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Cover: 34th Surgeon General of the Navy, VADM Michael L. Cowan, MC, USN

Change of Command for Navy Medicine

VADM Michael L. Cowan became the 34th Surgeon General of the Navy and Chief, Bureau of Medicine and Surgery on 10 August 2001. Previously, VADM Cowan served as the Deputy Executive Director, Chief Operating Officer, and Program Evaluation Officer for the TRICARE Management Activity, Office of the Assistant Secretary of Defense for Health Affairs.

Raised in Fort Morgan, CO, he did his undergraduate studies at the University of Colorado in Boulder, and received his M.D. degree in 1969 from Washington University School of Medicine in St. Louis. His postgraduate training began at Temple University Hospital and was completed at the National Naval Medical Center, Bethesda, MD. He is board certified in internal medicine, a Diplomate and Certified Physician Executive (CPE) in the American College of Physician Executives.

Dr. Cowan entered naval service as a general medical officer at Camp Lejeune, NC, in 1971, and was promoted to flag rank while serving as commanding officer at the same hospital in 1996. During his career, he has held a wide variety of clinical, research, operational, staff, and leadership positions, including:

Chief of Staff, Assistant Secretary of Defense (Health Affairs); Surgeon to the Joint Staff Commander, Defense Medical Readiness Training Institute; Commanding Officer, Naval Hospital, Camp Lejeune; Task Force Surgeon, Operation Restore Hope, Somalia.

His awards include: Defense Distinguished Service Medal (with two gold stars); Defense Superior Service Medal; Legion of Merit (with two gold stars); Nathan Davis Award (American Medical Association); University Medal (Uniformed Services University of the Health Sciences); Order of Military Medical Merit (U.S. Army); U.S. Army Expert Field Medical Badge; Navy PMO Society "Gihon Medal." ❑

BUMED's Biomedical Research and Development Laboratories

The Bureau of Medicine and Surgery's biomedical research and development laboratories are committed to providing the biomedical research needed to support the men and women of the Navy and Marine Corps. Researchers conduct basic, clinical, and field research directly related to military requirements and operational needs. Current studies focus on military recruits, special training groups, and personnel in the surface, submarine, air, and amphibious warfare communities.

In this special issue of *Navy Medicine*, representative R&D stories are featured. For more information on the Navy' biomedical laboratories and current research initiatives visit the web sites below.

Bureau of Medicine and Surgery
(http://navymedicine.med.navy.mil/med26/)
Operational Medicine and Fleet Support (MED-02), Research and Development (MED-26)

Naval Medical Research Center (NMRC), Silver Spring, MD. ***(www.nmrc.navy.mil/)***
Areas of Research: Combat Casualty Care; Infectious Diseases; Biological Defense; Bone Marrow Research.

Naval Medical Research Unit No. 2, Jakarta, Indonesia. ***(www.namru2.med.navy.mil/)***
Areas of Research: Parasitic Diseases; Emerging Diseases; Bacterial Diseases; Viral Diseases.

Naval Medical Research Unit No. 3, Cairo, Egypt. ***(www.nmrc.navy.mil)***
Areas of Research: Emerging Infectious Diseases; Entomology; Virology; Enterics.

NMRC Detachment, Lima, Peru. ***(www.nmrc.navy.mil/)***
Areas of Research: Microbiology; Entomology; Parasitology; Virology.

Naval Dental Research Institute, Great Lakes. ***(http://bumed.med.navy.mil/ndri/)***
Areas of Research: Dental Support of Forward Deployed Troops; Biometrics and Public Health Dentistry; Salivary Tests for Infectious Diseases and Biological Agents; Mercury Abatement in Dental Wastewater.

Naval Health Research Center (NHRC), San Diego, CA. ***(www.nhrc.navy.mil/)***
Areas of Research: DOD Center for Deployment Health Research; Field Medical Technologies; Modeling and Simulation; Human Performance; Operational Readiness.

Naval Aerospace Medical Research Laboratory, Pensacola, FL. ***(www.namrl.navy.mil/)***
Areas of Research: Operational Medicine; Spatial Orientation; Aviation Selection; Visual Sciences.

Naval Submarine Medical Research Laboratory, Groton, CT. ***(www.nhrc.navy.mil/nsmrl/)***
Areas of Research: Information Processing and Display; Submarine Escape and Rescue; Hearing Conservation; Submarine Medicine; Diving Bioeffects.

NHRC Detachment (Brooks), San Antonio, TX. ***(www.brooks.af.mil/NHRC/nhrc.htm)***
Areas of Research: Health and Safety in non-battle directed energy operating environments; Threat countermeasures in hostile directed energy operating environments; Care and management of directed energy casualties.

NHRC Detachment (Toxicology), WPAFB, OH. ***(www.navy.al.wpafb.af.mil/)***
Areas of Research: Environmental and Molecular Toxicology; Neurobehavioral Toxicology; Occupational Toxicology; Reproductive Toxicology; Analytical Toxicology; Inhalation Toxicology; Risk Assessment. ❑

NAVY MEDICAL RESEARCH PIONEER

CAPT Stephen J. Savarino, MC, USN

Official Navy photo

CAPT R. A. Phillips (then CDR) was OIC of NAMRU-3 from 1947-1949

September 19, 2001 marks the 25th anniversary of the death of CAPT Robert Allan Phillips, one of the Navy's most decorated medical scientists. Cradled in a small-town Iowa family locally renowned for its public service, CAPT Phillips graduated from Washington University School of Medicine in 1929. He then trained with some of the most brilliant physiologists and biochemists of the early twentieth century. As a lieutenant at the Naval Research Unit of the Rockefeller Institute during the early part of World War II, Phillips developed the remarkably simple copper sulfate method for rapid assessment of fluid loss in wounded servicemen. Greatly influenced by his service on the U.S.A. Typhus Commission in Egypt and Dachau towards the war's end, Phillips determinedly promoted the establishment of the Naval Medical Research Unit Number Three (NAMRU-3) in Cairo, Egypt in 1947 and NAMRU-2 in Taipei, Taiwan in 1955, long serving as the commanding officer of both units.

CAPT Phillips embarked on studies of cholera during the throes of the 1947 Egyptian epidemic and brought them to maturity during his service at NAMRU-2 (1955-1965), coincident with the advent of the seventh cholera pandemic. Under his ingenious direction, Navy and civilian scientists carefully elucidated the pathophysiologic derangements induced by cholera and demonstrated the remarkable efficacy of intravenous rehydration, using the copper sulfate method as a diagnostic rudder. After retirement from active duty in 1965, CAPT Phillips became the Director of the Pakistan-SEATO Cholera Research Laboratory in Dhaka, where his fitful dream of an even simpler treatment was realized in the late 1960s with development of glucose-based oral rehydration therapy (ORT) for cholera and related diseases. The progression of ORT from basic science to field application, to which many contributed, is indisputably one of the century's monumental medical breakthroughs.

CAPT Phillips was awarded the Albert Lasker Award in 1967, the nation's most coveted medical prize, "in recognition of his enormous contributions to the understanding of the mechanism of death in cholera, and the development of a lifesaving method of treating it." Previously, his other decorations had included the Military Order of the British Empire (1946), the Egyptian Cholera Medal (1947), The Edward Rhodes Stitt Award in Laboratory Medicine (1962), and the James D. Bruce Award in Preventive Medicine (1966). Perhaps the greatest emblem of his legacy is the applicability of his pioneering work has grown with time. Today, oral and intravenous fluid rehydration for diarrhea and dehydration are the stuff of everyday medical practice in military and civilian settings alike. In global terms, each year ORT is responsible for saving the lives of an estimated 2.5 million children who would otherwise succumb from the ravages of diarrhea. ❑

CAPT Savarino is with the Enteric Diseases Department, Naval Medical Research Center, Silver Spring, MD.

The Navy's Newest Infectious Disease Research Laboratory

CDR William Alexander, MSC, USN
LT Paul D. Mills, MSC, USN
CAPT James R. Campbell, MSC, USN
James Olson, Ph.D.
CAPT Andrew L. Corwin, MSC, USN
CAPT James Burans, MSC, USN
CDR Michael McCarthy, MC, USN

In April 1996 Naval Medical Research Unit 2 (NAMRU-2), located in Jakarta Indonesia, received a request for medical assistance from Kenneth M. Quinn, U.S. Ambassador to Cambodia. The request specifically discussed initiating first-time, collaborative infectious disease research between the U.S. and Cambodian Governments, in the Kingdom of Cambodia. The Commander in Chief, Pacific (CINCPAC) also recognized the positive public health and potential foreign policy implications of collaborative efforts and actively supported NAMRU-2's initial and subsequent research proposals. CINCPAC, NAMRU-2, and Ambassador Quinn presented this collaborative proposal to the Cambodian Ministry of Health. In December 1998 a formal agreement was signed between the U.S. Government and the Kingdom of Cambodia to begin infectious disease collaborative research projects.

As the number of opportunities for research quickly grew, the value of the information developed made it apparent that NAMRU-2 would need a more permanent laboratory facility within Cambodia to meet the logistical and support needs of the research effort. After discussions with CINCPAC, NAMRU-2 approached Ambassador Quinn and the Government of Cambodia with a proposal to open a satellite NAMRU-2 laboratory in Phnom Penh.

Any reticence quickly gave way to enthusiasm, in light of the opportunities that the proposed new lab facility would provide. The set-up and operation of a new, state-of-the-art lab, the ability to train personnel in-house, and the opportunity to extend research collaborations to include other international research organizations was very enticing. However the Cambodian government initially expressed some minor concerns about national security. They agreed with the concept of a permanent facility, but with the stipulation that the laboratory would not be operated by active duty, U.S. military personnel. Both NAMRU-2 and the U.S. Army's Armed Forces Research Institute of Medical Science (AFRIMS, Bangkok) would be allowed to work within the laboratory, but the permanent staff was required to be civilian personnel and Foreign Service nationals, citizens of Cambodia from the local area. Given the potential research opportunities, the U.S. Government quickly agreed to this requirement. With the concurrence of all parties, the Centers for Disease Control and Prevention (CDC) was approached to collaborate by entering into a contract with NAMRU-2 to provide a full-time laboratory manager in Phnom Penh.

Photos by Travis Clemens

The National Institute of Public Health Compound, Phnom Penh, Cambodia.

Dr. James Olson was selected and arrived in 1999 to begin set-up of the laboratory. He acquired buildings, procured equipment, hired administrative and research personnel and, in an amazingly short time, opened the lab.

Since its opening, the lab has been involved in several projects, including incidence and prevalence studies for malaria, tuberculosis, Human Immunodeficiency Virus (HIV), hepatitis, arboviral, and enteric diseases. DOD also recognized the public health value of maintaining such a facility in country, for U.S. personnel involved in Joint Task Force-Full Accounting (JTF-FA) missions. NAMRU-2, using advanced immunological and molecular biology techniques, began evaluating the immunological status of JTF-FA personnel pre and post deployment

in country, as sentinels for potential disease exposure in Cambodia. More recently, with the seasonal monsoon flooding in the region, the lab initiated studies to monitor outbreaks of *Vibrio cholerae*.

Today the lab is operating with a crew of 12, including Dr. Olson. It is housed in a 336-square-meter facility on the Cambodian Ministry of Health Compound in Phnom Penh. The laboratory's current capabilities include ELISA, culturing for *V. cholerae*, rapid diagnostics (e.g. Panbio for dengue), and microscopy (with electron microscopy support from NAMRU-2). The range of laboratory capabilities is growing rapidly, and concommitant plans to expand the facility have been approved by the Ministry of Health.

NAMRU-2 provides extensive training programs, including in-house training for research technicians and general public health awareness training for the community. In addition to the full-time personnel, the CDC sends post-doctoral individuals to conduct research and assist Dr. Olson in the laboratory's operations. The U.S. Embassy in Phnom Penh actively supports the laboratory by providing contracting, personnel, security, and other logistical expertise, and the laboratory is officially integrated into the management structure of the U.S. Defense Attaché's Office (DAO). The Cambodian Ministries of Health and Defense also provide personnel to support the lab. CINCPAC provides core funding for laboratory operations, but collaborative projects and funding support with DOD's Global Emerging Infections System (GEIS) expands the scope of the work. International and private sector funding partners are being aggressively pursued to supplement the laboratory's budget.

One very specific advantage has been derived from the set-up of the lab in Cambodia. NAMRU-2 operates a network of Early Warning Outbreak Recognition System (EWORS) surveillance sites for infectious disease throughout Southeast Asia (See *Navy Medicine* September-October 2001). Currently, there are nine EWORS sites, with the addition of the latest site at the Ministry of Health laboratory in Phnom Penh. Cambodia provides an unparalleled opportunity to test and develop EWORS for infectious diseases. Cambodia's climate, terrain, endemic diseases and geographical location make it high risk for infectious disease outbreaks including *V. cholerae, O. tsutsugamushi,* dengue, typhoid and malaria. As a sentinel site, Cambodia provides valuable information for development and validation of EWORS, and lessons learned there are essential to the development of an international EWORS network.

As Ambassador Quinn intended, the Phnom Penh laboratory is also providing opportunities beyond those in infectious disease research. Individuals in the laboratory and in the Cambodian Government are actively pursuing expansion of operations to other aspects of public health including sanitation, development of potable water and sewage control systems, environmental protection, and other issues. The set-up and operation of this collaborative infectious disease research laboratory in Cambodia is also opening other domestic and foreign policy doors. Cambodia's period of political unrest is resolving, and with the return of stability, the government is focusing resources on public health and the welfare of the populace. In close coordination with the Cambodian Ministry of Health, NAMRU-2, AFRIMS, CINCPAC, and the CDC have unquestionably opened doors in the public health arena between Cambodia and the international community.

This key nation in Indochina, long closed to the outside world, now offers an unequaled opportunity to answer key scientific questions about important infectious diseases endemic in the region. The NAMRU-2 laboratory on the National Institute of Public Health (NIPH) compound in Phnom Penh is a unique platform for research, and for advancing U.S. humanitarian and foreign policy goals in Southeast Asia. ❑

CDR Alexander is Executive Officer of NAMRU-2, Jakarta, Indonesia..

LT Mills is assigned to NAMRU-2's Emerging Disease Department.

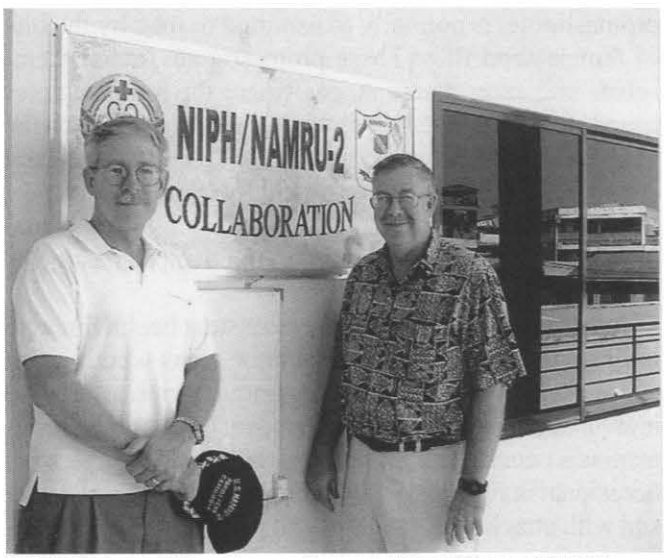
CAPT Campbell is Commanding Officer of NAMRU-2.

Dr. Olson is laboratory manager of NAMRU-2 Satellite Laboratory, Phnom Penh, Cambodia.

CAPT Corwin is Head, Emerging Diseases, NAMRU-2.

CAPT Burans is OIC, NMRID.

Dr. McCarthy is Executive Officer, NMRC.



CAPT Richard Hibbs, former Commanding Officer of NMRC, and Dr. James Olson, Laboratory Manager.

Leishmaniasis Research in Lima, Peru

LCDR Ellen M. Andersen, MSC, USN
CAPT James Burans, MSC, USN

Leishmaniasis is an infectious disease that has plagued mankind for millennia and continues to do so into the 21st Century. The disease in humans comprises a diverse group of clinical syndromes caused by various species of the protozoan parasite, *Leishmania*. Syndromes range from cutaneous to mucocutaneous to visceral manifestations, and can be both a psychologically and physically debilitating disease. The disease is transmitted from person to person via various species of the sand fly, *Lutzomyia* and *Phlebotomus*. This disease is found in Central and South America, Africa, Asia, the Middle East, and Southern Europe.

Cutaneous leishmaniasis manifests itself as a papule that often progresses into an ulcerative lesion that can become many centimeters in diameter. Mucocutaneous leishmaniasis develops in about 3 percent of those infected and involves erosion of the nasal, pharyngeal and buccal mucosa, eventually leading to destruction of the nasal septum, palates, lips, pharynx, and larynx.

The life cycle of the *Leishmania* parasite is complex. The form of the parasite found in the insect vector, the promastigote, is normally transmitted to man by the bite of female sand flies. These promastigotes attach themselves and enter macrophages where the promastigotes round up into amastigotes, the intracellular form of the parasite, that then divide, and are released from the cell and infect other cells. When a sand fly takes a blood meal from an infected host, the amastigotes are released into the sand fly gut and mature into infective promastigotes ready to repeat the cycle.

Leishmaniasis has become a persistent health threat to military forces deployed in endemic areas where it can cause significant morbidity in immunologically naive individuals. There are 10-25 new cases of cutaneous leishmaniasis occurring in military personnel each year, with occasional outbreaks yielding more than 50 cases per year and with attack rates as high as 50 percent. Cases of cutaneous and vicerotropic Leishmaniasis in U.S. Soldiers deployed during the Gulf War and numerous cases of cutaneous leishmaniasis, and some mucocutaneous, acquired in Central America have been evaluated at the Walter Reed Army Medical Center (WRAMC) (Martin et al., Leishmaniasis in the United States Military; Military Medicine 163:801).

The Naval Medical Research Center Detachment (NMRCD) in Lima, Peru, is currently involved in several research projects dealing with various aspects of the detection and treatment of cutaneous Leishmaniasis, in collaboration with various Peruvian scientific institutions. The types of leishmaniasis encountered in Peru are the cutaneous and mucocutaneous forms and these are endemic in 12 regional areas, primarily in the Andes and in the northern Amazon Basin. The population at risk numbers approximately 1,200,000 persons with approximately 7,000 to 9,000 cases per year, about half of which are actually confirmed by the visualization of parasites in smears of the lesions or in cultures taken from the lesions. The majority of cases in Peru are caused by *Leishmania braziliense*s, and occasionally by *L. peruviana*.

Licensure of a Leishmanial Treatment in the US

To date, there is no FDA approved drug for the treatment of cutaneous leishmaniasis in the U.S. The standard treatment worldwide is with pentavalent antimonials given intravenously daily at a dosage of 20 mg antimony (Sb)/kg/day for 20 days. The drug of choice for first-line therapy for cutaneous leishmaniasis for most of Latin America, including Peru, is Glucantime®, which is readily available but can be quite costly. In Peru, an average size adult needs approximately 75 ampules of Glucantime over the course of treatment, at a cost of approximately $7.00 per ampule. Glucantime is not approved by the FDA for use against leishmaniaisis in the U.S. Second line therapy for cases resistant to treatment the Glucantime is amphotericin B. Pentostam (sodium stibogluconate) is also used to treat cutaneous leishmaniasis and is available for treatment of leishmaniasis in the U.S. but only through an Investigational New Drug (IND) Protocol administered by the Centers for Disease Control and Prevention and the Surgeon General of the Army. An alternative treatment for cutaneous leishmaniasis is actively being sought by the U.S. military, as the future availability of Pentostam is in question.

Pentamidine isethionate, licensed in the United States since 1984 for use against pneumocystis, has proved efficacious against cutaneous leishmaniasis in several studies, but in order to license it for use against leishmaniasis in the U.S., trials that comply with Good Clinical Practices (GCP) remain to be performed. The U.S. military has funded a GCP trial in Peru comparing Glucantime with Pentamidine. This clinical trial is currently in progress and is being performed under the strict guidelines of GCP's. This is a collaborative effort between the Army, Navy, and the Institute of Tropical Medicine, Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru. The principal investigators are Dr. Maria Cruz Saldarriaga and Dr. Alejandro Llanos of UPCH, and LCDR Ellen Andersen of the Naval Medical Research Center Detachment (NMRCD).

Eighty patients from the Peruvian Andes with parasitologically confirmed cutaneous leishmaniasis are being enrolled and randomly assigned to receive either glucantime or pentamidine. Glucantime is given intravenously for 20 days, while pentamidine is given intravenously every other day for seven doses. During the 20-day (for Glucantime) or 14-day (for Pentamidine) treatment period the volunteers will be housed in a ward devoted to the project and monitored daily for any adverse effects by the nursing staff and physician on duty. Photos and measurements will be taken of their lesions before treatment is initiated, 2 weeks following the end of treatment, and at 3 months and 6 months post-treatment. Peruvian experts in leishmaniasis, that are blinded as to what drug was administered, will evaluate the photos and measurements at the different time points and assess the degree of healing. Statistical analysis of the results will yield information as to whether the efficacy of pentamidine against cutaneous leishmaniasis is comparable or better than that of glucantime. The data generated by this study will allow the FDA to make a judgment as to whether pentamidine should be licensed for use against cutaneous leishmaniasis in the U.S.

Skin Test for Leishmaniasis

One of the standard methods for the diagnosis of leishmaniasis, particularly in endemic areas, is the leishmanin (or Montenegro) skin test that elicits a delayed type hypersensitivity reaction in persons with exposure to *Leishmania*. Most leishmanin skin tests are made from promastigotes that are disrupted and the crude soluble solution is injected intradermally, usually on the arm. These preparations suffer from a lack of standardization, undefined sensitivity and specificity, unknown sensitizing capacity, and unknown dose response relationships between antigen content and clinical syndromes or the species of infecting parasite. In addition, no preparation has been made under the appropriate manufacturing and regulatory environment that would allow use in the U.S. as an investigational new drug or a commercially available product. A safe, effective, reproducible, and stable skin test for *Leishmania* produced under Good Manufacturing Practices (GMP) would be an important addition to the current methods used in the diagnosis of this disease.

In collaboration with investigators at Walter Reed Army Institute of Research (WRAIR), several new skin test antigens have become available that are species specific. The three species currently available are two New World Leishmania species, Leishmania guyanensis and L. mexicana, and and Old World species, L. tropica. A clinical trial comparing these three antigens will be performed at the University of San Marcos, in Lima, and at NMRCD, Peru, in collaboration with WRAIR.

The study will be initiated early in 2002 and will enroll 180 individuals divided into three clinical groups of 60. These groups will be composed of volunteers with active cutaneous leishmaniasis, those with a history of healed leishmaniasis, and healthy volunteers without any history of leishmaniasis. The skin test preparations will be tested first in healthy volunteers, followed by the healed leishmania cases, and finally the volunteers with active cutaneous leishmaniasis or visceral leishmaniasis. In order to better determine the magnitude of cross reactivity of each of these preparations by recording the intensity of the delayed type hypersensitivity responses, all three antigens will be injected intradermally into the same volunteer. This will allow a direct comparison of the three antigens, and will reduce the number of volunteers in the study. Several aspects will be carefully monitored; primarily the occurrence of local or systemic reactions to the skin or the occurrence of non-specific immune responses to the skin tests, the size of the induration which accompanies the hypersensitivity response which will indicate potency, and the sensitivity and specificity of each antigen.

NMRCD has continued to develop its research program in leishmaniasis and has become an ideal site for a variety of studies on cutaneous and mucocutaneous leishmaniasis. The collaborative relationships that have developed between NMRCD and scientific institutions, as well as the professionalism and expertise of Peruvian collaborators and the endemnicity of leishmaniasis ensures that Peru will continue as a top-notch location for research in leishmaniasis. ❑

Both authors are assigned to the Naval Medical Research Center Detachment, Lima Peru.

Naval Dental Research Institute: The Navy's Resource for Dental Research

LCDR Michael C. Bilak, MSC, USN
Dr. John W. Simecek
CDR Michael E. Levine, DC, USN
CAPT James C. Ragain, Jr., DC, USN

Photos by DT2 Scott A. Bacon, USN, Naval Dental Research Institute

The original Naval Hospital Great Lakes now houses the Naval Dental Research Institute.

The Naval Dental Research Institute (NDRI), the Navy's re-source for dental research is located at the Great Lakes Naval Training Center's original Naval Hospital. The Navy has been conducting research in dental and allied sciences relative to the dental health of Navy and Marine Corps personnel for more than 50 years. Established on 15 April 1947, as the Dental Research Facility, the Naval Dental Research Institute has grown from a single dental officer who reported to the Dental Department, Naval Administrative Command, Naval Training Center, Great Lakes, IL, into a dynamic tri-service research facility.

Co-located with the Army Dental Research Detachment and the Air Force Dental Investigation Service, the Institute is now the primary site for all DOD sponsored dental research.

Dental Research

Unlike the civilian sector, the Navy and Marine Corps, with their unique military operational environments, have established mission requirements for operational dental readiness. The frequently hostile working conditions and challenging duty assignments faced by Sailors and Marines, can have significant implications on their dental

health and readiness. Dental emergencies experienced in operational settings have jeopardized essential military missions. Research conducted at NDRI is intended to identify better diagnostic and risk assessment techniques and develop improved methods of prevention and treatment for this unique patient population. The goals of increasing operational dental readiness, addressing emergent dental problems in Navy and Marine Corps personnel, enhancing the health care delivery system, and gathering data to provide valuable input for the Chief, Navy Dental Corps to use in formulating future Corps policy and direction, are factored into the research projects undertaken at the Institute.

Research Accomplishments

During its early years, NDRI pioneered research in saliva, fluoride use, and oral microbiology leading to an international reputation as one of the principal laboratories in determining etiologic agents of periodontal diseases. NDRI researchers were also instrumental in the identification of *Streptococcus mutans* as a primary etiologic agent of dental caries and developed and patented salivary test for dental caries.

The discovery of an important application for collagen products to reduce bleeding during surgery and other significant wound-healing research was conducted at NDRI, as well as the development of early sterilization strategies and dry-heat dental bur sterilization procedures. Research efforts at NDRI also lead to the development of a ballistic face shield for NAVSEA, a portable dental van for Marine Corps operational use, and portable dental chairs for use in the field.

More recently, NDRI researchers completed detailed studies of the incidence and distribution of dental emergencies in Marine Corps personnel during Operation Desert Storm (ODS) and the description of the treatment needs of Marine Corps reserve personnel called up during that conflict. Additional investigations in oral biology have resulted in the development of rapid, non-invasive salivary tests to diagnose oral diseases.

Ongoing Research

Today, NDRI researchers are focusing their expertise in oral biology, epidemiology, and materials science to provide meaningful information and develop products that will increase readiness, protect the warfighter, and reduce the need to evacuate Sailors and Marines for dental-related reasons. Exciting research is being conducted to develop rapid, non-invasive analytical tests using saliva to evaluate the immune status of warfighters for infectious diseases such as anthrax and tuberculosis. Researchers are also working toward providing a quick, easy to perform and cost-effective diagnosis for tuberculosis, dengue fever, and cholera.

NDRI researchers, with support of the Environmental Protection Agency, are continuing a pioneering study of the use of mercury pre-treatment systems in dentistry. NDRI maintains a dental mercury web site (http://www.dentalmercury.com) designed to inform all dental providers of the dangers of environmental mercury, to provide a source for up-to-date publications, and to hallmark new advances in the area of mercury removal. Additionally, NDRI has embarked on a Navy Dental Corps directed 5-year project funded by the Naval Environmental Health Center to install mercury removal systems in all Navy dental treatment facilities worldwide to protect patients, staff, and the environment.

NDRI continues to investigate the operational impact of dental emergencies. Investigators are conducting a retrospective cohort study to more accurately identify patients at high risk for dental emergencies and disease progression. They have developed, and are field-testing, a software-based Advanced Independent Duty (IDC) Dental Triage Informatics System that will enable independent duty corpsmen to diagnosis and treat dental emergencies in operational environments where dental officer support is unavailable. NDRI scientists are also developing a dental restorative system that could be used by auxiliary (dental or non-dental) personnel to treat temporarily dental injuries such as a fractured tooth or a lost restoration, thereby expediting treatment and allowing rapid return of a forward deployed Sailor or Marine to duty.

Summary

Research conducted at the Naval Dental Research Institute encompasses the systematic, scientific investigation of problems related to oral health, wellness, dental and systemic disease, and injury of Navy and Marine Corps personnel. During its 54-year history, NDRI has aggressively addressed these goals and has made valuable scientific advances that enhanced the readiness of Sailors and Marines. Into the future, NDRI continues to conduct cutting-edge research to provide the Navy with the most responsive and most cost-efficient methods to address the dental and medical needs of our fighting forces. ❑

LCDR Bilak is Director of Facilities Administration, Naval Dental Research Institute (DRI), Great Lakes, IL.

Dr. Simecek is Research Investigator, Applied Clinical Sciences Department, NDRI.

Dr. Levine is Executive Officer, NDRI.

Dr. Ragain is Commanding Officer, NDRI.

An Undersea View Research at the Naval Medical Research Center

Suzan Nadi, Ph.D.

The Environmental Physiology Department (EPD) at the Naval Medical Research Center devotes its research activities to three main areas of immediate interest to the fleet: decompression and decompression sickness, environmental stress responses, and hyperbaric oxygen toxicity. The department has been busy executing a variety of work from very basic research at the laboratory bench level investigating cellular mechanisms to the more applied research level investigating organ and whole-body physiology as well as engineering research.

Decompression Sickness

Decompression sickness (bends) is the result of uptake and release of absorbed gases in the human body as a result of pressure changes normally related to diving. Decompression sickness is avoided by Fleet and sport divers by strictly adhering to decompression schedules that dictate bottom time and ascent rates. Understanding these two factors—bottom time and ascent rate—are key to avoiding decompression sickness. EPD is probably most noted for the work that has been done to establish the safe limits of diving and establishing the decompression tables that are used by Navy, sport, and international divers.

EPD researchers are trying to identify the mechanisms responsible for the onset of decompression sickness. For a number of years, we have been investigating the biochemical events that occur following dives of various depths and for various periods of time. The research has focused on the very smallest part of the brain, the synaptosomes, which represent the very basic point at which nerve cells communicate with each other, to the way in which individuals respond to decompression. Early studies on synaptosomes showed that exposures to high pressures cause an increased release of a messenger called glutamate which when released in large quantities can be toxic to cells. This finding seemed to explain the observations of pathologic changes in the neuronal tissues such as the spinal cord and other brain areas resulting from very severe dives and severe decompressions.

Parallel investigations have addressed the issue of gases that get trapped in tissues as a result of high pressure exposures and how these gases may contribute to the problems of decompression following dives. Mathematical modeling studies were carried out to determine the theoretical basis of how gas bubbles form and how they behave with changes in pressure. These studies have given us a greater understanding of bubble contribution to decompression sickness and have provided many clues to the origins of decompression sickness.

Many different gas mixes have been tested to see if there is added benefit of one gas over another in decreasing the risk for decompression sickness to the diver. Hy-

drogen/oxygen and helium/oxygen combinations are two gas mixes that have been shown to decrease the risk for decompression sickness when compared to the risk of decompression sickness breathing plain air. Hydrogen/oxygen gas mix was chosen by the Navy as the gas of choice for deep dives of long duration. The use of the high concentration hydrogen gas presented results: the oxygen-induced seizures were either delayed significantly or were completely blocked. These findings make neuropeptide Y a very promising drug for the prevention of hyperbaric oxygen-induced seizures. There are disadvantages to using this compound, however, and at the present time our investigators are working with pharmaceutical companies to overcome these disadvantages and produce a potent anit-seizure drug for hyperbaric oxygen-induced seizures.

Other studies on brain oxygen toxicity have given us additional clues for novel therapies to prevent oxygen toxicity. The rodent model has been used to characterize biochemical changes resulting from oxygen-induced seizures. Of particular note is the evidence that potentially damaging free radicals are causing lipid and protein oxidation. There are also enzyme activity changes that result from oxygen exposures and these findings may help lead us to more efficient and safer means to combat hyperbaric oxygen toxicity.

Another exciting aspect of EPD research in oxygen toxicity is the recent identification of a specific biomarker that can be used to predict the onset of oxygen-induced seizures. Prior to the occurrence of a seizure the blood flow in the brains of rats increases. Based on this finding, experiments were repeated in swine (an animal model whose cardiovascular system closely parallels that of the human). The results of these experiments showed that the mean arterial blood pressure increases several minutes prior to a seizure. This observation has led us to develop a system to help forewarn divers of impending seizures. One can visualize an instrument the diver could wear which would transmit a signal letting the individual know that he/she would have, for example, 20 minutes to surface prior to a seizure. EPD investigators are now helping to advance this capability to the engineering level and, ultimately, produce an early warning device that offers the diver enough time to react and eliminate the onset of any seizures.

In the effort to understand how oxygen toxicity occurs we have been interested in answering the question: Are there molecules in the brain which specifically sense oxygen? In order to find answers we have turned to the area of gene chips. Gene chips are powerful experimental tools that allow researchers to scan thousands of nuclear changes in a single experiment. This state-of-the-art tool has allowed EPD to identify a number of metabolic enzymes that respond to oxygen changes. This is the very first such detailed insight into oxygen effects on genes. We are currently setting up comparative studies to focus in on the oxygen sensors of the brain.

EPD is also leading the way by using another powerful analytical tool, chaos and non-linear dynamical analysis, to help predict the onset of oxygen-induced seizures. Recent evidence suggests that the application of these analytical procedures to electrocardiogram data can result in information that can be used to reduce the risk for oxygen toxicity. The advantage of this type of early warning system is that the analysis can be individualized. These "smart algorithms" can be designed to an individual's personal physiology and they get "smarter" with added data. EPD investigators are presently collaborating with private industry to develop this personalized tool for future delivery to the fleet.

Long Is the Road and Short the Time But...

Bacterial scrubbing of dangerous gases, block of seizures by neuropeptide Y and other agents, prediction of seizures by mean arterial pressure and heart beat changes, and protection against the elements are all very interesting developments originated or confirmed by EPD investigators. We are striving to execute diving research so that we can increase the safety and expand the mission capability of Navy diving personnel. ❑

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Human and Environmental Health Issues Related to Use of Radio Frequency Chaff

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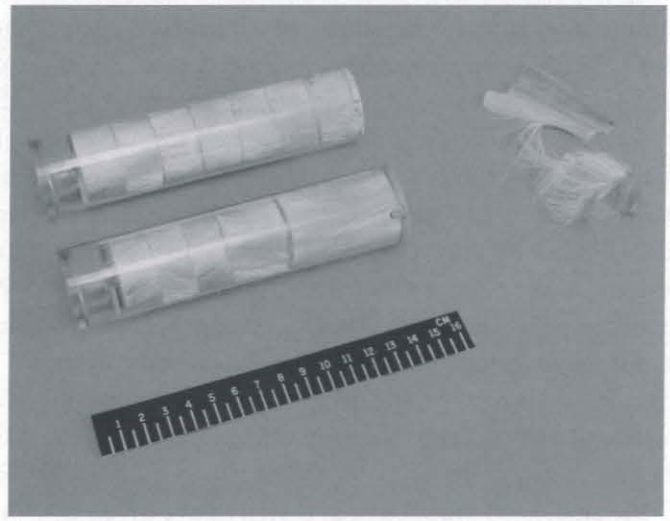

Figure 1. Radio frequency chaff cartridges (Air Force version RR-188/AL, top; Navy version RR-144/AL, bottom) and chaff fibers (right). Fibers of different lengths can be seen in the Navy operational version. These lengths correspond to the frequency modes of the radar spectrum. In training, however, cartridges containing only 1.8 cm fibers are used (not shown).

Radio frequency (RF) chaff is an electronic countermeasure designed to reflect radar waves and obscure planes, ships, and other assets from radar tracking sources. Chaff consists of aluminum-coated glass fibers (also referred to as dipoles) ranging in length from 0.8 to over 5 cm. Chaff is released or dispensed from military vehicles in cartridges or projectiles that contain millions of dipoles. When deployed, a diffuse cloud of dipoles is formed that is undetectable to the human eye from the ground. Chaff is a very light material that can remain suspended in air anywhere from 10 minutes to 10 hours and can travel considerable distances from its release point, depending on prevailing atmospheric conditions.(*1*) Training for military personnel, particularly aircraft pilots, in the use of chaff is necessary to deploy this electronic countermeasure effectively. As with most acquired skills, the deployment of chaff must be maintained by practicing in-flight release during training. It is estimated that the U.S. Armed Forces dispense about 500 tons of chaff per year, with most chaff being released during training exercises within the continental United States.(*1*)

Concerns have been raised since the early 1950s both by the public and government officials on the potential impacts of chaff on the environment. In response to these concerns, the Department of Defense (DOD) has sponsored or conducted research to address issues related to the use of chaff by the military including: (a) questions on its persistence and fate in the environment, (b) the effects of chaff on human, livestock, and wildlife health, and (c) the impact of chaff release on natural and cultural resources.(*2-8*) In this review, we address the historical and current use of chaff, the importance of its use in training and the effects of chaff on humans and the environment.

History and Use of Chaff

RF chaff was first used as a radar countermeasure in December 1943 by U.S. bombers flying over Bremen, Germany. At this time, chaff consisted of solid aluminum pieces of non-specific sizes that were tossed from cockpit windows or dropped from trap doors on the underside of bomber aircraft. Tactics of the time were to generate huge chaff plumes to provide slow-moving bombers with some protection against ground-based anti-aircraft fire.

Chaff technology has evolved considerably since World War II. Modern chaff is composed of glass fibers

coated with a 3 μm-thick layer of high purity (99 percent) aluminum, which gives chaff its radar-reflective properties (see Figure 1). Chaff fibers are approximately 60 percent glass and 40 percent aluminum by weight. Lead was used as a weighting material in early versions, but this metal is no longer incorporated into chaff (*2, 4*). Chaff fibers are also coated with a lipid to prevent clumping. Modern chaff is cut to specific lengths that correspond to one-half the wavelength of specified radar bands. Along with chaff, "chaff debris" is also dispensed during the release of chaff. Typical chaff debris includes paper, cardboard, styrene plastic caps, pistons, and miscellaneous plastic parts.

Chaff is typically deployed in cartridges or projectiles, but can also be dumped or tossed from military vehicles. Chaff cartridges typically contain up to 100 million chaff fibers or dipoles.(*2, 4*) Training cartridges used by Navy aircraft contain about 5 million dipoles per cartridge. (*3*) Zuni rockets, used by the Navy to screen surface vessels from radar contain about 8.5 pounds of chaff. Mortars are also used to launch chaff from ships and these projectiles contain up to 24 pounds of chaff.

Current DOD Chaff Use Policy and Initiatives

Currently, DOD severely restricts the use of chaff in training in order to reduce pollution of the environment and to protect civilian airspace. At the height of the Cold War, training with RF chaff was permissible at all military training ranges and Military Operating Areas (MOAs) within the United States. Since 1990, DOD has attempted to balance the chaff training needs of the Armed Services with concerns of the public and government for the possible negative impacts of chaff use on the environment.

In 1998, the Joint Chiefs of Staff issued a directive incorporating chaff use policies of each of the Armed Forces and placed significant restrictions on the use of chaff for training in the United States. (*9*) As a result, the number of training sites where chaff training is permitted has been reduced to approximately 50 selected ranges and MOA in and around the U.S. Additionally, flight rules were changed and now stipulate that chaff should not be released below certain altitudes during training to ensure chaff plumes are widely dispersed and dipole ground level concentrations are very low. Likewise, DOD policy for chaff operations requires that every effort be made to conduct chaff drops away from major air routes and air route hubs and to avoid frequent dispersal over the same ground points. DOD policy also specifies that all planned chaff releases and training flight plans be reported to the Federal Aviation Administration and local environmental agencies. (*9*)

In addition to making extensive policy changes in chaff use, DOD has initiated several cooperative relationships with Department of Interior agencies aimed at minimizing the impact of chaff on public lands. Among these efforts is a committee formed between the DOD and the Bureau of Land Management to evalute periodically the chaff deployment policies of each of the Armed Services for training conducted over public lands. (*2*)

Environmental Fate and Impact

Intact chaff fibers do not pose an inhalation risk to humans; however, degradation of the fiber might result in reduction to a size amenable to respiration and this is discussed further below. As such, degradation of chaff fibers under various environmental and mechanical conditions has also been of interest. The abrading of chaff dipoles to respirable diameters during pyrotechnic discharge or by weathering has been an issue of concern expressed by various parties.(*3*) The Air Force found no evidence that chaff dipoles are abraded to respirable particulate during pyrotechnic discharge under controlled conditions. (*4*) Further studies are needed to determine definitively whether respirable chaff dipoles are released or formed in the process of dispersal.

Because of its large diameter relative to other particulate contaminants, chaff does not add to particulate matter (i.e., PM_{10} or $PM_{2.5}$) emissions as defined by the EPA. To understand what affect chaff may have on human health, Hullar et al. (1999) assumed that chaff degraded into PM_{10} and $PM_{2.5}$ and estimated the contribution of chaff to the respirable fractions. In their estimates, chaff would account for less than 0.25 percent of the particulate emission measurements for Churchill County, NV (Fallon Naval Air Station). Similar predictions were made for St. Mary's County, MD, (Patuxent NAS), where chaff releases contribute no more than 0.008 percent of the total particulate matter emissions. Currently, the Navy is sponsoring studies to determine chaff air concentrations at ground level of training ranges and housing areas located at Fallon NAS. Preliminary results indicate that chaff plumes comprise less than 0.5 percent of the particulate matter present at these sampling areas.

Several investigations have demonstrated that aluminum-coated dipoles are resistant to weathering and breakdown under desert conditions. A 1977 Navy-sponsored study found no evidence to indicate that chaff degrades

significantly or quickly in water from the Chesapeake Bay nor did this material leach significant amounts of aluminum into the Bay. A recent study by our group found no evidence that over 20 years of chaff operations at the Naval Research Laboratory detachment at Chesapeake Beach, MD, resulted in a significant increase in sediment or soil aluminum concentrations. (*10*) However, additional studies are needed to determine the half-life of chaff dipoles in various soils and environmental conditions and whether dipoles break down to respirable particles. A current study at the University of Nevada, Desert Research Institute is examining the propensity of chaff dipoles to be reduced to respirable sizes by wind-driven sand abrasion.

Human Health Effects

It has been suggested that chaff poses an inhalation hazard and may induce diseases of the respiratory tract. This idea has been addressed in detail by several groups. (*3,11*) Chaff dipoles are manufactured at diameters that are too large (~40 M) to be inhaled into the lung. If inhaled, dipoles are predicted to deposit in the nose, mouth, or trachea and are either swallowed or expelled. Although there is no definitive evidence from the epidemiological literature that chaff exposure is not harmful, there is epidemiological information available on workers involved in the glass fiber manufacturing industry. Data from these studies suggests that exposure to fibrous glass is not associated with increased risk of death from respiratory disease.

There are reports that occupational exposure to aluminum may increase the risk of asthma (*12,13*) and pulmonary fibrosis. (*14,15*) We are not aware of any cases of occupationally induced asthma or pulmonary fibrosis among workers involved in the manufacture or handling of RF chaff. Intact chaff dipoles are not expected to penetrate the lungs and therefore, would not be expected to increase the risk of either asthma or pulmonary fibrosis among exposed persons. Dermal contact with RF chaff is a possible exposure scenario for Sailors and ground troops during training exercises or combat. A review of historical medical records of military personnel at potential risk will be conducted in the near future. However, to date there is no data on the ability of chaff to cause dermal or ocular irritation in humans or animals. Occupational exposure to fibrous glass has been linked to eye and skin irritation and irritation of the nasal and oral mucous membranes. (*16*)

Ingestion of chaff dipoles could occur through drinking unfiltered water drawn from a source containing chaff or by swallowing fibers that become trapped in the mouth and upper airway following inhalation of chaff. Children that consume large amounts of soil (i.e., geophageous) are potentially at risk of ingesting chaff if this material is present in the soil. There are no reports of children or adults that have developed adverse health effects after ingestion of chaff. However, studies in which laboratory animals were dosed with chaff at varying doses revealed no gross or histological signs of toxicity or mechanical injury upon postmortem examination.(*17*)

It has been speculated for some time that aluminum may be associated with several neurodegenerative diseases (*18*) and chaff dipoles are a potential source of aluminum in cases of accidental ingestion. However, the link between dietary aluminum ingestion and development of neurodegenerative diseases remains tenuous. Absorption of aluminum by the human gastrointestinal tract is minimal (<1 percent), with most ingested aluminum being passed out of the body in the feces.(*19*) It has been shown that the bioavailability of aluminum from ingested chaff in both *in vitro* and *in vivo* models is considerably less than that of $Al(OH)_3$, which is a source of aluminum in common aluminum-based antacids.(*17*)

Health Effects on Livestock & Wildlife

The potential negative impact of chaff on wildlife and livestock health has been a major issue for DOD since the 1950's. A number of legal claims have been filed against the Air Force alleging that livestock had died from ingesting chaff while grazing.(*7*) Studies conducted in cattle and goats at the University of Wisconsin found no evidence that chaff ingestion posed a significant health hazard for farm animals.(*7*) In similar studies, the Canadian Department of Agriculture found no evidence of toxicity in calves fed RF chaff.(*20*)

At least one study (*4*) describes several ground surveys of two chaff use MOAs and reports that chaff debris, including plastic end caps, foil, and paper wrappers, was visible on the training ranges. Clumps of chaff from cartridges that did not deploy correctly were also observed. However, animal abundance and nesting activities of rodents or birds were considered normal. It was concluded from the results of this study that chaff interference with wildlife activities is negligible.

Chaff has also been deployed over estuarine environments, and several federal agencies have commissioned

studies of the effects of chaff on these ecosystems. Multiple marine organisms, including benthic polychaetes, American oyster, blue mussel, Blue crab, filter-feeding menhaden, and killifish, were utilized in studies investigating the impact of chaff on organisms in the Chesapeake Bay and no evidence was found suggesting that RF chaff was acutely toxic to any of the species tested. Concentrations of chaff used in these studies were described 10 to 100 times the exposure level expected to be found in the Chesapeake Bay.

Degradable Chaff

Recently, the Navy considered developing chaff that could be quickly degraded.(*2*) One candidate under consideration for use as training chaff consisted of aluminum-coated degradable glass fibers. Contact with water results in degradation of the fiber. However, problems with incomplete degradation and lack of evidence that chaff is harmful to the environment resulted in suspension of further development of a degradable chaff in 1999.

Discarded styrene dispenser pistons and endcaps are visible to the human eye and account for about 95 percent of the total mass of product released to the environment during chaff deployment. As such, the Navy is considering the use of chaff dispenser pistons and endcaps constructed with biodegradable polymers. This program is in its preliminary stages and studies are now on-going at the Naval Research Laboratory and Naval Health Research Center Toxicology Detachment to identify biodegradable materials with little potential for ecotoxicity. The Navy plans to field biodegradable chaff dispensers and endcaps by FY2003.

The Future of Chaff

Any military pilot will tell you the importance of chaff. This material, usually dispersed a couple of handfuls at a time, in a time often no greater than seconds, means the difference between the loss of life and destruction of a multi-million dollar aircraft in air-to-air combat and survival. Split second timing while executing a number of operations at Mach speed can only be acquired by training. Chaff, its composition and its use in training, has changed dramatically over the past few decades. The changes have resulted from research advances and an appreciation for potential environmental impacts of military activities. While dramatic advances in chaff are not anticipated, its use in training and combat will continue for the foreseeable future.

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The Fight Against Dengue
The Viral Nemesis of Military Operations

CDR Kevin R. Porter, MC, USNR

Dengue fever (DF) is the most common arboviral infection worldwide, with an estimated 100 million infections occurring per year.(*1*) DF is caused by dengue virus, which belongs to the family *Flaviviridae*, genus *Flavivirus*. There are four antigenic types of dengue, dengue 1 through 4. DF occurs primarily in tropical and sub-tropical regions of the world and is transmitted primarily by the *Aedes aegypti* mosquito. This mosquito is unique in that peak biting times occur during daylight hours and it preferably feeds on humans. As a result, dengue is seen mostly in highly populated urban areas.

Dengue fever is clinically manifested by a rather abrupt onset of fever that is usually associated with retro-orbital headache, rash, gastrointestinal symptoms, myalgias, and bone pain. The bone pain can be rather intense at times and hence DF has also been referred to as "break bone fever." Severe forms of dengue are classified as either dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).

The principal pathogenic mechanism responsible for DHF is the occurrence of plasma leakage. DHF is subdivided into four grades. Criteria for grade I includes the presence of mild to moderate plasma leakage manifested by hemoconcentration, pleural effusion, or ascites. The presence of spontaneous hemorrhage in the presence of plasma leakage indicates grade II. The onset of hypotension or frank shock, with or without hemorrhage, satisfies criteria for grades III and IV (DSS), respectively. Mortality for DF is very low whereas that for DHF/DSS is usually around 5 percent, but can be as high as 30 percent to 40 percent if left untreated. There is no therapy for dengue and effective treatment consists of supportive care and close monitoring of hemodynamic status.

Dengue and the Military

Dengue has had a negative impact on military operations dating back as far as World War II. During that conflict, dengue caused epidemics that resulted in the incapacitation of large numbers of military personnel. For example, in the Southwest Pacific, dengue resulted in over 50,000 cases per annum per 1,000 average strength between 1942 and 1945.(*2*) In New Guinea and adjacent islands, over 24,000 cases were reported in 1944. During the Vietnam War, DF was reported to be the most common cause of undiagnosed fever among deployed troops. During "Operation Uphold Democracy in Haiti," one study showed that over 30 percent of cases of fever oc-

curring in troops was due to dengue.(*3*) More recently, large numbers of dengue cases occurred among Australian peacekeeping soldiers stationed in East Timor, an area where all four serotypes of dengue are known to circulate.

The war-stopping potential of dengue infection is great. Since dengue is not endemic in the U.S., American troops represent a large population of dengue naïve individuals who if deployed to dengue endemic areas, are at great risk for acquiring primary infections. Although primary infections are rarely fatal in adults, they are associated with significant morbidity. Dengue infection may also occasionally give rise to a post-illness depression that can be rather severe and require the use of anti-depressant medication.

A study conducted by Hayes et al. in the Philippines showed that dengue infection resulted in an average loss of 8 days of duty per individual suffering from dengue.(*4*) In Somalia, during "Operation Restore Hope," a study conducted among deployed troops revealed that dengue accounted for 20 percent of all febrile admissions to military hospitals.(*5*) Of 289 troops hospitalized for evaluation of febrile illness, 129 (45 percent) were discharged with a diagnosis of unspecified febrile illness. Forty-five percent of these were later confirmed to be dengue by either virus isolation or anti-dengue IgM serology using acute and convalescent sera.

Somalia is an area where multiple serotypes of dengue are known to circulate. In a scenario where 10,000 U.S. troops and Sailors are deployed to this dengue endemic region, an estimated 4,500 troops may develop an unspecified febrile illness and 2,025 of these cases would be caused by dengue based on the Somalia dengue surveillance study. Assuming an average loss of 8 days of active duty per dengue case, during this deployment, a loss of 16,200 man-days of active duty would occur. This number re-emphasizes the need to develop an effective dengue vaccine and justifies dengue vaccine development as being a top priority for military research and development efforts.

Dengue Vaccine Development

The U.S. military is taking many approaches to develop a safe and effective vaccine against dengue. Traditional methods, patterned after the successful development scheme for the 17D Yellow Fever vaccine, have involved serial passage of selected dengue strains multiple times in tissue culture to produce an attenuated strain for use as a live-attenuated vaccine. These efforts have met with variable success. The difficulties encountered in the development process may be attributed to an incomplete knowledge of the biology of the virus in humans and lack of a thorough understanding of the pathophysiology of the virus attenuation process.

Investigators at the Naval Medical Research Center (NMRC), Silver Spring, MD, have taken a new innovative approach to developing a dengue vaccine. This approach involves the use of naked DNA. The gene for each dengue serotype that codes for the viral envelope proteins is inserted into a circular DNA molecule known as a plasmid vector. Millions of copies of the newly constructed DNA are made by transforming it into *E. coli* and growing many liters of the bacteria. The plasmid DNA is then extracted from the bacteria, purified, and tested to see if the inserted gene is capable of producing the correct envelope protein in mammalian cells. This DNA is then used as the vaccine.

The first-ever animal trial of an experimental dengue 2 DNA vaccine was conducted at the Naval Medical Research Institute (now NMRC) in 1996.(*6*) This vaccine was also shown to provide protection against dengue infection in mice.(*7*) Follow-up studies have been conducted in non-human primate trials to evaluate dengue 1 DNA vaccine candidates.(*8,9*) These studies collectively prove that the DNA vaccine approach is a viable one. New and more immunogenic dengue DNA vaccines have been developed. These vaccines are currently being evaluated in non-human primate trials at NAMRU-2 in Jakarta, Indonesia. Data generated from these studies will be used to plan human trials of a dengue DNA vaccine.

Field Studies in Dengue

To gain more insight into the pathophysiology of this disease, investigators at NAMRU-2 have recently completed the follow up phase of a prospective study of DF and DHF in a cohort of 2,400 children. Although the laboratory analysis of samples collected from this study is ongoing, the first year study results have been published.(*10*)

Given the desire to better define the pathophysiology of dengue in adults, a prospective study of DF and DHF in young adults is ongoing in Bandung, West Java, Indonesia. Data generated from this study will provide a better understanding of the immunological requirements for

protection against DF and DHF in a population similar in age to that of the U.S. military. Mimicking these immunological requirements in humans will be incorporated into the goals of the dengue vaccine development program.

Diagnosis of Dengue Infection

In febrile military personnel deployed to dengue endemic regions, making a diagnosis of dengue can be quite challenging given that the clinical presentation of DF can mimic other treatable infectious diseases that exist in these regions including typhoid and malaria. It is therefore important to rule out dengue illness in a timely manner. One of the goals of the dengue research program is to develop or validate methods for making a rapid and accurate diagnosis of dengue in deployed military personnel. Field deployable diagnostic assays have been developed by commercial companies and evaluated by NMRC and NAMRU-2 investigators.(*11,12*) These rapid assays were shown to reliably diagnose dengue infection and have utility under field conditions. One assay takes only 5 minutes and has a high sensitivity and specificity for detecting anti-dengue IgM antibodies that develop during acute infection. The lack of the need for any specialized equipment makes this assay extremely useful for medical officers, hospital corpsman, and field medics.

The virology laboratory at NAMRU-2 possesses state-of-the-art tissue culture, serology, and molecular biology capabilities. Because of its unique location in Southeast Asia, the facility can serve as a tertiary back-up laboratory for extensive analysis of any infectious diseases samples collected in the region. The capability also exists to perform DNA and RNA sequence analysis, techniques needed to conduct detailed analysis of viruses as well as unknown infectious agents.

Dengue infection occurs frequently in military personnel deployed to dengue endemic regions and causes great morbidity, which can interfere with important military operations. The Navy's dengue research program is making significant progress toward reducing the impact of this disease on Sailors and Soldiers.

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Imagine Flying Blindfolded

Not many of us would have the nerve to fly upside down and blindfolded, but that actually was a goal of CAPT Angus Rupert, MC, USN, at the Naval Aerospace Medical Research Laboratory in Pensacola, FL. For the past 12 years, he has been perfecting a wearable device for pilots called the "Tactile Situation Awareness System" in a joint venture with NASA. The purpose of his invention is to provide pilots with orientation cues through the sense of touch so that they always know which way is up.

It all started in the 1970s with an unusual *au naturel* sky dive in which Dr. Rupert noticed how the air felt on his skin. He explains, "On the ground, in our day-to-day activities, spatial orientation is continuously maintained by accurate information from three independent, redundant, and concordant sensory systems—vision, the vestibular system (inner ear), and the somatosensory system (skin, muscle, joints). We walk upright without giving a second thought to the complex processes at play within our bodies. The brain integrates information from the eyes; inner ear; and skin, muscles, and joints to make smooth, accurate movements. Our sensory mechanisms have spent millennia evolving to their present level of sophistication, well able to cope with most terrestrial experiences. Spatial orientation, which even on the ground involves a simultaneous integration of information from multiple sensory systems, poses an even more complex problem in the aerial environment." In other words, our bodies are uniquely designed to provide us with enough information to keep us oriented in an upright position naturally on land.

That works well enough on dry ground with plenty of visual cues, but in an airplane other factors come into play. Nighttime conditions, heavy cloud cover, blowing sand or snow, and/or task saturation can easily obscure or compete with visual cues necessary to maintain straight-and-level flight. In those instances, the body will tend to provide false but compelling "seat-of-the-pants" orientation information that may cause pilots to incorrectly perceive the position of their aircraft. This is partly due to the effects of gravity and centrifugal acceleration. In flight, only visual orientation cues will override these illusions created by the seat-of-the-pants sensations.

When pilots are not able to maintain their upright orientation in flight, they are said to be suffering from spatial disorientation. Spatial disorientation is the main cause of pilot-related mishaps in the Navy and the Air Force and tends to occur when pilots incorrectly perceive the attitude, altitude, or motion of their aircraft. This is most likely to happen when a pilot's gaze is temporarily directed away from visual information provided by the aircraft's instruments and the earth's horizon. The central nervous system is left to compute unreliable orientation information from the vestibular and somatosensory systems. This serious problem annually costs the Department of Defense more than $300 million in destroyed aircraft and an average of 40 lives.

The Tactile Situation Awareness System (TSAS, pronounced tee sass) is a flight vest containing miniature tactor vibrators that are interfaced with the aircraft's instruments and computers. The vibrators activate continuously to update the pilot's awareness of position. Worn under a flight suit, TSAS works like this. If the plane leans too far to the left, the vibrators on the left side of the vest pulse to alert the pilot. Likewise, corresponding

Photo by HM2 Alex Eakle, USN

CAPT Rupert (on the right) explaining TSAS at the Paris Air show.


Photograph by: Cary Wolinsky

vibrators alert the pilot if the plane banks too far right, forward, and so forth. During level flight, the tactors are not firing. Thus, the pilot can maintain correct orientation with the vest alone—without relying on vision at all. This unique device frees the pilot to devote more time to weapons delivery systems, target locations, threat warnings, instrument approaches, and other tasks requiring visual attention.

A prototype has been tested on two occasions in helicopters and fixed-wing aircraft. With only 20 minutes of training, pilots performed complex aerial maneuvers relying solely on TSAS. They had no visual cues or instruments whatsoever. Last December, the Air Force Special Operations Command (AFSOC) successfully tested TSAS in the MH-53M helicopter and CV-22 simulator. The purpose of the testing was to evaluate the potential of TSAS to provide increased situational awareness and reduced aircrew workload through the sense of touch. Results indicated that TSAS successfully improved situational awareness and reduced pilot workload.

The device also has the ability to provide navigational information in underwater environments of reduced visibility. Turbidity, low light, visual distortions, and lack of visual references can interact to affect a diver's ability to determine or maintain his/her true position or orientation. Special Forces underwater operators are particularly interested in TSAS because current visual displays are tiring and can ultimately degrade performance. In an underwater test in 1997, Navy divers found TSAS easier to use than visual displays and preferred having the sense of touch in addition to visual displays. The tests showed that divers using TSAS had improved situation awareness, reduced workload and improved performance in navigation and underwater mine detection. TSAS also has the capability of providing information in a clandestine, "eyes-free" manner to Navy and Marine Special Forces. By providing constant orientation information, it could be used to improve the safety of water and land rescue operations.

In the aerospace environments, TSAS could provide orientation information to astronauts to prevent disorientation due to weightlessness. It could also help crewmembers of the International Space Station navigate if they become disoriented moving around the large structure even if there is no gravity. Other possible aerospace applications include shuttle landings, extra vehicular activity, tele-operation of robots and unmanned aerial vehicles, and space motion sickness.

In the medical community, TSAS could be adapted for people who have difficulty maintaining their balance (injuries and deaths exceed that of motor vehicle accidents). According to the Centers for Disease Control, "falls are a serious public health problem among older adults. In the United States, one of every three people 65 years and older falls each year. Older adults are hospitalized for fall-related injuries five times more often than they are for injuries from other causes." By 2020, the cost of fall-related injuries is expected to reach $32.4 billion. These costs do not account for the long-term consequences of fall-related injuries, such as disability, decreased productivity, or quality of life.

By invitation, CAPT Rupert and his team took TSAS to the 44th Paris Air Show at Le Bourget fairgrounds, just outside of Paris, France, 17-24 June. The Air Show attracts more exhibitors (1,861 from 42 countries) and visitors (500,000) than any other air show in the world. It is the premier international event in the aeronautics and space industry, featuring the full range of aerospace business activities—from parts suppliers to aircraft manufacturers. Interest in TSAS was so phenomenal that the supply of promotional materials was quickly exhausted on attendees eager to "fly" without visual cues.

The device, costing about $5,000 each to produce, will most likely be available first in the entertainment industry. Computer gaming, amusement parks, and virtual reality environments will probably have the means to produce the technology before the military can afford to make it available. In the meantime, CAPT Rupert and company continue to miniaturize the tactors and make the equipment even less intrusive and expensive. It is truly a work in progress.

Albert Einstein once said, "Imagination is more important than knowledge." CAPT Rupert is using both to address a complex and costly problem. ❑

—Story by Kathy Mayer, Public Affairs, Naval Aerospace Medical Research Laboratory, Pensacola, FL.

Centerfold: CAPT Angus Rupert tests the Tactile Situation Awareness System (TSAS) in a Stearman biplane upside down. For the purpose of the photograph an LED display indicates when the vest is vibrating in the upper chest region. Photo by Cary Wolinsky.

Malaria Vaccine Research at the Naval Medical Research Center

CAPT Daniel J. Carucci, MC, USN

At a time in bioscience when many people assume that vaccines are available for most infectious diseases, it often comes as a surprise that the ancient disease, malaria, is still the most important parasitic infectious disease in the world today. It also poses one of the greatest threats to the U.S. military operational forces than any other naturally-occurring infectious disease. In fact, in every campaign this century fought where malaria was present, more casualties resulted from malaria than from bullets. During the war in Vietnam, entire divisions were rendered ineffective due to large numbers of malaria cases.(*1*) Even more importantly for the world population there are between 300 and 500 million cases each year and between 1.5 and 2.7 million deaths annually, mostly in children living in Sub Saharan Africa.(*2*)

Drugs used to prevent malaria infection, though universally effective until the 1960's and 1970's, are either no longer effective or are becoming less effective in many parts of the world due to the development of drug resistance. And yet despite over 15 years of research, there is still no licensed vaccine against malaria.

Navy malaria researchers are developing approaches to preventing and treating malaria through drug and vaccine development at the Naval Medical Research Center (NMRC) core Malaria Program located in Silver Spring, MD, and also through a network of overseas research commands—Naval Medical Research Units (NMRU) working throughout Southeast Asia (NMRU-2), South America (NMRC-DET), Africa (NMRU-3) and most recently in Ghana, West Africa. In addition, NMRC has established the first Navy Clinical Trials Center at the National Naval Medical Center, Bethesda, MD, the only clinical trials center dedicated for malaria vaccine testing and development.

Malaria Life Cycle

So why is there no vaccine against a disease that causes such an incalculable costs in terms of human lives and suffering and results in the death of more than a million children each year? Many feel that the answer lies in the complexity of the parasite itself. Unlike most viruses and bacteria, pathogens such as malaria live a complex life. The single cell parasite *Plasmodium* starts its life in humans as "sporozoite" forms injected by the bite of an infected female *Anopheles* mosquito. Hundreds of sporozoites enter the blood stream with the mosquito's saliva and within minutes, invade individual cells in the liver. Inside these liver cells the parasites multiply to over 10,000 in 1 week.

As the parasites at this stage appear to cause no signs of illness, many feel this is an ideal time to attack the parasite with drugs and vaccines. If left unchecked, the parasites (now called "merozoites" and numbering over one million) burst out of the liver cells into the blood stream and attach themselves to red blood cells.

Individual parasites enter the red blood cells and multiply to 16-20 parasites in approximately 2 days. All manifestations of disease occur at this stage of the parasite's life cycle.

Approximately, every 2 days parasites burst from the infected red blood cells, invade new red blood cells, and multiply an additional 10-20 times. Within a few days the numbers of parasites in the body reach many billions and cause fevers, chills, fatigue, and lethargy. In severe cases, especially in children, the parasites destroy so many red cells and suppress the production of new red cells that severe anemia develops. In some cases, the infected red cells become "sticky" and attach to the inner surface of capillaries, especially in the major organs, causing blockages.

When the parasites block the blood flow in the brain "cerebral malaria" develops resulting in seizures and coma. These two syndromes, severe anemia or cerebral malaria, are the predominant causes of death in children and non-immune travelers such as military personnel.

In order to reproduce, some parasites in the red cells do not divide and multiply, but transform into male and female "gametocytes." These gametocytes are taken up by feeding mosquitoes and sexually reproduce in the mosquito's stomach. The resulting sporozoites travel to the mosquito salivary glands ready to be injected on the next blood meal and to infect another individual.

Malaria Vaccine Development

Recognizing the complexity of the parasite, many scientists feel that an effective vaccine may need to attack multiple stages of the parasite's life cycle. In addition, the vaccine will have to mount different immune responses to attack the parasite at its different stages. For example, soluble circulating antibodies may be needed to attack the sporozoites while in the blood stream, killer immune cells (T-cells) may be needed to attack the parasites within the liver cells, and a combination of antibodies and T-cells may be required to attack the parasites inside the red cells. Further, antibodies may be needed to prevent the reproduction of the parasites within the mosquito stomach.

No vaccine to date has been shown to provide the breadth of immune responses that may be required for preventing malaria. The challenge is daunting, though there are two models that suggest that a protective malaria vaccine is feasible. If *Plasmodium* infected mosquitoes are bombarded with a precise amount of gamma irradiation, the parasites living inside the mosquito salivary glands become weakened but are not killed. When the mosquitoes are allowed to feed on an animal or human, the "irradiated sporozoites" invade liver cells normally, but they do not divide and do not develop further. The immune system recognizes the parasite proteins present in the liver cells and mounts an attack on these cells killing the parasite. This "irradiated sporozoite vaccine" is comprised of allowing 150 mosquitoes to feed on the arm of an individual once a month for 6 months. Individuals immunized by this method are completely protected against infection with malaria for at least 9 months. Unfortunately, this effective vaccine is completely impractical except as an experimental model.

A second vaccine model is that of "naturally acquired" immunity. Children raised in malarious areas who are continually exposed to the bites of infected mosquitoes and who survive to the age of about 10 years old, generally develop immunity to malaria. This immunity does not result in sterile protection, but does protect against severe disease. In fact, in many areas of the world, it is not uncommon to find nearly all adolescents and adults with malaria parasites in their blood yet they are apparently quite healthy. In these individuals the immune system keeps the number of parasites in the blood low and prevents the manifestations of severe disease. Interestingly, when these individuals travel to non-malarious areas, they often lose a substantial part of their immunity and are at risk for more severe malaria when they return.

Armed with these two models of malaria vaccines, it is convenient to approach vaccine development in one of three ways. The first is to assume that there are one or two "key" proteins that the parasite expresses and can be targeted for vaccine development. One would construct a vaccine that produces a very strong immune response against these one or two proteins and hope that this will be sufficient for killing the malaria parasite. For example, one protein expressed at the liver stage and one protein expressed at the blood stage could be targeted. In fact, the best experimental malaria vaccine to date is based on a single protein expressed at the sporozoite and liver stages. This vaccine, RTS,S, is a recombinant protein vaccine (a protein produced in the laboratory that is similar to a protein actually made by the parasite) and has been shown to provide 30 percent protection for several weeks in studies.(*3*) It is hoped that this vaccine can be improved upon sufficiently, perhaps by adding additional recombinant proteins, to provide long-term protection.

However, it may be that the parasite is sufficiently complex and has the ability to evade the host's immune

system as to require an attack at many targets simultaneously. This second approach targets all known proteins (10 to 15) expressed at multiple stages of the parasite life cycle. Unfortunately, it may not be practical to produce the multiple recombinant proteins required due to their expense, complexity of production and difficulty in purification.

To develop this type of multistage vaccine, a nontraditional approach may be needed. Researchers at the Malaria Program, Naval Medical Research Center, have been developing novel DNA-based vaccines used alone or in combination with recombinant proteins and viruses to target multiple stages of the parasite life cycle as well as exploiting the two models of immunity to malaria, irradiated sporozoites and naturally-acquired immunity. A third approach would target all expressed proteins from a particular stage, in essence reproducing the "whole organism" immunity seen in both the irradiated sporozoite vaccine and the naturally-acquired immunity models. To do this would require the identification and pattern of expression of all known genes and proteins from each of the stages of the parasite that are the targets of these vaccines, as well knowing which are those that generate protective immune responses, an approach that is actively being developed at the Navy's malaria program.

DNA-based vaccines

DNA vaccines are different from any other licensed vaccine available. Instead of immunizing with a foreign protein, DNA vaccines immunize with the genetic blueprint that encodes for that foreign protein. Cells from immunized individuals take up a "ring of DNA" containing the foreign gene and uses its own cellular machinery to translate the injected genetic material to produce the foreign protein. The immune system then responds to the foreign protein much in the same way that it would if the protein was introduced intact.

Thus DNA vaccines offer significant advantages over other types of vaccines. They are relatively easy to produce and purify, and thus are easy to modify; stimulate strong T-cell responses; may not require refrigeration; and have the potential for combination allowing the targeting of multiple foreign proteins simultaneously. During the past 6 years the NMRC Malaria Program has developed extensive experience with DNA-based vaccines demonstrating that DNA vaccines can protect mice from infection with malaria,(*4*) can be combined to overcome the differences in responses between different strains of mice,(*5*) can be combined with recombinant protein or recombinant pox viruses to increase protection in mice,(*6*) are immunogenic in monkeys(*7*) and can protect monkeys from lethal infection with malaria (Rogers, et al, submitted).

Based on these findings and others, NMRC's Malaria Program, conducted the first-ever clinical trial in healthy humans using a DNA vaccine.(*8*) This vaccine, though not designed to be protective, was shown to be safe, well tolerated and to produce strong cellular immunity.(*9*) A second trial evaluated this same DNA vaccine in a novel vaccine delivery system, the needle-less Biojector system (Epstein/Wang, et al submitted).

To assess the safety and immune responses to multiple genes introduced simultaneously a clinical trial was conducted using a combination of five malaria genes, targeted to the liver stage of the parasite life cycle. During the development of this five-gene vaccine, researchers at NMRC's Malaria Program, demonstrated that if these malaria genes were reengineered in the laboratory each had the potential to function significantly better than the original native malaria genes. Since *Plasmodium* DNA uses a very different balance in its genetic code as compared to humans, by changing the genetic code in the malaria genes to be more like that of human genes, they were able to show these genes could produce 10-20 times more foreign protein than the native malaria genes.

In studies in mice, these "synthetic genes" stimulated an immune response in mice 3-20 times greater than the native genes. Clinical trials are now being planned to assess the effectiveness of these synthetic vaccines.

Although DNA-based vaccines hold tremendous promise, not only for malaria vaccines, but for a variety of other diseases, based on results to date, they may not be able to simulate sufficiently strong immune responses in monkeys and humans on their own to confer complete protection against malaria. Researchers at NMRC and elsewhere have shown that combining a DNA vaccine "prime" followed with the same genes expressed by a modified virus, similar to the smallpox vaccine, or to recombinant protein, provides better immune responses and protection in animal models than either alone.(*10-12*)

A major effort, therefore, is underway focusing on improving malaria vaccine development by this "prime-boost" approach.. Because DNA vaccines on their own offer such a tremendous potential advantage over all other types of vaccines available today, a major area of research is focusing on improvements in vaccine delivery systems to make DNA vaccines on their own as effective

as the prime-boost vaccines. This includes novel means of getting the DNA into the cells, using absorbable micro particles, coated gold-beads, specialized polymers, and others; improving the DNA sequences in the vaccines used by the host cell machinery; and adding additional DNA vaccines expressing proteins helpful in recruiting immune cells to the area of vaccine delivery.

Genomics

The future of vaccine development for malaria and a range of other pathogens may actually lie within the genetic code itself. In order to duplicate whole organism immunity, such as occurs in both the irradiated sporozoite model and the naturally acquired immunity model, it may be necessary for the immune system to mount multiple types of immune responses simultaneously against multiple targets. Herein lies that power of the genetic code.

In 1996, Malaria Program researchers in an international collaboration with The Institute for Genomic Research (TIGR), the Sanger Centre, and Stanford University, with funding from the Department of Defense, the NIH, the Burroughs Wellcome Fund, and the Wellcome Trust, embarked on a project to determine the entire genetic sequence of the human malaria parasite, *P. falciparum.*(*13*) With the complete genomic sequence of the malaria parasite in hand, researchers would have the ability to identify every potential drug and vaccine target, elucidate complex biochemical pathways, and be able to develop tools to study fundamental parasite biological processes.

Within 18 months of starting the project, NMRC/TIGR researchers published the first complete genetic sequence of a malaria parasite chromosome.(*14*) A second chromosome was published shortly after.(*15*) Plans are now underway to publish a series of articles by early 2002 including the complete genomic sequence of *P. falciparum.*

As part of the DNA sequencing consortium's effort, all of the genomic sequence data has been released to the public during the 4-year history of the project. This early released data has enabled researchers to "jump start" their research already leading to the identification of two potentially important targets for new antimalarial drugs.(*16,17*) The consortium has made such progress with the completion of the *P. falciparum* project, including overcoming several technical hurdles as well as developing improved and more cost effective means of sequencing, that the genomes from at least two additional species of malaria parasite will be completed by the end of 2002, including the second most important malaria parasite in humans, *P. vivax*.

Functional Genomics

NMRC researchers have also been on the forefront in developing and utilizing novel technologies to exploit the enormous amounts of data generated from the malaria genome project toward drug and vaccine development. Working broadly on several fronts, the NMRC team has produced the first chromosome-specific DNA microarray, enabling the study of the expression of thousands of genes simultaneously, for example in response to antimalarial drugs and from various stages of the parasite life cycle.

In collaboration with Scripps Research Institute (SRI) they have employed a method to identify hundreds to thousands of parasite proteins from various stages of the life cycle using high-throughput liquid chromatography coupled with tandem mass spectrometry, have partnered with San Diego Supercomputing Center and the U.S. Navy High Performance Computing Center (supercomputers) to dramatically improve computer performance used in protein identification, deployed recombinational cloning systems to produce hundreds of plasmid clones in a fraction of the time by traditional methods, and developed in-house relational database capabilities needed to handle the enormous volumes of information generated from these functional genomics projects.(*18*)

DNA-based vaccines offer a unique opportunity to transform genomic sequence data into deployable vaccines. Although "whole genes" are currently being investigated as potential DNA vaccines, researchers at the NMRC malaria program are also constructing "minigene" vaccines, comprised of a series of "epitopes," small regions of individual genes predicted to be important in stimulating immune responses, particularly T-cell responses.(*19-21*) The next generation of DNA-based vaccines that will result from the data from the Malaria Genome Project will likely be composed of dozens to hundreds of epitopes strung together like beads on a string.

Conclusion

By the end of 2002, researchers will have at their disposal the complete genomic sequence of *P. falciparum*, and its two hosts: humans(*22*) and the mosquito, *Anopheles gambiae*. In this nascent field of

genomics, it is as yet unclear how these data will be best used to elucidate the complex interactions between the parasite and its host(s). However, combined with technical advances in functional genomics and rational drug and vaccine design, including DNA-based vaccines, these genomic data may provide the foundation for entirely novel approaches to drug and vaccine development, and may lead to new strategies to combat not only malaria but many other infectious and emerging diseases. The challenge over the next decade will be to use these novel approaches to better understand the malaria parasite and its interactions with its hosts, to develop strategies to intervene and reduce the tremendous human toll, and to provide effective vaccines and drugs to protect DOD forces against the threat of this destructive disease. Navy researchers are at the cutting edge in this 21st century era of biomedicine.

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Using Estimating Supplies Progarm (ESP) to Estimate Medical Resource Requirements

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The Naval Health Research Center (NHRC) recently evaluated several Marine Corps medical supply blocks and achieved significant reductions in materiel requirements by modeling the clinically relevant elements of the theater of operations. Only those items with an identified clinical requirement were included in the supply stream. An extensive database was developed that catalogues patient conditions (PCs) and the medical tasks and supplies required to treat them. More than 130 Subject Matter Experts (SME's) with operational experience participated in the database development by reviewing treatment briefs, tasks, supplies, and equipment, and by examining their usefulness to Marine Corps medical providers in forward areas of care. Substantial reductions (approximately 30 percent) in the weight, cube, and number of items were achieved with the NHRC supply model.(*1-7*)

By establishing the clinical requirement for each item pushed forward, the NHRC model was able to reduce the logistical burden carried by Marine Corps units and enhance far-forward clinical capability. In addition, establishing a clinical requirement for each supply produces an audit trail for each item and allows existing AMAL/ADAL configurations to be optimized for more current scenarios or revised as Marine Corps policy and doctrine change. The result of this effort is a database that can be accessed to estimate supplies and equipment based on a given patient stream distribution.

That database was incorporated into an exciting new computer application, the Estimating Supplies Program (ESP), to provide users with the ability to calculate supplies and equipment needed to treat a particular patient distribution. Under the sponsorship of the Office of Naval Research and the Marine Corps Systems Command, NHRC incorporated years of research in supply requirements into a user-friendly computer program for medical providers, trainers, and planners.

ESP generates the supplies and equipment necessary to treat a given patient distribution using casualty estimates, level of care, and functional area. ESP produces output in the form of easy-to-read reports that detail supply quantity, weight, cube, and cost. In addition to estimating the supply requirements for a particular patient stream, ESP offers a valuable query tool that is helpful in understanding the relationship among PC's, medical tasks, supplies, and equipment. The user can query the ESP database to obtain output that lists the supplies and equipment required to perform a task or to treat a specific PC.

ESP generates the supplies and equipment necessary to treat a given patient distribution by using casualty estimates, level of care, and functional area.(*8*) The user (1) selects a medical mission scenario by manually en-

tering casualty flow data into ESP; (2) imports a patient stream from a casualty estimation program; or (3) generates the supply requirements for one of ESP's predefined casualty streams. The user identifies the level of care and functional area expected to provide treatment for the patients. ESP then produces output in the form of easy-to-read reports that detail supply quantity, weight, cube, and cost.

By offering alternatives for patient stream selection as well as the option to query, ESP can be used to:

Generate the supplies and equipment, including weight, cube, and cost, needed to treat a user-defined patient distribution. Medical planners routinely determine medical supply transportation requirements. By selecting a "canned" scenario or generating a new patient stream, medical planners can use ESP to estimate the weight, cube, and cost for the specified patient stream. These data are used to project the transportation assets needed to move the materiel. If adequate space is not available for the medical resources, ESP can be used to justify the requirements by identifying how the lack of materiel impacts the treatment options available to patients.

Calculate the supplies needed for a specific operational deployment or training exercise. Medical officers preparing for a deployment or field training exercise must determine the supply list and the quantity of each supply required to treat possible injuries and illnesses incurred by personnel. Medical officers can input data, including any information they may have about the types of injuries and illnesses likely to be encountered while deployed, into ESP to generate the supply requirements.

Query the database when conducting an AMAL review to understand the relationship among PCs, medical tasks, consumables, and equipment. ESP can be used during AMAL reviews to monitor the complex relationships between clinical functions and the required medical supply items. New medical items are routinely incorporated into AMALs as a result of changing protocols, technological advances that improve the medical mission, and the availability of more effective drugs. Adding new materiel may create redundancies, increase costs unnecessarily by duplicating treatment options, or fail to achieve interoperability with existing materiel both within the Navy and among the services. ESP quickly and clearly identifies the relationships between the clinical requirements and the necessary supplies, providing valuable data for AMAL reviews.

Query the database to develop training guidelines. ESP can help medical officers develop refresher training for

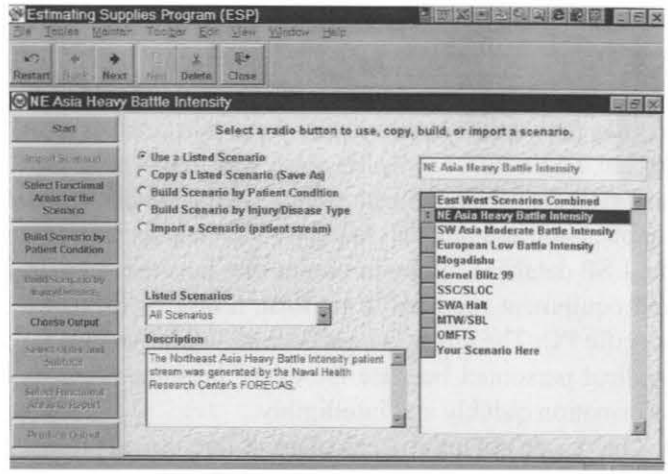

Figure 1. ESP main screen used for selecting or building the patient stream scenario.

first responders, independent duty corpsman (IDC's), nurses, and physicians. Because combat injuries are seldom encountered in civilian trauma centers, military medical care providers must be familiar with both the level of care and the supply items used to deliver combat casualty care. ESP can be used to review both the medical tasks and the associated supplies required to treat each injury and disease.

Use ESP in Four Easy Steps

Step 1: Once logged onto the system, the ESP main screen opens (see Figure 1). ESP offers the user five choices: (1) use a listed scenario, (2) copy a listed scenario, (3) build a scenario by PC, (4) build a scenario by injury and disease type, or (5) import a scenario. The user clicks the radio button that corresponds to the desired option.

Step 2: The next step in the process is to identify level of care and functional area (see Figure 2). Currently ESP offers the following levels of care: First Responder, Battalion Aid Station, Forward Resuscitative Surgery, Surgical Company, and Small Ships/ IDC. Additional functional areas are available for the Forward Resuscitative Surgery, Surgical Company, and the Small Ship Medical Departments/IDC. For example, as in Figure 2, Surgical Company is highlighted in the drop-down menu so the checklist displays operating room, triage, x-ray, ward, and so on.

Step 3: ESP reports and queries are organized in a clear, easy-to-read format and offer sorting options where appropriate. ESP can report the data relevant to a particular functional area. This tool is helpful for users who select more than one functional area for a scenario but want to

view only those supplies needed for one of those areas. Reports are run after entering level of care, functional area, and patient stream information. In addition to estimating the supply requirements for a particular patient stream, ESP offers a valuable query tool that is helpful in understanding the relationship among PCs, medical tasks, supplies, and equipment (see Figure 3). The user can query the ESP database to obtain output that lists the supplies and equipment required to perform a task or to treat a specific PC. The query is a particularly effective tool for medical personnel because the query presents complex information quickly and intelligibly.

Queries do not involve calculations but instead prompt the program to search the database and gather information from its tables. However, users must identify level of care and functional area because the supply requirements for a PC vary according to where the patient is treated.

Step 4: In addition to offering different types for reports and queries, ESP also provides users with output viewing options (see Figure 4). Users can preview, save, email, and print ESP reports and queries. All report and data style options can be previewed and printed. The following formats can be saved and emailed: ASCII Text Report, Microsoft Word, .DBF, ASCII Text File, Excel, and HTML. ESP's email option is compatible with Microsoft Outlook, Outlook Express, Eudora, and MSMail. ESP automatically opens these email systems, attaches the output in the desired format, and composes a generic memo that describes the contents of the attachment.

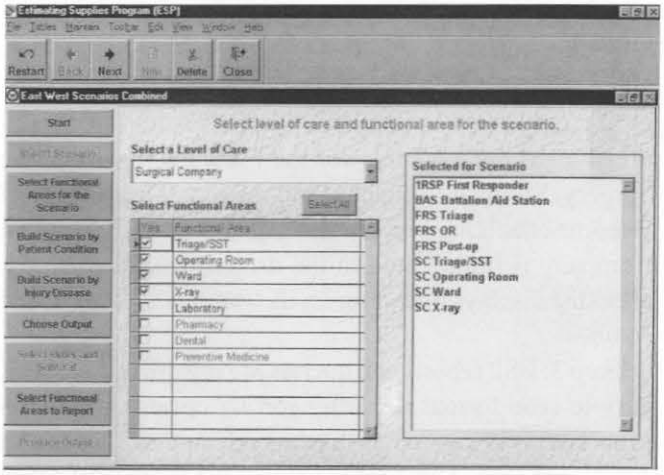

Figure 2. ESP screen used to identify levels of care and functional areas to be included.

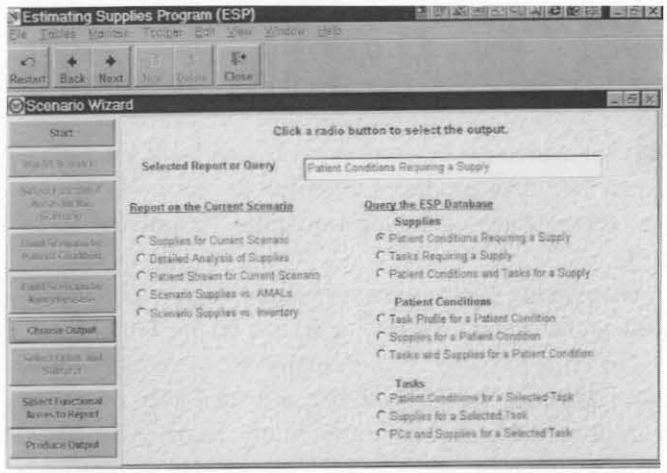

Figure 3. ESP screen used to select type of report or query.

ESP Tables: ESP offers three tables that provide the PCs, tasks, and supplies applicable to each functional area (see Figure 5). The tables aid the user in answering questions that may arise when using the program. For example, if the user is building a scenario and wants to know at which functional area PC003 is treated, the user can look at the PC by FA table to obtain a list of each PC and where it is treated. The Supply by FA table describes the functional areas where each supply is used. If a supply has been identified for deletion, the Supply by FA table can be used to see the levels of care and functional areas where it is used. The Task by FA table shows the functional areas where each task is performed.

ESP is being expanded and its capability enhanced by the addition of Operations Other Than War, shipboard and urban warfare scenarios. The new scenarios will include patient streams that may be anticipated specifically in Humanitarian Assistance, Disaster Relief, and Peacekeeping missions. Patient streams representative of (1) injuries and illness incurred during routine ship deployments, (2) injury rates generated using NHRC's SHIPCAS casualty generating program and (3) specific shipboard disasters will also be included. PCs that reflect injuries likely to be incurred during urban warfighting (falls from height, blasts) will also be included.

Due to the importance of assessing medical readiness, NHRC is incorporating a new readiness reporting capability into ESP that will allow the user to compare current consumable and equipment inventory (1) with what should be in the AMALs, and (2) with the supplies estimated by ESP for a particular patient stream. These data are essential; the user will know what supplies are missing as well as gain an accurate picture of how the current

inventory will impact the patient treatment options if the supplies are not purchased.

The goals of the Marine Corps include being more flexible and responding more quickly to operational situations. NHRC has designed a software program in keeping with this philosophy; ESP is structured to accommodate policy changes, growth, and new directions in which the Marine Corps may travel. Its structure is such that ESP can be tailored to the unique needs of any branch of the U.S. military.

As the medical community moves toward supporting the use of "precision logistics alternatives" ESP can be used to provide consumable and equipment data configured for specific unit sizes and operational needs. The current AMAL configurations assume an equal consumption rate for all supply items. For example, each AMAL block carries a certain number of bottles of medication and a certain number of blankets, yet blankets are used at a much higher rate than some medications. ESP can be used to configure the initial operating supply capability as well as the resupply requirements.

For more information on ESP, visit the ESP website at http://www.nhrc.navy.mil/programs/esp/

The ESP software and user's guide are available for download from the site. Updated versions of ESP are posted quarterly.

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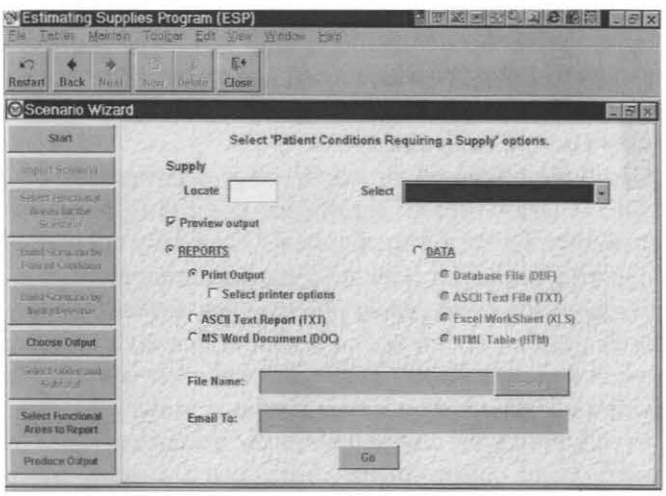


Figure 4. ESP screen used to select output format.

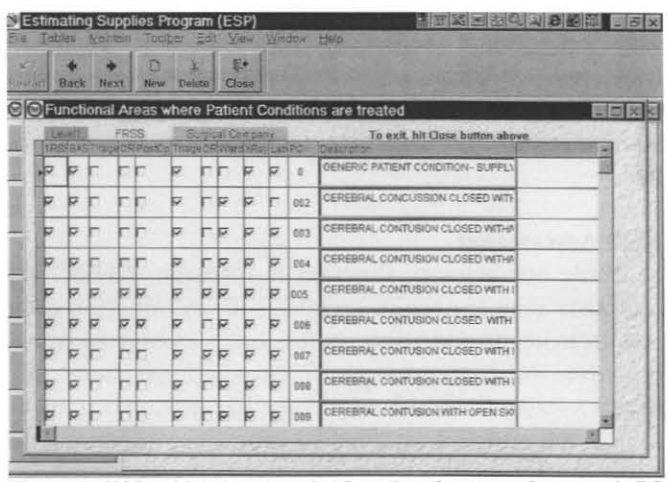


Figure 5. ESP table showing the functional areas where each PC is treated.

Chemical Hazards in the Military Environment

LT Andrew J. Bobb, MSC, USNR
CAPT Kenneth R. Still, MSC, USN
CDR John Rossi, MSC, USN
LCDR Linda Kane, MSC, USN
Robert L. Carpenter, Ph.D.

When the discussion of chemical hazards for military members comes up, the immediate thought is of chemical weapons. Further reflection may bring to mind depleted uranium and smoke from oil fires; but service members regularly employ potentially hazardous occupational chemicals in the course of non-operational work: copier toner, insecticides, fuels, disinfectants, even the proverbial boot polish. It is necessary to establish acceptable exposure limits for these chemicals, to protect the immediate and long-term health of our Sailors, Marines, Soldiers and Airmen. These standards must be developed using tested and reliable procedures based on rigorous scientific research.

The Naval Health Research Center, Toxicology Detachment (NHRC/TD) is a Navy laboratory with the mission of identifying and quantifying chemical hazards for the protection of military personnel and civilian workers. We are part of a toxicology consortium, including personnel of the Army and Air Force, housed at Wright Patterson AFB in Dayton, OH. We perform research on hazardous chemicals to determine what level of necessary occupational chemicals is acceptable for humans to be exposed to occupationally. We also provide expert consultative services to military, government, and, under some circumstances, private, health and safety personnel.

Risk Assessment

While our primary function is research, NHRC/TD scientists answer over 200 requests for information each year from health and safety professionals around the world regarding the dangers of specific occupational chemicals. In many cases these requests come because an organization is changing an established procedure and needs to know the safety of a chemical used in the new process; recent examples include a naval hospital switching to a new sterilization product for its ultrasound probes, and the U.S. Coast Guard considering pepper spray to restrain violent individuals in refugee boats. We use our technical library and networked resources to collect scientific research data from both internal and external studies on the chemicals at issue. In many cases the substance of concern is not a pure chemical, and the component chemicals must be determined in order to properly determine what studies relate to its toxicity. In the event that no information is available on the substance or its major components, our scientists must seek information on structurally similar chemicals. From the collected information we develop a concise report detailing the likely health concerns of the substance, with references for more detailed scientific information. Additionally, NHRC/TD assists Navy Bureau of Medicine and NAVSEA through the Closed Living Space Environmental Concerns Working Group (CLSECWG) and the Submarine Atmosphere Health Assessment Program (SAHAP) project, to develop occupational/environmental exposure limits for submarine atmosheres.

The Toxicology Detachment partners with the Navy Environmental Health Center (NEHC), using United States Environmental Protection Agency (USEPA) recommended models to develop Occupational Exposure Limits (OEL's) for naval personnel in operational environments. The Detachment works with the Naval SubmarineMmedical Research Laboratory (NSMRL) to develop Submarine Escape Action Levels (SEAL's) to assist operational commanders with various scenario decisions that must be made when underway.

Operational Toxicology

In the operational, or warfighting, environment, certain scenarios present significant possibility of troops encountering hazardous chemicals, especially operations involving industrial centers. Water treatment plants usually have stocks of deadly chlorine gas. Insecticide factories produce chemicals very similar in nature to nerve gas, and many industries use acids and other compounds with toxic vapors. Some agencies have proposed a short list of highly toxic compounds as the primary concern of warfighting environments, but there are many more chemicals that do, in fact, pose an immediate or long-

term threat to combat forces and deployed medical personnel. To help identify these compounds and develop plans for exposure response, NHRC/TD serves as an available "reachback" resource for operational units, and a part of our organization is prepared to go to the field in support of major operations.

Reproductive Toxicology

It is essential to safeguard not only the immediate health of our service members, but also to prevent long term consequences from occupational chemical exposure. The Reproductive Toxicology program performs research toward establishing exposure levels that prevent reduced fertility or damage to developing embryos. Current works includes studies on the impact of DBNP, a substance found in the submarine environment, and jet fuel, JP-8, on the male reproductive system. Planning is currently underway for a large project to set exposure standards for women in submarines, including reproductive health exposure limits for over 220 chemicals.

Environmental and Molecular Toxicology

Classical toxicology focuses primarily on quantifying the danger to living systems posed by chemicals. The newest department at NHRC/TD uses cutting-edge molecular biology technology to examine the underlying mechanisms through which chemicals disrupt living systems. It also has responsibility to examine the impact of military substances on the environment.

One current study of the Department of Environmental and Molecular Toxicology looks at the interaction of the Jet Fuel, JP-8, (under consideration for installment as the standard fuel by all U.S. armed services) with enzymes of the cytochrome p-450 family and functionally similar enzymes. These enzymes are involved in the breakdown of most therapeutic drugs, with various effects: in some cases the breakdown product is the toxic (and dose-limiting) form of the drug. In other cases, breakdown of therapeutic drugs is necessary to prevent toxicity. As a result, if JP-8 affects the way these enzymes function, individuals regularly exposed to JP-8 could be susceptible to toxic effects from medically prescribed or even over-the-counter drugs at doses that are safe under normal circumstances. The primary goal is to determine the impact exposure has on the expression of these important enzymes. A secondary goal of the project is to identify testable biochemical changes that occur in JP-8-exposed individuals, to help determine the extent of an individual's exposure.

Another current research project involves the impact of chaff on the marine environment. Chaff is a radar-reflective substance released by aircraft to confuse incoming missiles. As aluminum, known to be harmful, is one of the primary components of chaff, initial studies focused on the leaching of aluminum from chaff to the immediate surroundings, using laboratory analysis of chaff in aqueous solutions and testing an estuarine environment regularly exposed to chaff for elevated aluminum levels. Direct absorption through the mammalian intestine has been tested in animal models (see Naval Medical Research Addresses Concerns Over Radar-Reflecting Chaff, page), as well.

In collaboration with the Department of Inhalation Toxicology and researchers from the Naval Postgraduate School in Monterey, CA., the Department of Environmental and Molecular Toxicology is currently involved in developing mathematical/computer models for liver toxicity. In contrast to the "bottom-up" method used by molecular biology, mathematical modeling allows a "top-down" approach. Cellular behavior (cell death, the disappearance or alteration of normal cell compounds, etc) in response to varying concentrations of chemical can be predicted based on mathematical assumptions, which are based on hypotheses of how the cells are responding to the chemical. When the system is tested in the laboratory, it either agrees with or defies the predicted behavior. This information is used to reject or support the hypotheses of cellular response. The current study uses toxicity of acetaminophen (Tylenol) as the basis for building the model. To test the model, we have developed an "artificial liver" system using cultured liver cells attached to beads in a flow-through column. This will allow more accurate simulation of blood flow through the liver. Ultimately we want to meet the molecular biologists in the middle, and derive an effective model of organ and even organism toxicology. This would allow us to better predict the toxicity of compounds without expensive and time-consuming *in vivo* testing.

Inhalation Toxicology

It must be recognized that every individual involuntarily inhales approximately 22 cubic meters of air each day and thus is exposed to the vapors and particulate matter present in that air. Within military operations, the atmosphere being inhaled may be present in a confined space and may require significant activity to maintain its ability to support life. The aerosol and inhalation toxicology group at NHRC/TD provides a capability to study the respiratory tract as a route of entry into the body and as a target organ in its own right. Members of this group have expertise in pulmonary function, inhalation toxicology, and pulmonary cell biology. As a whole, the group also has the knowledge of physics and physical chemistry necessary to understand and characterize the distribu-

tion of toxic materials between the vapor and particulate phases of an inhaled atmosphere.

Recent activities include the study of laboratory rodents as a model for fire-smoke induced acute lung injury (ALI) and the development of methods to measure such injury. These ongoing studies are intended to study the onset of ALI in a dosimetric fashion using surrogate combustion atmospheres of known composition. As a complementary activity, the group has studied the combustion toxicity of composite materials from advanced aircraft to gain insight into the hazards associated with aircraft crashes when these materials constitute part of the airframe structure. These studies demonstrate that acute airway hypersensitivity responses are possible upon inhalation of low levels of smoke from such fires.

The group has also conducted several studies involving inhalation of JP-8 vapors as part of a series of studies to assess the neurobehavioral toxicity of inhaled jet fuel vapors. These studies involve the delivery and characterization of jet fuel vapors to laboratory animals whose behavior will be assessed after exposure to these vapors.

Neurobehavioral Toxicology

The Neurobehavioral Effects Laboratory (NEL) conducts research and development to provide tools for predicting the effects of exposure to chemical toxicants or stressors on performance of mission critical tasks. Neurobehavioral risks are evaluated through three major R&D approach directions. The first is prediction of human risk from the exposure of laboratory animals to chemicals of military interest. The second is prediction of human risk from the exposure of *in vitro* or cellular-level *in vivo* preparations. The third involves the direct testing of humans exposed to chemicals and other stressors either occupationally or during military deployment.

The first research objective of the NEL was accomplished through the development and validation of a battery of laboratory tests to predict human exposure risk. The Neurobehavioral Toxicity Assessment Battery (NTAB) is a well-accepted battery of 32 tests that measure the effects of acute or repeated exposure in eight sub-areas of human performance. Prediction of human neurobehavioral risk is simplified by the fact that NTAB tests are topographically similar to tests commonly used to assess performance deficits in humans. The NTAB has been recently used to predict human neurobehavioral compromise from exposure to refrigerant gases, pyrolysis products of turbine lubricants, jet fuel vapors, and a submarine atmospheric contaminant.

The second research objective of the NEL is being addressed through development of a series of cellular-level tests. The Neuromolecular Toxicity Assessment System (NTAS) includes a wide range of in vitro and cellular level in vivo tests that can be used individually, or in combination, to predict risk of incapacitation. An exciting area of ongoing NTAS research involves development of a tissue-based toxicant biosensor. Prototypes of the tissue-based biosensor are currently being tested at the NEL. These sensors employ cultured brain tissue slices that can be maintained to provide reliable environmental testing for up to 90 days. This tissue-based detection system is exquisitely sensitive to very weak concentrations of a wide variety of potentially harmful chemicals. The system is currently being considered for use by the pharmaceutical industry as a drug discovery tool.

Finally, the NEL is developing a comprehensive battery of neurobehavioral tests to evaluate the performance capacity of mission readiness of human subjects. The Global Assessment System for Humans (GASH) can be used in laboratory, occupational or combat deployment settings. Human subjects can be evaluated before, during and following exposures to evaluate both incapacitating effects as well as recovery. Most recently, portions of the GASH were used to measure performance capacity of over 300 military aircraft personnel chronically exposed to jet-fuel. The GASH provides an exclusive electroencephalographic (EEG) capability. Using computational paradigms exclusive to the NEL, the system provides a comprehensive analysis of brain cognitive and emotional processing that can be used to assess the integrity of specific neural systems underlying performance changes identified by other GASH tests. Collectively, the GASH provides a rapid portrait of the immediate mission readiness of military personnel, as well as a complex analysis of exposure-related changes in brain functioning.

The Tri-Service Consortium

The Navy, Army, and Air Force each maintains a toxicology unit to research the effects of occupational chemicals on its service members. These units cooperate to cover a broader range of fields than could be studied by one unit alone. In addition to the areas discussed above, tri-service toxicology studies pharmacokinetics (the study of the interaction of foreign substances with the body), aerosol formation, and biotransformation (the formation and elimination of metabolic products from the body). It is our common mission to protect the armed forces of the United States from chemical hazards in the work and combat environment. NHRC/TD is the lead service in reproductive, neurobehavioral, and inhalation toxicology studies in risk assessment. ❑

All authors are assigned to the Naval Health Research Center, Toxicology Detachment at Wright-Patterson AFB, Dayton, OH.

From the Assistant Editor

Dear Readers:

Several months ago when we decided to do a Research & Development issue of *Navy Medicine*, we had no idea what we were getting into. After sending out a request to the R & D community, the response was just short of a stampede, and we were inundated with articles. We want to thank everyone who responded to our call.

Because the response was so outstanding you will note that this magazine is larger than usual. Even with expanding the printed issue there is still an overflow of articles worthy of publication.

In order to allow all the contributors their 15 minutes of fame, Mr. Andre´ Sobocinski, our Assistant Historian, has set up a designated web address on the NAVY MEDICINE/Navy Medicine History homepage at: http://navymedicine.med.navy.mil/med09h. Select the "Research and Development" link. At this site you will find the following articles.

Again, we would like to thank the R & D community for such a prolific response. We hope to do this again next year.

Janice Marie Hores
Assistant Editor
Navy Medicine

- **OZ: A Human Centered Suite of Cockpit Instruments**
- **Tri-Service Medical Research in the Twenty-first Century**
- **New Horizons 2000, Antigua: Demonstration of Preventive Medicine MMART Capabilities**
- **A New Method for Measuring Atmospheric Contaminants Onboard U.S. Navy Nuclear Submarines**
- **NAMRU-3 Field Facility in Ethiopia**
- **DOD's Rickettsial Diseases Research Program**
- **Why Can You Weld Hot Dogs Together with Microwaves and What is Microwave Dosimetry Modeling?**
- **Submarine Watchstanding Study**
- **Blood Requirement in Combat Casualty Care**
- **Diarrheal Diseases Then and Now**
- **A Neural Tissue Based Biosensor for the Detection of Neurobehavioral Toxicants**
- **Solving the Risk of Malaria in the Fleet**
- **Naval Health Rearch Center**

In Memoriam

Dorothy Still Danner, 87, Navy nurse and former prisoner of war, died on 16 June 2001 at the Boise State Veterans Home in Boise, ID. She was buried with full military honors at Arlington National Cemetery.

LCDR Still was born in Saginaw, MI. After graduating as a registered nurse from the Los Angeles County General Hospital School of Nursing, and working in surgery at Hollywood Hospital, she joined the Navy in 1937. She saw duty at Naval Hospital San Diego before receiving orders for Naval Hospital Cañacao, the Philippines in late 1939. In a 1991 oral history, Danner talked nostalgically about her "slow boat" voyage across the Pacific aboard the USS *Henderson* (AP-1).

"It was a festive trip. We first stopped at Honolulu. I can still see the people on the dock there with their lais and the hula dancers." Although the Philippines was not quite as spectacular as Hawaii, she became very fond of tropical duty and the very active social life.

Social concerns, however, were put on the back burner as tension with Japan escalated. Following the attack on Pearl Harbor, the Japanese bombed the Cavite Navy Yard. Still rushed to the hospital to find it swarming with grievously wounded Filipino civilians and Sailors from the Navy Yard. Working day and night, she and Cañacao's other medical personnel treated the casualties and awaited the Japanese onslaught.

When Manila fell in January 1942, Dorothy Still and 10 of her comrades became prisoners of the Japanese, spending the next 3 years in captivity at Santo Tomás and Los Baños. On 23 February 1945, they were liberated by U.S. Army troops of the Eleventh

Airborne Division and Filipino guerrillas in a daring raid on the Los Baños prison camp. She later described what happened that day. "All of a sudden we saw a formation of aircraft coming over. As the paratroopers started jumping out, the guerrillas and soldiers around the guard houses began killing the Japanese there. Then the amtracs came in, crashing through the swali-covered fence near the front gate. An amtrac pulled up in front of the hospital and the American troops jumped out. Oh, we never saw anything so handsome in our lives."

Despite their ordeal, all 11 survived their captivity because they were nurses with a mission--to care for their patients regardless of the circumstances. They ran their prison hospital as a Navy hospital despite the lack of medicine and near absence of nourishment.

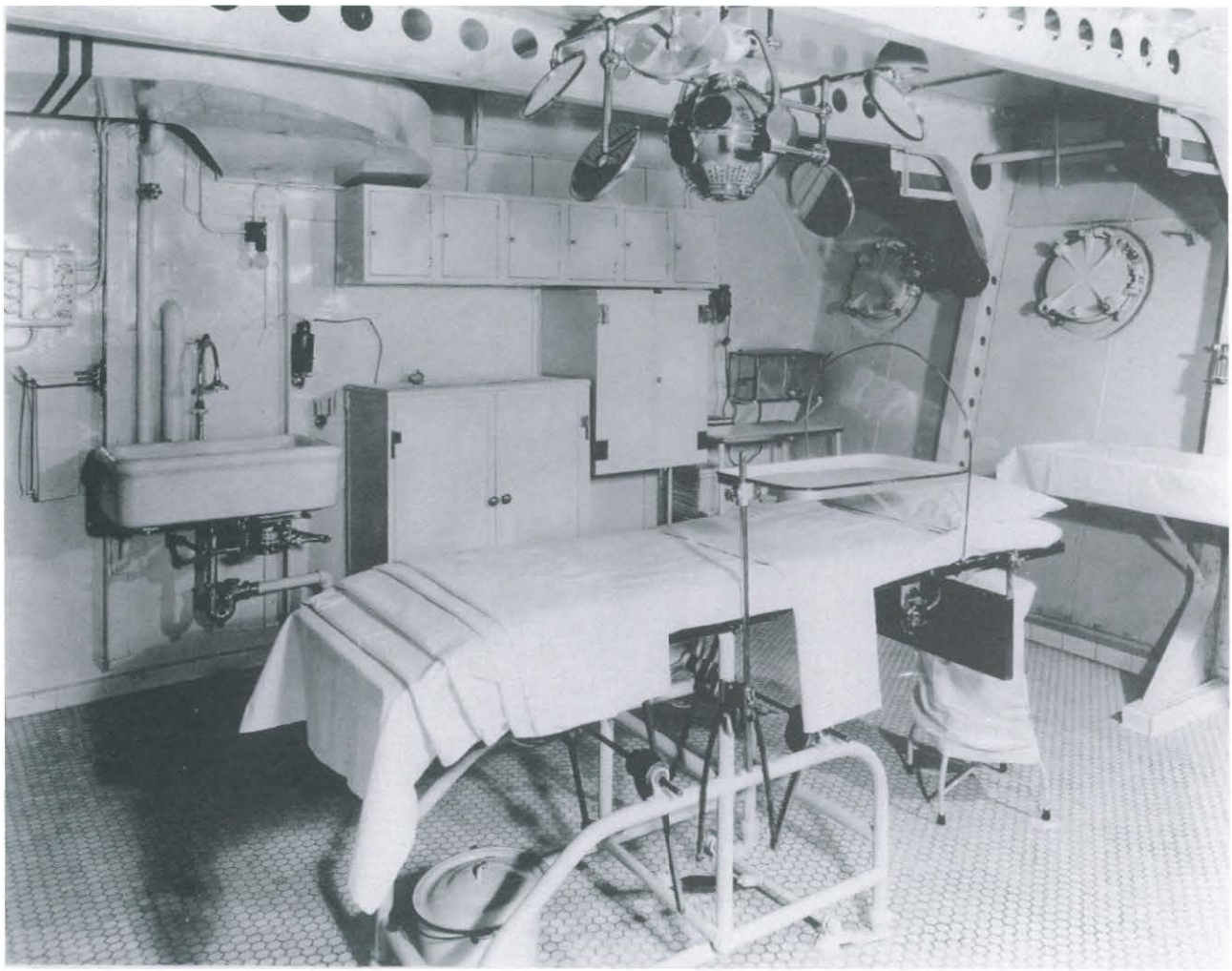
Following her liberation and recuperation, Nurse Still traveled throughout the U.S. promoting the sale of war bonds. Soon thereafter, she was discharged as a lieutenant commander with a Bronze Star and POW medal.

Dorothy Still married in 1947, had two children, and lost her husband to a heart attack while expecting her third. She was then forced to support her family single-handedly, working as a nurse and hospital supervisor.

In 1995 she published a memoir of her captivity, *What a Way to Spend a War*, (Naval Institute Press).

Dorothy Still Danner never would have used the word hero to describe herself. Rather, she often said, "We were just Navy nurses doing our jobs." Fifty-six years after World War II ended, she and the 10 Navy nurses who shared her experiences are almost all gone now. Nevertheless, their example and single-minded dedication to their patients mark them all as heroes by any standards.—JKH ❑

Navy Medicine ca. 1935



BUMED Archives

Operating room on a U.S. Navy battleship. Note the "low tech" but very practical operating lamp. The mirrors could be manually adjusted to direct light exactly where it was needed.

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