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History of U.S. Military Contributions to the Understanding, Prevention, and Treatment of Infectious Diseases: An Overview

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The contributions of U.S. military and affiliated civilian personnel to the advancement of mankind's understanding, prevention, and treatment of infectious diseases are innumerable. This supplement of *Military Medicine* has been produced by the Armed Forces Infectious Diseases Society (AFIDS) to review and highlight the accomplishments of U.S. Department of Defense military and civilian researchers in this field of study. Contributions by U.S. Armed Forces investigators to better the health of the world are documented in the 11 articles that follow.

Introduction

Uniformed and civilian personnel of the U.S. military services have contributed to mankind's battle against infectious diseases since the formation of the Continental Army in the 1770s. Efforts to preserve the fighting strength have included development of vaccines, therapeutics, vector control agents, and other preventive strategies. To improve the health of the military forces, the epidemiologies of many infectious diseases have been extensively examined to develop means and strategies of prevention and control. To support these efforts, basic science research into the structure, genome, growth, pathogenicity, and virulence of the bacteria, parasites, viruses, and occasionally fungi causing human disease have been examined by military researchers.

Armed Forces Infectious Diseases Society

The Armed Forces Infectious Diseases Society (AFIDS) is a chapter of the Infectious Diseases Society of America (IDSA). It is composed of physicians and other health care professionals or researchers who are presently or have been previously affiliated with the U.S. Department of Defense. The Society and its annual scientific conference emerged in 1995 from the Annual Tri-Service Infectious Disease Meeting. As both names imply, AFIDS is composed chiefly of physicians from the U.S. Air Force, U.S. Army, and U.S. Navy with subspecialty training and board certification in infectious diseases. The Society is and has been represented by officers and councilors from each of these three services, including both adult and pediatric infectious disease specialists (Tables I and 2). Other nonphysician and/or nonmilitary, but Department of Defense-affiliated, personnel with interests in research and the treatment of infectious diseases make up a small percentage of AFIDS membership. The Society was established to

TABLE I

CURRENT ARMED FORCES INFECTIOUS DISEASES SOCIETY OFFICERS AND COUNSELORS

Officers	
President	LtCol George W. Christopher, USAF MC
Vice President	CAPT Glenn A. Schnepf, MC USN
Secretary-Treasurer	COL Ted J. Cieslak, MC USA
Board of Councilors	
U.S. Air Force	Maj Michael A. Forgione, USAF, MC
U.S. Army	COL David P. Dooley, MC USA
U.S. Navy	CAPT Mark R. Wallace, MC USN
Pediatrics	Col Martin G. Ottolini, USAF MC

TABLE II

PAST ARMED FORCES INFECTIOUS DISEASES SOCIETY PRESIDENTS

LTC Duane R. Hospenthal, MC USA	2003–2004
CAPT Norman J. Waecker, Jr., MC USN	2002–2003
Col Matthew J. Dolan, USAF MC	2001–2002
COL Raymond C.Y. Chung, MC USA (Ret.)	2000–2001
CAPT John D. Malone, MC USN (Ret.)	1999–2000
Col David P. Ascher, USAF MC (Ret.)	1998–1999
COL David P. Dooley, MC USA	1997–1998
CAPT Douglas L. Mayers, MC USN (Ret.)	1996–1997
Col George E. Crawford, USAF MC (Ret.)	1995–1996
Col Gregory P. Melcher, USAF MC (Ret.)	1994–1995

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TABLE III

RECIPIENTS OF THE JAY P. SANFORD MEMORIAL AWARD FOR EXCELLENCE IN MILITARY INFECTIOUS DISEASES[a]

CAPT Kenneth F. Wagner, MC USN (Ret.)	2004
Col Gregory P. Melcher, USAF MC (Ret.)	2003
COL Gerald W. Fischer, MC USA (Ret.)	2002
CAPT Edward C. Oldfield III, MC USN (Ret.)	2001
Col George E. Crawford, USAF MC (Ret.)	2000
COL James W. Bass, MC USA (Ret.)	1999
CAPT Walter W. Karney, MC USN (Ret.)	1998
COL Edmund C. Tramont, MC USA (Ret.)	1997

[a] Awarded for a career achievement in military infectious diseases.

further communication and cooperation among infectious diseases specialists within the U.S. military and between this group and the national society, IDSA. Over the brief history of AFIDS, the Society has honored seven infectious disease clinicians for their careers in military infectious diseases (Table III), with an award named for one of infectious diseases' and the U.S. military's greats, Jay P. Sanford, MD, the first dean of the military medical school at the Uniformed Services University of the Health Sciences, Bethesda, Maryland. Additional information about the Society and how to join can be found online at www.afids.org.

The History Project

As a society representing the current U.S. military infectious disease community, and indirectly the past and future of that community, AFIDS is proud of the heritage that has been established by our predecessors in the armed forces research community. The program of the 2004 annual meeting included presentations that were meant to make the membership aware of the tremendous scope of the infectious disease contributions of these predecessors. These brief presentations only scratched the surface of these labors and were subsequently expanded into the full-length articles herein. The goal of this supplement is an attempt to record and present to a greater audience the extensive contributions of the U.S. military to the field of infectious diseases.

Although it would be nearly impossible to document all of the contributions made by U.S. military and affiliated civilian personnel, the following articles highlight major contributions and areas examined by these researchers and clinicians. For those contributions that have been overlooked in this sea of information, we apologize in advance, but hopefully the reader will at least appreciate the depth and breadth of infectious disease contributions of investigators.

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History of U.S. Military Contributions to the Study of Viral Hemorrhagic Fevers

Guarantor: COL Timothy P. Endy, MC USA
Contributors: MAJ Stephen J. Thomas, MC USA*; LCDR James V. Lawler, MC USN†; COL Timothy P. Endy, MC USA‡

The viral hemorrhagic fever viruses represent a unique group of viruses that can produce large outbreaks of both animal and human disease and produce severe, highly fatal, human illnesses. The viral hemorrhagic fever viruses display a great deal of diversity in their genetic organization, vectors for transmission, and geographic distribution. They share common features in being able to induce a great deal of cellular damage and to elicit an immune response among humans that can result in severe hemorrhage, coagulopathy, shock, and death. The characteristics of the viral hemorrhagic fever viruses as arthropod-borne or rodent-borne viruses that can result in human illnesses with high morbidity and mortality rates make these viruses a unique threat, historically, currently, and in the future, to deployed soldiers around the world. In response to this threat, U.S. military scientists have been world leaders in the development of knowledge on the viral hemorrhagic fever viruses, from extensive fieldwork in areas in which these viruses are endemic, outbreak investigations of epidemics, and careful clinical studies elucidating the pathogenesis of severe disease. Defining the disease threat and creating practical countermeasures through the development of drugs and vaccines has been the major mission of military scientists and has resulted in numerous candidate vaccines currently in animal and human clinical trials.

Introduction

The viral hemorrhagic fever viruses are arthropod-borne or rodent-borne viral infections that can result in hemorrhage and shock. In the case of the filoviruses, the transmission to humans and the natural reservoir are not known. The viral hemorrhagic fever viruses can produce a clinical syndrome that is characterized by fever, severe systemic symptoms such as headache, myalgias, arthralgias, nausea, vomiting, and diarrhea, and varying degrees of coagulopathy. Coagulopathy is a distinguishing feature of the viral hemorrhagic fever viruses and is manifested by hemorrhage into the skin as petechiae or ecchymoses, oozing at puncture sites, epistaxis, gingival bleeding, hematemesis, melena, and severe vaginal bleeding. Cardiovascular collapse and shock syndrome can occur through blood loss or intravascular plasma leakage into the extravascular space.

The viral hemorrhagic fever viruses are represented by a variety of RNA viruses with varying vectors of transmission, epidemiology, pathogenesis, and case fatality rates. The RNA viruses are highly susceptible to point mutations, in the range of 10^{-4} to 10^{-5} substitutions per nucleotide copied, and undergo homologous and heterologous recombination, gene reassortments, and formation of quasispecies during replication.[1,2] The high mutation and recombination rates observed explain in part the great deal of genetic diversity seen among the RNA viruses.[3] The result is a virus that undergoes rapid evolution and that can become highly adaptable to the host and the environment. The diversity of the viral hemorrhagic fever viruses and their adaptability to the host and the environment result in a group of pathogens that have been in the past, are currently, and potentially will be in the future major disease threats to military personnel deployed in virus-endemic areas. This article is a review of the military significance of the viral hemorrhagic fever viruses and the contributions of military scientists toward understanding the viruses.

Dengue

Dengue is an expanding public health problem in the tropics and subtropics. Reports suggest that 2.5 billion people are at risk for dengue, with up to 100 million dengue virus infections occurring each year and more than 60,000 reported deaths.[4–6] Dengue transmission occurs in Central and South America, South and Southeast Asia, Africa, and the Caribbean and Pacific regions. There have been recent outbreaks in Texas, Florida, and Hawaii.[7–9] Population growth, urbanization, and regional and international travel sustain the continually worsening global dengue situation.[10,11]

The U.S. military has made great contributions to the understanding of the etiology, epidemiology, immunology, and pathogenesis of dengue virus infections. Numerous dengue vaccine candidates have been developed by the U.S. military and are being evaluated in Phase I/II clinical trials.

Dengue viruses belong to the genus *Flavivirus* and the family Flaviviridae.[12] The virion is a single-strand, positive-sense, RNA genome coding for capsid, membrane, and envelope proteins and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5).[13] The dengue viruses exhibit substantial genetic diversity, exemplified by the existence of four distinct serotypes (DEN-1–4).[13,14] The genetic diversity and phylogenetic relationships of dengue virus strains isolated from different parts of the world suggest the existence of numerous DEN-1, -2, -3, and -4 genotypes.[15–25]

The pathogenesis and pathophysiology of severe dengue virus infections (dengue hemorrhagic fever) remain incompletely understood. Early theories were based on clinical observations and seroepidemiological studies.[26–28] An extensive body of work describing clinical and basic science observations on pathogenesis has been completed by U.S. military scientists and their collaborators at the Walter Reed Army Institute of Research (WRAIR)

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than 3,000 United Nation soldiers developing hemorrhagic disease, with renal failure, shock, and death in 10 to 15% of cases.[214,215] The etiological agent of this disease in Korea was isolated in 1967 from the rodent *A. agrarius* and was named Hantaan virus after the Hantaan River.

Military scientists continued to investigate HFRS, with numerous publications and the development of a vaccine program that continues in the Military Infectious Disease Research Program. Intravenous ribavirin (Viratek Pharmaceuticals) therapy was found to be effective for HFRS, and this is currently an Investigational New Drug with the U.S. Food and Drug Administration (U.S. Department of Defense Investigational New Drug 16,666). The only double-blind, placebo-controlled, clinical trial of intravenous ribavirin therapy was conducted among 242 patients with HFRS in the People's Republic of China by scientists from the USAMRIID.[216] Mortality rates were reduced sevenfold for the ribavirin-treated patients, and ribavirin therapy resulted in significant reductions in the risks of entering the oliguric renal phase and of developing hemorrhagic manifestations.[216]

Today military scientists continue to address the hantaviruses as a military threat and have published seminal articles on the epidemiology, pathogenesis, and virology of these viruses.[202,211,217-236] The Department of Defense Military Infectious Disease Research Program continues in its efforts to develop an effective vaccine against HFRS.

Rift Valley Fever

Rift Valley fever (RVF) virus is in the family Bunyaviridae, genus *Phlebovirus*. As previously noted, the Bunyaviridae share similar morphological features, with a spherical virion and a size between 80 and 120 nm.[198]

U.S. Military Significance

RVF is an acute zoonotic disease that affects both ruminant animals and humans and occurs as an epizootic, with transmission to humans primarily from infected mosquitoes (*Culex, Aedes*, and *Anopheles* species) and secondarily from the handling of infected animal carcasses.[214] RVF virus was isolated in 1930 in the Rift Valley of Kenya, in East Africa, and has been responsible for more than 30 large outbreaks of animal and human disease in East Africa since the 1930s. Weather pattern analysis demonstrated that RVF outbreaks followed periods of abnormally high rainfall, which were predictive up to 5 months in advance of outbreaks.[237] In 1977, RVF was responsible for a large outbreak of animal and human disease in Egypt, involving more than 18,000 clinical cases and 598 deaths.[238] Subsequent outbreaks occurred in Mauritania in 1987, again in Egypt during 1993, and recently in Yemen and the Kingdom of Saudi Arabia in 2000. Saudi Arabia reported a total of 886 cases and a case fatality rate of 13.9%.[239] The majority of cases in Saudi Arabia occurred among adult men with significant risk factors for exposure to mosquito bites and infected animals. Age-specific mortality rates were greatest for the elderly, with an overall mortality rate in the population of 14%.[240] RVF virus is considered an emerging pathogen, causing considerable economic loss among domestic animals and human disease. Factors responsible for its emergence include the movement of infected livestock and mosquito vectors, global weather pattern changes, and economic development resulting in environmental conditions favoring mosquito breeding, such as periods of heavy rainfall or the building of dams, with associated flooding of plains.[239]

The major clinical characteristics of RVF include hepatocellular failure, acute renal failure, and hemorrhagic manifestations.[241] Development of retinitis and meningoencephalitis is a late complication of the disease. Death has been observed in 33.9% of cases. Hepatorenal failure, shock, and severe anemia were all factors associated with death.[241]

U.S. Military Contributions

Military scientists have contributed to the understanding of the epidemiology, pathogenesis, and diagnosis of RVF. The full potential of RVF as a human pathogen and military threat was determined by military scientists from the Naval Medical Research Unit in Cairo, Egypt, during a large outbreak of RVF in Egypt in 1977.[238] Four clinical syndromes were documented during that outbreak, i.e., a febrile illness, encephalitis, ocular complications, and hemorrhagic disease. Other contributions have been characterization of the virus and its vector and transmission cycle and the development of diagnostic assays.[239,242-244] One of the most significant achievements by military scientists was in the analysis of weather patterns as a predictive model for RVF outbreaks.[237,245-247]

Chikungunya

Chikungunya (CHIK) virus is classified in the family Togaviridae, genus *Alphavirus*. The alphaviruses contain a nucleocapsid enclosed within a lipoprotein envelope containing a single strand of positive-polarity RNA. Two viral envelope glycoproteins, termed E1 and E2, exist and function as a heterodimer and the site for antibody neutralization.[248] CHIK is antigenically closely related to other alphaviruses, including O'nyong-nyong, Mayaro, and Semliki Forest viruses, and is serologically indistinct from O'nyong-nyong virus. CHIK is transmitted to humans by *Aedes* mosquitoes, primarily *A. aegypti* and *Aedes africanus*.[249,250]

Human infection with CHIK is manifested by the sudden onset of fever, myalgia, headache, ocular pain, sore throat, nausea, and vomiting.[250] A maculopapular rash develops and is accompanied by enlarged tender lymph nodes. Severe joint arthralgias are common; they occur during the acute period and can last for several months into convalescence. Hemorrhagic manifestations can occur during acute CHIK infection and were observed during outbreaks in India and Southeast Asia. The hemorrhagic manifestations of CHIK were first observed during the early 1960s in Bangkok, Thailand, where approximately 10% of children admitted for dengue hemorrhagic fever were in fact suffering from CHIK virus.[250-254] Outbreaks of CHIK have been identified in Southeast Asia, India, Zambia, southeastern Zimbabwe, and Zaire.

U.S. Military Significance

CHIK was not a major problem among U.S. forces deployed in Vietnam and was not a significant factor in previous military operations. As an arbovirus with epidemic potential that can produce a sudden debilitating disease, its potential as a serious military threat is considerable.

U.S. Military Contributions

Military scientists have contributed to our understanding of the epidemiology, transmission, and pathogenesis of CHIK virus infections. The significance of CHIK virus as a human pathogen was demonstrated during the early part of the dengue hemorrhagic fever outbreak in Southeast Asia, where its clinical manifestations and potential as a hemorrhagic fever virus were described. Military scientists also have contributed significantly in the development of both killed and live attenuated CHIK vaccines, demonstrating low reactogenicity and high immunogenicity in Phase I clinical studies.[253-258]

Summary of Key U.S. Military Contributions

The viral hemorrhagic fever viruses are a unique group of viruses that can produce severe, highly fatal human illnesses following the bites of mosquitoes or ticks, infected rodent or domestic animal exposure, or contact with other infected humans. They share common features in being able to directly induce cellular damage and to elicit an immune response among humans that can result in severe hemorrhage, coagulopathy, shock, and death. The characteristics of arthropod-borne or rodent-borne transmission, combined with illnesses that result in high morbidity and mortality rates, make the viral hemorrhagic fever viruses a unique threat to deployed soldiers around the world. The viral hemorrhagic fever viruses have historically been a major cause of disease for both U.S. and foreign soldiers, are currently a major cause of morbidity among U.S. soldiers, and will certainly be an ever-present disease threat for the U.S. military. The key military contributions are as follows: (1) leaders in the development of knowledge on the epidemiology and pathogenesis of dengue fever and dengue hemorrhagic fever, (2) development of numerous candidate dengue vaccines and a live attenuated dengue tetravalent vaccine currently in human clinical trials, (3) instrumental in gaining knowledge on the epidemiology and pathogenesis of YF, including the discovery of its transmission to humans from the bites of mosquitoes, (4) development of fundamental knowledge on the epidemiology and pathogenesis of the arenaviruses, (5) contributions in the characterization and testing of the Junin vaccine, (6) development of fundamental knowledge on the epidemiology and pathogenesis of filoviruses and filovirus vaccine development, (7) leaders in the development of knowledge on the epidemiology and pathogenesis of HFRS, (8) development of an effective antiviral drug against HFRS, ribavirin, and the vaccine development program, and (9) development of fundamental knowledge on the epidemiology and pathogenesis of RVF and CHIK.

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