

# Outlook

Naval Medical Research and Development Command



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## THIRTEEN PROPOSALS SELECTED FOR FY93 INDEPENDENT RESEARCH/INDEPENDENT EXPLORATORY DEVELOPMENT PROGRAM

by Christine Eisemann, NMRDC Associate Director for Research Management

Six new proposals and six continuing studies were selected for NMRDC's FY93 Independent Research (IR) program, and one new proposal will be funded as Independent Exploratory Development (IED) work. These proposals were selected from a total of 38 IR/IED candidates submitted in the April, 1992 competition. Each proposal was evaluated for technical merit by three external reviewers and for management issues by the NMRDC research program staff. As always, there were many more deserving proposals than could be funded with our modest IR budget and all the investigators participating in the competition should be congratulated on their efforts.

The IR program provides a way for investigators to compete for basic research funding, with technical quality and creativity as the main selection criteria. For investigators who seek this outlet for their imaginative ideas, the competition maintains creative tension and lets the best, most convincing proposals rise to the top. Without an IR dollar or project quota to be filled for each NMRDC laboratory, our Command-wide IR program encompasses the best innovative research from our entire R&D system.

One facet making the IR program more attractive to investigators is that typical funds invested in each proposal have risen dramatically. In the past ten years, with approximately level funding in the program, the number of IR proposals each year has fallen from 49 to 12. The average annual funding per proposal has risen from \$15K to \$104K. Some would argue, validly, that this trend limits participation in the IR program. However, in general, it provides a better opportunity for investigators to develop their ideas into significant research products. The results will be twelve great products from a million dollar-a-year program to support the operational Navy (besides, this thinking is consistent with specific guidance from the IR program sponsor, the Office of Naval Research!).

A list of the proposals is on page 12.

*Holiday Greetings*

Have a Safe  
and Festive Holiday  
Season



# ELECTRONIC MAIL

by LCDR M.E. Dobson, MSC, USN, NMRDC Director of Facilities & Equipment Management

**NMRDC and the subordinate laboratories have the ability to exchange electronic mail (E-Mail) and files, not only among the Commands but also with colleagues around the world. E-Mail is a generic name for non-interactive communications of text, data or image messages between a sender and a designated receiver by systems using telecommunications links. It is a combination of hardware and software.**

E-Mail is provided through Command user accounts sponsored by NMRDC on the Naval Research Laboratory's VAX Front End Cluster for CONUS laboratories or the WRAIR, Division of Biometrics' VAX for OCONUS laboratories plus those CONUS laboratories involved in epidemiological studies. Since these systems are part of the Defense Data Network (DDN), also referred to as Milnet, which is part of the world-wide collection of interconnected networks known as Internet, communicating with thousands of other researchers is possible. As powerful as these tools are, they have not received widespread use except by the OCONUS laboratories. One reason is that all messages for a Command were funneled through a single account that did not provide ready access for individuals. In

recent years, some of the laboratories, along with NMRDC, have taken steps to provide individual access to Local Area Networks (LANs). LANs connected to the DDN and the Internet are available at NMRDC, the Naval Health Research Center (NHRC), San Diego, CA, and the Naval Medical Research Institute (NMRI), Bethesda, MD. Multiple user accounts on host activity systems connected to DDN are available for NMRI Toxicology Detachment, Dayton, OH and the Naval Submarine Medical Research Laboratory, Groton, CT. Individual researchers at various laboratories have arranged for their own accounts on DDN connected systems as well. Only NMRDC and NHRC are currently providing these services to all users.

A second reason for low user rates

is the lack of "user friendliness" of many of these systems. At NMRDC, we have addressed this issue by implementing POPMail /PC. This program is an MS-DOS E-Mail client that communicates across the LAN to a UNIX minicomputer that acts as an electronic post office connected to the Internet. This minicomputer also functions as a DOS file and printer server across the network. POPMail /PC provides an easy to use, "point and shoot" interface to the E-mail system. It includes the ability to send binary files as attachments to other POPMail/PC users and to create files of E-mail addresses that can be rapidly searched and pasted into outgoing messages. After a year of testing by NMRDC and the Naval Medical Information Management Command (formerly the Naval Medical Data Services Center), Bethesda, MD, POPMail /PC is being included as part of BUMED's Medical Open Architecture (MED-OA) suite of LAN software. It is highly recommended for use at all NMRDC activities. The requirements for providing this capability are relatively simple. If you already have an Ethernet based LAN, you are well on your way. In addition, you need a UNIX based system such as an 80386 or 80486 PC with 300 Meg or more of hard disk space or a small minicomputer such as a Sun, HP-9000, Silicon Graphics, AT&T 3B2/600GR, etc. The software to turn the UNIX computer into an electronic post office as well as POPMail/PC is available from NMRDC. If your LAN is not connected to DDN, you will also need a high speed modem to link with NMRDC.

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND	
<b>Commanding Officer</b> E. T. Flynn Jr. CAPT, MC, USN 301-295-0287	<b>Executive Officer</b> R.L. Chaput, CAPT, MSC, USN 301-295-2163
<b>Director of Research and Development</b> R.C. Carter, CAPT, MSC, USN 301-295-0883	<b>Associate Director for Research Management</b> C. S. Eisemann 301-295-0882
<b>Outlook Editor</b> D.M. Ryan 301-295-0875	
<b>Research Area Managers (RAMs)</b>	
<b>Submarine and Diving Medicine</b> B.A. Schibly, CDR, MC, USN 301-295-0879	<b>Fleet Occupational Health</b> J.R. Beddard, CDR, MSC, USN 301-295-0885
<b>Aviation Medicine and Human Performance</b> T.J. Singer, CDR, MSC, USN 301-295-0878	<b>Infectious Diseases</b> C.J. Schlagel, CDR, MSC, USN 301-295-0881
<b>Combat Casualty Care</b> P.D. Kent, CDR, MC, USN 301-295-0880	<b>Dental Research</b> S.A. Ralls, CAPT, DC, USN 202-653-0463
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For information contact LCDR Michael Dobson, NMRDC Code 03 at 301-295-0815, DSN 295-0815 or E-mail rdc30@nmrdc1.nmrdc.nnmc.navy.mil.

## VIEW FROM THE TOWER

by CAPT Edward T. Flynn, NMRDC Commanding Officer

Since I last wrote this column in the early spring, a great deal has happened. I want to share just a few of the highpoints with you.

### FY93

NMRDC's funding, personnel authorizations, and facilities look strong for FY93. The funds that were transferred from the Navy to the Assistant Secretary of Defense for Health Affairs (ASD(HA)) late last year during the FY93 budget development were returned to the Navy by Congressional action. When the FY93 budget dust settles, I expect a 10% increase in total research funding.

On the personnel side, we have managed to avoid officer and enlisted cuts and have suffered only a slight reduction in civilian manage-to-payroll celling. We have successfully proposed and defended military construction projects that will add 100,000 square feet of new laboratory space to our system.

### The ASBREM Committee

The ASBREM Committee has been greatly strengthened by the addition of co-chairpersons, Dr. Enrique Mendez, Jr., ASD(HA) and Dr. J. Osterman, Office of the Director, Defense Research & Engineering. These individuals are willing to listen to opposing Service arguments and then make binding decisions. The infectious disease program already has benefited greatly from this new arrangement. A new charter for the ASBREM Committee should be signed by the time you read this.

### Peer Review

There is heightened interest in external peer review. Resource sponsors are asking for peer review to assure the quality of the programs and to assist in the reallocation of funds. The recent review of the Army-Navy effort in infectious disease is an example of what is in store for the future.

### Strategic Planning

We have been active in strategic planning and hope to have a final plan in place by the end of the year. This plan will emphasize the need for aggressive marketing, enhancement of the quality of programs, and open participation in decision making. Each of these actions is essential to our future success. I want to thank all those who worked so hard on this plan during our many meetings.

### Tri-Service Consolidation

In the coming months, we are likely to see new and much greater pressures for the tri-Service consolidation of medical research. NMRDC has spent a great deal of effort this past year analyzing possible consolidation moves within our own system. With this data in hand we are in a good position to respond to consolidation plans.

More information on these items in the April 1993 OUTLOOK

## UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER ENVIRONMENTAL BIOMEDICAL RESEARCH DATA CENTER

Twenty-five years ago a joint action by BUMED and the University of Pennsylvania established an active research applications center, with primary emphasis on decompression safety. Initial developmental assistance by BUMED and the Office of Naval Research led to the evolution of the present International Environmental Biomedical Research Data Center within the Institute for Environmental Medicine at the University of Pennsylvania. This data center has aided universities, federal agencies, and offshore industries in diving physiology research and in the application of undersea physiology to safety in aerospace activities. The continuing technical and scientific communication with Navy, NASA, in-

dustry and universities has resulted in a broadened scope of activity which now encompasses work in atmospheric, undersea, and aerospace environments. The data center's components include:

1. Extensive biomedical and bioengineering research information records from multiple programs and cooperating laboratories
2. Diving, compression and decompression analysis and development information
3. Operational exposure information
4. Technical documents system correlated with the Undersea and Hyperbaric Medical Society abstract system

Each data system component is utilized in performing analytic func-

tions of experimental program design, development of predictive/preventive models of environmental stress, and advancement of operational capability. Access to the data center for information or collaborative analytic projects may be accomplished by direct communication with the technical supervisor, Eleanor Hopkin.

Environmental Biomedical Research Data Center, University of Pennsylvania Medical Center, Institute for Environmental Medicine  
1 John Morgan Building  
Philadelphia, PA 19104-6068  
at 215-898-8692 FAX 215-898-6120

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## NOTES FROM THE PATENT COUNSEL

by A. David Spevack, NMRDC Patent Attorney

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### What is the Navy's Policy on Copyright?

Federal employees cannot copyright materials that were prepared as part of work for the Navy. Section 105 of the copyright statute denies copyright protection to any work of the U.S. Government which is a work prepared by a federal employee, whether it is published by the Government or by a commercial publisher. The rationale for this is that Government work is financed with tax funds and should be available for use by the public.

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### Copyrights and Contracting for Computer Services

Any work done under a Navy contract may be copyrighted by a contractor in the name of the contractor. Several situations have arisen where a computer program, created under a Government contract, resulted in a contractor-owned copyright which caused problems involving Government use. Any contract that encompasses the preparation of a computer program should contain clauses guaranteeing the Government at least a license to use the program for Governmental purposes. The program may be an important product applicable to future Government work, in which case the contract should include provisions that require the contractor to take out a copyright on the program and assign that copyright to the Government. The Government can own a copyright if it acquires the right by purchase.

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### What To Do When You Want to Copy Copyrighted Material

Any time a Government employee wants to use a copyrighted item owned by the Navy in a Government work, it is necessary to write and obtain permission for such use. SECNAVINST 5870.5 of 26 August 1988 is directed to the sub-

ject of obtaining such permission. Likewise, SECNAVINST 5870.4 pertains to copyrights in sound and video recordings, and has a suggested letter for requesting permission to use an excerpt from a sound or video recording. Counsel will assist in preparing a letter or obtaining permission.

It is the express policy of the Navy to respect the rights of employees to assert a copyright in those works not prepared as part of their assigned duties. It is also Navy policy to not condone, facilitate or permit the unlawful use or copying of copyrighted work for private or personal use. If you do not obtain copyright permission and still use the copyrighted material, you will have committed copyright infringement.

Any infringing user is liable for monetary damages, and the Navy has no exemption from copyright infringement liability. The Navy will protect the rights it has in any copyrights it owns.

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### Copyrights in Journal or Symposia Articles and Sections of Books

The substance of articles submitted to journals or symposia and chapters or sections of handbooks or textbooks that were prepared as part of your work for the Navy cannot be copyrighted by the publisher. The publisher can copyright the form used to present the information. When you submit your manuscript to the publisher, you must inform the publisher that your material cannot be copyrighted. The best way to do this is to include the following statement on your manuscript: **This is the work of a U.S. Government employee and may not be copyrighted (17USC 105). No copyright notice may be placed on this work.** The publisher must include this statement with your article or chapter when it is published. This will allow readers of the publication

to know that they can freely reproduce the information in the article (but they cannot copy and use the article as it appears in the publication).

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### Contracts for R&D Services Must Include Patent Rights and Data Clauses

The Government can obtain patent rights to inventions by contract personnel *only* if the contract provides the Government with that right. When a subordinate command asks the local contracting department to prepare a services contract for a consultant or contract technician, that is exactly what they get — a contract for either goods or services. Standard contracts for goods and services do not contain patent rights or data clauses giving the Government either an express right to a royalty-free license to practice what it has paid for, or an opportunity to take title to the invention. When contracting for consultation or technical services you should inform the contracting officer that the agreement must be in the form of a research and development agreement for the services and must include patent rights and data clauses so the Government is properly protected.

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### Material Transfer

Biological materials created by researchers with Government time, money and materials as part of their assigned duties, is considered Government property and can only be transferred with proper authority. Counsel is in the process of preparing a "blanket" CRDA for such transfers. Counsel also has prepared a draft agreement for use in obtaining transfers from non-federal providers. There is also a draft MOU for obtaining transfer of a biological material from another Government agency.

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For more information contact A. David Spevack, NMRDC Patent Attorney at 301-295-6760 or DSN 295-7670 or FAX 301-295-1022

# OPNAV REORGANIZATION - Effective January 1, 1993

On July 22, 1992, the Chief of Naval Operations (CNO) and the Secretary of the Navy (SECNAV) announced a reorganization of the Office of the Chief of Naval Operations (OPNAV) as part of the Navy's overall plan to improve productivity and quality, to eliminate duplication within organizations and enhance overall effectiveness and to realign functions to parallel the Joint Staff. OPNAV codes will correspond to Joint Staff directorate numbers which will allow for easier identification.

## Organization Code Changes

As a result of the reorganization, OPNAV offices will now reflect new N Codes. Old OP Codes will no longer be used. Under the reorganization, the current OP-02 (Undersea Warfare), OP-03 (Surface Warfare), and OP-05 (Air Warfare) will be consolidated under N8, Deputy Chief of Naval Operations (Resources, Warfare Requirements and Assessment). This achieves SECNAV's objective of improving coordination among the warfare communities in program planning and warfare requirements. The cur-

rent OP-01 will retain Manpower and Personnel responsibilities and will be recoded N1. The Chief of Naval Education and Training (CNET) will be dual-hatted to a new OPNAV office, N7, titled Director of Naval Training.

## N Codes

The titles for the CNO, Vice CNO, and Special Assistants to the CNO are not affected; their codes remain the same prefaced with N vice OP.

The following summarizes the movement of major OPNAV offices:

OP-01, Deputy CNO (DCNO) (Manpower, Personnel, and Training) becomes N1, DCNO (Manpower and Personnel).

OP-11, Training and Education Policy Division, will be disestablished and functions assumed by either N7 or CNET.

OP-02, ACNO (Undersea Warfare), becomes N87, Director, Submarine Warfare Division.

OP-03, ACNO (Surface Warfare), becomes N86, Director, Surface Warfare Division.

OP-04, DCNO (Logistics) becomes N4 and retains the same title.

OP-05, ACNO (Air Warfare), becomes N88,

Director, Air Warfare Division.

OP-06, DCNO (Plans, Policy and Operations), becomes N3/N5 and retains the same title.

OP-65, Nuclear Warfare and Arms Control Division is disestablished and functions assumed by other divisions under N3/N5.

OP-07, DCNO (Naval Warfare), is disestablished and functions assumed by various OPNAV offices.

OP-08, DCNO (Navy Program Planning), becomes N8, DCNO (Resources, Warfare Requirements and Assessment).

OP-091, Director, Test and Evaluation and Technology Requirements, becomes N091 and retains the same title.

OP-092, Director, Naval Intelligence, becomes N2 and retains the same title.

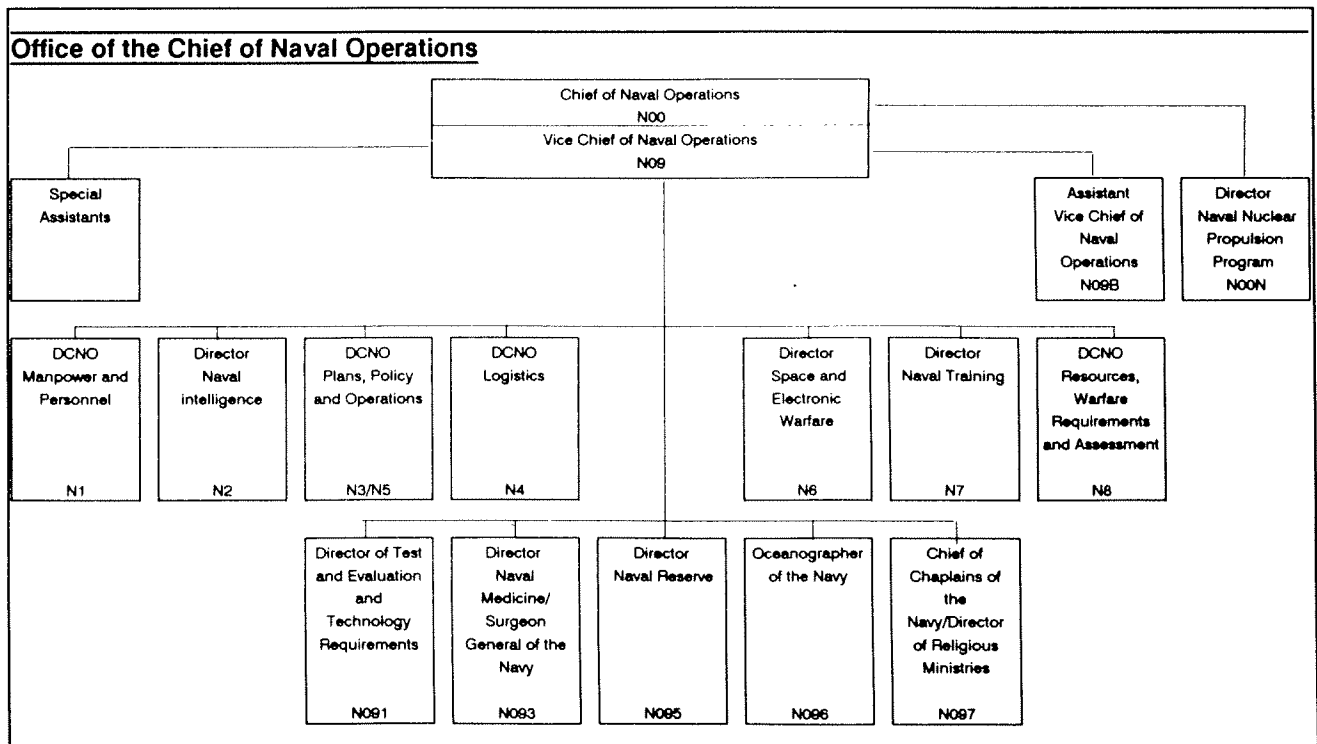
OP-093, Director, Naval Medicine/Surgeon General of the Navy, becomes N093 and retains the same title.

OP-094, Director, Space and Electronic Warfare, becomes N6, Director of Space and Electronic Warfare.

OP-095, Director, Naval Reserve, becomes N095 and retains the same title.

OP-096, Oceanographer of the Navy, becomes N096 and retains the same title.

OP-097, Chief of Chaplains of the Navy/Director of Religious Ministries, becomes N097 and retains the same title.



# TRI-SERVICE TOXICOLOGY PROGRAMS SPONSOR CONFERENCE SESSION ON "ALTERNATIVES TO ANIMALS IN TOXICOLOGY RESEARCH: POLICY CONSIDERATIONS"

by LCDR John Wyman, MSC, USN, Naval Medical Research Institute Toxicology Detachment

**The use of animals in biomedical research is a very important and a very controversial subject. Animal welfare and protection is a concern to all of us, and the increased requirements for documenting and justifying the use of animals causes us to be better stewards of our resources and to thoroughly examine our proposed research.**

To clarify the issues, the annual Tri-Service Toxicology Conference devoted an entire session this year to addressing the policy considerations involved with the use of animals in biomedical research. This was one of five sessions at this year's conference (19-21 May 92) on Applications of Advances in Toxicology to Risk Assessment.

The objectives of the animal use session included discussions that stimulated thinking about animal welfare and toxicology research, focusing on the specific advantages and obstacles facing bench scientists and regulatory agencies. This was accomplished by helping researchers evaluate the ethics of animal research and by educating researchers concerning the global nature of the interest and concern about the use of animals in biomedical research.

**Individuals interested in reviewing the entire content of the presentations may do so by obtaining the proceedings of this conference which will be published as the February or March 1993 issue of Toxicology Letters.**

## Symposium Background

The Tri-Service Toxicology Conference is held annually at Wright-Patterson AFB, Dayton, OH, the site of the BRAC/Project Reliance-directed collocation for the Services' toxicology research programs. The conference can trace its roots back to a session on toxicity that was part of the "Symposium on Submarine and Space Medicine" held in New London, CT

in 1958 at the Naval Submarine Medical Research Laboratory. Widespread interest and increasing demand for the critical application of toxicology to these operational environments led to an entire symposium on this subject. The first Tri-Service toxicology symposium was held during 29-31 July 1963 and the topic was "Toxicity in the Closed Ecological System". This symposium was cosponsored by the Lockheed Missiles and Space Company and the Navy's Special Projects Office (Nuclear Submarines and the Fleet Ballistic Missile project). The focus of the symposium was on the hazards from chemicals in submarines and space craft, exposures unique to the military. Among the many participants were the Navy Toxicology Unit, the Army Chemical R&D Laboratories, the Air Force Aerospace Medical Research Laboratory, NASA, the National Research Council's Advisory Center on Toxicology and many distinguished toxicologists.

## NMRI TOXDET

The Naval Medical Research Institute Toxicology Detachment (NMRI TOXDET) is the Navy's sole toxicology research laboratory. The TOXDET currently supports programs in materials and systems research and acquisition, occupational safety and health, environmental protection, damage control, and fire prevention. TOXDET research is concerned with materials of Navy interest and the conditions of their use. In coordination with other Navy Medical Department activities, the TOXDET performs health hazard evaluations and risk assessments to provide program

managers and line commanders with information for decision-making.

## Session Presenters

### **Animal Issues and Society**

Maj. John H. Grabau, VC, USA  
Armstrong Laboratory, AL/OEVM  
Wright-Patterson AFB, OH

### **Current DOD Policy on Use of Animals in Medical Research**

COL John W. Kolmer, MC, USA  
Officer of the Under Secretary of  
Defense for Acquisition,  
DDR&E(S&T)SPP  
Washington, DC

### **Formulation of Ethical Standards for Use of Animals in Medical Research**

Andrew N. Rowan, Ph.D.  
Tufts Center for Animals and Public  
Policy  
Tufts University  
N. Grafton, MA

### **In Vitro Models for Toxicological Research and Testing**

John M. Frazier, Ph.D.  
Johns Hopkins University  
Baltimore, MD

### **In Vitro Methodologies for Enhanced Toxicity Testing**

Nicholas J. DeRaso  
Armstrong Laboratory, AL/OETB  
Wright-Patterson AFB, OH

### **Coupling of Computer Modeling with In Vitro Methodologies to Reduce Animal Usage in Toxicity Testing**

Harvey J. Ciewell III  
ManTech Environmental  
Technology, Inc.  
Dayton, OH

### **Regulatory Agency Requirements for Validation of Toxicity Tests Alternatives**

Sidney Green, Ph. D.  
Food and Drug Administration  
Laurel, MD

### **Rapporteur:**

Shayne Gad, Ph.D., D.A.B.T.  
Becton Dickinson Research Center  
Research Triangle Park, NC

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## UPDATE FROM U.S. NAVAL MEDICAL RESEARCH UNIT NO.3, CAIRO, EGYPT

The U.S. Naval Medical Research Unit No. 3 (NAMRU-3) conducts a multi-faceted basic, clinical, and field research program relating to the health and operational readiness of military personnel assigned or deployed to Southwest Asia or Africa. NAMRU-3 is fully capable of deploying highly qualified field-trained personnel and state-of-the-art field-applicable laboratory diagnostic capabilities to any remote area in the region. In addition, NAMRU-3 is a state-of-the-art medical research facility equipped to conduct the most technologically advanced basic science research.

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### Project Marco Polo 1992

During July 1992, NAMRU-3 provided logistical support and a facility tour to a large (40+) group participating in Project Marco Polo 1992. This joint program between the Navy and the National Geographic Society is an effort to motivate American students in the study of science and geography.

A group of high school students and teachers, and representatives from the Naval Oceanographic Command and the National Geographic Society, visited Egypt and NAMRU-3 during their geographic and oceanographic educational exercise. During the visit, briefings were presented by LCDR Richard Hedstrom on molecular biology, Dr. Fouad Yousef on parasites, MAJ Craig Calamaio and LT Stan Cope on zoology, and Dr. Beverly Mangold and Dr. Robert Harrison on the schistosomiasis laboratory. HMCMTerry Thurman, who acted as the group's corpsman while they were in Egypt, set up the tour and visit to NAMRU-3.

The students and teachers participating in Project Marco Polo 1992 went home with a greater knowledge of the real day-to-day operations of the Navy's medical research efforts and the students' unique experience may very well produce some future Navy medical researchers and corpsmen.

Project Marco Polo 1992 will be featured in *Navy Medicine* (Nov/Dec 1992 issue), *All Hands Magazine*, the *National Geographic Society Magazine*, on *Navy News This Week* and in an upcoming television *Explorer* program.

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### Co-sponsoring Symposium

NAMRU-3 will be co-sponsoring, along with the Royal Society of Tropical Medicine and Hygiene and the Pathological Society of Great Britain and Ireland, a symposium in London on 6-7 January 1993 entitled "Diarrheal Disease: Current Concepts and Future Challenges." Presentations in this symposium will be published in a supplement to the journal *Transactions of the Royal Society of Tropical Medicine and Hygiene*, as was the previously co-sponsored symposium on "Meningitis" in 1992.

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### Uniformed Services University of the Health Sciences and NAMRU-3

NAMRU-3 has received the *green light* from the Uniformed Services University of Health Sciences (USUHS), Bethesda, MD to provide an overseas elective option, as travel and per diem funds allow, for their senior medical students and graduate students in the Masters of Tropical Medicine and Hygiene program. Applications from the NAMRU-3 staff will soon be considered by USUHS for adjunct faculty appointments. This promises to be an exciting collaboration for both institutions.

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### Oral and Poster Presentations

NAMRU-3 staff presented 15 oral and poster presentations at the American Society of Tropical Medicine and Hygiene's Annual Meeting in Seattle, Washington, in November 1992, and will present at least six oral and poster presentations during the Naval Environmental Health Center's annual workshop in February 1993.

In addition, NAMRU-3 is providing

presentations and organizational assistance at the International Congress on Schistosomiasis in Cairo, scheduled for February 1993.

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### Operational Medical Support

NAMRU-3 staff provided operational medical support during a famine relief exercise in Madagascar in July 1992, and also participated with NMRI and NEPMU-7 in a vaccine trial onboard USS Saratoga during a Mediterranean deployment.

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### CENTCOM Visit

A recent (second) visit by the U.S. Central Command's (CENTCOM) command surgeon, COL Randolph, solidified the recognition of NAMRU-3 as a valuable infectious disease resource to USCINCENT during future potential contingency operations in this region of the CENTCOM Area of Responsibility.

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### Intensive Care Unit

To enhance the quality of health care and infectious disease research involving seriously ill hospitalized patients, NAMRU-3 is working with the Egyptian Ministry of Health to develop an Intensive Care Unit at Abbassia Fever Hospital, the largest (1500 bed) fever hospital in Egypt. The Abbassia Fever Hospital is adjacent to NAMRU-3. This ICU also will be a valuable resource for training and experience for clinical tropical medicine students from USUHS and elsewhere, and for infectious disease residents and fellows who choose NAMRU-3 as an elective training or research option.

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Detailed information on the history and accomplishments of NAMRU-3 will be featured in a forthcoming article in *Military Medicine* entitled "NAMRU-3, 46 Years of Infectious Disease Research".

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## NMRDC MAJOR RESEARCH AREAS

Current NMRDC research and development efforts are linked to the requirements for Medical Department support of the operational Navy and Fleet Marine Force. In order to preserve the health and safety of military personnel who work in a wide variety of occupational environments, NMRDC's laboratory and field research extends to almost every activity undertaken by the Navy and Marine Corps. By developing research programs that focus on the unique medical problems of the military, NMRDC ensures that the men and women in the Navy and Marine Corps are prepared to complete their missions.

NMRDC research deals with operational medicine, which is different from traditional health care provided in hospitals and clinics. Operational medicine is clinical and occupational medicine practiced in military settings around the globe. NMRDC's research programs are organized into six areas: Combat Casualty Care, Infectious Disease, Diving and Submarine Medicine, Fleet Occupational Health, Aerospace Medicine and Human Performance, and Dental Research.

An NMRDC staff member is assigned as the Research Area Manager (RAM) for each research program area. The RAM provides an important link between the laboratories, where the research takes place, and NMRDC where budget allocation decisions are made and research and development planning efforts are designed to meet sponsor-directed operational requirements.

Also, each RAM monitors a research-area-related contract program from the initial award of the contract through completion.

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### Combat Casualty Care Program

**Research Area Manager**  
P. D. Kent, CDR, MC, USN  
301-295-0880/DSN 295-0880

Timely and effective treatment for disease, non-battle injury, and combat trauma remain essential for optimal return to duty of personnel, overall mission effectiveness, and elimination or reduction of injury complications and sequelae. Currently, researchers are working on efforts to meet the unique medical needs of the Navy's operational environments by improving availability for a range of blood and resuscitation products, by improv-

ing diagnostic and treatment consumables, by extending shelf-life for essential drugs and biologicals, by exploring biosensor technology, and by developing rapid and effective field treatments to sustain casualties prior to evacuation and definitive care. Medical complications from severe hemorrhage, wound contamination, shock lung, septic shock, severe burns, radiation exposures, non-freezing cold injuries, immersion hypothermia, and injuries due to chemical and biological warfare agents continue to be the focus of innovative research and development efforts.

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### Infectious Disease Program

**Research Area Manager**  
C. J. Schlagel, CDR, MSC, USN  
301-295-0881/DSN 295-0081

Because the Navy and Marine Corps are deployed around the globe, NMRDC's laboratories in the United States and overseas are constantly assessing infectious diseases that could threaten military operations. This research area program includes basic and applied studies related to the prevention, diagnosis, and treatment of militarily relevant infectious diseases. Basic research in microbiology, immunology, pathogenesis, disease prevention, and vector transmission provides insight into developing prevention and treatment measures.

Applied research focuses on the development and testing of vaccines, prophylactic and therapeutic drugs, as well as rapid identification and diagnostic methods and equipment. Current studies address diarrheal diseases, arboviral diseases, malaria, HIV-AIDS, hepatitis and sexually transmitted diseases,

respiratory diseases, and other tropical diseases and disease threats. Current research also includes the collection and analysis of epidemiological data required for risk assessment and the selection of test sites for vaccines, drugs, and equipment.

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### Diving and Submarine Medicine Program

**Research Area Manager**  
B.A. Schibly, CDR, MC, USN  
301-295-0879/DSN 295-0879

NMRDC's Diving and Submarine Medicine Program focuses on the safety and readiness of Navy divers and submariners. The Navy's diving research program represents a unique center of expertise that investigates a wide range of medical and physiological problems related to diving. Major efforts include diving decompression procedures, biomedical criteria for diver equipment, improved treatments for decompression sickness and arterial gas embolism, divers' hearing conservation standards inclusive of all operational diving scenarios, and methods to monitor the long term health of Navy saturation divers.

The unique working environment of a submarine is the focus of researchers who evaluate the environmental controls and occupational medical aspects of submarine operations. The major efforts include sonarman performance, medical conditions effecting qualifications for submarine duty and methods to improve crew health and safety.

Continued on page 9



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## **Aerospace Medicine and Human Performance Program**

**Research Area Manager**  
**T. J. Singer, CDR, MSC, USN**  
**301-295-0878/DSN 295-0878**

NMRDC's Aerospace Medicine and Human Performance Program concentrates on the interaction between military personnel and their working environment. Current research efforts are planned to parallel the research being done by the Navy's warfare technology laboratories. Complex, high tech Navy defense systems are creating more physically and intellectually demanding work environments and NMRDC's scientists are assessing the medical requirements of these developing systems in order to provide support for the designers and users.

Current efforts include improved selection techniques for Navy and Marine Corps aviators, microclimate cooling systems for use by combat personnel, and laser eye protection. Researchers are working on ways to improve electro-optical devices and to enhance visual performance at night. Current studies also include evaluating various biomedical interventions to enhance performance during sustained and continuous combat operations.

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## **Fleet Occupational Health Program**

**Research Area Manager**  
**J.R. Beddard, CDR, MSC, USN**  
**301-295-0885/DSN 295-0885**

NMRDC assists Navy decision-makers by performing research aimed at identifying and quantifying health risks associated with Navy and Marine Corps operational environments. Current research involving the health hazards of military materiel will define the physiological and biological impact of new systems and technologies and leads to the development of injury prevention standards and health

protection criteria. Medical factors that limit performance are studied to assess and minimize the effects of operational and environmental stressors on health and safety. Examples of stressors studied include phased array radar, high frequency radio equipment, high intensity noise, solvents, OTTO Fuel II, lubricants, propellants, hydraulic fluids, and freon replacement compounds.

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## **Dental Research Program**

**Research Area Manager**  
**S. Ralls, CAPT, DC, USN**  
**202-653-0463/DSN 294-0463**

The Dental Research Program at NMRDC encompasses dental and allied sciences research projects which have direct application to the Navy and Marine Corps. Navy scientists are developing and evaluating methods to prevent or intercept acute dental conditions and

improve dental readiness. Current research efforts focus on the development of rapid diagnostic enzymatic indicators used to identify military patients at high risk for dental diseases.

Current research also focuses on reducing dental emergencies in military personnel through the epidemiologic assessment of dental treatment needs, evaluation of methods to assist in the diagnosis and documentation of orificial diseases, and evaluation of preventive and treatment methodologies to promote dental wellness. The program also supports studies as part of the dental residency program at the Naval Dental School, NNMC, Bethesda, MD. In conjunction with the National Institute of Standards and Technology and the Air Force Dental Investigative Service, scientists are also evaluating new techniques, materials, drugs, and equipment for use in the Navy.

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## **NMRDC's Research Facilities**

NMRDC's laboratory facilities equal those available at modern academic and industrial institutions. A number of the laboratories provide unique test equipment and specialized software for pursuing research on current and projected biomedical problems relevant to the Navy. The military and civilian personnel are highly trained in a variety of different disciplines and offer a blend of research experience and technology development to reach short- and long-term solutions which enhance the Navy's operational capabilities.

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### **NMRDC Research Facilities**

Naval Medical Research Institute, Bethesda, MD  
Naval Medical Research Institute, Toxicology Det., Dayton, OH  
Naval Health Research Center, San Diego, CA  
Naval Aerospace Medical Research Laboratory, Pensacola, FL  
Naval Biodynamics Laboratory, New Orleans, LA  
Naval Submarine Medical Research Laboratory, Groton, CT  
Naval Dental Research Institute, Great Lakes, IL  
Naval Dental Research Institute Det., Bethesda, MD  
Naval Dental Research Institute Det., San Antonio, TX  
U.S. Naval Medical Research Institute Det., Lima, Peru  
U.S. Naval Medical Research Unit No. 2, Jakarta, Indonesia  
U.S. Naval Medical Research Unit No. 2 Det., Manila, Republic of the Philippines  
U.S. Naval Medical Research Institute Det., Nairobi, Kenya  
U.S. Naval Medical Research Unit No. 3, Cairo, Egypt

# NMRDC INSTRUCTIONS IN THE MAKING- Let Your Ideas Be Heard

by R.C. Carter, CAPT, MSC, USN, NMRDC Director of Research and Development

NMRDC is planning three new Instructions for completion early in FY93. These instructions will deal with DD1498 and Addendum, Human Use, and the Approval Process for Work Units. Instructions in these areas should help by providing uniform policies, interpreting higher-level policies for implementation in Navy Medical R&D, and recording routine procedures in a way that is widely and easily accessible.

## DD1498 and Addendum

An instruction on DD1498 and Addendum will replace the enclosure on this subject that is distributed with each year's planning guidance. The instruction will help the laboratories by making policy available well in advance of the guidance, and it will help NMRDC by eliminating the need for the development of that enclosure for each issue of the guidance.

A concept to be included in the DD1498 and Addendum instruction is the increased use of electronic media to facilitate incremental changes to DD 1498s and Addenda. Electronic updates will reduce the volume of paper-processing involved in present procedures.

The point of contact is Ms. Christine Eisemann, NMRDC Associate Director for Research Management, 301-295-0882, DSN 295-0882, E-Mail rdc04a @nmrdc1.nmrdc.nmnc.navy.mil.

## Human Use

An instruction on Human Use is needed to ensure that everyone understands what is required in this sensitive area. The instruction is intended to provide examples of forms and procedures to be used, to familiarize investigators with recent national policies for human use, and to provide answers to frequently encountered questions that are more specific than the answers found in DOD and SECNAV instruc-

tions on human use. The new instruction will be based on a lapsed BUMED instruction and on previous draft OPNAV instructions.

The point of contact is CAPT (sel) Fred Paleologo, NMRDC Special Assistant to the Commanding Officer, 301-295-1771, DSN 295-1771.

## Approval Process for Work Units

The process of work unit approval is a mystery to many outside of NMRDC. NMRDC's commitment to Total Quality Leadership requires this instruction. How can you have continuous process improvement when the process is poorly understood by those it effects?

Features of this instruction will include a flow diagram for work unit approval at NMRDC, a check list for review of documents prior to input into the approval process, a format for output of the process, clear delineation of responsibilities, and analytic methods (graphs, charts, tables) for tracking the annual cycle of the approval process. One intention is to make the approval process visible with weekly reports to the laboratories and RAMs, so all stakeholders can detect and help resolve any problems.

The point of contact is Ms. Beth Harris, NMRDC Research Administrator, 301-295-0355, DSN 205-0355.

## STANDARD OF CONDUCT AND ETHICS

The Office of Government Ethics (OGE) has published standards of conduct and ethics regulations in the Federal Register dated August 7, 1992. During January or February 1993 the DOD is expected to issue the implementing regulations of the new OGE regulations.

In the interim, the current standards of conduct and ethics instruc-

tion SECAVINST 5370.2J of 16 March 1980 will continue to apply to all Navy employees. The new OGE regulations and their impact will be further addressed during annual ethics training.

For more information contact A. David Spevack, NMRDC Office of Patent Attorney, 301-295-6760 or DSN 295-6760.

### DATES TO REMEMBER

#### DECEMBER 1992

**December 15** - FY94 IR/IED proposals due NMRDC

**December 15** - Full ARI proposals IR/IED due NMRDC

**December 31** - Information Systems Management Plan (ISMP) due NMRDC

#### JANUARY 1993

**January 4** - Mid-year reviews (PARS/PMRS; sign/date)

**January 18** - Interim Report - 1 due NMRDC

#### FEBRUARY 1993

**February 10** - Preliminary FY94 Guidance due laboratories

#### MARCH 1993

**March 4** - ARI FY95 Competition (tentative)

#### APRIL 1993

**April 13 - 15** - Navy R&D Conference, San Diego

**April 26 - 30** - Cold Physiology Review

## FIRE SAFETY IN SUBJECT SLEEP QUARTERS

by Kip Johnson, NMRDC Staff Assistant for Occupational Safety

Research protocols at many NMRDC research facilities include the testing of human subjects over long periods of time. In many cases, this means that human volunteers are being studied overnight and on weekends.

Modifying work spaces to accommodate overnight occupancies does not simply mean bringing in a bed, a night stand and possibly a small TV or refrigerator. We must also ensure that the fire safety code is adhered to.

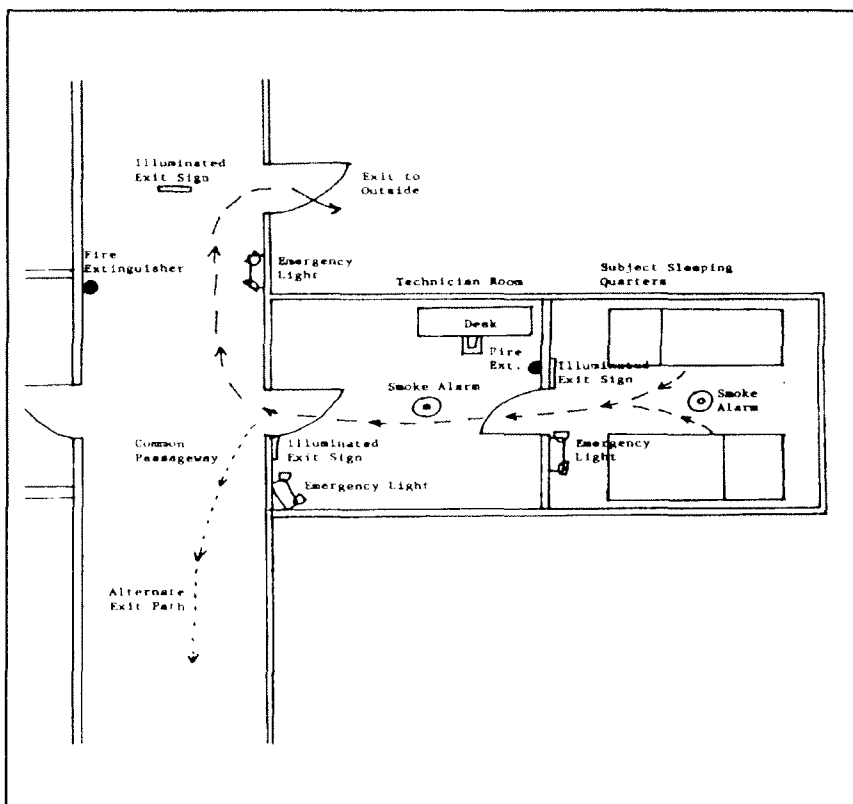
Laboratory spaces modified for overnight occupancy of human volunteer and technicians must include fire safety additions.

The illustration on the right shows a former laboratory work space that has been modified for overnight occupancy. Note how additional emergency lights, lighted exit lights, fire extinguishers and a clear and illuminated exit path are available as required by the fire safety code.

Contact your host Fire Department to inspect the modified spaces

before human volunteers and technicians begin staying overnight for experiments.

**We must continue to provide the safest environment.**



## RADIO FREQUENCY REWARMING TECHNIQUES FOR HYPOTHERMIA RESUSCITATION: Status of Clinical Trials and Potential Payoffs

A prototype Radio Frequency (RF) rewarming apparatus was produced at the Naval Aerospace Medical Research Laboratory (NAMRL), Pensacola, FL in the late 1980s after many successful animal experiments showed the comparative advantages over conventional rewarming techniques. After NAMRL obtained a Navy patent and an FDA Investigation Device Exemption, researchers at the Naval Medical Research Institute (NMRI), Bethesda, MD conducted the first human trials in 1988 and published their findings in the *Journal of Applied Physiology*. The NMRI study used a fiber-optic esophageal temperature probe to show that RF energy warmed the body's core much faster than did

warm-water immersion. Since then, smaller-scale human experiments have been conducted at the Naval Air Warfare Center (Warminster, PA) and the Naval Surface Warfare Center (Coronado, CA), but no esophageal probes were used. Currently, Dr. Duncan Harveil is conducting a clinically oriented (emergency room) study of RF rewarming at the Washington Hospital Center, Washington, DC but few subjects have been studied to date.

Several commercial interests in this technology have surfaced during the past years. They envisioned that it might be possible to place an RF rewarming system in every emergency room. Unfortunately,

the hardware remains in a prototype stage and an insufficient number of "safety and effectiveness" experiments have been conducted to satisfy the FDA. Commercial interest, therefore, has languished, but the solid potential of the technique remains viable.

The pattern of internal body warmth produced by RF energy, as applied with the Navy's resonant coil system, is unique and potentially very beneficial. As stated by Maj. Gen. Knud Jessen (Danish Armed Forces Health Service), an international expert, this system has the potential to become the "treatment of choice" in hypothermia resuscitation.

# THIRTEEN PROPOSALS SELECTED FOR FY93 IR/IED Cont. from page one

## **NEW IRs first year**

### **Evoked Otoacoustic Emissions (EOAEs) and Inner Ear Damage from Previous Noise Exposure**

**Dr. Lynne Marshall, NSMRL**

This study will determine whether changes in evoked otoacoustic emissions ("noise" produced by the ear in response to a stimulus) can be used as a non-invasive, objective measure of inner ear damage resulting from noise exposure. The long-term goal is to minimize the incidence of job-related hearing loss, ensure that Navy personnel can perform their jobs, and save large sums of compensation money. (This study was chosen last Spring as NMRDC's winning FY94 Accelerated Research Initiative (ARI)).

### **Identification of Human Receptors for Dengue Virus and Analysis of Virus-Receptor Interactions**

**CDR Mitchell Carl, NMRI**

This study's goal is to identify the interactions between host cell receptors and dengue virus proteins which allow the virus to enter the cell. The information gained will aid in the design of antivirals to block the entry of the virus into the host cell and decrease the incidence of this debilitating disease.

### **The Role of Cytokines in Recovery from Enteric Compromise Following Hemorrhagic Shock**

**Dr. Florence Rollwagen, NMRI**

This study will determine the role of selected cytokines in healing the intestinal mucosa and the responses of the local and systemic immune systems following hemorrhagic shock. This information will lead to new ways to speed repair after intestinal injury and to prevent overwhelming infection by controlling the translocation of bacteria from the gut into the peritoneal cavity.

### **Evaluation of the Influence of Superantigens and Polyclonal B-Cell Activators in Periodontal Diseases**

**Dr. Glenn Miller, NDRI Det Bethesda**

This study will determine whether superantigens (bacterial products that stimulate T-cells) and polyclonal B-cell activators can function as virulence factors which modulate the host immune response and establish the conditions necessary for the development of periodontitis, apical periodontitis, and other localized inflammatory diseases.

### **The Development of Flow Injection Analysis Methodologies in Toxicology**

**CDR Nathan Lacy, NMRI TOXDET**

This project intends to establish a

new technique for studies in Navy toxicology by determining if pertinent analytes can be evaluated accurately through the use of Flow Injection Analysis. If successful, this approach will allow comprehensive, realtime, kinetic evaluations of toxicological action.

### **Immunity to Malaria Infection and T Cell Reactivity to the Circumsporozoite Protein**

**CDR Walter Weiss, NMRI Det Kenya**

This study will determine whether T cell reactivity to the circumsporozoite (CS) protein of *Plasmodium falciparum* correlates with natural protection in Kenyan subjects. CS proteins from infected individuals will be amino acid-sequenced to determine the T cell reactivity of CS protein variants. This information will provide new insight on the importance of the cellular immune response in protecting against malaria.

## **CONTINUING IRs second year**

### **Plasma Volume, Vasopressin, and the Genetics of Motion Sickness**

**Dr. Warren Lockette, NHRC**

This study will determine whether plasma volume influences an individual's susceptibility to motion sickness, whether the synthetic hormone, 1-desamino-8-D-arginine vasopressin, modulates motion sickness, and whether motion sickness susceptibility is genetically controlled. (Note: First year work in this IR led to its successful submission as an FY95 ARI candidate).

### **The Performance of Neuropeptide Y on the Acquisition and Performance of Response Sequences During Heat Stress**

**Dr. John Schrot, NMRI**

This study will define the basic mechanisms by which neuropeptides, released in response to heat stress, exert profound effects on learning and memory. The information from this study will contribute to the development of pharmacological strategies to protect personnel from the deleterious effects of heat. (Progress in the first year of this IR supported its successful evolution into an FY95 ARI candidate).

### **Role of the Rec A Gene in the Antigenic Variation of Campylobacter**

**Dr. Patricia Guerry, NMRI**

This study will determine whether a generalized recombination system (Rec A) controls campylobacter's (a bacterium) ability to vary its surface antigens and virulence determinants, and to be naturally transformed. Success in this project will provide the

basis for unique experimental genetic manipulation systems for campylobacter.

### **Idiotypic Mimicry of Endotoxin and Endotoxin Receptors**

**Dr. C-H Lee, NMRI**

This study will clarify the mechanisms of lipopolysaccharide (LPS) binding to endothelial cells and will identify anti-idiotypic and monoclonal antibodies that mimic or neutralize LPS. This information will help clarify the LPS-host interactions that result in septic shock and will lead to new approaches for septic shock prevention.

### **The Use of LEET and Bright Light Separately and Together for Shifting the Work/Rest Cycle**

**Dr. Tamsin Kelly, NHRC**

This study will determine the effects of electromagnetic fields and timed bright light exposure on the adaptation of subjects to a ten hour shift in the wake/sleep cycle. Such studies on the adaptation of personnel to circadian rhythm/time zone changes have been specifically requested by the Marine Corps.

### **Modulation of Cell Surface Adhesion Molecules and Cytoskeletal Reorganization by Cytokines in Monocyte-Endothelial Cell Interactions**

**Dr. Y-H Kang, NMRI**

This study will clarify the cellular mechanisms regulating inflammation. Specific goals include determining the effects of cytokines, LPS, and thrombin on the expression of monocyte and endothelial cell surface adhesion molecules and receptors; the interaction between monocytes and endothelial cells; and, the reorganization of the cytoskeleton.

## **NEW IED first year**

### **The Effect of Stress on Performance and Decision Making Within the Realm of Complex Human-Machine Interfaces**

**LT Karl Van Orden, NSMRL**

This project will examine the effects of exogenous stress (such as fear or command pressure) on cognitive processes, including information assimilation and decision-making. Operator performance on the Navy Advanced Information Management Evaluation System (NAIMES) will be monitored under stressful and control conditions (NAIMES is a computer-based, scripted, unfolding AEGIS-like tactical scenario that requires the user to answer questions by seeking out information within the display and to make decisions regarding tactical action).

# FIVE PROPOSALS VIE FOR FY95 ACCELERATED RESEARCH INITIATIVE FUNDING

by Christine Eisemann, NMRDC Associate Director for Research Management

In the 6.1 arena, the second round of the FY95 Accelerated Research Initiative (ARI) competition is in full swing. Investigators are preparing their full research proposals for submission (15 December 1992) and review prior to their oral presentations to the NMRDC Basic Research Selection Committee in March, 1993.

The ARI competition began last July. Sixteen preproposals from NHRC, NMRI, NAMRL, NSMRL, and NBDL were evaluated for Navy need, research merit, basic (vice applied) character, and compliance with the Office of Naval Research's (ONR) definition of an ARI. The July review, which included both in-house Navy managers and outside technical experts, aimed to identify the top 3-5 ARI concepts, any of which NMRDC could solidly stand up for approval by ONR.

This initial down-selection allowed for a manageable group of detailed proposals for the Selection Panel to review and a better chance of payoff for the investigators who put time and energy into writing full research proposals. The reward for a winning ARI proposal isn't trivial: ballpark funding for an ARI is \$450K for 4-5 years (\$ 1.8M - \$ 2.3M total).

## **NMRDC's ARI Selection Process Is TQL in Action**

Just a few years ago, the ARI selection process was very different than it is today. In the past, NMRDC could enter one ARI candidate into the Office of Naval Research's (ONR) competition to compete against other research proposals ranging from oceanography to space physics. We had a possibility of winning up to \$500K each year for five years. Non-selection meant a substantial cut in our basic research program.

For the POM-91 cycle, ONR revised the ARI management process, citing a number of good reasons, i.e. greater claimant participation and team management in ONR's investment process, claimants' tailoring of procedures to their unique scientific and organizational environments, and

reducing fiscal uncertainty to allow for better claimant planning, reasons that reflect true commitment to the principles of Total Quality Leadership (TQL). The new process has worked exceptionally well for NMRDC.

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**Bravo Zulu to ONR for unparalleled and very appreciated TQL practices!**

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## **The five ARI candidates**

### **The Genetics of Motion Sickness**

**Dr. Warren Lockette, NHRC**

This hypothesis of this proposal is that susceptibility to motion sickness and vestibular disorientation is under genetic control. The discrete genes which modulate susceptibility to motion sickness, the inheritance patterns, and the cellular mechanisms by which motion sickness develops will be identified. Understanding the etiology of motion sickness at the molecular level will result in improved countermeasures for troops subjected to untoward motion in various operational environments.

### **Production of Dengue Vaccine Candidates by Genetic Engineering**

**LCDR Kevin Porter, NMRI**

This proposal suggests that by comparing differences in the nucleotide sequences of virulent/immunogenic parent dengue virus strains and avirulent/non-immunogenic strains, the genetic mutations associated with avirulence and immunogenicity can be determined. Once the specific mutations responsible for avirulence and optimum immunogenicity are known, a safe and effective live virus vaccine can be engineered for Dengue Fever, a major health problem for the military during both wartime and peace.

### **In Vitro Tissue Constructs for Wound Repair**

**Dr. Thor Nielsen, Dr. Henry Chang, and Dr. Florence Rollwagen, NMRI; Dr. Barry Spargo, and Dr. Alan Rudolph, NRL**

Investigators will combine advanced polymer and small molecule organic chemistry; techniques for cell isolation, adhesion, and growth; fibroblast and muscle cell molecular biology; and cell transplantation im-

munology to create a novel model for improved wound therapy. Basic efforts to identify and optimize individual components and combinations in this new tissue construct will lead to the ultimate envisioned product, a field-deployable, implantable, revascularized living skin substitute.

### **Virtual Reality Displays in Acceleration Environments**

**CDR Angus Rupert, NAMRL**

With virtual reality displays planned for use in future Navy aircraft, there is concern (based on preliminary data) that using these displays while under multiple acceleration forces will distort the pilot's perceptions of orientation or velocity and lead to aviation mishaps costing aircrew lives and lost aircraft. This effort proposes to determine the magnitude of position and velocity misperceptions experienced by pilots using virtual reality displays in high acceleration environments, identify the parameters that facilitate these illusions, and develop techniques to minimize them.

### **Modulation of Heat Stress Effects on Learning and Memory by Endogenous CNS Neurotransmitters and Neuromodulators**

**Dr. John Schrot, NMRI**

Ambient air temperatures as low as 100° F can cause a progressive decline in learning and memory in a relatively short period of time (hours). Reaction time, tracking ability, time estimation and other military-critical skills all reliably worsen during heat exposure. This proposal will investigate the basic neurochemical mechanisms by which heat stress impacts cognitive processes and will then suggest prophylactic or treatment regimens to counteract these decrements.

## THE THOMAS DOMES

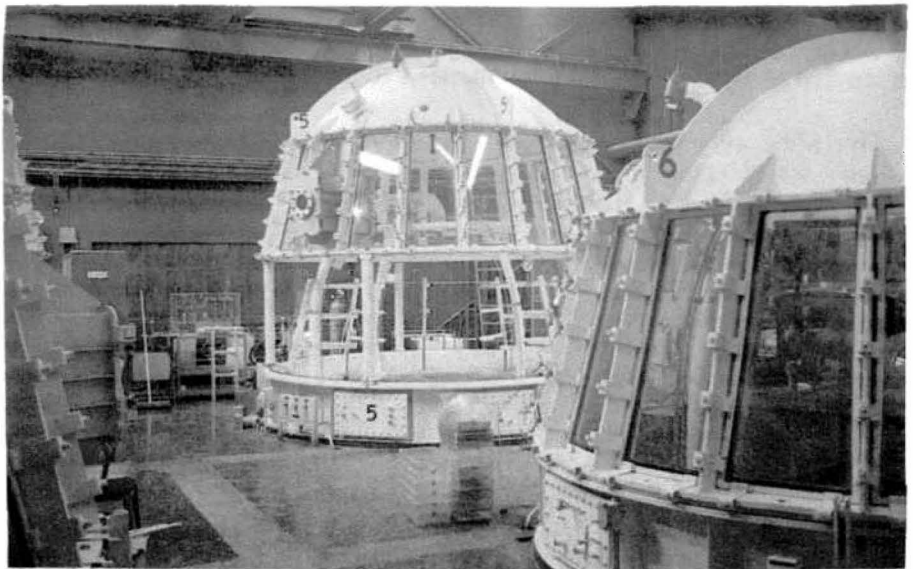
### A Successful History of Supporting Operational Requirements for 28 Years

CAPT David A. Macys MSC, USN, OIC, Naval Medical Research Institute Detachment (Toxicology), WPAFB OH

The Thomas Domes, built in 1964, are individually airlocked domes, built as a set of four (for three exposure levels and one control level). The Domes were funded to support the man-in-space program and were designed to operate at hypobaric pressures between 0.33 and 0.95 ATM. Each dome is nine feet tall and twelve feet in diameter. Access is either from the floor below through the dome's own airlock, or by having the overhead crane in the two-story dome room lift the top two-thirds of the dome off the dome ring wall. Air-tightness is assured by an o-ring between the ring wall and the dome, which is held in place by atmospheric pressure. The removable portion of the dome consists of a steel top plate and shatterproof, one inch thick glass panels to facilitate observation. All experimental manipulations, normal husbandry and cleaning operations can be carried out while maintaining the integrity and continuity of the exposure environment.

A second set of four domes was later constructed with improvements based on experience with the originals. The most significant improvement was the joining of the airlocks by a single large airlocked suite. This allows the staff to lock into the domes at their operating pressure and stay until all work is finished, rather than locking in and out of each dome. The large lower level suite also provides significant work space for procedures to be performed on animals at the operating pressure, rather than removing and returning them.

The original set of domes is still in use but only as a secondary containment for experiments involving highly hazardous materials on a short-term exposure basis. A proposal to remove the original set of domes has been included as part of the project to accommodate the relocation of elements of the



Army's toxicology program at Wright Patterson Air Force Base (WPAFB), Dayton, OH as part of the Base Realignment and Closure Act of 1991. The original domes will be replaced with three stories of office and laboratory space totalling about 4300 square feet.

The newer set of domes remains in active use as a primary exposure facility. Estimates to build an equivalent replacement facility have ranged up to \$20M, although no such replacement is envisioned. The major application remains the same: to generate extended continuous inhalation exposures of contaminants whose toxicity is not sufficiently characterized to permit accurate assessment of the hazard they represent under those exposure conditions. The Navy continues to perform such experiments in support of the nuclear submarine fleet since new materials are periodically introduced (a recent example: a new non-flammable hydraulic fluid) and unanticipated reaction products continue to be found (a recent example: a new anti-oxidant for hydraulic fluids reacting with oxides of nitrogen from electrical equipment and electrostatic precipitators).

#### Future Uses for the Domes

A new class of submarine is in design. Issues of toxicity from contaminant exposure during the course of the typical patrol cycle, as well as the extreme cycle profile, are likely to surface during this process as they did almost forty years ago with the launching of the USS Nautilus in 1954. The new design effort relies on the professional expertise of the National Academy of Sciences/National Research Council (NAS/NRC) through its Committee on Toxicology (CoT) for interim guidance and recommendations. Their expert judgment is based on a great deal of knowledge about the metabolic fate of and effects from many of the known chemicals of concern. For many other chemicals, however, little is known and the process of finding out the needed information remains laborious. For now, the gold standard for ensuring that a chemical can be introduced into the submarine environment without posing an unacceptable risk to the health and performance of the crew remains the 90 day continuous exposure as performed in the Thomas Domes.

It should be noted that the Air Force has no plans for further use of the Thomas Domes and, in fact, has not used them in several years. NASA is currently pursuing the assessment of airborne chemical hazards for the six month space station missions and for the two year Mars mission profiles. Guidance from the CoT is relied on to set exposure control levels. No decisions regarding experimental validation of the numbers set through the "Spacecraft Maximum Allowable Concentration" process have been announced. NASA has also let a contract to a consortium of universities and private corporations to evaluate toxicological issues related to these two mission profiles, focusing specifically on very long term, low level exposures and their impact on crew performance, with a secondary focus on the impact of occasional peak exposures due to accidents of various sorts, including any lingering, long term effects. The NMRI TOXDET at WPAFB is a consulting member of the consortium.

Environmental concerns have even been identified as one of the major new threats facing the United States. Most of the exposures of concern are long term ones, lasting substantial portions of a lifetime; some of them are inhalation exposures. Some of these exposures may have to be experimentally evaluated to determine more precisely the hazard they present.

### **Technology to Replace the Domes**

For decades, the mathematical tools of pharmacokinetics have been used to describe the absorption, distribution, metabolism and excretion of xenobiotics. Ten to fifteen years ago, a revolution in this descriptive process was initiated with the application of partial differential mass balance equations to model what was actually happening in the body.

These physiologically-based pharmacokinetics (PBPK) led to mathematical models which were not only much more descriptive, they were also predictive that existing models. In the last five years, PBPK models have left the laboratory and have influenced the national regulatory process for both environmental and occupational exposure standards setting.

As knowledge of the fundamental biochemistry and physiology underlying toxic effects has advanced, the precision of predictive PBPK models based on them has improved. As confidence in this new tool builds, and as understanding of the fundamental processes advances, the frequency with which purely descriptive toxicity studies, such as the 90 day continuous exposure, need to be performed will decline drastically.

The process by which chemicals are evaluated for degree and type of hazard presented in submarine environments has already begun to change to incorporate these advances, and studies which were considered 6.1/6.2 research ten years ago are now the starting point for assessing the toxicity of materials.

### **Will We Give Up the Domes?**

Almost certainly. When? Five years? Ten years? The answer is likely to be closer to ten years, with decreasing frequency of use throughout that period. Already usage averages less than one study per year. If for no other reason than economics (a dome study costs at least \$500K), new approaches are required.

**Better science means better, more precise evaluation of a hazard and therefore better decisions regarding how and how much to control the hazard. This has been the goal of the Navy's Toxicology Research Program for over thirty five years, and remains the goal for the future.**

## **THOMAS DOMES — BACKGROUND**

In 1954, the launching of the USS Nautilus led to immediate concerns about the effects on the crew of continuous, long-duration exposures to contaminants in the submarine's atmosphere.

In 1957, the Navy established a dedicated research command, the Navy Toxicology Unit (NTU), and the National Academy of Sciences /National Research Council (NAS/NRC) established the Toxicology Information Center. This was the first long-term association to bring to bear expert scientific judgement on toxicological unknowns investigated in the laboratory.

In 1958 the concerns about the contamination of existing closed environments aboard nuclear submarines was joined by concern about the contamination of a proposed closed environment, that of spacecraft.

In 1963, interest in this subject matter burgeoned, resulting in a complete symposium being devoted to "Toxicity in the Closed Ecological System". Reports from the NTU and the Air Force's Aerospace Medical Research Laboratory (AFAMRL) confirmed that exposure control levels developed for standard industrial-type exposures could not be applied to extended continuous exposure conditions. It was at this symposium that Anthony A. Thomas, M.D. of AFAMRL announced the construction of a unique new inhalation exposure facility at Wright-Patterson AFB (WPAFB).

In 1964, construction of the Domes was completed and the first comprehensive description of their functioning was presented at what was to be the first of the annual toxicology conferences to be held at WPAFB, the "Conference on Atmospheric Contamination in Confined Spaces", 30 Mar - 1 Apr 1965 (AMRL-TR-65-230). A description was also published in a paper in the September 1965 issue of the Archives of Environmental Health (11:316-322 - "Low Ambient Pressure Environments and Toxicity: A New Approach to Space Cabin Toxicology").

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## HIGHLIGHTS OF NMRDC RESEARCH

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### **MEASURING BLOOD ANALYTES USING A NON-INVASIVE TECHNIQUE**

Current methods of performing laboratory tests for the rapid evaluation of a critical care patient require analyzers, reagents, and the procurement of a blood specimen from the patient. Performing these tests in the field or operational environments is logistically very difficult. A NMRDC-sponsored Small Business Innovation Research Project is developing a promising solution to this problem. Investigators of Biotronics Technologies, Inc., Waukesha, WI are working with researchers at the National Naval Medical Center (NNMC), Bethesda, MD in the development phase of an analyzer that will use infrared light reflectance from the skin to provide results for blood analytes. A study, conducted at NNMC on 250 subjects from whom infrared light spectra and correlating chemistry profiles were collected and compared, has provided data for the computer algorithms that will be used in the development of the final prototype analyzer. The analyzer, which will be of a portable size, will analyze infrared light spectra that is reflected from the patients' skin to give results for sodium, potassium, chloride, carbon dioxide, glucose, hematocrit, and blood urea nitrogen. Upon completion, this project will provide the solution to overcome the difficulties of measuring blood analyte levels in the field or in operational environments, and will allow rapid, noninvasive evaluation of patient status.

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### **NDRI EXPLORES NON-INVASIVE PHYSIOLOGIC MONITORS**

The early detection of infection is essential to the safety of military personnel when faced with delayed medical evacuation. For personnel stationed in conditions of constant environmental stress (e.g. climatic extremes, undersea habitats, space evolutions, endemic disease), frequent monitoring of salivary chemistry may be a useful alternative to venipuncture. Salivary components which may provide early warning signals of physiologic compromise were evaluated by researchers in the Clinical Investigation Department at the Naval Dental Research Institute (NDRI), Great Lakes, IL in a collaborative study of acoustic stress effects in humans, at the Naval Submarine Medical Research Laboratory, Groton, CT. Salivary C-reactive protein (CRP) and cyclic AMP-dependent protein kinase regulatory subunits (cARP) showed changes associated with catecholamine release. CRP and cARP are indicators of inflammation and metabolic dysfunction, respectively. While it may be of forensic interest that the cARP protein banding patterns were unique to each subject (N = 21), this evidence of pleomorphism suggests that cARP may also have protein isoforms specific to diseases which trigger immune response. CRP, as an "acute phase" protein, may also show disease-specific pleomorphism. Both cARP and CRP may respond to the immunologic stimuli of infection by showing genetically reprogrammed disease-specific protein isoforms.

Such isoforms could provide monoclonal antibodies for early disease detection by salivary ELISA or Western Blot tests. NDRI has proposed expanded studies to explore these hypotheses.

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### **RESEARCHERS INVESTIGATE REPLACEMENT TISSUE FOR SKIN GRAFTING**

Open wounds and burns are a major problem in combat situations, frequently leading to infection and further complications, especially when large areas of the epidermal surface are burned or scarred. Future combat casualty care scenarios will have a field surgeon quickly and safely cover the wound with cryogenically stored ready-to-use sterile sheets of epidermal cells attached to an underlying dermal equivalent. Navy sponsored researchers at Case Western Reserve University School of Medicine, Cleveland, OH are developing a skin-like tissue using keratinocytes, a basal lamina, and dermal fibroblasts as a replacement tissue for skin wounds. They are also investigating the technology for transferring genetic information into skin cells to enhance the therapeutic value for grafting and reduce rejection by the host immune system. In addition, researchers are planning to design DNA vectors that can carry biologically important genes into keratinocytes. The availability of such a set of vectors would potentially make it possible to express genes encoding antibiotics in the cells. This would render the cells resistant to bacterial infection, a further advantage in combat situations. The number of potentially useful genes that could be inserted into the cells with such a vector system is unlimited.

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### **NHRC DEVELOPS AN AUTOMATED ALERTNESS MONITORING SYSTEM**

Sonar, radar, and air traffic control operators; pilots; and long-haul drivers, often need to remain alert during long periods when little or no new information is received. Many studies have shown that under these circumstances, operator vigilance tends to decline after only a few minutes on the job. Researchers in the Department of Cognitive Performance and Psychophysiology, Naval Health Research Center (NHRC), San Diego, CA, have demonstrated that this decline is actually made up of wide-ranging fluctuations in alertness over seconds and minutes, that could result in delayed or absent responses to important events. New studies have shown that fluctuations in alertness can be detected by computer analysis of brain electroencephalogram (EEG) patterns. NHRC scientists have developed an Alertness Monitoring System that uses individualized neural net software to deliver real time feedback to the operator when alertness levels drop. Once implemented, the system could improve both operator and total system performance and save operating costs by reducing the need for redundant staffing. Potential applications include sonar, radar and air traffic control; air and land vehicle operations, and plant engineering.