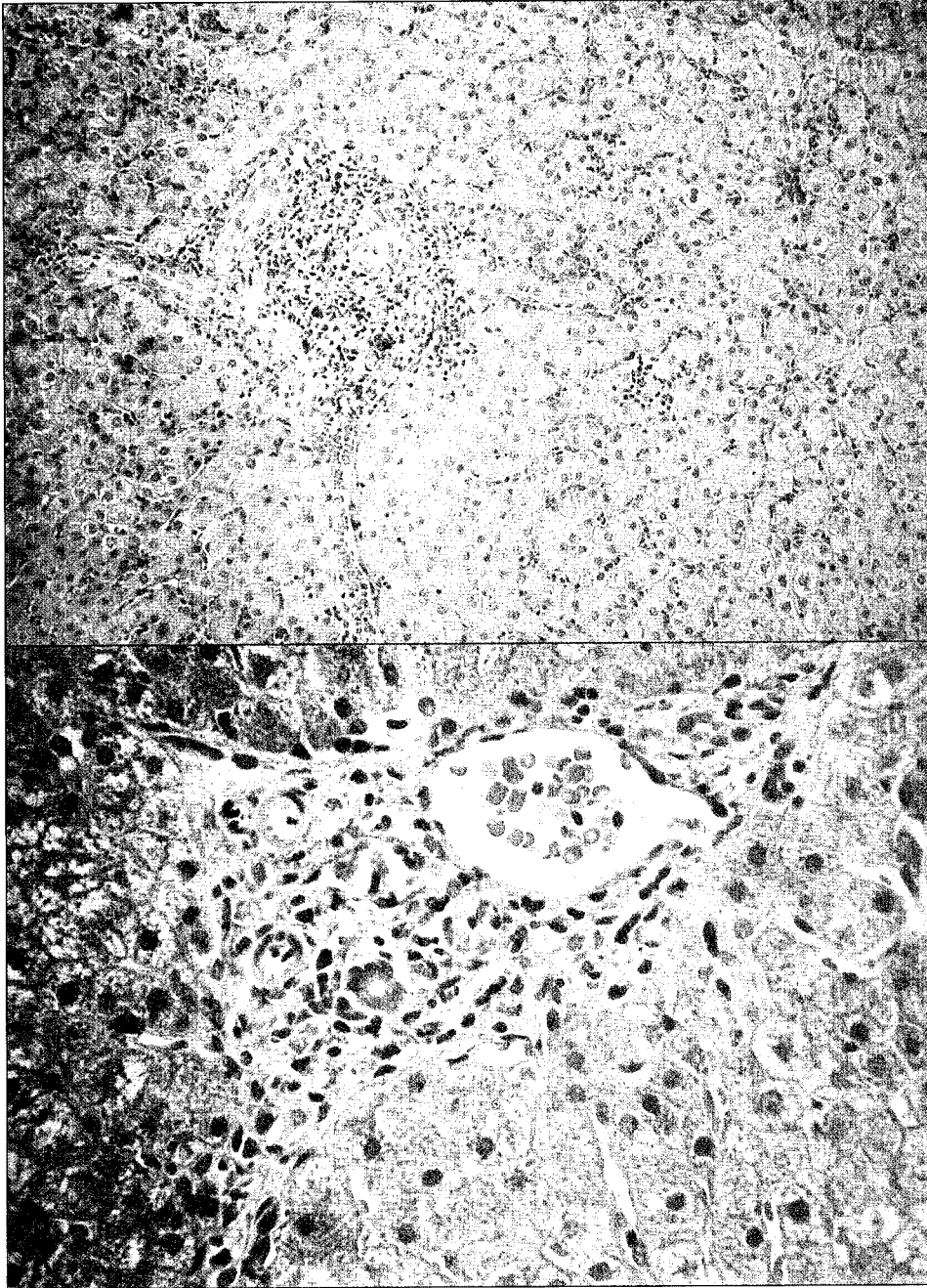


FIGURE 79.—Top: High power microscopic view (hematoxylin-eosin) of hepatic parenchyma in chronic persistent hepatitis showing minimal necrosis, preservation of limiting plate, and round cell infiltration. Bottom: Same, with Masson stain.

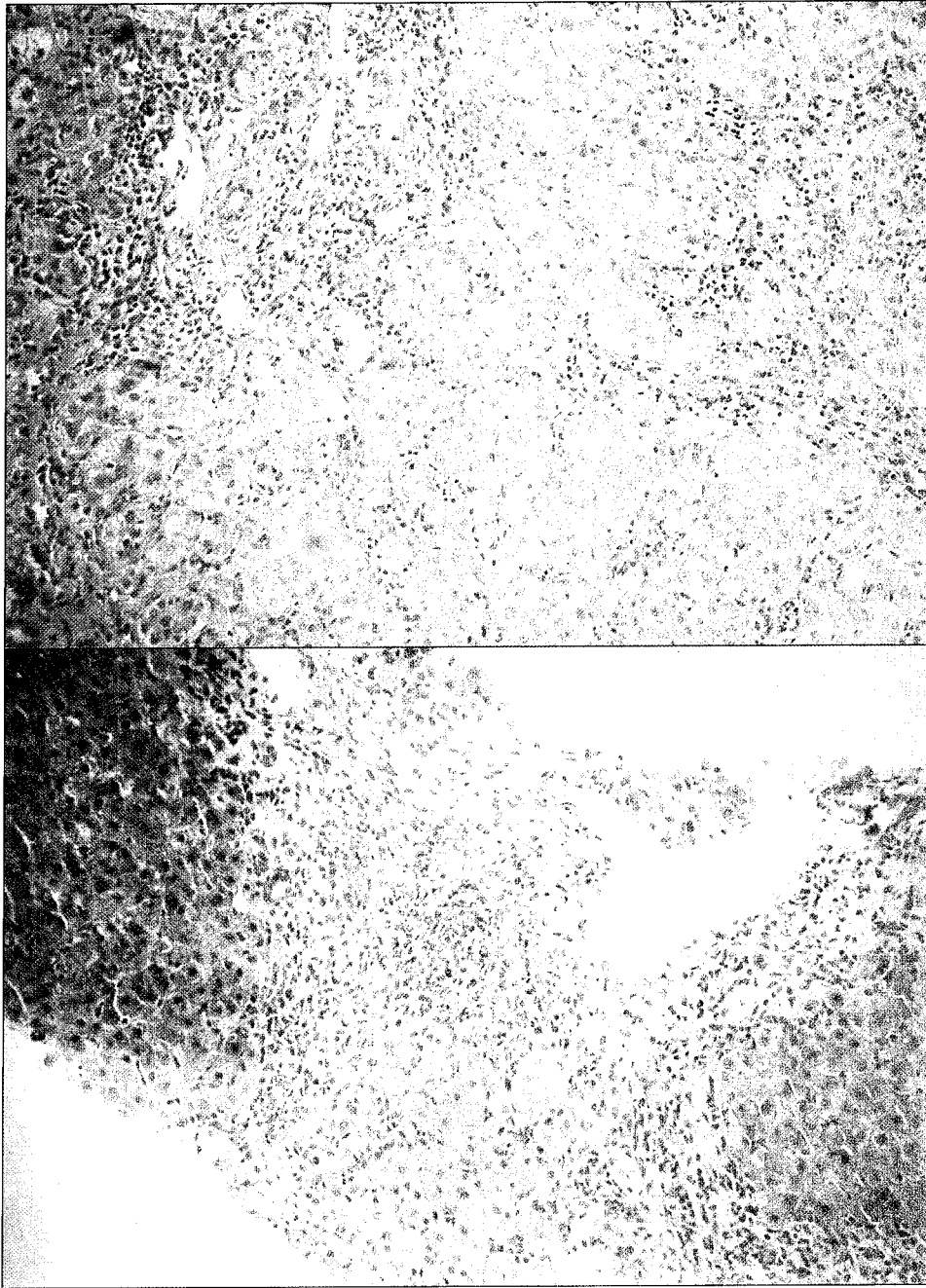


FIGURE 80.—Top: High power microscopic view (hematoxylin-eosin) of hepatic parenchyma in chronic active hepatitis showing piecemeal necrosis, limiting plate loss, periportal hepatocyte entrapment, and bridging necrosis. Bottom: Low power view (Masson) of same.

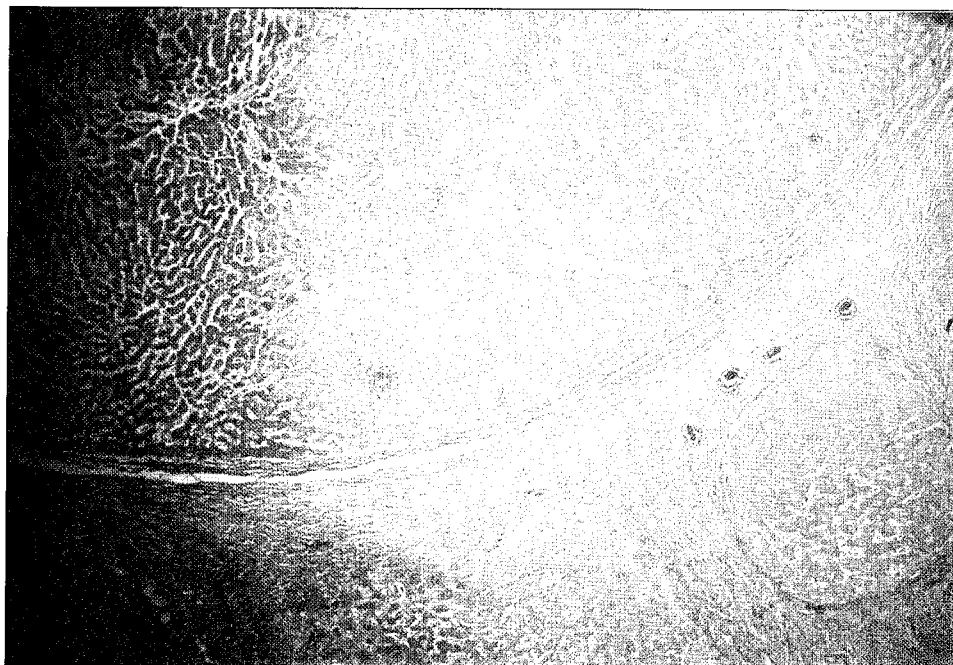


FIGURE 81.—Low power microscopic view (hematoxylin-eosin) of postnecrotic (macronodular) cirrhosis demonstrating large bands of fibrous tissue encircling regenerating macronodules.

resolution of this form of hepatitis is poor; thus, these nonspecific treatment modalities are difficult to assess. They have been shown to have beneficial effects on survival, hepatic histology, and laboratory tests in non-B hepatitis patients, but such evidence is lacking for Type B chronic active hepatitis (Cook, Mulligan, and Sherlock 1971; Soloway et al. 1972).

VIETNAM EXPERIENCE

Organized study of the large numbers of troops afflicted with hepatitis was not undertaken in Vietnam; attention was focused on prevention and therapy. As early as the 1940's, Stokes and Neefe (1945) reported that epidemic icteric hepatitis could be either prevented or attenuated by the parenteral administration of human serum gamma globulin. In 1964, a program designed to protect all military personnel stationed in Asia against hepatitis was instituted. A 16-percent solution of human serum gamma globulin in a dose of 0.05 ml/lb was used. The gamma globulin was prepared from blood donated in the United States. A significant decrease in the prevalence of hepatitis during that year as compared to the previous year was seen in preliminary observations in both Korea and Vietnam. However, close examination of monthly hepatitis rates revealed that the decrease had begun 4 months before the gamma globulin prophylaxis program was initiated. Thus it was impossible to determine whether

the incidence of icteric hepatitis in American troops hospitalized in Southeast Asia was significantly affected by the administration of gamma globulin from the United States (Conrad 1972).

With the increasing involvement in Vietnam after 1965, national stockpiles of gamma globulin were significantly depleted and a reassessment of the prophylactic program was necessary. The dose of gamma globulin administered to soldiers was reduced to 5 ml of a 16-percent solution after arrival overseas, with a second injection 5 months later (DA Circ). It was decided, in 1966, that only persons under high risk of exposure to infectious hepatitis would receive the inoculations of gamma globulin. A continuing incidence greater than five cases per 1,000 per year in particular units was suggested as a guideline for this high risk group.

No significant increases in the incidence of hepatitis during the next year were associated with the decreased utilization and dosage of gamma globulin. In Vietnam, the case rates for viral hepatitis ranged between 4 and 10 per 1,000 troops per annum (HOA). A systematic study of the policy of prophylactic gamma globulin administration in high risk patients was never accomplished in Vietnam.

However, a large body of data was available from the Korean era (Conrad 1969). Conrad (1972) did a study of all soldiers arriving in Korea through a single airport. Between May 1967 and August 1969, 107,803 troops were given, upon arrival, either a 10-ml injection containing 2 ml, 5 ml, or 10 ml of a 16-percent human serum gamma globulin or a 10-ml albumin-sucrose-potassium glutamate solution. A second injection of the same material was given to 65 percent of these soldiers 5 to 7 months later. Soldiers having symptoms or physical findings of hepatitis were hospitalized and examined. A liver biopsy specimen was obtained from 82 percent of the patients. Results showed 467 documented cases of icteric viral hepatitis in the subjects studied. The calculated incidence was 5.67 cases per 1,000 among the control subjects, who received the albumin, while among soldiers given various amounts of gamma globulin it was 4.04 (2 ml group), 3.39 (10 ml group), and 2.90 (5 ml group) cases per 1,000. Significant protection was provided to those receiving 2 ml of gamma globulin but slightly less than that which was observed with 5 ml. The larger dose of 10 ml did not produce a further reduction in the incidence of viral hepatitis.

In addition, there was no significant difference between the incidence of other infectious diseases in the gamma globulin-protected group and in the control group. Conrad also compared the hospital records of patients who received the 5- or 10-ml dose of gamma globulin with those of patients injected with placebo, to determine whether gamma globulin affected the severity of the illness. Again, no significant differences appeared between the groups. Since almost none of the patients studied had had blood transfusions, it was believed that most were infected orally. The availability of data showing minimal differences between treated and untreated groups in mass prophylaxis reinforced the policy in Vietnam of providing only 2 ml of gamma globulin to individuals in whose units a significant epidemic exposure was manifest. There is no evidence that this policy had any effect on the incidence or severity of disease.

As the number of troops, and consequently the number of cases of hepatitis, increased and the necessity for air evacuation of these patients from Vietnam became apparent, the prolonged period of treatment and hospitalization not only caused a loss of duty time but also produced a logistical problem of evacuation and replacement. The opening of the 6th Convalescent Center at Cam Ranh Bay, Vietnam, on 16 May 1966, provided a way station to which hepatitis patients could be evacuated for convalescence. However, the prolonged recovery phase was still a major factor contributing to the number of man-days lost to combat units.

In examining the problem of treating hundreds of patients with infectious hepatitis at the 6th Convalescent Center, Repsher and Freebern (1969) were impressed by the benignity of the clinical course in most of the patients, the occurrence of relapses despite adherence to a bed rest regimen, and the uneventful clinical course of patients who engaged in physical activity contrary to advice. Based on these observations, they performed a pilot study on the effect of vigorous reconditioning on patients whose liver function tests had not completely returned to normal values. The effect of exercise on recovery from viral hepatitis had been reviewed earlier by Chalmers et al. (1955) and Nefzger and Chalmers (1963), whose extensive studies led to the conclusion that patients allowed *ad libitum* activity improved just as rapidly as those kept on strict bed rest. In addition, patients who returned to active physical rehabilitation as soon as the results of their liver function tests were relatively normal were found to have an uncomplicated convalescence similar to that of patients returned to duty much more gradually. Nelson and coworkers (1954) had reexamined, 2 to 3 years after onset of disease, patients who had had *ad libitum* exercise. Their studies included hepatic biopsies in 40 of the 80 patients, all of which showed no evidence of residual liver disease. Furthermore, Repsher and Freebern's review of existing literature indicated an absence of controlled or prospective studies demonstrating any benefit from the traditional enforced bed rest regimen.

Repsher and Freebern (1969) then undertook a prospective study of 398 American servicemen at the 6th Convalescent Center. Inclusion in the study required elevations of serum bilirubin concentration and SGOT. Patients were examined to preclude the presence of malaria, infectious mononucleosis, pneumonia, or other illnesses. They were required to have been asymptomatic with return of appetite for less than 5 days despite the persistence of abnormal liver function. Evidence of previous hepatitis or history of blood transfusion in the preceding year excluded patients from the study. Patients were divided randomly into rest and exercise groups. The rest group's activity was restricted to a 100-yard walk to the messhall and a walk to the theater or post exchange; they were otherwise confined to the ward. The exercise group participated in a 1-hour session of calisthenics 6 mornings a week, including a 1-mile run and, for 4 afternoons a week, a 2-hour work detail filling sandbags, painting buildings, and constructing bunkers. This group also participated in supervised athletics including softball, swimming, volleyball, and basketball. During the period of study, all groups were under the direct observation of the assigned physicians.

Comparison of these groups showed no difference in duration of illness. In one-third of the cases, the SGOT was still elevated when the serum bilirubin had returned to normal, a situation no more frequent in the exercise group than in the rest group. While recovery time was unchanged in the two groups, the time to return to duty was shorter for the exercise group. The exercise group was shown to be fit for return to combat duty immediately on completion of hospitalization. The rest group, however, required conditioning and observation before discharge and appropriate disposition could be made. As a result of this study, individuals recovered from hepatitis were returned to combat duty earlier than had been possible in the past. Repsher and Freebern cautioned against making generalizations about infectious hepatitis in all adults from studies of the disease in this military population of otherwise healthy young men. Furthermore, the origin of the disease may differ in different parts of the world. They also warned against applying their findings to Type B hepatitis, inasmuch as presumably their cases were caused by Type A virus.

The studies of Krugman, Ward, and Giles (1962) indicated that in most cases virus is excreted from about 16 days before icterus to about 8 days after its appearance. Based on this information, no attempt was made to separate the exercise group from the other patients at the 6th Convalescent Center. Most patients had been hospitalized primarily at an evacuation or field hospital before transfer to the convalescent center, with an average of 8 days' delay before arrival there. Normal hygiene was maintained but isolation procedures for hepatitis patients were not practiced. They shared common dining facilities with the staff and with other patients. During the 6 months of the study, none of the patient contacts developed hepatitis; only one case was identified in a staff member in the year that followed, but it could be attributed to eating in a local village. Thus, this study was responsible for simplifying hospital care for hepatitis patients in addition to significantly reducing combat man-days lost. Returning the individual to his parent unit reduced the need for out-of-country evacuation and replacement from the continental United States.

Table 81 lists the number of cases of hepatitis, by month, in Vietnam for 1965-72 and the numbers of noneffective days for 1965-70. While the number of cases per year remained fairly constant, the noneffective days decreased by 65,986 between 1968 and 1970. The average time lost from duty per individual thus decreased from 35.7 days to 18.6 days during that period.

While an exercise program for the patient with uncomplicated hepatitis was shown to be appropriate in a combat theater, considerable concern arose regarding those patients who might have chronic active hepatitis. Studies by Anand, Tamburo, and Leevy (1971) had shown some detrimental effect of exercise on hepatic function in patients with chronic active hepatitis. At the 6th Convalescent Center, Jolson and Blailock (1970) studied 26 patients with a clinical diagnosis of viral hepatitis, randomly selected for aspiration liver biopsy by the Menghini technique. Six of these patients were noted to have some increase in portal collagen and minimal fibrous interconnecting bridging. Three of the six had evidence of focal, piecemeal necrosis at the limiting plate compatible with chronic active hepatitis. Followup of these three patients was obtained with

TABLE 81.—*New cases of hepatitis, by month, among active-duty Army personnel in Vietnam, 1965-72*

Month	1965	1966	1967	1968	1969	1970	1971	1972
January	4	42	101	192	140	167	132	-----
February	4	43	99	141	166	141	162	64
March	4	45	121	209	224	189	215	66
April	1	53	234	232	167	187	151	42
May	7	68	185	325	204	171	259	32
June	26	67	167	253	217	196	196	33
July	8	56	191	339	168	188	130	27
August	20	49	222	387	187	217	120	28
September	24	53	208	283	176	153	105	14
October	44	49	192	219	158	179	84	-----
November	48	74	181	237	183	135	95	19
December	41	79	169	165	231	180	64	21
Total	231	678	2,070	2,982	2,221	2,103	1,713	346
Man-days lost	8,085	42,244	82,789	107,124	82,511	41,138	-----	-----

Sources: Patient Administration Division, Health Services Command, Department of the Army. (1) Morbidity Report (MED-78), 1965-1972. (2) Individual Medical Records (IMR), 1965-1970.

biopsies 30 to 90 days later. The pathological changes in each case progressively decreased in severity as fibrous interportal bands disappeared. Results were inconclusive, though they suggested that additional studies on larger numbers of patients might be considered.

The success of the 6th Convalescent Center's programs in returning hepatitis patients to duty resulted in publication of an official fact sheet on management and evacuation policy by Col. Philip J. Noel, Jr., MC, USARV (U.S. Army, Vietnam) surgeon (1970). The text of the fact sheet follows:

The projected possibility of a shortage of convalescent beds has not materialized. Therefore, the following management practices for viral hepatitis patients are being established.

All patients with viral hepatitis will be admitted to an acute treatment facility. When subjective symptomatology improves, the patient will be transferred to the 6th Convalescent Center.

Patients contracting viral hepatitis with over ten months in-country will be evacuated directly from the acute treatment facility to CONUS. Their clinical status should be stable prior to disposition.

Those patients transferred to the 6th Convalescent Center will undergo a program of treatment and graded physical exercise and reconditioning. This program will allow most of the affected individuals to be returned to full duty. Those patients whose clinical states do not warrant return to full duty within the limits of the established evacuation policies will be returned to CONUS.

The important point is the requirement for a physical activity program. However, with American withdrawal and the increase in hepatitis related to drug abuse, definitive conclusions about the long-term followup of patients treated with daily exercise could not be reached. Many questions remain for future study in large troop populations with hepatitis, especially if therapy continues to include early ambulation, exercise, and early return to duty.

It was indeed fortunate that the major complications of hepatitis were infrequently seen in Vietnam. Although a limited number of patients developed fulminant hepatitis, as a general rule most patients had uncomplicated

recoveries without significant sequelae. Problems with hepatitis in drug abusers will be discussed in volume III of this series on internal medicine in Vietnam.

Following the discovery of hepatitis B antigen, viral hepatitis could be divided into two major groups based on the antigen's presence or absence. To determine the importance of HB_s Ag positive hepatitis in Vietnam, Neumann and Benenson (1974) studied patients admitted to four U.S. military hospitals with a diagnosis of acute viral hepatitis. From August to December 1970, 175 American servicemen with acute viral hepatitis were studied and information was gathered on possible exposure to other persons with hepatitis and other epidemiological variables. HB_s Ag was detected in the serum of 71 of these soldiers. There appeared to be no relationship between the presence of the antigen and race, sex, location, eating habits, drug use, or contact with other hepatitis cases. The signs and symptoms of disease among all patients are noted in table 82.

The epidemiology of Type B hepatitis was studied only late in the conflict and includes Thai and Cambodian population samples as well as American. Table 83 demonstrates the prevalence of antigenic markers of hepatitis B subgroups in varied populations. The antigenic subtypes of Americans stationed in Southeast Asia were unlike those of the indigenous populations and those of Americans in the United States (Snitbhan et al. 1975). The adr subtype, present in 85 percent of asymptomatic Asians, is noted in only 2.5 percent of Americans in the United States. However, it is found in 40 percent of American asymptomatic carriers in Asia. Such differences indicate that Americans acquire HB_s Ag of subtype adr in Asia. Subtypes are region-dependent and not solely related to national origin. The presence of adr in Americans with hepatitis suggests transmission from the local population and the frequency of ayw confirms passage of infection from one American to another. The future study of subtypes can offer an effective epidemiological tool in review of large populations.

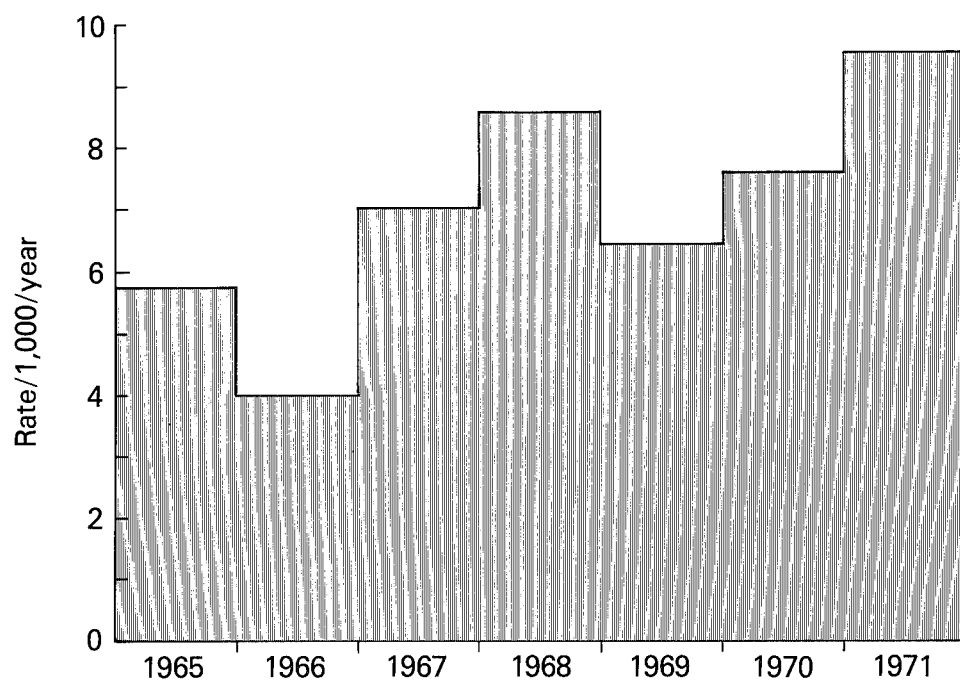
Epidemics related to Type A hepatitis were documented in units in Vietnam (Kunkel 1967). An episode of 71 cases of viral hepatitis among 1st Infantry Division personnel occurred between 3 April and 1 June 1967, while they were engaged in Operation JUNCTION CITY in War Zone C near the Cambodian border. All of the afflicted individuals had been in the field during the estimated time of the exposure; 92 percent were found to have been in one of the villages in the operations area, and 94 percent had been assigned duties at a single bridge site. Further investigation incriminated nonpotable ice supplies. Waterborne Type A hepatitis was well documented as far back as the 1930's and 1940's; however, it did not become part of everyday epidemiological consideration until the Delhi epidemic of 1955-56, which involved 29,300 cases (Mosley 1972). Scattered reports of epidemic outbreaks most likely related to iceborne or waterborne routes were characteristic of the Vietnam experience.

An analysis of hepatitis rates (chart 27) for the Vietnam war reflects three major phases. The first years, when activities were limited, were characterized by a low incidence rate. This was soon followed by rising rates as more troops became exposed to the environment and as established principles of hygiene and discipline were less effectively enforced. In 1968-69, however, personal hygiene

TABLE 82.—*Clinical findings among 175 American servicemen in Vietnam with acute viral hepatitis, August-December 1970*

Signs and symptoms	Number of patients	Percent of total
Sore throat	40	23
Cough	48	27
Nausea	150	86
Vomiting	117	67
Diarrhea	56	32
Abdominal discomfort	130	74
Malaise	157	90
Anorexia	158	90
Frank jaundice	105	60
Headache	80	46
Fever	84	48
Dark urine	170	97
Arthralgia	66	38
Lymphadenopathy	27	15
Splenomegaly	10	6
Hepatomegaly	55	31

Source: Neumann, D. A., and Benenson, M. W. 1974. Hepatitis B antigen in American personnel with acute hepatitis in the Republic of Vietnam. *Mil Med.* 139: 693-95.

CHART 27.—*Hepatitis incidence rates during the Vietnam war*

Source: Office of the Surgeon General, Department of the Army. Health of the Army, May 1966, May 1967, May 1968, May 1969, May 1970, May 1971, and May 1972.

was emphasized and unit awareness was aroused. This was followed by a drop in the incidence rate. However, as the problem of drug abuse developed, rates again rose. Studies at that time (Neumann and Benenson 1974) revealed 41 percent of the patients were afflicted with type B hepatitis; this was the first time such data were available in Vietnam and reflected a shift in the epidemiology of the disease. With U.S. withdrawal, further study was aborted.

TABLE 83.—Prevalence of hepatitis B surface antigen¹ and relative frequency of HB_s Ag subtypes in various populations in Southeast Asia

Nationality and population type	Number of people	HB _s Ag-positive		Subtyped/tested for subtype		Subtype frequency (percent)				
		Number	Percent	Number	Percent	adr	adw	ad	ayw	Other
Thai:										
Persons with acute hepatitis	119	51	42.9	24/51	47.0	92	0	8	0	0
Pregnant women	1,625	93	5.7	² 42/51	82.3	71	10	19	0	0
Female										
prostitutes	681	51	7.5	² 43/45	95.5	81	9	9	0	0
Urban dwellers (Bangkok)	695	59	8.5	48/59	81.3	81	13	6	0	0
Residents of northern Thailand	606	28	4.6	² 20/23	86.9	95	0	5	0	0
Blood donors	8,801	958	10.9	² 80/101	79.2	81	9	10	0	0
Cambodian blood donors	210	25	11.9	16/25	64.0	81	13	6	0	0
Vietnamese blood donors	35	5	14.3	3/5	60.0	67	0	33	0	0
American:										
Persons with acute hepatitis	174	68	39.1	² 40/60	66.7	20	5	23	52	0
Asymptomatic persons	2,365	16	0.7	14/16	87.5	40	27	0	27	6

¹HB_s Ag, detected by immunoelectro-osmophoresis.

²Selected for testing on the basis of CF titers $\geq 1:16$.

Source: Snitbhan, R.; Scott, R. M.; Bancroft, W. H.; Top, F. H., Jr.; and Chiwailp, D. 1975. Subtypes of hepatitis B surface antigen in Southeast Asia. *J. Infect. Dis.* 131: 708-11. Reprinted by permission of The University of Chicago Press. © 1975 by the University of Chicago. All rights reserved.

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Tropical Sprue

*Brigadier General Andre J. Ognibene, MC, USA, Donald Catino, M.D.,
Robert F. Proctor, M.D.,
Colonel Llewellyn J. Legters, MC, USA (Ret.), Edward J. Colwell, M.D., and
Joe A. Dean, M.D.*

HISTORY AND BACKGROUND

Tropical sprue has been defined as a syndrome consisting of chronic diarrhea, malabsorption of fat, xylose, and vitamin B₁₂, megaloblastic anemia, and nonspecific intestinal morphological abnormalities, other conditions having been excluded from the diagnosis, which responds to folic acid and/or antibiotic therapy (Lindenbaum 1973). It may have been described in an Indian medical textbook written between 1300 and 600 B.C., which mentions a wasting disease with chronic diarrhea, "a weakness of the digestive fire" leading to "impaired assimilation of ingested food" (Mathan 1973). The term "sprue" was first used by Sir Patrick Manson in 1830 (Klipstein and Baker 1970); an anglicized word, it is derived from the Dutch "sprouw," and is perhaps related to the Flemish word "spruwen" meaning "to sprinkle" (Oxford English Dictionary). Manson's description of the syndrome is remarkably similar to the now classic clinical description offered by Bahr (1915, p. 8), who characterized it as follows:

* * * a disease, essentially of the tropics. It is characterized by symptoms suggestive of a chronic affection of the alimentary tract and of the glandular organs subserving digestion.

The disease rarely runs an acute course, usually its progress is subject to periods of quiescence and exacerbation; it may remain latent even for a number of years.

In typical cases the tongue presents at first a peculiar raw appearance, most marked at the tip and edges, due to inflammation of the fungiform papillae. This process eventually leads to atrophy of all the papillae and to an eroded condition of the entire mucous surface of the mouth. Associated with these changes small yellow apthous ulcers often appear periodically on the tongue and the buccal mucosa, especially on the inner surface of the lower lip, the cheeks, the frenulum or the soft palate.

Flatulent dyspepsia is generally a marked feature and is accompanied by distension of the entire intestinal canal, particularly of the small intestine. This distension is only relieved by the frequent passage, especially in the early morning, of large, pale, frothy acid stools and of much flatus.

In many instances the inflammatory disturbance spreads down the oesophagus, causing great pain and difficulty swallowing; there may be, and usually is, extreme hyperaesthesia of the mouth parts, and the sense of taste is often in abeyance. In the later and profoundly anaemic stage there is a tendency to patchy pigmentation between the scapulae and on the interior aspect of the thighs.

Symptoms persisting, atrophy of all the organs of the body, particularly of the liver, and profound anaemia ensue. The disease unless promptly and properly treated ultimately proves fatal.

A significant portion of this chapter is from the unpublished paper by Catino et al. (undated): Tropical sprue. Prospective studies on incidence, early manifestations, and association with abnormal bacterial flora and intestinal parasitemia, January 1967-March 1968.

Tropical sprue was first discussed in the English language by Hillary in 1759, when small bowel disease was generally ignored (Mathan 1973, p. 978). This attitude persisted for a century and a half; one physician, Dr. Evan Evans, is quoted by Crohn, a student of his, as stating, around 1906, "There are no diseases of the small intestine, and what is more, we know nothing about them" (Lepore et al. 1957).

Since Evans's comment, tropical sprue has accounted for 30,000 deaths among 100,000 cases in one Indian epidemic (1960-62) alone (Mathan 1973, p. 979). Although it was ignored in the United States Army volumes on internal medicine in World War II, it accounted for significant morbidity and mortality during that war, with more than 1,500 cases described in Burma (Wellcome Trust 1971, pp. 13-23) and 1,069 cases reported among Italian prisoners of war in India (Stefanini 1948).

As is true of many diseases, variations are now reported in the severity and geographic distribution of tropical sprue-like illness. These reports have led to division of the syndrome into "tropical enteropathy," "subclinical enteropathy," and "idiopathic enteropathy." However, idiopathic enteropathy is in fact tropical enteropathy occurring in nonendemic geographical regions. Further discussion, therefore, will follow the nomenclature and definition of Klipstein and Baker (1970). They proposed that, until its etiology or etiologies could be determined, "tropical sprue should be regarded as a *syndrome* which occurs among the indigenous population and visitors to certain tropical regions that has variable clinical and laboratory manifestations which are related, in part at least, to the duration of the disorder and to the nutritional reserves of the individual." Malabsorption of two or more unrelated substances for which no etiology can be ascertained would be included in this definition.

Behind this statement are three basic tenets which summarize the current understanding of the illness:

1. The etiology and pathogenesis of the disease are unknown. It is now generally accepted that mucosal damage, probably of an infectious nature, must occur initially, followed by secondary events such as B₁₂ or folate deficiency which promote the illness.

2. Tropical sprue is confined to endemic tropical regions and affects both visitors and the indigenous population.

3. The phenotype of the illness varies from subclinical indolent disease to severe and fatal disease.

The subclinical enteropathy occurs in asymptomatic individuals (usually selected as control subjects) who reside in endemic areas and have a very high incidence of abnormal small bowel function and morphology. Nutritional status affects the expression of the disease (Mata et al. 1972).

The diagnosis is one of exclusion. Therefore, other causes of malabsorption syndromes, such as *Giardia lamblia*, *Strongyloides stercoralis*, *Capillaria philippinensis*, Coccidia, gluten-sensitive celiac disease, protein-calorie deficiency, intestinal tuberculosis, regional enteritis, Whipple's disease, and pancreatic exocrine insufficiency, must be eliminated as possibilities.

PATHOLOGY

Morphological changes of the small intestinal mucosa in tropical sprue as well as in subclinical enteropathy are well described by Haghighi and Nasr (1975) in a recent review. These changes are not specific. They may include fragmented or indistinct brush border, decrease in cell height so that cuboidal epithelium replaces the normal columnar epithelium, pseudostratification and loss of polarity and regularity of epithelial cell nuclei, various degrees of transepithelial migration of lymphocytes, pallor and enlargement of the crypt epithelial cell nuclei (megalocytosis), nuclear enlargement and rounding of villous epithelial cells with alteration in position of cell nuclei, subnuclear vacuolization, subepithelial edema sometimes involving vesicle formation (Gruenhagen spaces), basophilia of the villous epithelial cytoplasm, villous core edema, villous core lymphangiectasis, loss of the delicate ruffling of the villi, and thickening of the basement membrane with a change from the tinctorial characteristics of reticulin to those of collagen fibers (figs. 82 and 83).

The total absorptive surface is decreased; however, the mucosal thickness may be normal because of shortening of the villi associated with lengthening or tortuosity of the crypts. The villous shortening has been called partial villous atrophy; however, flat mucosa is rarely a feature of tropical sprue. All of the preceding changes are more severe in the proximal small intestine; the ileum may sometimes be spared. The proximal changes probably antedate the distal abnormalities.

ETIOLOGY

The unique epidemiological features of tropical sprue have suggested a possible infectious etiology, as indicated by the following studies. During an outbreak of dengue fever among Puerto Ricans, Sheehy, Artenstein, and Green (1964) obtained two jejunal biopsies. In one of these, villi were shortened and a striking inflammatory exudate was present in the lamina propria; the other specimen had a normal appearance. No d-xylose absorption tests were performed in these patients, and no patients without dengue were included as controls. Tropical sprue is known to be endemic in Puerto Rico.

In this study, adenovirus-4 was isolated from three asymptomatic patients with mild jejunitis and villous blunting, but polio virus and herpes simplex virus were also recovered from two of these patients. Adenovirus 2 infection has been associated with partial villous atrophy of the jejunum.* Reovirus was isolated from several members of a family with "steatorrheic enteritis" in a study by Sabin (1956). Stanley (1961) reviewed the subject of reoviruses and noted that three strains of this virus have been isolated in seven cases of steatorrhea in children. He also noted that steatorrhea is a regular feature of reovirus infection in mice. Thomas (1952) reported an epidemic of gastroenteritis with steatorrhea in children. An exhaustive search failed to reveal a bacterial or parasitic pathogen; a viral agent was suggested.

*Joe A. Dean, M.D.: Personal experience.



FIGURE 82.—Mucosa from proximal jejunum of a patient with tropical sprue, demonstrating shortened villi, crypt hypertrophy and inflammatory cell infiltration of the lamina propria. X 80.

Astaldi and associates (1964) were among the first to describe jejunitis and villous atrophy in "epidemic hepatitis." Partial villous atrophy and steatorrhea with normal d-xylose excretion were demonstrated by Sheehy, Artenstein, and Green (1964, p. 1025) in four American soldiers with hepatitis, but no control subjects were included for comparison. Conrad, Schwartz, and Young (1964) studied 25 American soldiers who contracted hepatitis in Korea after 6 weeks to 13 months of service there. They found diffuse granulomatous inflammation of the jejunum in all subjects and partial villous atrophy in those with a prolonged clinical course. During convalescence, the crypt areas were prominent and contained many Paneth's cells; the villi varied markedly in length and shape, and fusion of adjacent villi was apparent. The results of biopsies performed after com-

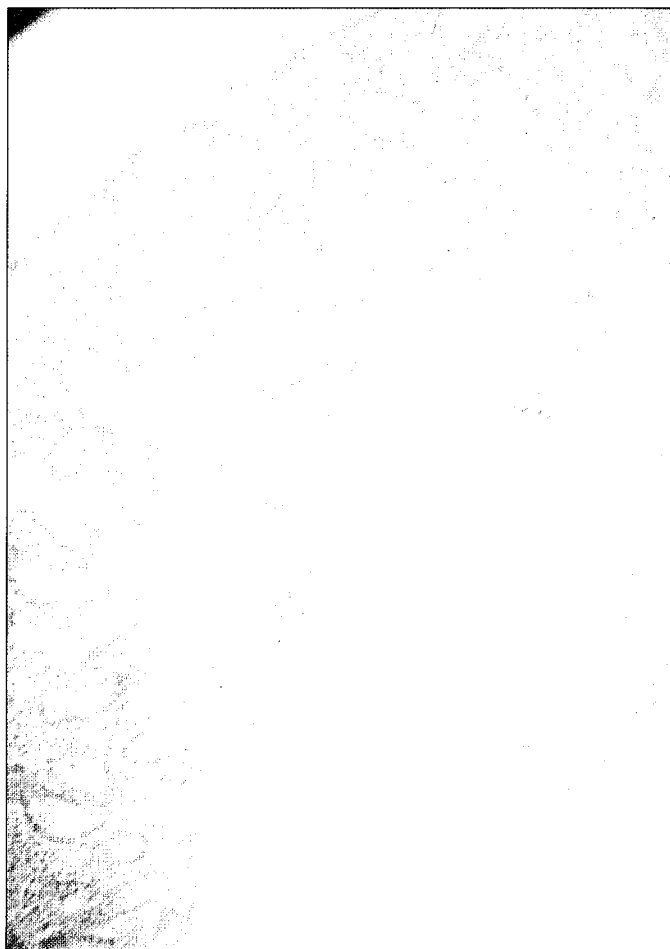


FIGURE 83.—Mucosal biopsy from jejunum of more severely ill tropical sprue patient, demonstrating moderately severe villous atrophy and crypt hypertrophy. X 80.

plete recovery were not given. The illustrations provided suggest that the villous atrophy seen could have been caused by tangential sectioning or Brunner's gland artifact. No control subjects were included and no attempt was made to rule out tropical sprue or adult celiac disease. LIVIM (lethal intestinal virus infection of mice) in newborn mice is also associated with subtotal villous atrophy of the intestinal tract (Biggers, Kraft, and Sprinz 1964).

Bacterial infections have, in several studies, been associated with acute and chronic malabsorptive states. Among the causative agents were *Salmonella*, *Staphylococcus*, *Vibrio cholerae*, nonvibrio cholera organisms, and *Shigella* (King and Joske 1960; Alexander 1958; Lindenbaum 1965). In some cases, malabsorption persisted for a year or more after the acute infection; these studies, which

were done on Pakistanis, who often have asymptomatic jejunitis and malabsorption (Lindenbaum, Jamiul Alam, and Kent 1966), did not include controls.

Kent (1966) demonstrated jejunitis and villous atrophy in the jejunal mucosa of rhesus monkeys given staphylococcus enterotoxin B but attributed the change to a nonspecific reaction of the jejunum to injury. Sprinz and coworkers (1966) demonstrated nonspecific, chronic, nonsuppurative inflammation or an acute granulomatous jejunitis in typhoid fever patients; these changes disappeared during the convalescent stage of the illness. In another study, Sprinz et al. (1962) showed the jejunal histopathology and results of absorption studies in asymptomatic natives of Thailand to be identical with those in Thais with a history of cholera or other gastroenteritis. Both groups show the nonspecific changes typical of socioeconomically depressed areas of the Middle and Far East. Rubin and Dobbins (1965) apparently agree that this picture is identical to that seen in tropical sprue.

Parasitic infections have also been implicated in certain malabsorptive states. Olsson and Johnston (1969) demonstrated jejunitis and duodenitis without villous atrophy in 20 U.S. Army personnel in Vietnam with *Plasmodium falciparum* malaria; 8 of 10 men tested failed to absorb d-xylose normally. No followup biopsies were done.

Necator americanus (hookworm) and *Strongyloides stercoralis* (strongyloidiasis) infections have been associated with malabsorption and jejunitis with partial villous atrophy in some patients (O'Brien and England 1966; Sheehy et al. 1962; Chaudhuri and Saha 1964; Milner et al. 1965). None of these studies was well enough controlled to rule out tropical sprue or the nonspecific jejunal changes seen in tropical areas. Other investigators have noted the absence of jejunitis in ancylostomiasis (Layrisse et al. 1964), and the histological response to adequate treatment is not well documented.

Giardiasis has been found in association with nonspecific jejunitis, villous atrophy, and steatorrhea, usually in pediatric patients (Hoskins et al. 1963; Yardley, Takano, and Hendrix 1964; Amini 1963). Da Silva et al. (1964) reported five adult Brazilian patients with giardiasis and jejunitis with villous atrophy, but all had other parasitic infections as well. Studies in adult populations in underdeveloped tropical areas have not been well enough controlled to exclude commonly occurring nonspecific jejunitis, tropical sprue, and adult celiac disease.

Subtotal villous atrophy of the jejunum and steatorrhea have been reported with *Isospora belli* infection. Nitrofurantoin therapy relieved the steatorrhea but produced no change in the biopsy picture (French, Whitby, and Whitfield 1964). A gluten-free diet to rule out adult celiac disease was not tried.

An unidentified species of the nematode *Capillaria* caused 500 cases of chronic malabsorption with 80 deaths in the Philippines. Autopsies were performed, but the nature of the jejunal lesion was not mentioned (NamruGram).

The past decades have been marked by multiple studies of intestinal microflora. Improvements in such studies have recently been made through new and more accurate anaerobic culture systems. Bacterial overgrowth in the small

intestine has been reported (Gorbach et al. 1970; Bhat et al. 1972). There is debate about the normal flora in the control group patients; in the series by Bhat and associates, there was no difference between the flora of healthy subjects and that of those with sprue.

The observations which follow, along with the studies just discussed, support the hypothesis that tropical sprue is an infectious disease. The beneficial effect of long-term antibiotic therapy provides the most impressive indirect evidence that antibiotic-sensitive infectious agents play an important part in the pathogenesis of the syndrome (French, Gaddie, and Smith 1956; Klipstein 1964; Guerra, Wheby, and Bayless 1965).

Epidemiologically, tropical sprue can behave like an infectious disease, as demonstrated by an outbreak reported from India (Keele and Bound 1946). It presented as an acute, explosive enteritis among British soldiers on a well-balanced diet during the Burma campaign (Keele 1946), and it was observed to spread through an isolated family in a manner suggestive of an infectious disease (Mathan, Ignatius, and Baker 1966).

The tropical distribution of the illness, affecting both permanent and transient inhabitants, suggests an endemic infectious agent. If patients with mild tropical sprue are evacuated to a temperate climate, they often have remission of symptoms without antibiotic or folate treatment, suggesting that they are thus freed from continued exposure to a tropical infectious agent (Gardner 1958).

The occasional clinical presentation of tropical sprue as an explosive enteritis is compatible with enterovirus infection. Coxsackie B3 virus has been isolated in tissue cultures of rectal swab material from 1 of 50 patients with untreated, symptomatic tropical sprue. However, the same virus was isolated from 1 of 10 asymptomatic patients with treated sprue. ECHO 8 virus was isolated from 1 of 48 controls (Bayless, Guardiola-Rotger, and Wheby 1966).

Many different parasites have been recovered from the stools of patients with tropical sprue, but with no greater frequency than in control groups of the general population. Milanes and associates (1946) found no parasites in the stools of 44 percent of the sprue patients they studied.

Ashford (1930-31) isolated *Candida albicans* in 80 percent of sprue patients. On the other hand, Swanson, Haley, and Wheby (1965) found no evidence of fungal elements in jejunal biopsy samples from 15 patients with tropical sprue cultured on Sabouraud's agar, nor in tissue sections stained with periodic acid-Schiff, Gomori methenamine silver, or hematoxylin-eosin which were examined specifically for hyphal elements. The data to date still do not conclusively establish a specific infectious etiology for tropical sprue.

RADIOLOGY

One of the most constant radiographic features of tropical sprue is dilatation of the lumen of the small intestine, especially of the distal jejunum. Generally, the dilated loops are long and tortuous, and the valvulae conniventes are

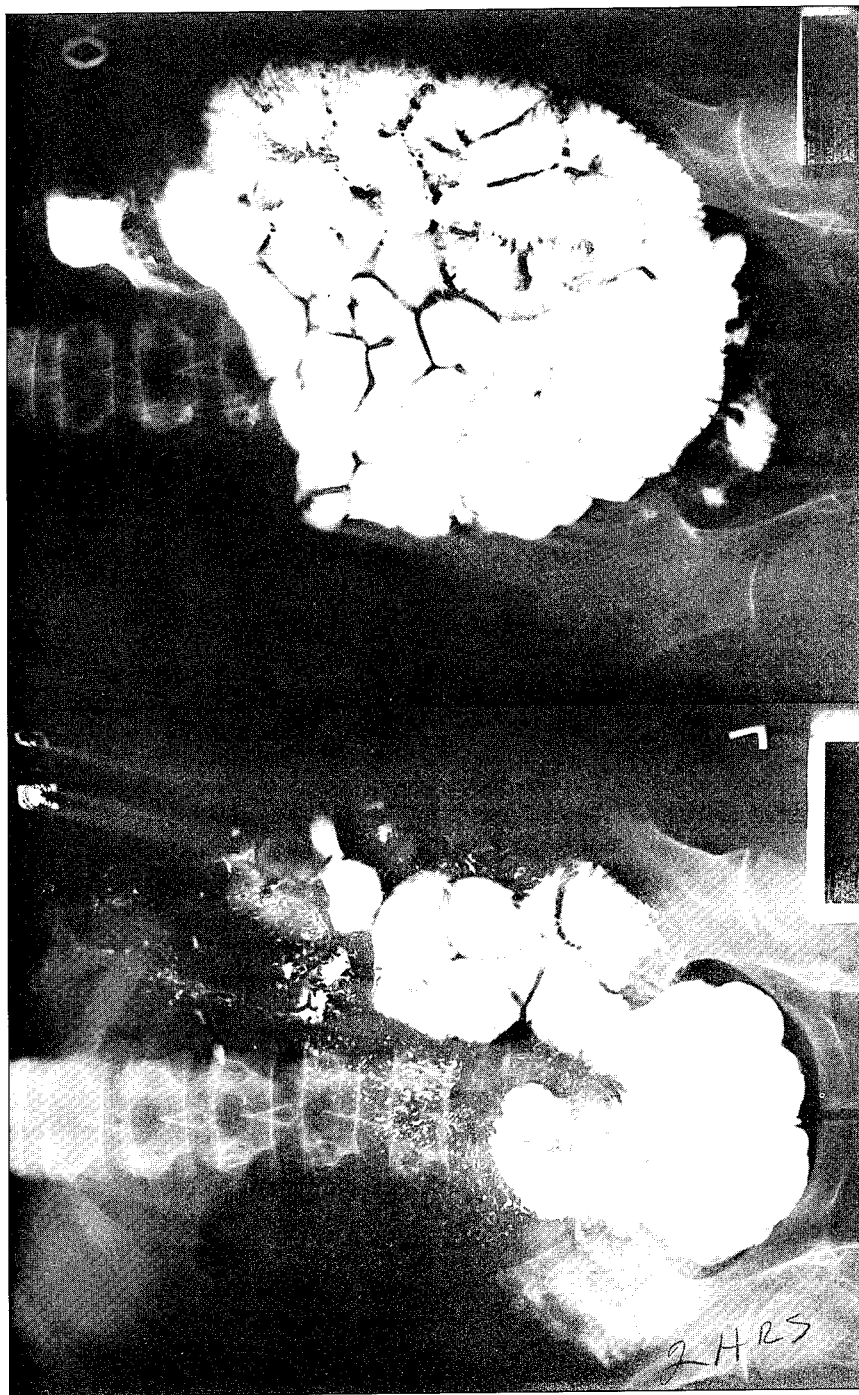


FIGURE 84.—Left and right: Barium radiographs from a patient with tropical sprue, showing dilatation of the loops of the small bowel, with thickening of mucosal valves, fragmentation of barium column, and moulage sign.

prominent. Dilatation may also be seen in the large intestine, where it may be pronounced. Segmentation is the second most common finding; this is usually most prominent in the ileum and is best seen in more advanced cases. Another constant phenomenon in most cases is excessive secretion in the intestinal tract (Lepore et al. 1957, pp. 119-20).

The term "moulage sign" describes the X-ray appearance of the jejunum, in which the folds appear to be entirely obliterated and the barium column resembles a tube filled with hardened wax. This picture is most frequently associated with hypersecretion and segmentation (Lepore et al. 1957, pp. 121-22). The X-ray patterns are shown in figure 84.

DIAGNOSIS AND TREATMENT

The diagnosis of tropical sprue is suggested by red cell macrocytosis, hypersegmentation of the polymorphonuclear leukocytes, and malabsorption as demonstrated by oral glucose tolerance, xylose excretion, and 72-hour fecal fat, in patients residing in tropical environments. Hypokalemia, hyponatremia, and hypochloremia are common. Hypocalcemia may be present, and hypoproteinemia is a frequent finding. IgG synthesis may be depressed. Bone marrow aspiration or biopsy may reveal a megaloblastic pattern. Anemia is generally present. Serum iron is normal to low, and serum vitamin B₁₂ levels are usually depressed. Serum folate levels may be low but are not necessarily depressed. Macrocytosis may be demonstrated in the gastric mucosa. Small bowel biopsy will disclose the morphologic changes previously discussed. Lactase deficiency is expected, but sucrase and maltase activity may be normal. Chronic sucrosuria may occur and reflects deficiency of disaccharidase activity. The presence of steatorrhea depends upon the severity of the mucosal lesion (Spiro 1970, pp. 465-71).

Tropical sprue usually resolves when the patient leaves the tropical endemic area and returns to a temperate climate. Therapy for patients with ongoing disease should aim at managing diarrhea, correcting nutritional deficiencies, and reversing the intestinal mucosal lesion. Diarrhea can usually be controlled with Lomotil, belladonna, opium, paregoric, or bismuth subcarbonate. Attention should be paid to fluid and electrolyte balance. Specific therapy for dehydration, lactic acidosis, hypokalemia, and hyponatremia should be instituted. Appropriate therapy for megaloblastic anemia and iron deficiency is also indicated. Orally administered iron and folic acid appear to be absorbed satisfactorily; however, vitamin B₁₂ should be given parenterally. A high-calorie and high-protein diet should be given, but unfortunately there are no clear guidelines for diet therapy in tropical sprue patients (Mathan 1973, pp. 986-87).

In addition to therapy with folic acid and vitamin B₁₂, broad spectrum antimicrobial agents have been reported to be effective. Tetracycline has been used most widely and has had the most success. Erythromycin is ineffective. Lincomycin may be effective, as may some sulfonamides (Lindenbaum 1973, p. 644). A short course of antibiotics (2 weeks) is usually effective; however, therapy may be continued up to 6 months, when necessary, to achieve a higher percentage of remission (Mathan 1973, p. 987). The overall prognosis is generally good, especially in those patients repatriated to temperate zones.

VIETNAM STUDIES

Data collected by the Surgeon's Office, U.S. Army John F. Kennedy Center for Special Warfare (Airborne), in collaboration with the Division of Medicine, WRAIR (Walter Reed Army Institute of Research), attest to the military significance of diarrheal disease and tropical sprue in operations by U.S. Army Special Forces in Southeast Asia (OS-CSW). Of the SF (Special Forces) troops studied, 56 percent experienced one or more attacks of acute diarrhea during a 6-month tour of duty; 5 percent experienced a diarrheal illness lasting longer than 2 weeks. Of randomly selected SF troops studied after return from a 6-month tour in Vietnam, 6.5 percent were found to have jejunitis associated with malabsorption. The continued deployment of troops to an area in which preliminary data showed a high incidence of acute diarrheal illness and jejunitis with malabsorption provided a unique opportunity for prospective studies of the natural history of early tropical sprue.

The U.S. Army Medical Research Team (WRAIR) Vietnam was deployed to the Special Forces operations detachment C in Can Tho, IV CTZ (Corps Tactical Zone) to study the tropical sprue syndrome (Catino et al.). Tropical sprue was known to be endemic in this area of the Mekong Delta (Colwell et al. 1968; 1971). Sixty-nine soldiers volunteered for a continuing study of intestinal absorption and small bowel mucosal abnormalities during their tour of duty. They were initially studied 1 to 2 weeks after arrival in Vietnam; all but two had normal small bowel biopsies. The importance of the further findings of the WRAIR team in these soldiers requires that they be discussed in some detail.

The relative proportion of fingerlike villi found, plotted according to the length of swallowed tubing, was progressively greater in biopsies taken from more distal sites, although there were wide individual variations. The association between the proportion of fingerlike villi and tube length was statistically significant ($p < .001$). Mean villous width in the 67 normal jejunal biopsies plotted against tube length showed a decrease with increase in tube length, but the association was not statistically significant ($p > 0.1$).

Histologic sections indicated that duodenal or very early jejunal tissue with Brunner's glands was found at tube lengths of 80 cm or less. The average tube length of initial jejunal biopsies was 107 cm, similar to the tube lengths used by

other investigators (Hirsch, Ahrens, and Blankenhorn 1956; Sprinz et al. 1962; Blankenhorn, Hirsch, and Ahrens 1955; Madanagopalan, Shiner, and Rowe 1965).

Mucosal measurements of 48 perpendicularly sectioned initial jejunal biopsies are summarized in table 84. There was close agreement between these results and those of other investigators (Madanagopalan, Shiner, and Rowe 1965; Doniach and Shiner 1957). The ratio of VH:CD (villus height to crypt depth) has been used as a measure of villous atrophy; a ratio of 4:1 is usually considered normal (Kent and Lindenbaum 1967; Swanson and Thomassen 1965). While the average VH:CD ratio was 3.59 in these subjects, the normal range was wide (2.39-5.09).

TABLE 84.—*Jejunal mucosal measurements of 48 Americans on arrival in Vietnam*

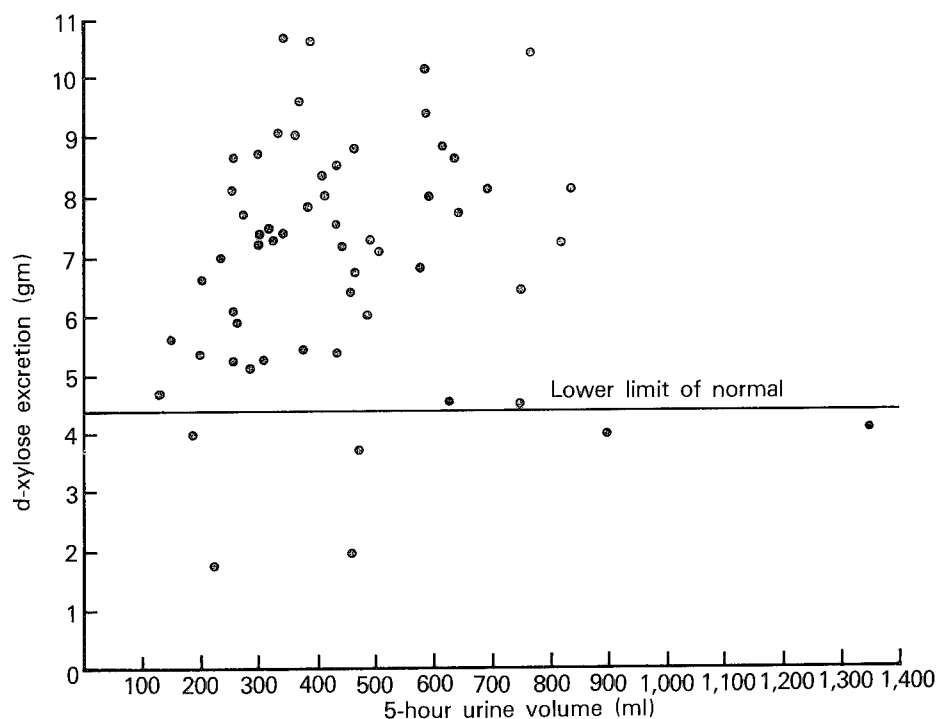
Item	Range	Mean	95 percent confidence limit
Total mucosal thickness, μ	491-915	670	470-869
Villus height, μ	349-671	498	335-660
Crypt depth, μ	96-208	140	80-200
Villus height to crypt depth ratio	2.39-5.09	3.59	2.47-471

Source: Catino, Capt. Donald; Proctor, Maj. Robert F.; Colwell, Capt. Edward J.; Legters, Lt. Col. Llewellyn J.; and Webb, Lt. Col. Charles R., Jr. Tropical sprue. Prospective studies on incidence, early manifestations, and association with abnormal bacterial flora and intestinal parasitemia, January 1967-March 1968, p. 30. Unpublished paper, undated.

The results of initial d-xylose excretion tests are shown in chart 28 with d-xylose excretion plotted against 5-hour urine volume. Subjects who excreted less than 200 ml of urine in 5 hours tended to have lower levels of d-xylose excretion. Repeat testing, with the ingestion of at least 700 cc of water over the 5-hour collection period, produced larger urine volumes and normal d-xylose excretion. However, after excluding "low volume" tests, the lower limit of d-xylose excretion in initial studies was still 3.01 g (normal 6.99 ± 1.99 g). The prospective approach allowed judging of each patient's variation in d-xylose excretion against his own initial value. The 13 patients who eventually developed tropical sprue had an initial d-xylose excretion of 8.2 g (7.10-9.51 g) in 5 hours.

Qualitative and quantitative bacteriology was done on 52 patients in the initial group. The results are shown in tables 85 and 86. These are similar to other published data on normal patients (Kalser et al. 1966; Dellipiani and Girdwood 1964; Cohen et al. 1967).

There was a statistically significant association ($p < 0.025$) between mild or moderate jejunitis and recent ADI (acute diarrheal illness), using Fisher's exact probability test. The two patients who had jejunitis with villous atrophy on initial examination had acute idiopathic gastroenteritis at the time of study. They were not considered to have had tropical sprue. Thirteen patients went on to develop tropical sprue, representing 19 percent of the total group (table 87).

CHART 28.—*d*-Xylose excretion and 5-hour urine volume at initial examination of Americans in Vietnam

Source: Catino, Capt. Donald; Proctor, Maj. Robert F.; Colwell, Capt. Edward J.; Legters, Lt. Col. Llewellyn J.; and Webb, Lt. Col. Charles R., Jr. Tropical sprue. Prospective studies on incidence, early manifestations and association with abnormal bacterial flora and intestinal parasitemia, January 1967-March 1968, p. 31. Unpublished paper, undated.

TABLE 85.—*Quantitative jejunal bacteriology of tropical sprue patients versus patients newly arrived in Vietnam*

Patient group	Number of patients	Total number intestinal bacteria/cc					
		< 10 ²		10 ² -10 ³		10 ⁴ -10 ⁸	
		Number	Percent	Number	Percent	Number	Percent
New arrivals	52	23	44	17	33	12	23
Tropical sprue patients	13	4	31	5	38	4	31

Source: Catino et al. (unpublished paper), p. 32.

Earlier studies of Special Forces returnees from Vietnam (OS-CSW) revealed that almost all those who developed tropical sprue had been deployed in IV CTZ. When the detachment locations of the patients who developed tropical sprue during the course of this study were plotted on a map of the Mekong River Delta, it appeared that most cases occurred in the Plain of Reeds area and the U

TABLE 86.—*Qualitative jejunal bacteriology of tropical sprue patients versus patients newly arrived in Vietnam*

Organism	Sprue patients (13)		New arrivals (52)	
	Number	Percent	Number	Percent
Oral flora:				
Alpha streptococcus	5	39	21	41
Beta streptococcus	0	0	2	4
Gamma streptococcus	0	0	9	17
<i>Staphylococcus aureus</i>	1	8	7	13
<i>Staphylococcus epidermidis</i>	4	31	12	23
<i>Staphylococcus citreus</i>	1	8	0	0
Diphtheroids	3	23	4	8
<i>Bacillus</i> species	1	8	7	13
<i>Neisseria flavescens</i>	1	8	0	0
<i>Hemophilus</i> species	0	0	1	2
Mimeae tribe	0	0	2	4
Fecal flora:				
<i>Aerobacter</i> species	2	15	6	12
<i>Pseudomonas</i> species	2	15	2	4
<i>Escherichia coli</i>	0	0	3	6
<i>Alcaligenes</i>	0	0	4	8
Paracolon	0	0	3	6

Source: Catino et al. (unpublished paper), p. 33.

TABLE 87.—*Incidence of tropical sprue in Vietnam*

Month of serial study	Number of biopsies on normal patients	Patients with sprue	
		Number	Percent
Initial	69	0	
Third	36	4	11
Sixth	24	4	17
Ninth to fourteenth	18	5	28
Total	147	13	9

Source: Catino et al. (unpublished paper), p. 35.

Minh Forest. Both are low, inundated areas of sparsely inhabited swampland where conditions favor the spread of waterborne or mosquitoborne diseases.

Twelve of the 13 patients with tropical sprue in the study of Catino et al. served as members of the remote Special Forces A detachments. Only one patient with sprue served at an urban B detachment headquarters; his illness was mild and abated spontaneously. The relationship of tropical sprue and service in A detachments is statistically significant ($p < 0.025$). Other data collected by the WRAIR team at the Dong Tam base of the 9th Infantry Division indicated that personnel at this location did not develop tropical sprue. They remained on this large post most of the time and went on 2- to 3-day combat operations, returning to the "protected" base environment.

There were no significant differences between the normal and sprue groups with regard to age, race, or rank. Prior duty in tropical areas did not seem to protect from or predispose to the development of tropical sprue. There was no relationship between the frequent ingestion of Vietnamese food, protein-deficient diet, scarcity of fresh vegetables in the diet, or consumption of contaminated food or water or of rancid fats, and the development of tropical sprue. Those who took army vitamins ("Non-A-Vits") were not protected; however, this preparation does not contain folic acid.

Two of the tropical sprue patients had FUO (fever of undetermined origin) during the 3-month interval before diagnosis, while none of the normal subjects had such an illness. Those with sprue had a total weight loss almost double that of the control group. In general, these 13 patients were not severely ill and would fall into Gardner's (1958) categories of stage 1 or 2 tropical sprue. Complaints of weakness, malaise, intermittent noneffectiveness, anorexia, nausea, vomiting, dyspepsia, and flatulence were all more common in patients with sprue than in controls, but these complaints did not permit clinical diagnosis of tropical sprue. Both groups had complaints of diarrhea, but the tropical sprue group had more days of diarrhea per month and more bowel movements per day during these episodes. Those with sprue more often had a constant diarrhea with loose, fatty-looking stools. However, these characteristics were not unique, and the symptoms of individual patients varied considerably. Three of the tropical sprue patients had subclinical disease, while those with normal intestinal biopsies occasionally had a classical clinical picture of sprue (table 88).

TABLE 88.—*Symptoms during the 3-month interval before diagnosis of sprue versus symptoms of patients without sprue, duodenitis, or parasitic diseases*

Symptom	Sprue patients (13)	Nonsprue patients (23)
Fever	2	0
Total weight loss (average)	16 lb.	9 lb.
Weakness/malaise	5	3
Intermittent noneffectiveness	3	2
Anorexia	5	4
Nausea/vomiting	5	4
Dyspepsia	6	2
Abdominal pain (with acute diarrheal illness)	6	8
Flatulence	4	3
Constipation	0	1
Diarrhea:		
Episodic	9	16
Constant (1 to 3 months)	2	1
Stool:		
Watery	7	13
Loose	4	4
Steatorrhea	3	2
Onset:		
Acute	8	14
Insidious	3	3
Average number days of diarrhea per month	9.1	5.6
Average number of stools per day with ADI	5.7	3.3

Source: Catino et al. (unpublished paper), p. 40.

The jejunal biopsies in the sprue patients were obtained at an average tube length of 99.1 cm (range 75 to 110 cm). None contained Brunner's glands, so they must have been taken from the first portion of the jejunum, just past the ligament of Treitz. Although most jejunal mucosal specimens from sprue patients were not grossly abnormal upon examination through the dissecting microscope, fingerlike villi always appeared decreased. Ridgelike villi and/or thick leaflike villi were present in all; two specimens contained convoluted villus ridges. Only two specimens showed white, dull, poorly defined, shortened villi with increased mucus adherent to them. Therefore, although the mucosal appearance with stereoscopic microscopy was often suggestive, the diagnosis of tropical sprue was of necessity made by light microscopy.

Inflammation of the lamina propria of the villi and subvillous thickness of the mucosa was moderate to severe in most cases, though one patient had minimal changes (table 89). Branching and fusion of villi were often seen. Mucosal measurements were abnormal; they showed the characteristic decrease in total mucosal thickness, villous shortening, and some broadening, with distinct deepening of the glandular crypts. Thus, the villus:crypt ratios were low (0.9 to 2.4) and always less than the initial values.

TABLE 89.—Clinical picture and laboratory data of 13 tropical sprue patients, Vietnam

Patient	Month at diagnosis	Symptoms ¹	Weight loss (lbs.)	Jejunitis	Villus crypt ratio	Xylose	Carotene	Total jejunal bacteria	Stool pathogens
1 —	3	+	21	minimal	2.4	5.0	89.5	< 10 ³	0
2 —	4	0	11	mild	1.2	4.4	110.7	10 ⁵	0
3 —	4	0	—	severe	1.4	5.4	106.5	0	0
4 —	4	0	24	mild	1.9	7.4	197.0	< 10 ³	0
5 —	6	+	10	severe	0.9	2.2	71.4	0	0
6 —	6	+	—	moderate	2.3	2.2	—	0	<i>Bethesda ballerup</i>
7 —	6	+	14	severe	1.1	4.9	121.4	< 10 ³	0
8 —	7	+	9	mild	2.2	6.9	—	0	0
9 —	9	+	—	mild	2.1	5.8	—	10 ²	0
10 —	9	+	17	severe	0.9	2.0	71.4	10 ⁷	0
11 —	9	+	9	severe	1.1	2.8	107.1	10 ⁶	0
12 —	9	+	23	moderate	1.6	2.4	—	10 ²	0
13 —	14	+	18	moderate	1.3	4.6	—	10 ⁴	0

¹(+) indicates presence; (0) indicates absence; (—) indicates not measured.

Source: Catino et al. (unpublished paper), p. 41.

The average d-xylose excretion for the 13 tropical sprue patients was 4.3 g/5 hours. While five patients had d-xylose excretion above the "lower limit of normal" (5 g/5 hours), all of them excreted 1.2 to 4.7 g less than they had in their baseline studies; and thus these later findings may be considered abnormal. These five patients tended to have milder inflammatory (minimal to mild) and atrophic (1.4 to 2.4) changes than the patients with grossly abnormal d-xylose excretion. Six patients with normal intestinal biopsies demonstrated abnormal xylose absorption (0.93 to 3.45 g/5 hr). All of these patients had acute diarrheal illness; five of the six had 10⁴ to 10⁶ intestinal bacteria/cc of aspirate, but none had parasitism or enteric bacterial pathogens.

Only 3 of the 13 patients with sprue had low serum carotene. Carotene is stored in the liver and may take months to become depleted. The short duration of illness in these 13 patients may explain the normal serum carotene found in most cases.

A comparison of normal jejunal flora with the flora of the 13 sprue patients is presented in table 85. There was no significant difference between the two groups. Table 86 shows a comparison of the types of bacteria found in the jejunal aspirate of tropical sprue patients and the control population. Both groups had a predominance of swallowed oral and upper respiratory organisms; there is no evidence of a predominance of fecal flora in sprue patients. In fact, most oral and fecal organisms were more common in the group without tropical sprue.

Only 1 of the 13 patients with tropical sprue harbored an organism which might be construed as a pathogen, *Bethesda ballerup*. The same organism was isolated from one other patient with sprue 6 months after the diagnosis was made, and from another sprue patient 4 months after diagnosis, following a spontaneous remission. *Bethesda ballerup* was also isolated from a patient with duodenitis and villous atrophy and one with ADI. *Shigella* species and *Providencia* species were isolated from 12 patients without sprue, some of whom had enteritis at the time.

No parasites were found in the stool or jejunal aspirate of patients with sprue at the time of diagnosis. *Ascaris lumbricoides* was found in one patient 5 months before the development of sprue. In another patient, hookworm infection developed 5 months after the diagnosis of sprue was made; mild jejunitis and villous atrophy were still present in this patient despite folate and tetracycline therapy. *Giardia lamblia* was identified in two patients with diarrheal illness. *G. lamblia* and hookworm species were isolated from another patient who was asymptomatic. The latter three patients did not have tropical sprue.

The WRAIR team studies were undertaken following the report of Sheehy and associates (1965) in which histologic abnormalities and malabsorption had been noted in 12 percent of American servicemen returning from Vietnam. The WRAIR team found a 28-percent peak incidence in selected troops in the Mekong Delta. Despite these dramatic reports, the impact of tropical sprue upon U.S. troops in Vietnam was never fully investigated. McCloy, who served as a gastroenterologist at the 8th Field Hospital, and Hofmann, of the Mayo Clinic, suggested the existence of tropical sprue in the Nha Trang area in their treatise (1971) on tropical diarrhea. Air Force physicians at nearby Cam Ranh Bay reported 12 cases in a 1-year period (Miller et al. 1974). Although biopsies were not performed, clinical findings were extensively summarized (table 90). Laboratory abnormalities found in the 12 sprue patients, plus two patients with clinical evidence of sprue, were as follows (number with finding/number tested) (Miller et al. 1974, p. 20):

Abnormal d-xylose.....	14/14	Low carotene.....	3/3
Flat glucose tolerance.....	9/10	Anemia.....	4/?
Neutral fat in stools.....	11/12	Abnormal small bowel biopsy.....	8/10
Low cholesterol.....	6/7		

TABLE 90.—Findings in 12 patients with tropical sprue, 12th USAF Hospital, Cam Ranh Bay, January 1968-January 1969

Clinical manifestation	Patient											
	1	2	3	4	5	6	7	8	9	10	11	12
Diarrhea (weeks)	8	16	4	8	16	16	4	12	2	12	4	9
Weight loss (lbs.)	17	26	21	15	45	30	11	35	10	10	28	20
Stools (per day)	6	8	15	10	9	7	12	8	10	10	8	7
Characteristic stools ¹	+	+	+	+	+	+	+	+	+	+	+	+
Bloating/cramping	+	+	+	+	0	+	+	0	+	+	+	+
Weakness/fatigue	+	+	+	+	+	+	+	+	0	+	+	+
Anorexia	0	+	+	+	0	0	+	0	+	+	+	+
Abnormal d-xylose	+	+	+	+	+	+	+	+	+	+	+	+
Flat glucose tolerance	+	+	0	+	+	+	—	—	—	—	—	—
Increased stool fat	+	+	+	+	+	+	+	+	+	+	+	+
Abnormal bowel X-ray	+	+	+	+	+	0	+	+	0	—	—	+
Low serum lipids	—	+	+	+	0	+	—	0	+	—	+	—
Anemia	+	0	0	0	+	+	0	+	0	0	0	0

¹(+) indicates presence; (0) indicates absence; (—) indicates not measured or not recorded.

Source: Miller, M. B.; Loftus, P. M.; Lohr, D. C.; Reynolds, R. D.; Bratton, J. L.; Hanson, J. P.; and Keil, P. G. 1974. Tropical sprue in South Vietnam. *Mil. Med.* 139: 17-20.

The presence of U.S. forces in Vietnam allowed further elucidation of the syndrome of tropical sprue. The spectrum of disease, subclinical to moderately severe, was reemphasized, as was the lack of specificity of clinical symptomatology. The overall impact on the combat effort is unknown, but understanding of diarrheal syndromes was increased and tropical sprue was shown to be a cause of noneffectiveness, especially in troops operating with indigenous populations in tropical areas.

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Part V

CLINICAL DISORDERS: RENAL DISEASES

Renal Care

*Daniel L. Macken, M.D., James H. Kneppshield, M.D.,
James V. Donadio, Jr., M.D., and Andrew Whelton, M.D.*

Section I. The 629th Medical Detachment (Renal)

Daniel L. Macken, M.D., and James H. Kneppshield, M.D.

The 629th Medical Detachment (Renal) was a specialized intensive care unit capable of sustaining patients with renal failure by hemodialysis or peritoneal dialysis. The renal unit served as a referral center for all four CTZ's (Corps Tactical Zones) in the Republic of Vietnam, and provided care to U.S. civilians, Vietnamese civilians and military personnel, and other foreign nationals with ARI (acute renal insufficiency). American military and civilian patients with chronic renal failure underwent dialysis until their conditions stabilized and then were evacuated as rapidly as possible to CONUS (continental United States). If hemodialysis was required en route, it was available at Tachikawa Air Force Base Hospital in Japan, Clark Air Force Base Hospital in the Republic of the Philippines, Tripler General Hospital in Honolulu, and Travis Air Force Base near San Francisco.

ARI has been a significant medical problem in combat zones. During World War II, before the advent of the artificial kidney, the fatality rate among severely wounded ARI patients exceeded 90 percent. The time lapse between injury and definitive treatment often ranged from 1 to 3 days (MD-S2). By the 1950's, the artificial kidney had been developed. Shortly after the United States entered the Korean conflict, the WRAIR (Walter Reed Army Institute of Research) Surgical Team, which included Maj. (later Brig. Gen.) William Meroney, MC, Maj. (later Col.) Paul Teschan, MC, Capt. Lloyd H. Smith, MC, Dr. George Schreiner, and many others, established an artificial kidney unit in the field at the 11th Evacuation Hospital. With a great deal of ingenuity, a fuel tank from an aircraft, a cookstove, yards of rubber tubing, and a roller drum artificial kidney of that era, the unit started work.* Mortality from posttraumatic ARI

*Col. Paul Teschan, MC: Personal communication.

was reduced to 68 percent when dialysis was required and 30 percent when medical treatment alone was needed (Smith et al. 1955). During this conflict, the delivery of medical care was facilitated by the development of battalion aid stations in forward areas, and helicopters were used to hasten the evacuation of seriously wounded patients to surgical hospitals. The average evacuation time for patients not developing ARI was reduced from days to 3½ hours (Teschman et al. 1955).

The acceleration of U.S. involvement in the Vietnam conflict prompted the decision, in 1965, to establish a renal unit in South Vietnam. The 629th Medical Detachment, formed from WRAIR personnel, arrived in Saigon in April 1966. For a short time before arrival in Vietnam, the renal unit was housed at Camp Zama, Japan, and supported by the 406th Medical Laboratory. This was the beginning of a close association with the laboratory, which provided support for patient care and research in later years.

The initial planning and deployment of the renal unit were directed by Colonel Teschan, then heading the Division of Medicine at WRAIR. Capt. (later Maj.) Ronald Easterling, MC, and Capt. Gary Cordis, MC, were sent from Washington, D.C., to Vietnam. Soon after the unit became functional at the 3d Field Hospital in Saigon, Maj. (later Col.) Craig Canfield, MC, joined it.

Capt. (later Maj.) Andrew Whelton, MC, and Capt. James V. Donadio, Jr., MC, were assigned to the renal unit in 1966 and became the first permanent members. They developed the unit's ability to manage a large number of seriously wounded ARI patients. They established the unit's research capabilities with studies on the dialysance of quinine and recorded experiences with post-traumatic ARI and renal failure in association with malaria, typhus, G6PD (glucose-6-phosphate dehydrogenase) deficiency, and phosphorus burns. They attempted to establish communication channels to disseminate information to hospitals countrywide about the prevention and early management of ARI, and they developed a working relationship with the University of Saigon School of Medicine.

Capt. Rolland F. Regester, MC, and Capt. M. David Cohen, MC, followed in late 1967 and 1968, respectively. At this time use of the renal unit's services was increasing; during their stay the number of admissions was approximately double that of the preceding year. They were responsible for operation of the unit during the *Tet* offensive of 1968, which brought a heavy influx of serious casualties. After their departure, the unit was managed by Capt. Frederick Oerther, MC, and Capt. Robin Oxman, MC.

An evaluation of the unit's operation and goals was undertaken by Colonel Teschan, Col. Samuel Jefferson, MC, and Maj. (later Lt. Col.) James H. Kneppshield, MC. Unfortunately, separate parallel command channels had led to administrative uncertainty and misunderstanding; the complete autonomy originally contemplated was not practical in the operational setting of the 3d Field Hospital. After Major Kneppshield and Capt. (later Maj.) William Stone, MC, arrived in Vietnam in 1968-69, they recommended that the unit come under the direct command of the hospital commander, Col. Merle Thomas, MC, instead of that of the USARV (U.S. Army, Vietnam) surgeon.

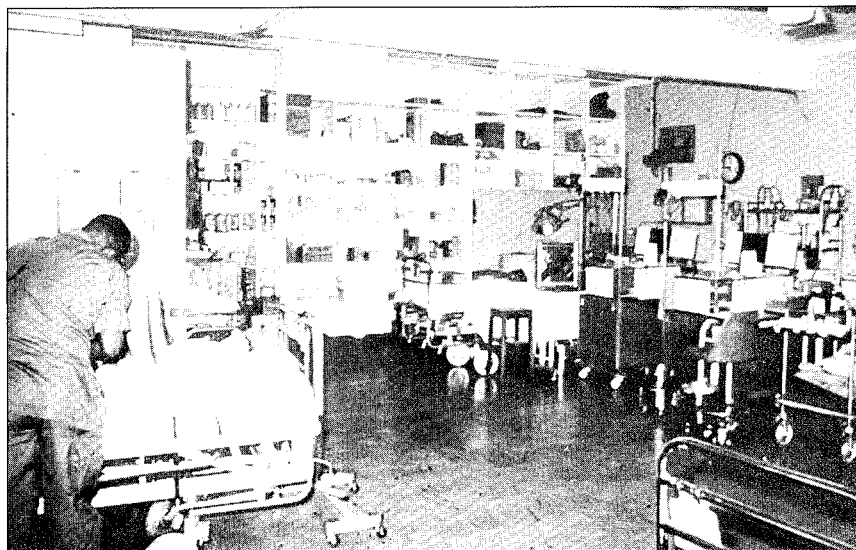


FIGURE 85.—View of the 629th Medical Detachment (Renal), 3d Field Hospital, 1969.

The unit's successes in reducing mortality were well documented, but it was apparent that broader expertise in the management of renal failure patients was necessary if treatment was to be more successful. Two more physicians were added to the staff. Maj. (later Lt. Col.) Ronald Fischer, MC, brought experienced judgment in the surgical management of renal failure patients and improved the liaison with the surgical service of the hospital. Capt. (later Lt. Col.) Daniel Macken, MC, broadened the acute care resources of the unit, particularly in the management of cardiopulmonary complications and shock. In addition, the technician and nursing complements were increased and the unit was expanded from 6 beds to 11 (fig. 85). The renal unit accepted more patients in 1969 than in any previous year.

The high mortality among the large surgical population of the unit stimulated the staff to seek methods to prevent or manage such complications of renal failure as sepsis, coagulation defects, stress ulcers, and respiratory, hepatic, and circulatory failure.

A campaign stressing ARI prevention and early management was launched by means of consultant visits to many outlying hospitals, distribution of printed material countrywide, and formal lectures given at in-country medical meetings. This resulted in improved medical care for the renal failure patient at all levels in the chain of medical evacuation.

Greater involvement in the medical education of Vietnamese physicians was initiated through lectures on electrolyte balance and the management of renal failure patients at the University of Saigon School of Medicine, participation in ward rounds at Cong Hoa Military Hospital and Cho Ray Hospital, and efforts to establish hemodialysis capability in the civilian community and at Cong Hoa Military Hospital. Vietnamese physicians began tours involving patient care at the renal unit, and Vietnamese nurses and corpsmen were trained in the

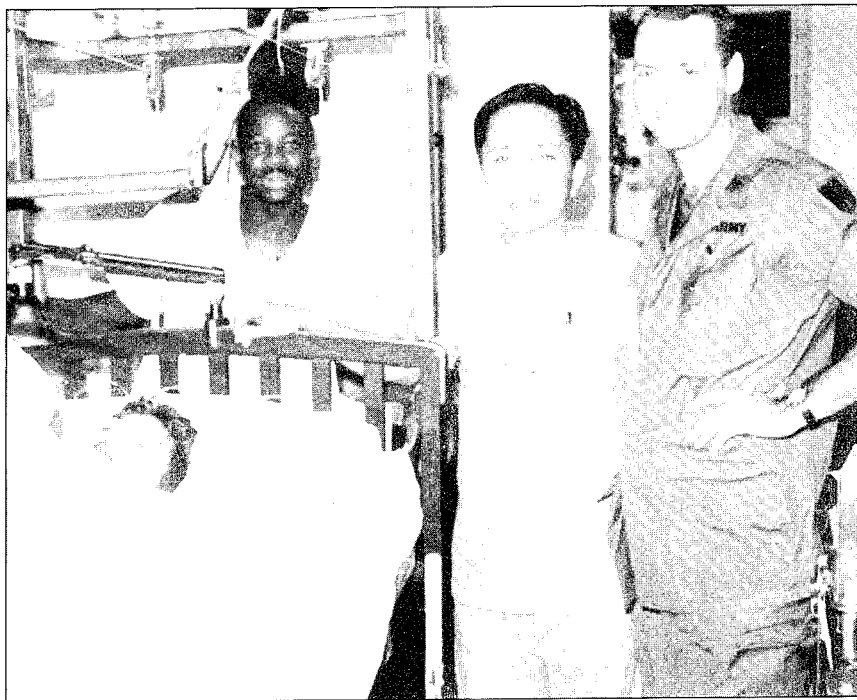


FIGURE 86.—U.S. Army Sergeant Osborn, ARVN Sergeant Chew, and Maj. James H. Kneppshield with patient during training of ARVN (Army of the Republic of Vietnam) dialysis technicians for Cong Hoa Military Hospital.

techniques of intensive care nursing and dialysis. As an outgrowth of this close relationship with the community, a related-donor kidney transplant was performed on a 20-year-old Vietnamese man at a local civilian hospital in a joint effort by Vietnamese and American medical teams (see chapter 23). The favorable publicity surrounding this operation gave impetus to the development of an artificial kidney unit in a Vietnamese hospital.

Later in 1969, Maj. William Miller, MC, arrived in the unit, followed by Maj. David Kessler, MC, and Capt. William Chenitz, MC. During this period, the equipment was augmented and updated. The immunologic behavior of patients with renal insufficiency was explored in an investigation of granulocyte motility. Beginning in 1970, the number of monthly admissions to the unit gradually decreased as American involvement in hostilities declined.

In mid-1970, a new team—Maj. Jay Dennis Morton, MC, and Maj. Paul Balter, MC—arrived. They continued the research protocols and further developed techniques for peritoneal lavage in patients with abdominal wounds, using the Tenckhoff catheter. Personnel from Cong Hoa Military Hospital were trained as dialysis technicians (fig. 86); these trainees became proficient in peritoneal dialysis and set up a unit at their own hospital. Later, under the direction of Maj. James D. Flynn, MC, an artificial kidney center was established at Cong Hoa Military Hospital after physicians and technicians were trained in the 629th Medical Detachment. Major Flynn arrived as American involvement in

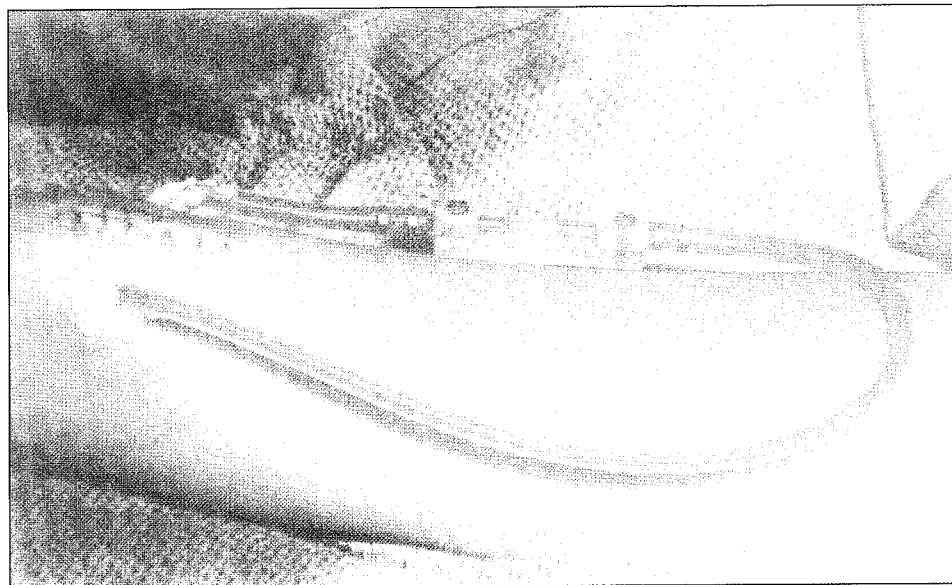


FIGURE 87.—The Teflon-Silastic arteriovenous shunt used by the 629th Medical Detachment (Renal).

hostilities was ending, and because of progressively decreasing admissions he deactivated the unit on 1 February 1972. The dialysis equipment was given to the South Vietnamese Medical Corps at Cong Hoa Military Hospital.

Section II. Renal Center Operation in a Combat Zone

James V. Donadio, Jr., M.D., and Andrew Whelton, M.D.

Hemodialysis for clinical treatment of ARI (acute renal insufficiency) was first used during the late 1940's. The development of dialysis and the progress in the management of ARI patients since that time represent two of the great milestones in the history of medicine. Much of our present-day knowledge of posttraumatic ARI stems from the original experience gained during the Korean war (Meroney and Herndon 1954; Teschan et al. 1955; Smith et al. 1955). Therefore, it is not surprising that in the conflict in Vietnam much interest focused on the problem of renal failure.

LOCATION

The physical plant of the renal unit included a six-bed ward containing a dialysis area; laboratory space and equipment for performing basic blood and

urinary examinations were also located in the unit. Two Kolff twin-coil artificial kidney units were used for hemodialysis, as were Teflon-Silastic arteriovenous shunts (fig. 87). Peritoneal dialysis was carried out using commercially prepared dialysis fluid and administration sets and straight polyethylene peritoneal catheters.

However, merely having the requisite equipment and personnel was not sufficient; an appropriate location was also important. Requirements included: an adjacent aircraft landing strip and heliport; laboratory support on a 24-hour basis for serum electrolyte, creatinine, and urea nitrogen determinations; adequate and reliable electrical power; availability of preheated processed water at all times (100 gallons per hemodialysis); and adequate medical maintenance facilities. The location in Saigon fulfilled all these requirements.

The significance of the in-country location of the renal unit deserves discussion here. Air evacuation of most types of patients from Vietnam to other hospitals in the Pacific area or to the continental United States was well established and was a remarkable achievement. However, transferring a patient from the referring hospital to an air facility and, in turn, from the air facility to the eventual receiving hospital, required as much as 24 hours. Thus, precious time was lost in the early critical phase of illness in patients with ARI. Hyperkalemia and unrecognized extracellular fluid volume excess with pulmonary edema were likely to occur in many of these patients (Teschner et al. 1955).

Those unavoidable delays in patient evacuation from the combat zone were reduced by the strategic location of the renal unit. The 3d Field Hospital was located adjacent to the large U.S. Air Force Base at Tan Son Nhut, Saigon, a hub of in-country air traffic, and patients were rapidly transported by fixed-wing aircraft and helicopter to this base. With prior notification by telephone of patient referral, no time was lost in coordinating and continuing intensive medical or surgical care and initiating dialysis when necessary. Accompaniment of patients by an attending physician from the referring hospital was recommended, to maintain continuity of patient care.

Laboratory support is an integral part of any renal unit, and laboratory personnel must be constantly ready to provide prompt and reliable service. The renal unit received excellent support from the 406th Mobile Laboratory, 3d Field Hospital. All routine hematologic and chemical tests, including blood gas determinations, were rapidly available. The more esoteric chemical or serologic study specimens were shipped by air freight to U.S. Army research laboratories in Japan or the United States. Electrical power failures during hemodialysis procedures were, fortunately, infrequent, and the use of twin-coil artificial kidneys with roller-pump mechanisms allowed the pump mechanism to be cranked by hand when necessary. However, when finger-pump mechanisms (Sigma-motor) were used, dialysis had to be discontinued during power failures. Spare parts for artificial kidneys were not readily available in the combat zone; therefore, a supply of additional parts was maintained locally. Servicing and upkeep of renal unit equipment were carried out by the medical maintenance personnel of the 3d Field Hospital.

PERSONNEL

Dialysis is but one element in the medical and surgical management of ARI patients. The renal center in Vietnam provided total care to its intensive care and dialysis patients, avoiding the too narrow concept of a "dialysis service." Patients with ARI are better managed when total primary care is under the direction of one team of physicians and nurses.

Experience in 1967 showed that two physicians were adequate to staff the unit. However, a third physician with renal training was added to the 3d Field Hospital general medical staff and provided backup assistance when necessary. Two nurses were insufficient to staff the unit, since this required that they work 12-hour shifts, 7 days a week. Nursing support was augmented with personnel of the 3d Field Hospital.

Although peritoneal dialysis and hemodialysis are now considered standard treatment techniques, it is mandatory that physicians with renal and dialysis training supervise and conduct these procedures; such physicians must obviously staff the renal unit. Unfortunately an MOS (military occupational specialty) identifying nephrologists was not established until after the war's end (AR-chg).

The number and MOS breakdown of corpsmen assigned to the renal unit were adequate for proper patient care and the operation of dialysis equipment. At the time of the unit's initiation, there was no primary or secondary MOS for enlisted personnel to indicate prior training or experience in renal dialysis work. Later, recognition of this specialized training by an appropriate MOS designation ensured assignment to a renal unit. Meanwhile, recommendations had to be made to the USARV surgeon to assign trained dialysis technicians to the unit so that their specialized training could be used for a full tour of duty in Vietnam.

CLINICAL RESULTS

Fifty-seven patients with ARI were referred to the unit during the first 16 months of operation. The authors' experience included 45 cases treated during a 12-month period (September 1966-September 1967). Thirty-one of these patients with established renal failure required prolonged dialysis treatment, using either hemodialysis or peritoneal dialysis (table 91).

The spectrum of contributing etiologies was quite varied. There were three main categories: medical causes, posttraumatic renal failure, and miscellaneous causes (table 92). Among the medical causes, tropical illnesses played a prominent role. Although malaria, leptospirosis, amebiasis, and rickettsial infections were observed with some degree of frequency among U.S. personnel in Vietnam, the development of ARI offered additional challenge in diagnosis and management. Peritoneal dialysis, a simple, safe, and effective procedure, was particularly favored in the nontraumatic cases.

Twenty-four cases of posttraumatic renal failure were referred to the unit. Many factors led to the development of ARI in these patients. The majority received multiple organ and extremity wounds with hemorrhage, oligemic shock,

TABLE 91.—*Dialysis procedures, 629th Medical Detachment (Renal), September 1966-September 1967*

Type	Number of patients	Number of dialyses	Total hours
Hemodialysis	17	68	472
Peritoneal dialysis	14	23	1,003
Total	31	91	1,475

Source: Donadio, J. V., Jr., and Whelton, A. 1968. Operation of a renal center in a combat zone. *Mil. Med.* 133: 833-37.

TABLE 92.—*Causes of acute renal insufficiency in Vietnam, 629th Medical Detachment (Renal), September 1966-September 1967*

Item	Number of patients	Number of survivors
Medical causes:		
Acute falciparum malaria with blackwater fever	4	3
Glucose-6-phosphate dehydrogenase deficiency (2 typhus infections)	3	3
Leptospirosis	2	2
Amebic hepatic abscess	1	1
Pneumonia-kanamycin toxicity	1	1
Sulfonamide toxicity	1	1
Acute bacterial endocarditis and cardiac arrest	1	0
Viral hepatitis, massive hepatocellular necrosis	1	0
Total	14	11
Cases treated	12	11 (92%)
Posttraumatic renal insufficiency:		
Cases referred to unit	24	
Cases treated	18	6 (33.3%)
Miscellaneous:		
White phosphorus burns (20%)	1	0
Thermal burns (flare grenade, 10%)	1	0
Methanol toxicity	1	0
Chronic renal insufficiency with acute decompensation	4	3

Source: Donadio, J. V., Jr., and Whelton, A. 1968. Operation of a renal center in a combat zone. *Mil. Med.* 133: 833-37.

bowel trauma, and infection. Intravascular hemolysis following incompatible whole blood transfusion was observed in four patients, with ABO reactions occurring in three patients and apparent Rh (rhesus factor) incompatibility in the other. Extensive injury, hemorrhagic diathesis, and intractable hypotension, despite volume replacement and vasopressor administration, precluded hemodialysis in six patients; these six were moribund on admission and died within the first several hours of hospitalization in the renal unit. Hemodialysis was used in the management of 15 patients. One patient with ARI following a hemolytic transfusion reaction received peritoneal dialysis and two patients were managed without dialysis. Of the 18 patients in this "treatable" group, 12 (67 percent) died.

It is interesting to contrast this group of posttraumatic renal failure patients with those observed in Korea (Meroney and Herndon 1954; Teschan et al. 1955; Smith et al. 1955). Overall mortality among patients referred to the renal insufficiency center in Korea was 53 percent. Comparing this figure with that of the current group is not entirely valid, however, since patient selection was substantially different. During the Korean conflict, delay in evacuation of seriously wounded patients from battlefield to hospital (mean time = 4.6 hours), prolonged hypotension, and use of blood drawn some 2 weeks ahead of time were major factors in the occurrence of renal failure. Many extensively wounded soldiers did not survive to develop renal failure. In Vietnam, seriously wounded individuals were evacuated from the battlefield by helicopter and arrived within a mean time of 35 to 40 minutes at a hospital, where rapid resuscitation and definitive surgery were provided (Hardaway 1967).^{*} Renal failure in this type of patient did not occur immediately after injury but followed multiple postoperative complications, many of which were associated with gastrointestinal injury and peritonitis.

In addition to patients with acute and chronic renal failure, other individuals were referred to the unit for evaluation and treatment. These included patients with hypertension, proteinuria, and various fluid and electrolyte disturbances.

Because of the uncommon etiologies of ARI encountered, a number of clinical research projects were undertaken by members of the renal team in the early period to further elucidate them. The subjects of these studies included: establishment of quinine dosage schedules in patients with ARI complicating acute falciparum malaria (Donadio, Whelton, and Kazyak 1968); the hazard of glucose-6-phosphate dehydrogenase-deficient individuals developing ARI in response to infection from a tropical disease (Whelton, Donadio, and Elisberg 1968); the role of dialysis and long term followup of patients developing renal failure with leptospirosis; the role of iatrogenic copper poisoning in the treatment of phosphorus-burned patients; and the role of antibiotic lavage in post-traumatic renal failure complicated by gastrointestinal injury (Whelton and Donadio 1969).

SUMMARY

Posttraumatic renal failure developed in the setting of multiple postoperative complications, many of which were associated with gastrointestinal injury and peritonitis.

Review of clinical results of 45 cases at the renal unit during 12 months (September 1966-September 1967) revealed a mortality rate of 8 percent among patients with medical causes of renal failure and 67 percent among those with posttraumatic renal failure.

Although an awareness of the principles of ARI prevention existed among

^{*}This estimate is also based on the personal observations of the authors in Vietnam.

the military physicians in Vietnam, renal failure continued to occur in varied circumstances. When renal failure was established, the immediate availability of either hemodialysis or peritoneal dialysis was crucial for managing these patients.

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Posttraumatic Acute Renal Insufficiency

William J. Stone, M.D., and James H. Kneppshield, M.D.

The single largest category of patients with ARI (acute renal insufficiency) seen in the 629th Medical Detachment (Renal) developed this complication following trauma. Posttraumatic ARI usually followed wounding in battle but occasionally was seen in nonbattle injury. This report reviews the clinical courses of 62 consecutive patients with posttraumatic ARI referred to the renal unit between August 1967 and February 1969.

Posttraumatic ARI was first recognized in World War II, first treated with hemodialysis in the Korean war, and probably first prevented on a large scale in the Vietnam conflict by appropriate physician education. In Vietnam, rapid evacuation by helicopter brought casualties with unusually severe injuries to well-equipped facilities within 30 minutes of wounding. Immediate resuscitation by physicians and nurses, with large volumes of plasma expanders and universal donor blood, resulted in the survival of many patients with extensive trauma for varying periods. Undoubtedly ARI was prevented frequently by this rapid resuscitation and the ready availability of sophisticated surgical facilities. A rough estimate is that ARI occurred in only 1 in 600 seriously wounded battle casualties in Vietnam as opposed to 1 in 200 in Korea (Whelton and Donadio 1969). The mortality of posttraumatic ARI has changed very little in the last 30 years despite improvement in methods of treating renal failure, shock, and infection; about two of three patients still die (Whelton and Donadio 1969, pp. 100-101; Teschan et al. 1955; Smith et al. 1955; Lordon and Burton 1972). A consideration of possible reasons and solutions for this perplexing situation was attempted.

MATERIALS AND METHODS

Cases of posttraumatic ARI between 1968 and 1969 were reviewed in detail, and the records of patients treated by the 629th Medical Detachment in 1967 and 1968 were extensively abstracted. Most patients were referred from outlying U.S. military hospitals, although a few cases developed in the 3d Field Hospital (site of the renal unit) and in Saigon community hospitals.

A total of 62 patients with posttraumatic ARI were studied. An additional

This chapter is a revised version of the following article by the authors (1974): Post-traumatic acute renal insufficiency in Vietnam. *Clin. Nephrol.* 2: 186-90.

17 patients were excluded because they presented in irreversible shock. The average age of both fatalities and survivors was 25.7 years, with a range of 10 to 75 years. All but one of the patients were male. Table 93 summarizes the patients by race and civilian or military status. Eight (13 percent) were civilian while 54 (87 percent) were in the military. U.S. servicemen made up the largest group (79 percent).

TABLE 93.—*Patient population with posttraumatic acute renal insufficiency, 629th Medical Detachment (Renal), August 1967-February 1969*

Category	Deaths	Survivors
U.S. military:		
White	29	13
Black	5	1
Not known	1	
U.S. civilian:		
White	2	
Black		
Australian civilian	1	
Vietnamese:		
Military	2	1
Civilian	2	3
Korean military	1	1
Total	43	19

Source: Stone, W. J., and Kneppshield, J. H. 1974. Post-traumatic acute renal insufficiency in Vietnam. *Clin. Nephrol.* 2: 186-90.

Patients were admitted to a 6-bed (later expanded to an 11-bed) intensive care area separated by partitions from an adjacent medical ward. Nurses and medical corpsmen trained in hemodialysis and peritoneal dialysis worked a 12-hour shift, 7 days a week. Two internist-nephrologists made up the medical staff. Consultant urologists and surgeons provided additional care to nearly every patient.

All hemodialyses were performed in the same intensive care area using a Travenol Standard twin-coil artificial kidney and a 100-liter tub dialysate delivery system (fig. 88). Dialysate was changed every 2 hours. Patients usually underwent dialysis every other day for 6 hours using regional heparinization. Extremely catabolic patients received dialysis more frequently. External Quinton-Scribner shunts were uniformly employed for vascular access. Peritoneal dialyses were performed at the patient's bedside. Respiratory assistance was provided with volume-controlled ventilators (Emerson) humidified at room temperature.

The following parameters were determined serially by standard laboratory techniques: (1) blood: urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, osmolality, arterial pO_2 , arterial pCO_2 , arterial pH, hematocrit, white blood cell count, differential, platelet count, and prothrombin time; (2) urine: urea nitrogen, creatinine, sodium, potassium, and osmolality. Cultures of blood, urine, wounds, and other body fluids were performed at frequent intervals when deemed necessary.

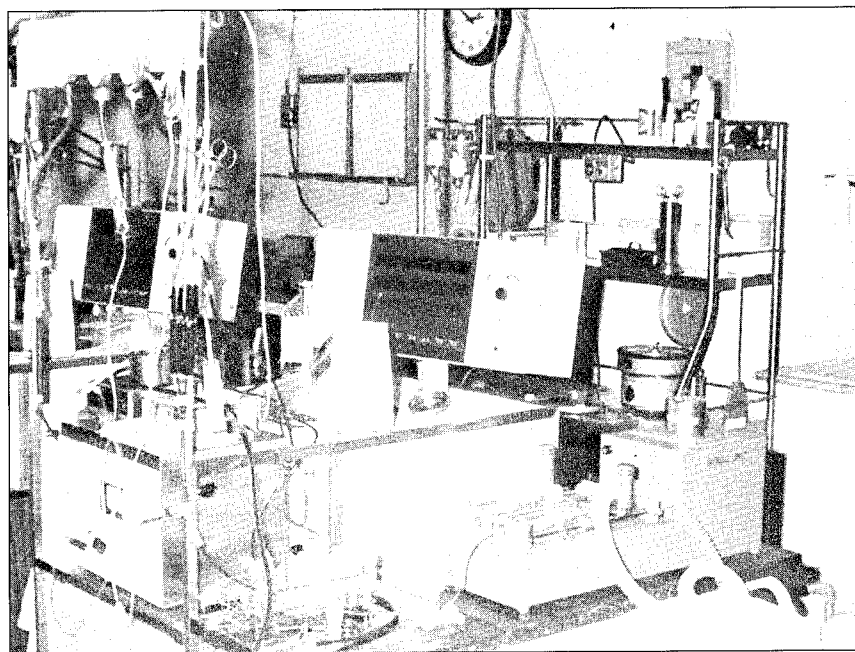


FIGURE 88.—Modernization of the 629th Medical Detachment (Renal) in 1969 and 1970 included acquisition of a Travenol RSP artificial kidney.

ARI was defined as a sudden progressive rise in the BUN (blood urea nitrogen) and serum creatinine following an inciting event without evidence of other causes of renal failure such as lower urinary tract obstruction. Oliguria meant a urine volume of less than 500 ml per day. A high output state was defined as a urine volume of greater than 500 ml per day in the presence of renal failure.

Multiple fragment wounds were defined as wounds resulting from the explosion of rockets, grenades, boobytraps, mines, and mortar shells; more than one fragment usually penetrated the body, resulting in injury to many organs. Blunt trauma was defined as trauma resulting from falls or vehicular accidents without penetration of the skin. Blast injury followed an explosion when no fragments penetrated the body.

RESULTS

Table 94 summarizes the types of trauma which initiated ARI. Of the two types of injury studied in significant numbers, gunshot wound causing ARI carried a better prognosis (11 of 27 survived); 22 of 26 patients with ARI following multiple fragment wounds died. This was a statistically significant difference ($p < 0.05$). The overall mortality from posttraumatic ARI was 69 percent.

Table 95 lists the organs injured. The two postoperative patients are omitted. Differences in survival depended on the areas wounded. For instance, 17% of patients who died had pancreatic injuries, while none of those who survived did ($p < 0.05$). There was also a significant difference between percentage of fatalities and of survivors with injuries of the small bowel (43/6), and the large bowel (45/17).

Table 96 contrasts causes of posttraumatic ARI in fatalities and survivors. Hemorrhagic shock was by far the leading antecedent event (66 percent). In 90 percent of these cases, ARI occurred within the first postwounding day. Transfusion of massive amounts of uncrossmatched blood was frequently required in the initial resuscitation (90 percent of patients received more than 5,000 ml of blood). The average amount received by those with hemorrhagic shock was 14,000 ml (fig. 89). Transfusion reactions were common and were believed to have led directly to ARI in 13 percent of cases. ABO (blood group) incompatibility was documented in one-third of these. Nephrotoxic antibiotics (kanamycin sulfate and/or sodium colistimethate) caused ARI in another 13 percent, but the use of these potent drugs was required to treat life-threatening infections. Usually excessive dosage was implicated.

Of the patients who died, a total of 33 were managed with hemodialysis (3.3 dialyses per patient), 3 underwent peritoneal dialysis (1 per patient), and 7 were treated conservatively. Of the survivors, 9 received hemodialysis (4 per patient), 3 underwent peritoneal dialysis, and 7 were treated conservatively with diet and fluid restriction alone.

Complications signifying a poor prognosis were: coagulation defects resulting in a bleeding diathesis, respiratory insufficiency with persistent hypoxemia, significant upper gastrointestinal hemorrhage, jaundice, and a clinical picture of septicemia. Only 19 of 38 patients with clinical septicemia (high spiking fever, shaking chills, hypotension, and cutaneous flushing) had positive blood cultures. All organisms were gram-negative rods. Fourteen patients had only one organism cultured from their blood, while five had two. *Pseudomonas aeruginosa* predominated, with *Klebsiella-Aerobacter* species next in incidence. Debilitation and weight loss were also frequently encountered. Acute psychoses were an infrequent but difficult problem to manage.

Causes of death were: septic shock in 28 (65 percent); respiratory insufficiency in 10 (23 percent); uncontrollable bleeding in 3 (7 percent); head injury in 1 (2 percent); and hyperkalemia in 1 (2 percent).

Table 97 shows days survived from injury, days spent in the renal unit until death or evacuation, days of oliguria, and percentages of patients with oliguria or a high output state among both survivors and fatalities. Oliguria occurred equally in both groups. Survivors were not evacuated until their clinical condition had stabilized and dialysis was no longer necessary.

DISCUSSION

The critically ill combat casualty was resuscitated almost immediately and then rapidly transported by helicopter to sophisticated treatment facilities. The

TABLE 94.—Types of trauma in patients with posttraumatic acute renal insufficiency, 629th Medical Detachment (Renal), August 1967-February 1969

Type of trauma	Fatalities		Survivors		Total	
	Number injured	Percent injured	Number injured	Percent injured	Number injured	Percent injured
Multiple fragment wounds	22	51	4	21	26	42
Gunshot wound	16	37	11	58	27	43
Blunt trauma	2	5	2	11	4	6
Gunshot and multiple fragment wounds	1	2	0		1	2
Blast	1	2	0		1	2
Postoperative	1	2	1	5	2	3
Burn	0		1	5	1	2
Total	43		19		62	

Source: Stone, W. J., and Kneppshield, J. H. 1974. Post-traumatic acute renal insufficiency in Vietnam. *Clin. Nephrol.* 2: 186-90.

TABLE 95.—Organs or organ systems injured, 629th Medical Detachment (Renal), August 1967-February 1969

Organ or system ¹	42 Fatalities		18 Survivors	
	Number injured	Percent injured	Number injured	Percent injured
Lung	12	29	2	11
Liver	11	26	2	11
Spleen	9	21	1	6
Pancreas	7	17	0	
Kidneys	15	36	6	33
Stomach	3	7	0	
Small bowel	18	43	1	6
Large bowel	19	45	3	17
Muscles	28	67	14	78
Skeleton	18	43	9	50
Arteries	9	21	3	17
Heart	1	2	0	
Brain	3	7	0	
Spinal cord	2	5	1	6
Total wounds	155		42	
Areas wounded per patient	3.7		2.3	

¹Multiple organs were involved in nearly all patients.

Source: Stone, W. J., and Kneppshield, J. H. 1974. Post-traumatic acute renal insufficiency in Vietnam. *Clin. Nephrol.* 2: 186-90.

incidence of ARI in these severely wounded individuals has progressively fallen (Whelton and Donadio 1969, pp. 98-99). However, an inordinately high mortality persists in those who do develop ARI. The mortality of 69 percent in these 62 patients is in agreement with the other studies cited (Whelton and Donadio 1969; Teschan et al. 1955; Smith et al. 1955; Lordon and Burton 1972).

Multiple fragment wounds were more perilous than gunshot wounds. Involvement of large bowel, small bowel, or pancreas signified an even more dismal prognosis. The patients received adequate dialysis; they did not die of the complications of renal failure but succumbed to progressive sepsis and shock. A

TABLE 96.—*Causes of posttraumatic acute renal insufficiency, 629th Medical Detachment (Renal), August 1967-February 1969*

Cause	Fatalities		Survivors		Total	
	Number	Percent	Number	Percent	Number	Percent
Hemorrhagic shock	32	74	9	47	41	66
Nephrotoxic drugs	6	14	2	11	8	13
Transfusion reaction	3	7	5	26	8	13
Burns	0		1	5	1	2
Renal contusions	0		2	11	2	3
Septic shock	2	5	0		2	3
Total	43		19		62	

Source: Stone, W. J., and Knepshield, J. H. 1974. Post-traumatic acute renal insufficiency in Vietnam. *Clin. Nephrol.* 2: 186-90.

TABLE 97.—*Selected statistics, 629th Medical Detachment (Renal), August 1967-February 1969*

Statistics	Deaths ¹		Survivors ¹		Total ¹
Days survived from injury	18.0	(4-89)	Indefinite		
Days in renal unit	11.0	(3-40)	22.4	(5-58)	14.0
Oliguria	39/43	(91%)	17/19	(90%)	56/62 (90%)
Days of oliguria	11.7	(1-41)	10.1	(1-23)	11.3
High output state	4/43	(9%)	2/19	(10%)	6/62 (10%)

¹Ranges and percentages are given in parentheses.

Source: Stone, W. J., and Knepshield, J. H. 1974. Post-traumatic acute renal insufficiency in Vietnam. *Clin. Nephrol.* 2: 186-90.

common sequence of fatal events evolved. Following 24 to 48 hours of septic shock refractory to antibiotics, fluid therapy, and pressor drugs, the patient died in one of three ways: pulmonary hemorrhagic consolidation and hypoxemia, a bleeding diathesis probably due to DIC (disseminated intravascular coagulation), or progressive and irreversible shock. Often all three were present. Stress ulcers of the upper gastrointestinal tract were the usual site of uncontrollable bleeding. Depressed platelet counts and prolonged prothrombin times were almost always seen in the patient with bleeding disorders. More sophisticated tests for DIC were unavailable. Respiratory failure did not respond to volume-controlled ventilation, frequent suctioning, oxygen administration, or fluid removal by hemodialysis ultrafiltration.

The clinical picture of gram-negative septicemia preceded the above events. It was seen in 79 percent of deaths but in only 26 percent of survivors. An average of 2.4 major surgical procedures were performed on each patient. The following were implicated in contributing to fatal gram-negative septicemia in some: inadequate initial drainage of contaminated areas, particularly in the abdomen; placement of colostomies in or near incisions or drains; failure to re-explore when intra-abdominal infection was suspected on clinical grounds; use of surgical packs for extended periods; prolonged and inappropriate use of urethral catheters and plastic venous cannulas; withholding or inadequate use of antibiotics because of their potential nephrotoxicity; and poor wound healing possibly related to protein-calorie malnutrition.

Once posttraumatic ARI became associated with respiratory failure and

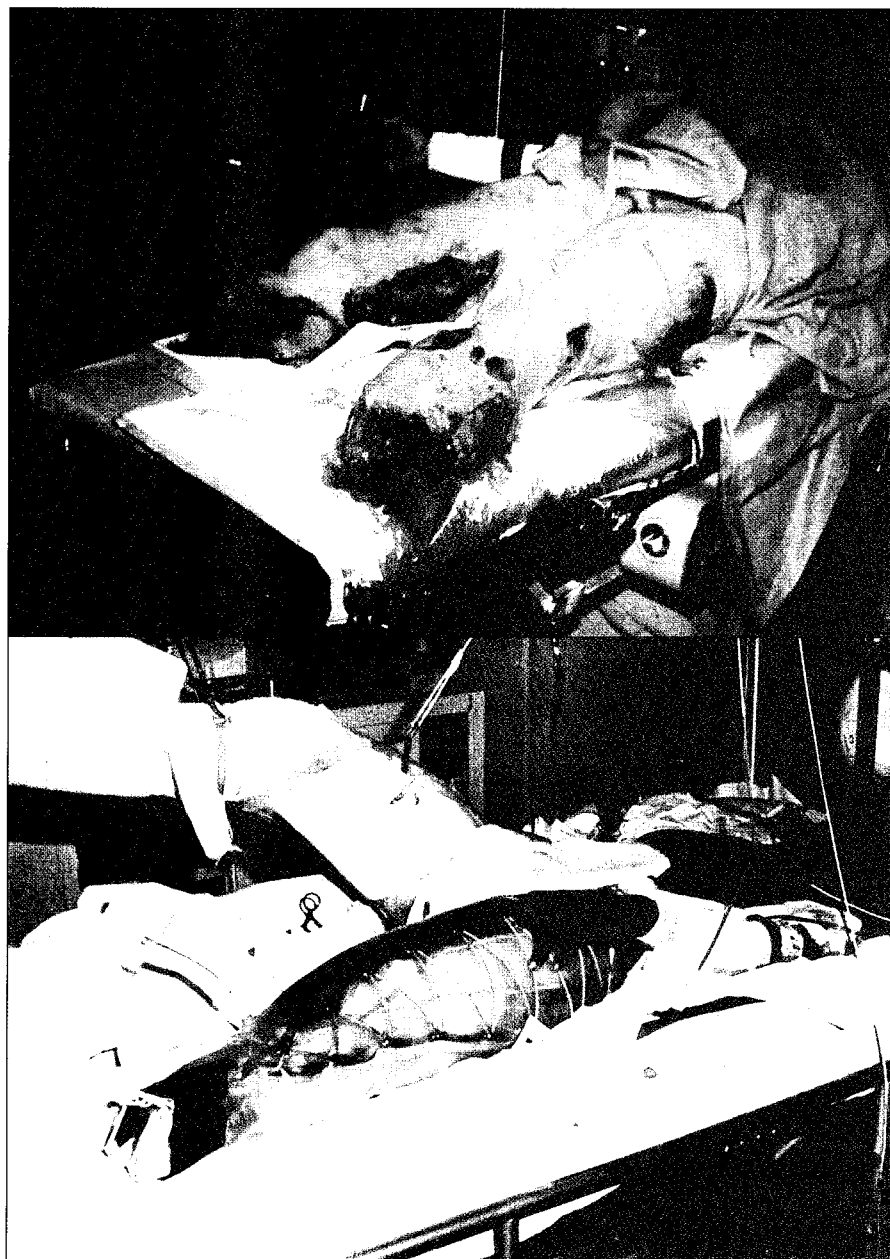


FIGURE 89.—Top: Typical wounded patient in shock and with renal failure, arriving at the 3d Field Hospital and transferred to the renal unit following debridement. Bottom: Treatment with immobilization and pressure dressings was included in the total care concept of the renal unit.

prolonged uncontrolled hypotension caused by septicemia, very little could be done to reverse the relentless downhill course of the patient. Meticulous patient care and frequent physical examinations by physicians can address the first five contributing factors listed above. Further attention to administration of aminoglycoside antibiotics at more frequent intervals and in doses appropriate to the level of renal function may be critical in preventing nephrotoxic ARI (Chan, Benner, and Hoeprich 1972).

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Medical Causes of Acute Renal Insufficiency

*William J. Stone, M.D., James E. Hanchett, M.D., and
James H. Knepshield, M.D.*

Section I. Acute Renal Insufficiency From Falciparum Malaria

*William J. Stone, M.D., James E. Hanchett, M.D., and
James H. Knepshield, M.D.*

During the 4 years between July 1965 and June 1969, 40 patients with ARI (acute renal insufficiency) caused by falciparum malaria were cared for in the three dialysis centers in the Asian war area (in Saigon; at Clark Air Force Base, Republic of the Philippines; and at Tachikawa Air Force Base, Japan). The pathogenesis, clinical features, and management of those cases are presented here.

MATERIALS AND METHODS

Forty-two cases of ARI caused by falciparum malaria comprise this study. Only patients with a positive blood smear for *Plasmodium falciparum* were considered. The patients ranged in age from 18 to 42 years, with an average of 22 years. Forty of these patients were members of the U.S. Armed Forces serving in Vietnam. Except in the cases of two soldiers on leave in the United States when symptoms began, initial evaluation and treatment were carried out in a number of hospitals throughout Vietnam. Results of laboratory tests reported were determined by standard methods. Percent parasitemia was calculated by a direct count of parasitized RBC.

Percutaneous renal biopsy was performed on six patients by Schreiner's (1963) technique. The tissue was fixed in formaldehyde solution (formalin) and stained with hematoxylin and eosin for light microscopy. Immunofluorescent studies by the method of Lange et al. (1966) were performed on heart, lung, and kidney tissue obtained from one patient at postmortem examination. Necropsy results of 10 of the 12 American servicemen who died were reviewed.

The definition of ARI was a sudden daily rise in levels of BUN (blood urea nitrogen) and serum creatinine in the absence of volume depletion and obstruction of the renovascular or collecting systems following an acute illness in patients with no prior history of renal disease. Oliguria (less than 500 ml of urine

This section is a revised version of the following article by the authors (1972): Acute renal insufficiency due to falciparum malaria. *Arch Int. Med.* 129: 620-28 (© 1972, American Medical Association).

per 24 hours) was usually present. All hemodialyses were performed under regional heparinization, using a twin-coil dialyzer (Kolff-Travenol).

RESULTS

Table 98 summarizes the clinical data obtained from the 42 patients included in this study, and table 99 gives the laboratory admission data. Thirty-six patients were oliguric; 6 were not. The average duration of symptoms before admission to a dialysis unit was 8 days. All patients manifested anemia; the majority—36 (86 percent)—showed significant hemolysis.

TABLE 98.—*Presenting symptoms and signs of 42 patients with acute renal insufficiency from falciparum malaria, July 1965-June 1969*

Symptoms and signs	Number of patients	Percent of 42 patients
Symptoms:		
Feverish feeling	37	88
Chills	29	68
Headache	18	43
Nausea	18	43
Vomiting	17	40
Diarrhea	15	35
Malaise	11	25
Dark urine	10	23
Signs:		
Hepatosplenomegaly	32	76
Jaundice	28	67
Mental obtundity	23	55
Fever	16	38
Respiratory distress	12	29
Rales or rhonchi	12	29
Edema	12	29
Purpura	7	16
Hyperactive deep tendon reflexes	7	16

Source: Stone, W. J.; Hanchett, J. E.; and Knepshield, J. H. 1972. Acute renal insufficiency due to falciparum malaria. *Arch. Int. Med.* 129: 620-28. © 1972, American Medical Association.

In 31 of the 42 patients, a parasite index was calculated on the basis of the blood smear obtained on admission to the original hospital. Twenty-two of 31 (71 percent) had at least 10-percent parasitemia. Eight (36 percent) of these had 60- to 90-percent parasitemia. The parasite index, as shown in table 100, tended to be lower in survivors than in fatal cases.

Hyperkalemia was found in only five patients (12 percent of admissions). In contrast, severe azotemia with evidence of hypercatabolism (BUN: creatinine ratio > 10) was the rule, as had been noted previously (Brooks et al. 1967; Jackson and Woodruff 1962). Hepatic dysfunction was seen in nearly all patients. Roentgenograms of the chest were abnormal in 23 of 42 (55 percent), with findings ranging from small infiltrates to extensive opacification of lung fields. Seven of 11 patients tested had a coagulation disorder suggesting a consumption

TABLE 99.—*Admission laboratory data of 42 patients with acute renal insufficiency from falciparum malaria, July 1965-June 1969*

Case	Hematocrit reading (percent)	Parasite index (percent)	Blood urea nitrogen (mg/100 ml)	Serum creatinine (mg/100 ml)	Serum potassium (mEq/liter)
1	22	1	126	14.0	6.4
2	28	20	200	12.5	5.4
3	21	10	145	6.8	4.1
4	25	60	75	3.0	4.0
5	23	3	97	4.1	4.2
6	39	1	14	1.4	2.9
7	25	1	155	9.5	4.4
8	32		93	10.0	3.8
9	15	60	140	5.4	4.5
10	19	25	140	4.5	4.8
11	17	60	160	6.6	5.5
12	22	1	165	10.0	3.6
13	29		115	15.0	5.6
14	23	70	116	3.1	4.3
15	19	50	175	8.0	4.8
16	27	1	225	15.0	3.7
17	17		98	14.5	3.7
18	16.5	10	145	10.5	4.7
19	30		119	16.0	5.0
20	25		59	2.4	4.9
21	31	60	100	16.0	5.1
22	22		183	16.5	4.6
23	35		220	5.3	4.9
24	31	90	98		4.3
25	34		180		5.5
26	43		280	7.4	5.1
27	34		164	7.1	4.4
28	51		126	3.6	5.5
29	44	15	68	4.0	6.1
30	45	45	147		4.2
31	45		135	2.3	3.8
32	35	70	76		4.7
33	40	75	80		6.4
34	45		150	6.8	
35	25	13	72		4.0
36	45		70	6.0	5.7
37	14	10	125	5.2	5.6
38	28	10	74		
39	21	8	85		6.2
40	35	1	29	4.0	3.5
41	12.5	40	236	4.0	7.0
42	22.5	20	54	5.7	4.9

Source: Stone, W. J.; Hanchett, J. E.; and Knepshield, J. H. 1972. Acute renal insufficiency due to falciparum malaria. *Arch. Int. Med.* 129: 620-28. © 1972, American Medical Association.

coagulopathy (table 101). Several other patients manifested a bleeding diathesis but had insufficient coagulation tests to establish a definite diagnosis.

TABLE 100.—*Parasite index of 31 patients with acute renal insufficiency from falciparum malaria, July 1965-June 1969*

Parasite index (percent)	Survivors		Fatalities	
	Number	Percent	Number	Percent
< 10	8	38	1	10
10-50	10	48	4	40
> 50	3	14	5	50
Total	21		10	

Source: Stone, W. J.; Hanchett, J. E.; and Knepshield, J. H. 1972. Acute renal insufficiency due to falciparum malaria. *Arch. Int. Med.* 129: 620-28. © 1972, American Medical Association.

TABLE 101.—*Coagulation disorders of seven patients with acute renal insufficiency from falciparum malaria, July 1965-June 1969*

Patient	Platelets (cu mm)	Prothrombin time ¹ (seconds)	Partial thromboplastin time ¹ (seconds)	Plasma fibrinogen (mg/100 ml)
9	(²)	25(13)	115(46)	105
11	(²)	27(15)	52(48)	100
13	62,000	14(15)	32(48)	70
15	35,000	18(13)	60(46)	140
21	58,000	17(13)	85(46)	210
24	(²)	32(13)	Over 250 (25-38)	
41	37,000	49(11)		

¹Control in parentheses.

²Markedly decreased on smear.

Source: Stone, W. J.; Hanchett, J. E.; and Knepshield, J. H. 1972. Acute renal insufficiency due to falciparum malaria. *Arch. Int. Med.* 129: 620-28. © 1972, American Medical Association.

Except for one patient (patient 24) who contracted his disease in 1965 (before the widespread recognition of chloroquine-resistant *P. falciparum*), all patients received quinine sulfate or quinine hydrochloride, administered orally or parenterally. Prompt clearing of parasitemia occurred in all patients receiving quinine. Other antimalarial agents employed were pyrimethamine, primaquine phosphate, chloroquine phosphate, sulfisoxazole, sulfadoxine, and dapsone. Large doses of corticosteroids were usually given to patients manifesting symptoms of cerebral malaria or respiratory distress associated with pulmonary edema or hemorrhage. Management of renal failure consisted of restriction of protein, sodium, potassium, and water intake alone (10 patients); peritoneal dialysis (6 patients); and hemodialysis (23 patients). The average duration of oliguria was 8 days, with a range of 1 to 19 days. An average of four hemodialyses were performed on the patients requiring dialysis. Peritoneal dialysis was employed when patients showed less severe catabolic changes. Three patients died before dialysis could be initiated.

Of the 42 patients included in this study, 12 died. All were oliguric and had at least one and usually both of the other potentially lethal complications (cerebral and pulmonary) of falciparum malaria. Eight patients (67 percent) who died had severe pulmonary involvement which was believed to be the primary cause of death in six (50 percent) (fig. 90). Eleven (92 percent) had cerebral

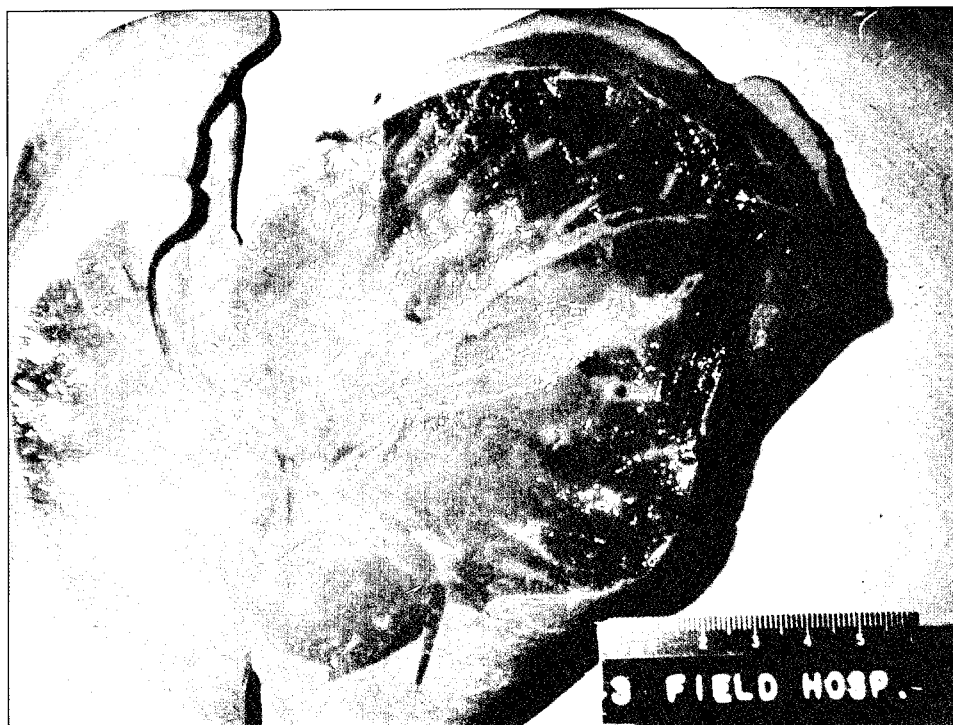


FIGURE 90.—Cross section of lung obtained at necropsy. Specimen shows massive hemorrhagic consolidation. (Stone, W. J.; Hanchett, J. E.; and Knepshield, J. H. 1972. Acute renal insufficiency due to falciparum malaria. *Arch. Int. Med.* 129: 620-28. © 1972, American Medical Association.)

malaria, which was considered the main cause of death in four (33 percent). One patient died of a massive upper gastrointestinal tract hemorrhage in association with marked thrombocytopenia and hypoprothrombinemia. Another died of gram-negative bacteremia secondary to peritoneal contamination at the time of peritoneal dialysis. No deaths resulted from uremia or hyperkalemia.

Among the 30 survivors, 1 (3 percent) had severe pulmonary involvement while 11 (37 percent) had moderate to severe cerebral malaria. Twenty of the survivors required some form of dialysis. All patients without oliguria lived, and none required dialysis therapy. The incidence of complications was much less in nonoliguric patients.

The renal pathologic findings in 10 necropsies and 6 percutaneous biopsies are summarized in table 102. At necropsy, the kidneys were enlarged with pallor of the cortex and hyperemia of the medulla. Findings on microscopic examination of both biopsy and necropsy material were similar. Evidence of a mild glomerulitis consisting of slightly increased cellularity was observed in eight (20 percent) of the specimens. Tubular changes included degeneration and dilatation of the proximal and distal nephron, patchy necrosis, and occasional interstitial

TABLE 102.—*Renal pathology in 16 cases of acute renal insufficiency from falciparum malaria, July 1965-June 1969*

Patient	Source of specimen	Status of renal function	Average weight of kidney (g)	Gross findings	Light microscopic examination			
					Glomeruli	Tubules	Casts	Vessels
2	A	OARI	250	Submucosal hemorrhages of renal pelvis.	Normal	Autolysis	Pigmented casts in DT and CD.	Congested medullary capillaries.
11	A	OARI		Swollen; pale cortex; hyperemic medulla.	Normal	Degeneration and dilatation of PT and DT.	Pigmented casts in DT.	Congestion of peritubular capillaries.
23	A	OARI	300	Pale cortex; hyperemic pelvis.	Mild proliferative glomerulitis.	Patchy tubular necrosis and regeneration.	Pigmented casts.	Normal.
24	A	OARI	265	Swollen	Normal	Degeneration and dilatation of PT and DT.	Pigmented casts in DT and CD.	Normal.
25	A	OARI	250	Pale cortex	Normal	Patchy tubular necrosis.	Hyaline casts in DT and CD.	Congestion of medullary capillaries.
26	PB	C _{cr} =77			Normal	Focal tubular dilatation; patchy tubular regeneration.	Pigmented casts.	Normal.
29	A	OARI	350	Pale cortex	Normal	DT regeneration.	Hyaline casts in DT.	Normal.
32	PB	HARI			Focal proliferative glomerulitis.			
33	A	OARI	215		Normal		Pigmented casts.	
34	PB	C _{cr} =30			Mild proliferative glomerulitis.	Marked tubular regeneration and interstitial fibrosis.		Occasional arterial wall thickening with eosinophilic deposits.
35	PB	C _{cr} =64			Normal	PT regeneration and dilatation and interstitial round cell infiltration and fibrosis.	Hyaline casts.	Normal.
36	PB	C _{cr} =64			Normal	Tubular regeneration and interstitial round cell infiltration and edema.	Pigmented casts.	Normal.
39	A	OARI	230		Mild proliferative glomerulitis.	DT degeneration.	Hyaline and pigmented casts.	Congestion of peritubular capillaries.

TABLE 102. — *Renal pathology in 16 cases of acute renal insufficiency from falciparum malaria, July 1956-June 1969—(Continued)*

Patient	Source of specimen	Status of renal function	Average weight of kidney (g)	Gross findings	Light microscopic examination			
					Glomeruli	Tubules	Casts	Vessels
40	PB	C _{cr} = 65			Normal	Mild degeneration and dilatation of DT and CD.	Pigmented casts.	Normal.
41	A	OARI	305	Swollen; slightly hemorrhagic cortex.	Normal	Degeneration and dilatation of PT, DT and CD.	Pigmented casts in CD.	Congestion of medullary capillaries.
42	A	OARI	200	Pale cortex; hyperemic medulla; submucosal hemorrhages of renal pelves.				

Abbreviations: ARI, acute renal insufficiency; A, autopsy; OARI, oliguric ARI; DT, distal tubules; CD, collecting ducts; PT, proximal tubules; PB, percutaneous biopsy; C_{cr}, uncorrected creatinine clearance (ml/min); and HARI, high output ARI.

Source: Stone, W. J.; Hanchett, J. E.; and Kneppshield, J. H. 1972. Acute renal insufficiency due to falciparum malaria. *Arch. Int. Med.* 129: 620-28. © 1972, American Medical Association.

round cell infiltration and edema. Most sections showed pigmented casts, particularly in the distal nephron. Striking medullary capillary congestion was seen in 30 percent of the cases (fig. 91). Immunofluorescent studies on renal tissue for immunoglobulins IgG, IgA, IgM, and β_2 C were negative in one patient studied.

DISCUSSION

Acute renal insufficiency has been recognized in many medical conditions, including thermal burns, gram-negative bacteremia, crush injury, and transfusion reaction, and following administration of certain drugs. It was commonly referred to as acute tubular necrosis in the past. Recovery is usual if the patient can be maintained by dialysis and other supportive measures during the oliguric phase. Renal histopathology during the acute period does not reflect the severe functional derangement seen (Finckh, Jeremy, and Whyte 1962; Olsen and Skjoldborg 1967; Brun and Munck 1957).

Many observations point to a similar situation occurring in ARI caused by falciparum malaria. Oliguria and subsequent diureses are common. Nonoliguric ARI has been noted less frequently (Sitprija et al. 1967).

Pathologic findings in the kidneys of patients with ARI caused by falciparum malaria have been mild to minimal. Spitz (1946) found evidence of glomerular involvement in 18 percent of 50 fatal cases of falciparum malaria during World War II. Light microscopic findings in these glomeruli consisted of

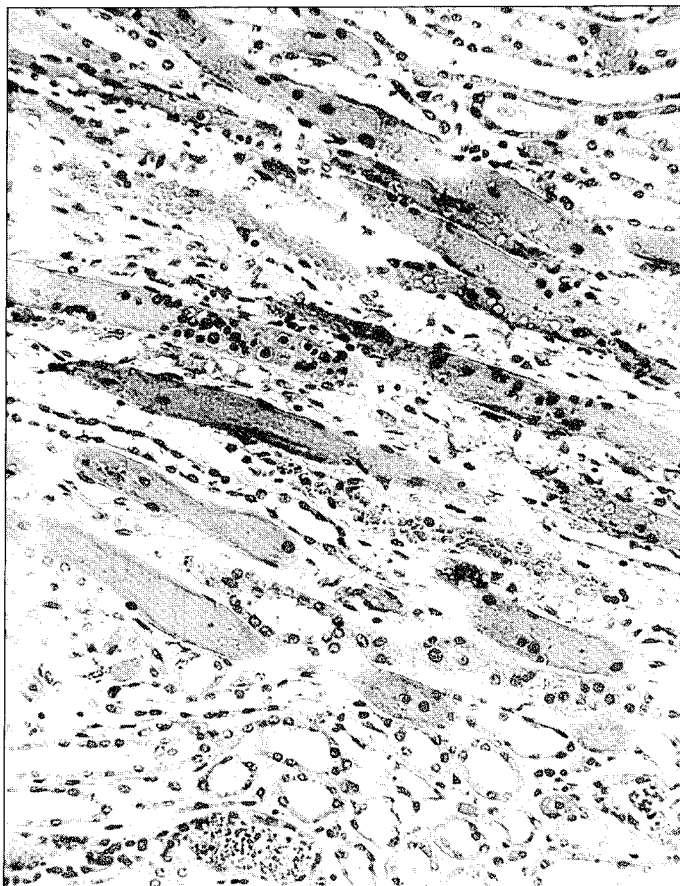


FIGURE 91.—Renal tissue obtained at necropsy from patient with falciparum malaria. Pigmented casts containing cellular elements are present in several collecting ducts. Congested capillaries are also prominent. Hematoxylin-eosin stain (X 190). (Stone, W. J.; Hanchett, J. E.; and Knepshield, J. H. 1972. Acute renal insufficiency due to falciparum malaria. *Arch. Int. Med.* 129: 620-28. © 1972, American Medical Association.)

“generalized ischemia, enlargement and increased cellularity of the glomerulus, hyperchromatism and swelling of the endothelium, and occasionally thickening of the basement membranes.” Pigmented casts were found in the distal nephrons of more than half of the cases; however, only 14 percent demonstrated tubular necrosis or degeneration. Proximal tubules were dilated and filled with proteinaceous fluid.

Maegraith and Findlay (1944; Maegraith 1944) found few RBC's in glomerular capillaries, “anemia” of the cortex, and congestion of the medulla. They suggested that a vasoconstrictive process produced the renal insufficiency.

Sitprijia and coworkers (1967) studied three patients with nonoliguric ARI caused by heavy *P. falciparum* infestation. There was no evidence of intravascular hemolysis. Renal biopsies showed normal glomeruli and only focal vacuolization of proximal tubules. Six patients from Central Africa with falciparum malaria and ARI demonstrated similar minimal changes consisting of tubular degeneration and casts on renal biopsy (Dukes, Sealey, and Forbes 1968).

Burdick reviewed three renal biopsies from patients with oliguric ARI caused by falciparum malaria. Light microscopy was normal. However, on electron microscopy he found moderate focal basement membrane thickening and small membrane-limited vacuoles within the basement membrane which may have been artifacts. Jackson and Woodruff (1962) reported on the renal findings in three cases of severe *P. falciparum* infection and renal failure. They found tubular necrosis of varying degree, and tubular casts, but no glomerular involvement.

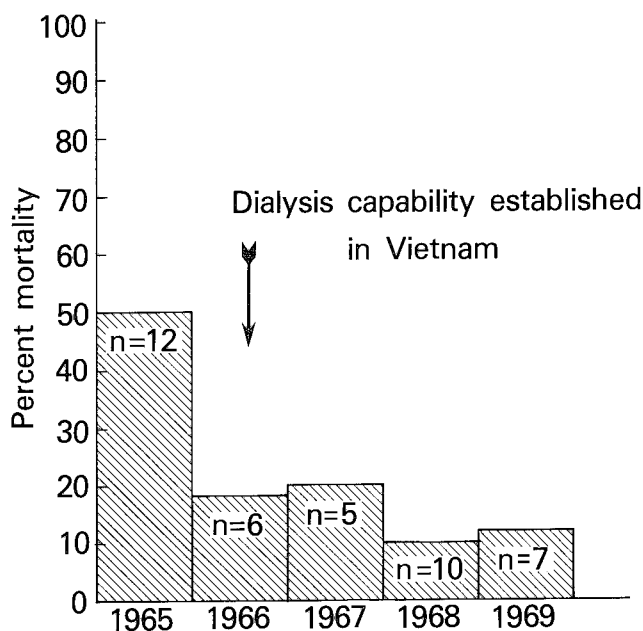
Rosen and coworkers (1968) studied renal biopsy specimens of six soldiers with "blackwater fever" from falciparum malaria, three of whom were oliguric. Pathologic changes included casts, tubular atrophy, and focal fibrosis. Two of the six cases had glomerular abnormalities consisting of epithelial inclusions and hyalinization.

Review of our necropsy and biopsy material supports the concept that the morphologic changes in the kidney in no way explain the excretory defect. Nearly all glomeruli appeared normal. The observed tubular abnormalities were mild and had focal distribution.

Glomerulonephritis of the immune complex type can occur in certain types of malaria. Deposition of immunoglobulins IgG and β_2C in glomeruli has been demonstrated by fluorescent antibody technique in rhesus monkeys infected with *P. cynomolgi* (Ward and Conran 1966) and in humans with *P. malariae* infestation (Kibukamusoke 1968; Allison et al. 1969). The nephrotic syndrome resulting from a proliferative glomerulonephritis has been described in three cases of falciparum malaria acquired in Vietnam (Berger, Birch, and Conte 1967). Unfortunately, immunologic techniques were not applied to these biopsies. However, glomerulonephritis as a cause of oliguria and azotemia is rare in falciparum malaria in comparison with ARI. Four cases in the current study showed evidence of a mild glomerulitis on biopsy. To the authors' knowledge, none subsequently developed the nephrotic syndrome or chronic renal insufficiency. In the only specimen studied for renal deposition of immune complexes, no IgG or β_2C was demonstrated.

The similarity between the clinical courses of these patients and of those previously reported on is striking (Jackson and Woodruff 1962; Reid, Goldsmith, and Wright 1967; Canfield et al. 1968; Donadio, Whelton, and Kazyak 1968). A significant interval between the onset of symptoms and the institution of appropriate therapy was typical. Marked anemia and parasitemia were usually present. Cerebral, hepatic, and pulmonary involvement frequently complicated the initial period, particularly when treatment was delayed. A bleeding tendency was evident. The patient had severe toxic and catabolic reactions. Acute renal insufficiency could be readily managed if peritoneal dialysis or hemodialysis

CHART 29.—Annual mortality of patients with acute renal insufficiency from falciparum malaria in Vietnam, 1965-69¹



¹ n = total patients, excluding deaths in transit.

Source: Stone, W. J.; Hanchett, J. E.; and Kneppshild, J. H. 1972. Acute renal insufficiency due to falciparum malaria. *Arch. Int. Med.* 129: 620-28. © 1972, American Medical Association.

facilities were available.

None of the patients in this study died of renal failure. However, the other complications of severe infestation with *P. falciparum* are less amenable to therapy and cause a significant mortality. Of the 12 fatalities, 6 died primarily of pulmonary involvement and 4 of cerebral involvement. All those who died had either pulmonary or cerebral complications and usually both. Initial delays in diagnosis and treatment may have contributed to the development of these lesions.

In the early period (1965-66) before a dialysis facility was established in Vietnam, patients requiring dialysis were flown to Japan or the Philippines. This critical delay of at least 12 hours may have contributed to the inordinate mortality (50 percent) observed in these patients. The later mortality (14 percent) probably reflects the value of early treatment (chart 29).

Similar delays have been recorded in the deaths from falciparum malaria in the U.S. civilian community. A low index of suspicion has been the single most troublesome factor. On therapeutic and epidemiological grounds, it is imperative that the diagnosis of malaria be sought in all individuals with unexplained febrile illnesses who return from endemic malarial regions.

Intravenously administered quinine hydrochloride was the cornerstone of therapy in severe *P. falciparum* infection. The usual daily dosage had to be decreased to 600 mg in the presence of oliguria to prevent toxic blood levels of quinine (Donadio, Whelton, and Kazyak 1968). This was given in 500 ml of dextrose solution over 24 hours and was continued for 10 to 14 days. Blood quinine levels were determined at regular intervals and the electrocardiogram was monitored for signs of toxic reaction (widened QRS complexes). In the absence of renal insufficiency, the recommended treatment regimen for falciparum malaria was the simultaneous initiation of quinine sulfate, 1,950 mg daily for 10 days; pyrimethamine, 25 mg twice daily for 3 days; and dapsone, 25 mg daily for 28 days (USARV Reg.) Sulfisoxazole, 500 mg four times daily for 5 days, was substituted for dapsone on occasion.

In treating patients with ARI from falciparum malaria, it was our practice to delay administration of pyrimethamine, dapsone, and sulfisoxazole until the recovery period. The dialysance of these drugs was not known, and recurrences of parasitemia did not occur when administration was delayed until the diuretic phase.

Section II. Acute Renal Insufficiency in Other Medical Disorders

James H. Kneppshield, M.D., and William J. Stone, M.D.

A review of the records of the 629th Medical Detachment (Renal) reveals 12 medical causes of renal failure resulting in admission to the unit. Distribution of cases by cause was as follows:

Falciparum malaria.....	13
Hemolytic anemia.....	12
C-4 plastic explosive.....	4
Chloroquine ingestion with overdose.....	1
Heat stroke.....	1
Hemolytic-uremic syndrome.....	1
<i>Serratia</i> pneumonia.....	1
Leptospirosis.....	1
Acute glomerulonephritis.....	4
Chronic glomerulonephritis with acute decompensation.....	4
Goodpasture's syndrome.....	1
Interstitial nephritis, phenacetin abuse.....	1

Hemolytic anemic states ranked second in frequency as a cause of acute renal failure. Considering the large population receiving malaria chemoprophylaxis, the actual number of severe hemolytic reactions was small. Acute infections added to the potential for hemolytic reaction among patients with G6PD (glucose-6-phosphate dehydrogenase) deficiency.

Acute renal insufficiency in a G6PD-deficient patient with viral hepatitis, who subsequently recovered, was described by Salen and coworkers (Salen et al. 1966). Drug-induced hemolysis, which had been well described since the early

1950's, produced severe degrees of hemolytic anemia uncomplicated by renal failure. In view of the frequency with which this red cell enzyme deficiency has been reported throughout the world, it is surprising that renal failure has not been more common.

The deployment of large numbers of American troops to Southeast Asia exposed individuals with the enzyme deficiency to the hemolyzing agent primaquine, as well as dapsone (diaminodiphenylsulfone) in some geographic sectors. The quantity of these drugs taken for routine chemoprophylaxis (primaquine, 45 mg base once per week; dapsone, 25 mg per day) was well below the amounts that have produced clinically overt hemolysis in most G6PD-deficient black American subjects; however, this was not always true in the white soldier (Carson and Frischer 1966).

Two cases of acute renal failure in G6PD-deficient black American troops in South Vietnam were reported. Massive intravascular hemolysis in these patients was not induced by the antimalarial agents or by other drugs per se but was associated with unsuspected rickettsial infections. One patient had scrub typhus and the other, murine typhus (Whelton, Donadio, and Elisberg 1968).

A review of 3 years' experience in Vietnam with acute renal insufficiency (table 103) shows that 31 percent of admissions were for medical causes. There was an overall survival rate of 79 percent in the medical group treated during that period.

TABLE 103.—*Survival rate of patients with acute renal insufficiency of medical etiology, 629th Medical Detachment (Renal)*

Item	September 1966- September 1967	1 Aug. 1967- 31 Aug. 1968	1 Aug. 1968- 31 July 1969
Total cases referred	45	102	130
Total acute renal insufficiency of medical etiology	14	27	44
Total survivors of medically caused acute renal insufficiency	11 (79%)	18 (66%)	38 (86%)

Source: Tabulated by James H. Knepshield, M.D., and William J. Stone, M.D., formerly of the 629th Medical Detachment.

Section III. Toxic Effects Following Ingestion of C-4 Plastic Explosive

James H. Knepshield, M.D., and William J. Stone, M.D.

Composition C-4, the most common plastic explosive used by field units in Vietnam, is a mixture of four potentially toxic substances: RDX (cyclonite), 91 percent; polyisobutylene, 2.1 percent; motor oil, 1.6 percent; and di(2-ethylhexyl) sebacate, 5.3 percent. Figure 92 shows the chemical structure for the major com-

This section is taken from the following article: Stone, W. J.; Paletta, T. L.; Heiman, E. M.; Bruce, J. I.; and Knepshield, J. H. 1969. Toxic effects following ingestion of C-4 plastic explosive. *Arch. Int. Med.* 124: 726-30 (© 1969, American Medical Association).

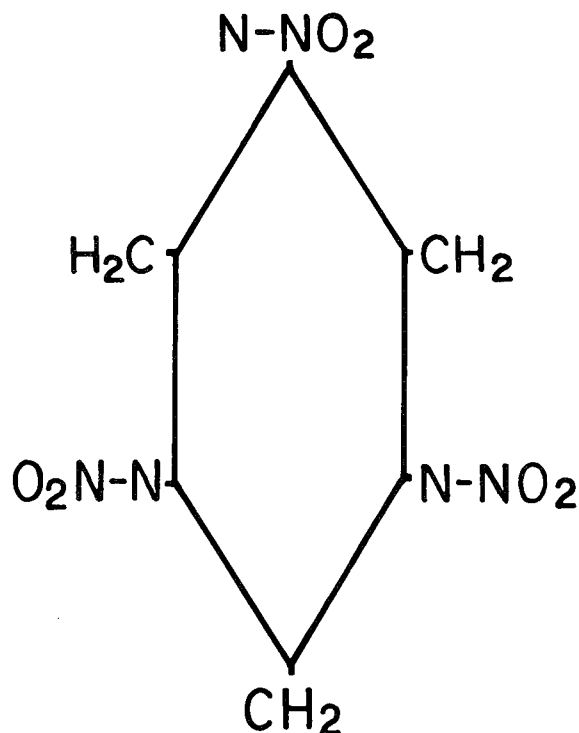


FIGURE 92.—Chemical structure of RDX (cyclotrimethylenetrinitramine, cyclonite, or Hexogen). (Stone, W. J.; Paletta, T. L.; Heiman, E. M.; Bruce, J. I.; and Knepshield, J. H. 1969. *Arch. Int. Med.* 124: 726-30. © 1969, American Medical Association.)

ponent, RDX, a colorless crystal which is highly insoluble in water (0.0076 g/100 g solvent at 25°C) (DA-TM). Because C-4 is a malleable solid, burns without explosion, and is relatively insensitive to impact or friction, it can be easily transported and stored without undue precautions (fig. 93). A blasting cap is employed as a detonator. C-4 may even be used as a field cooking fuel when other sources of heat are unavailable. However, when it is ingested or inhaled in significant quantities, by either accident or intent, a dramatic clinical picture develops within a few hours. Generalized seizures, gross hematuria, severe nausea and vomiting, muscle twitching, and mental changes occur.

It was common knowledge among the field troops in Vietnam that the ingestion of a small quantity of C-4 produces a "high" similar to that produced by alcohol. The exact frequency of ingestion of the material was not known; however, several serious intoxications from this agent were seen in every major military hospital in the Republic of Vietnam. Toxic effects of C-4 have also involved the civilian community in the United States. Inhalation of the dust was incriminated when factory workers who handled and packed the explosive experienced convulsions (Merrill 1968). C-4 is a potential health hazard in the



FIGURE 93.—Rounds of 105 mm white phosphorus are placed on top of C-4 explosive at an ammunition dump.

United States because of its availability on many military installations, although rigid control of its use makes this unlikely.

The six male patients summarized here had toxic effects from C-4 severe enough to warrant hospitalization (table 104). Their ages ranged from 20 to 35 years, with an average of 24 years. The estimated quantity of ingestion in three of the patients was 25 to 180 g (average 77 g). Data for two of the patients are from Merrill's report (1968).

TABLE 104.—Symptoms and signs of six patients with C-4 intoxication

Symptoms and signs	Number positive	Percent positive
Generalized seizures	6	100
Hematuria	5	83
Coma	4	67
Fever	4	67
Headaches	3	50
Lethargy	2	33
Nausea and vomiting	2	33
Oliguria	2	33

Sources: (1) Stone, W. J.; Paletta, T. L.; Heiman, E. M.; Bruce, J. L.; and Kneppshield, J. H. 1969. Toxic effects following ingestion of C-4 plastic explosive. *Arch. Int. Med.* 124: 726-30. © 1969, American Medical Association. (2) Merrill, S. L. 1968. Ingestion of an explosive material, composition C-4: A report of two cases. *USARV M. Bull.* (USARV Pam 40-8), March-April, pp. 5-11.

All patients were admitted to the hospital for the management of generalized seizures. When initially seen, most were conscious but stared into space confusedly. They were restless and unpredictable and required restraints. At frequent intervals, generalized seizures lasting 1 to 2 minutes occurred. Between seizures, the state of consciousness varied from coma to lethargy. Other prominent symptoms and signs were severe neuromuscular irritability with muscular twitching and hyperactive reflexes, myalgias, frontal headaches, nausea, vomiting, gross hematuria, and fever. Within 48 hours, the patients were able to answer simple questions and follow directions, but orientation, concentration, recall, and memory for recent and remote events were impaired. After 1 week, the sensorium cleared; however, remote memory continued to be defective with spotty recall for both personal experiences and well-known facts. Followup indicated that mental capacity had returned to normal in about 1 to 2 months. Neuromuscular irritability, gastrointestinal symptoms, hematuria, and fever abated within 48 hours. Headaches persisted for 1 to 3 weeks.

The abnormal laboratory findings are summarized in table 105. Within 2 weeks, all the abnormal values returned to normal except for the hematocrit in one patient and urinary protein excretion in another.

During the first week following ingestion of C-4, muscle, liver, and renal biopsies were performed on a patient with an elevated SGOT (serum glutamic-oxaloacetic transaminase) (354 units) and moderate azotemia with microscopic hematuria. Although the muscle biopsy was normal, muscle injury was still considered most likely because the patient complained of myalgias and muscle tenderness. Only a small portion of the latissimus dorsi was examined. The absence of hepatomegaly and of abnormal findings in the liver function studies and liver biopsy effectively excluded liver involvement. Renal biopsy showed minimal changes consisting of mild vacuolization of the proximal tubules most likely caused by mannitol therapy. There was transient hematuria and azotemia. Although a glomerulitis could also account for these abnormalities, the absence of glomerular changes by light and electron microscopy in the renal biopsy obtained 5 days after the ingestion made this diagnosis improbable. The early ad-

TABLE 105.—Laboratory data of patients with C-4 intoxication

Laboratory data	Number positive/ number patients	Percent positive
Anemia (hematocrit range 26-37%)	4/6	67
Leukocytosis (white blood cells range 11,900-41,000 cells/cu mm)	6/6	100
Azotemia (blood urea nitrogen range 20-69 mg %)	5/6	83
Hyperbilirubinemia	0/6	0
Elevated serum glutamic-oxaloacetic transaminase (range 170-1,030 units)	5/6	83
Elevated alkaline phosphatase (range 48-89 units)	2/4	50
Elevated Bromsulphalein retention (16.5%)	1/5	20
Normal liver biopsy	3/3	100

Sources: (1) Stone, W. J.; Paletta, T. L.; Heiman, E. M.; Bruce, J. I.; and Knepshield, J. H. 1969. Toxic effects following ingestion of C-4 plastic explosive. *Arch. Int. Med.* 124: 726-30. © 1969, American Medical Association. (2) Merrill, S. L. 1968. Ingestion of an explosive material, composition C-4: A report of two cases. *USARV M. Bull.* (USARV Pam 40-8), March-April, pp. 5-11.

ministration of mannitol may have modified the course of acute tubular necrosis in this patient. Prerenal azotemia was excluded because congestive heart failure and volume depletion were not present in any of the six patients. Additionally, a bone marrow aspiration was performed on the patient because of persistent normochromic, normocytic anemia. The findings of erythroid hypoplasia and a normal marrow iron content were consistent with toxic depression of the erythroid series. Mild anemia was found in three other patients.

Two abnormalities persisted in the patient who had ingested the largest quantity of C-4. At the time of evacuation on the 30th hospital day, anemia (hematocrit 33 percent) and loss of memory for recent events were still present. The patient's clinical course suggests that larger quantities may cause serious complications that persist for an extended period. The ingestion of a small quantity of C-4 (a few grams) is unlikely to produce any serious long term adverse effects.

The management of C-4 intoxication consisted of early gastric lavage; maintenance of an airway and prevention of aspiration of gastric contents; control of seizures with anticonvulsants; monitoring of hourly urine volume to detect acute renal insufficiency at its onset; and maintenance of normal fluid and electrolyte balance. In the presence of oliguria, a test dose of 25 g of mannitol or 200 mg of furosemide was given. If diuresis did not ensue, an acute renal insufficiency regimen was instituted. Because of its chemical structure and solubility characteristics, aqueous hemodialysis or peritoneal dialysis cannot remove significant quantities of RDX, which is presumed to be the cause of the toxic effects of C-4. The other constituents of composition C-4 are large molecules in low concentrations and are probably nontoxic in the quantities ingested. RDX is lipid-soluble; therefore, it is probably selectively accumulated in the central nervous system and body fat similarly to thiopental and glutethimide. This suggests that hemodialysis using soybean oil or cottonseed oil in the bath might be beneficial in the critically ill patient. No patient with C-4 intoxication in this study required dialysis.

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Renal Transplantation in Vietnam

*Daniel L. Macken, M.D., Ronald P. Fischer, M.D.,
William E. Miller, M.D., and James H. Kneppshield, M.D.*

Kidney transplantation has been performed in the United States for many years. A successful homograft was performed in the Republic of Vietnam during hostilities and was a step toward instituting a renal center in that country, ultimately strengthening the medical community in Vietnam as a whole. The U.S. Army Medical Department was instrumental in the success of this effort through its MEDCAP (Medical Civic Action Program).

MEDCAP was a voluntary activity among medical teams in Vietnam. At the 3d Field Hospital in Saigon and the 629th Medical Detachment (Renal), MEDCAP activities brought about a close association with the University of Saigon School of Medicine, which provided perspective into the capabilities and problems of the Vietnamese medical community in meeting the health needs of the country. With assistance from the American Medical Association, the Ministry of Health in Vietnam, the University of Saigon School of Medicine, the United States Agency for International Development, and the American and French Army Medical Departments, a high level of cooperation and interest in plans for renal transplantation evolved, resulting in other benefits as well. Saigon Hospital, ultimately chosen for the first operation, was a Ministry of Health facility used primarily as a teaching hospital by the medical school (fig. 94).

The recipient of the transplant was a 20-year-old male Vietnamese student who had had more than a year of vague flank pain, and a month of weakness, oliguria, nausea, and vomiting. He had been admitted to the French hospital, l'Hôpital Grall, in Saigon, on 3 March 1969, where azotemia, anemia, and hypertension were documented. On transfer to the 629th Medical Detachment 3 weeks later, he was considered moribund. He arrived in a stuporous state, with a blood pressure of 160/110 mm Hg, pulse 110/min, and deep respirations at 26/min. The neck veins were distended. Anasarca and ascites were present. The heart was clinically enlarged and there were prominent third and fourth heart sounds. A diagnosis of congestive heart failure and chronic renal failure was made.

Hemodialysis was instituted and his general condition improved. Urine volume was less than 100 ml/day. An open kidney biopsy revealed severe chronic glomerulonephritis. The patient's mother volunteered to donate her kidney; she was evaluated and found to be an acceptable donor. Compatibility was determined by ABO cross-matching alone as tissue typing was not available.

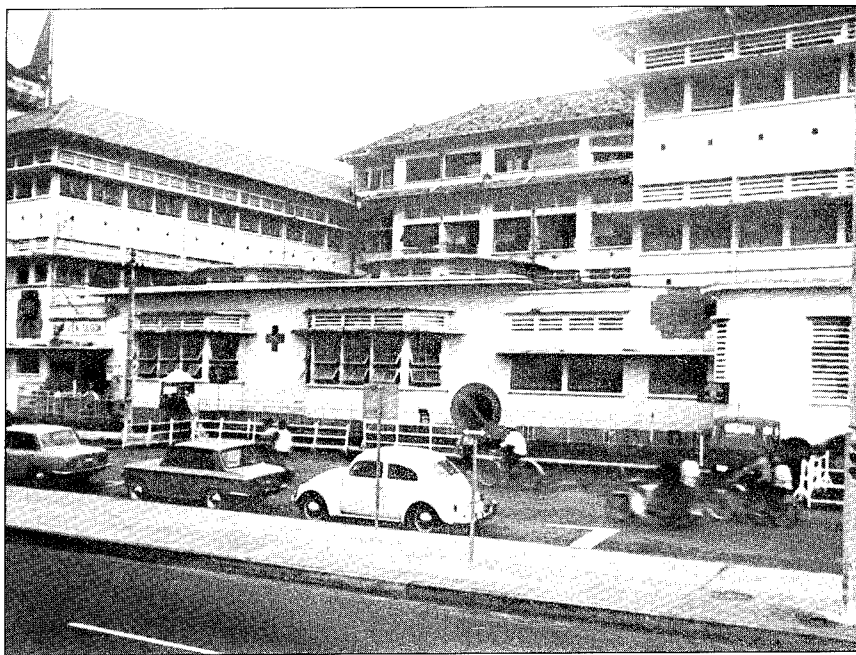


FIGURE 94.—Saigon Hospital, scene of the first U.S. military participation in a renal transplantation.

On 6 June 1969, the patient, pretreated with prednisone and azathioprine, was transported to Saigon Hospital where Dr. Nguyen Phuoc Dai, chief of surgery at the hospital and associate professor of surgery at the university, together with his team and one provided by the 3d Field Hospital, U.S. Army, performed the operation. The surgical team was composed of approximately equal numbers of Americans and Vietnamese (fig. 95). The donor kidney was perfused with a mixture of lactated Ringer's solution, papaverine, albumin, and heparin at approximately 5°C. Warm ischemia time was 2 min 25 sec. Cold ischemia time was 22 min 55 sec. After the intravenous administration of mannitol 25 g and furosemide 80 mg, a urine output of 3,920 ml was recorded in the first 24 hours.

On leaving the recovery room, the patient was readmitted to the 3d Field Hospital. On postoperative days 1, 3, 4, and 6, he was transported to l'Institut du Cancer du Vietnam where local irradiation to the kidney was delivered for a total tissue dose of 490 R. Two weeks after surgery, the creatinine clearance was 81.53 ml/min per 1.73 m². An intravenous pyelogram was consistent with normal function. The patient was discharged on the 14th hospital day on oral prednisone 30 mg and azathioprine 100 mg daily. The patient's mother was discharged from Saigon Hospital after an uncomplicated course.

On 3 July, the recipient was readmitted with fever and oliguria and was believed to have an early rejection episode. He was treated with high doses of



FIGURE 95.—The renal transplantation team. Front row (left to right): Lt. Col. Finn Gunderson, MC, Commander, 3d Field Hospital; U.S. Army nurse; Maj. Ronald Fischer, MC; Vietnamese nurses; Maj. Prentiss Smith, MC; Dr. Nguyen Phuoc Dai, Chief, Department of Surgery, Saigon Hospital; Maj. Daniel Macken, MC, medical coordinator for the operation (behind Vietnamese nurses); and Maj. James H. Kneppshield, MC, Chief, 629th Medical Detachment (Renal), 3d Field Hospital. Members of the team from the staffs of the 3d Field Hospital and the Saigon Hospital are present in the background.

prednisone and with 390 R of local irradiation. The BUN (blood urea nitrogen) reached 77 mg/100 ml before returning to normal. The patient recovered without incident and was discharged on prednisone 75 mg and azathioprine 100 mg daily.

Six-month followup studies were performed in December 1969. The blood pressure was 112/80 mm Hg; serum and urine electrolytes were normal. Twenty-four hour urine protein was 330 mg. The creatinine clearance was 76.22 ml/min per 1.73 m². The patient returned to school and was leading a normal life more than 2 years after the operation. He was lost to followup after cessation of the American effort in Vietnam.

Participation in a successful renal transplant by a U.S. Army medical team in Vietnam preceded the development of formal transplantation centers in U.S. military hospitals in the continental United States. The effort required international cooperation, using Vietnamese, French, and American facilities and personnel. It was a step forward in Vietnamese medicine at a time when planning for its future was difficult and troubled. The 629th Medical Detachment (Renal) became the first Army unit to accomplish a successful renal transplantation.

GLOSSARY

ACTH	Adrenocorticotrophic hormone
ADI	Acute diarrheal illness
AFEB	Armed Forces Epidemiological Board
AID	Agency for International Development
AMP	Adenosine monophosphate
ANC	Army Nurse Corps
Anti-HB _c Ab	Hepatitis B core antibody
Anti-HB _s Ab	Hepatitis B surface antibody
ARD	Acute respiratory disease
ARI	Acute renal insufficiency
ARVN	Army, Republic of Vietnam
ATP	Adenosine triphosphate
Average strength	Arithmetic mean (average) of daily morning report strengths, used in medical statistical reports for computing admission rates, mortality rates, and noneffective rates
BCOF	British Commonwealth Occupation Forces
BFP	Biologically false positivity; biologic false positive reaction
b.i.d.	Twice daily
BSP	Bromsulphalein
BTBST	Bromothymol-blue, salt, "Teepol" (culture medium)
BUN	Blood urea nitrogen
β_2 C	Complement, third component
CBI	China-Burma-India theater (World War II)
CCU	Coronary care unit
CDC	Center(s) for Disease Control
CF	Complement fixation
C5a	Complement, fifth component, activated
C-4	Plastic explosive
C'H ₅₀	Complement, hemolytic component
CIDG	Civilian Irregular Defense Group
CMV	Cytomegalovirus
C1	Complement, first component
CONUS	Continental United States
C-P	Chloroquine-primaquine (tablets)
CRD	Common respiratory disease
C.S.F.	Cerebrospinal fluid
C3	Complement, third component
C3a	Complement, third component, activated
CTZ	Corps Tactical Zone
CWCP	Civilian War Casualty Program
DC	Dental Corps
DDT	Dichlorodiphenyltrichloroethane
DFD	Diformaminodiphenylsulfone
DHF	Dengue hemorrhagic fever
DIC	Disseminated intravascular coagulation

DNA	Deoxyribonucleic acid
DSS	Dengue shock syndrome
EBV	Epstein-Barr virus
ECHO	Enteric cytopathogenic human orphan (virus)
EEG	Electroencephalogram
EMB	Eosin-methylene blue (agar)
E.S.R.	Erythrocyte sedimentation rate
EV	Live, attenuated strain of <i>Yersinia pestis</i>
FASCOM	Field Army Support Command
FUO	Fever of undetermined origin
G6PD	Glucose-6-phosphate dehydrogenase
HA	Hemagglutination
H antigen	Flagellar antigen of <i>Salmonella</i> genus
HB _c Ag	Hepatitis B core antigen
HB _s Ag	Hepatitis B surface antigen
HI	Hemagglutination inhibition
HOPE	Health Opportunity for People Everywhere
ID ₅₀	Median infective dose
IFA	Indirect fluorescent antibody
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHA	Indirect hemagglutination
I.U.	International units
JBE	Japanese B encephalitis
LGV	Lymphogranuloma venereum
LIVIM	Lethal intestinal virus infection of mice
MAAGV	Military Assistance Advisory Group, Vietnam
MACV	Military Assistance Command, Vietnam
MC	Medical Corps
MEDCAP	Medical Civic Action Program
MEDCON	Operation Medical Consultant
MEDICO	Medical International Cooperation Organization
MIC	Minimal inhibitory concentration
MILPHAP	Military Provincial Health Assistance Program
MOS	Military occupational specialty
MSC	Medical Service Corps
MUST	Medical unit, self-contained, transportable
NAD	Nicotinamide-adenine dinucleotide
NAGCV	Nutrient agar, glycerol, crystal violet
NAMRU	Naval Medical Research Unit
NCDC	National Communicable Disease Center
NSU	Nonspecific urethritis
NVA	North Vietnamese Army
O antigen	Somatic antigen of <i>Salmonella</i> genus
OX-K	O or somatic antigen of X strain of the <i>Proteus</i> bacillus, Kingsbury type
OX-19	O or somatic antigen of X strain of the <i>Proteus</i> bacillus, type 19
OX-2	O or somatic antigen of X strain of the <i>Proteus</i> bacillus, type 2
pCO ₂	Partial pressure of carbon dioxide
PGU	Postgonococcal urethritis
pH	Hydrogen ion concentration
P.M.N.	Polymorphonuclear neutrophil leukocyte
pO ₂	Partial pressure of oxygen
PRNT	Plaque red neutralization test

PT	Prothrombin time
PTT	Partial thromboplastin time
PVA	Polyvinylalcohol
P value	Statistical term expressing significance of data
q.d.	Daily
q.i.d.	Four times a day
q.o.d.	Every other day
R&R	Rest and recuperation
RBC	Red blood cells; red blood count
RDX	Cyclonite
R factor	Resistance factor
Rh	Rhesus factor
RNA	Ribonucleic acid
RPR	Rapid Plasma Reagin (test)
RS	Respiratory syncytial (virus)
RVN	Republic of Vietnam
RVNAF	Republic of Vietnam Armed Forces
SAFA	Soluble antigen fluorescent antibody
SEATO	Southeast Asia Treaty Organization
SGOT	Serum glutamic-oxaloacetic transaminase (aspartate aminotransferase)
SGPT	Serum glutamic-pyruvic transaminase (alanine aminotransferase)
SPA	South Pacific Area (World War II)
SWPA	Southwest Pacific Area (World War II)
TB Med	Technical Bulletin, Medical
TCBS	Thiosulfate, citrate, bile salts, sucrose (agar)
TD	Table of distribution
t.i.d.	Three times a day
TOE	Table of organization and equipment
TRIC	Trachoma inclusion conjunctivitis
TSH	Thyroid-stimulating hormone
"T" test	Statistical test to determine significance
URI	Upper respiratory infection
USAMCJ	U.S. Army Medical Command, Japan
USAMRTV	U.S. Army Medical Research Team, Vietnam
USARJ	U.S. Army, Japan
USARPAC	U.S. Army, Pacific
USARV	U.S. Army, Vietnam
USARYIS	U.S. Army, Ryukyu Islands
USASGV	U.S. Army Support Group, Vietnam
USATC	United States of America Typhus Commission
USOM	U.S. Operations Mission
USP	U.S. Pharmacopeia
USPHS	U.S. Public Health Service
V antigen	Antigenic fraction of plague bacillus that inhibits phagocytosis
VC	Veterinary Corps; Vietcong
VDRL	Venereal Disease Research Laboratory
VH:CD	Villus height to crypt depth ratio
Vi antigen	Virulence antigen of <i>Salmonella</i> genus
VN	Virus neutralization
W antigen	Antigenic fraction of plague bacillus that inhibits phagocytosis
WBC	White blood cells; white blood count
WFR	Weil-Felix reaction
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

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