Resident Research Associateships, Postdoctoral and Senior Research Awards: 1997 Opportunities for Research Tenable at the United States Army Medical Research and Materiel Command (0)

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National Research Council

Resident Research Associateships

Postdoctoral and Senior Research Awards

1997

OPPORTUNITIES FOR RESEARCH

tenable at the

US ARMY MEDICAL RESEARCH
AND MATERIEL COMMAND

Walter Reed Army Institute of Research (WRAIR)
US Army Medical Research Institute of Infectious Diseases
US Army Medical Research Institute of Chemical Defense
US Army Research Institute of Environmental Medicine
US Army Institute of Surgical Research

administered by the
NATIONAL RESEARCH COUNCIL
Washington, DC 20418

The National Research Council serves as an independent advisor to the federal government on scientific and technical questions of national importance. Established under the congressional charter of the private, nonprofit National Academy of Sciences, the Research Council brings the resources of the entire scientific and technical community to bear on national problems through its volunteer advisory committees. Today the Research Council stands as the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering and is administered jointly by the two academies and the Institute of Medicine. The National Academy of Engineering and the Institute of Medicine were established in 1964 and 1970, respectively, under the charter of the National Academy of Sciences.

The National Research Council has nine major divisions. One of these, the Office of Scientific and Engineering Personnel, is charged with administering Research Associateships through its Associateship Programs office.

Foreword

The US Army Medical Research and Materiel Command (AMRMC) is a major subordinate command of the US Army Medical Command. AMRMC conducts medical research and development in five Army medical research laboratories and institutes and in nongovernmental laboratories through contracts and grants with universities and industry. All research directly addresses the preservation of the health and safety of soldiers.

The Commander, AMRMC, is also the Assistant Surgeon General for Research and Development and is responsible to the Army Surgeon General for planning, coordinating, executing, and reviewing the Army-wide medical research, development, test, and evaluation programs.

The Command's annual budget of approximately 250 million dollars is expended at a rate of 50% for contracted research and 50% for in-house research. Approximately 50% is spent on basic research and 46% on advanced development. Research programs of the AMRMC are as follows:

Military Disease Hazards Technology. This program includes basic research related to medical defense against naturally occurring infectious diseases worldwide.

Combat Casualty Management and Combat Dentistry. This program is designed to improve battlefield medical care.

Army Systems and Combat Operations Hazards. This program fosters and maintains operational readiness and combat effectiveness by preserving the physical and mental fitness of soldiers.

Medical Biologic and Chemical Defense. This program comprises research on medical defense against potential biological threats, and medical research and development required to minimize deaths, disabilities, performance decrements, and patient loads in the event of chemical threats.

Contents

Introduction

History and Objectives

The National Research Council conducts the Research Associateship Programs in cooperation with sponsoring federal laboratories and research organizations approved for participation.

The Research Council, through its Associateship Programs office, conducts a national competition to recommend and make awards to outstanding scientists and engineers at recent postdoctoral and experienced senior levels for tenure as guest researchers at participating laboratories. These Programs have been conducted on behalf of a number of federal agencies since 1954.

The objectives of the Programs are (1) to provide postdoctoral scientists and engineers of unusual promise and ability opportunities for research on problems, largely of their own choice, that are compatible with the interests of the sponsoring laboratories and (2) to contribute thereby to the overall efforts of the federal laboratories.

For recent doctoral graduates, the Programs provide an opportunity for concentrated research in association with selected members of the permanent professional laboratory staff, often as a climax to formal career preparation.

For established scientists and engineers, the Programs afford an opportunity for research without the interruptions and distracting assignments of permanent career positions.

Participating laboratories receive a stimulus to their programs by the presence of bright, highly motivated, recent doctoral graduates and by senior investigators with established records of research productivity. New ideas, techniques, and approaches to problems contribute to the overall research climate of the laboratories. Indirectly, Associateships also make available to the broader scientific and engineering communities the excellent and often unique research facilities that exist in federal laboratories.

For the 1997 program year, an anticipated 1,300 applications will be received for the nearly 350 new awards to be made in the Associateship Programs.

Associates on Tenure

A Research Associate is a guest researcher, not an employee of the Research Council or of the laboratory. Associateships are analogous to fellowships or similar temporary programs at the postdoctoral level in universities and other organizations. They are not intended to be, or to compete with, permanent professional career positions.

No commitment on the part of an Associate, the sponsoring laboratory, or the Research Council with regard to later employment is implied or should be inferred by the offer or acceptance of an award.

Associates must devote their full-time effort to the research program proposed in their applications and must be in residence at the sponsoring laboratory during the entire period of the Associateship. No period of tenure may be spent in residence at another laboratory or institution. Associates have the status of visiting scientists or engineers but are subject to the general regulations of the laboratory.

No additional monetary aid or other remuneration may be accepted from another appointment, fellowship, or similar grant, except for sabbatical leave, during the period of the Associateship.

Postdoctoral or Senior Research Associate Status and Length of Tenure

Postdoctoral Research Associateships are awarded to persons who have held the doctorate less than five years at the time of application and are made initially for one year.

Senior Research Associateships are awarded only to applicants who have held the doctorate five years or more at the time of application. Senior Research Associateship applicants should have research experience that has resulted in significant contributions and recognition as established investigators in their specialized fields. Although awards to Senior Research Associates are usually for one year, awards for periods of six months or longer may be considered.

Under certain conditions, extensions may be granted to allow Associates to bring their research to a reasonable stage of completion. However,

extensions are not automatically granted, and applicants are advised to plan their research programs to conform to the length of tenure stated above.

Consideration

Qualified applicants will receive consideration without regard to race, creed, color, age, sex, or national origin.

Citizenship

Programs at the following laboratories are open to citizens of the United States and to citizens of other countries who have full command of the English language:

Walter Reed Army Institute of Research (WRAIR)
- US Army Dental Research Detachment-WRAIR
- US Army Medical Research Detachment-WRAIR
- US Army Medical Research Unit-Brazil
- US Army Medical Research Unit-Kenya
- Armed Forces Research Institute for Medical Sciences
  Bangkok, Thailand

US Army Medical Research Institute of Infectious Diseases
US Army Research Institute of Environmental Medicine
US Army Institute of Surgical Research

NOTE: The Research Institute of Environmental Medicine also requires an applicant who is a non-US national to secure a clearance through his or her embassy to the US Army Assistant Chief of Staff for Intelligence. Further details are available through the office of the Laboratory Program Representative.

Programs at the US Army Medical Research Institute of Chemical Defense are open only to citizens of the United States.

Visa Requirements

Non-US nationals who are offered awards must have valid visas throughout tenure. Only Exchange Visitor and Immigrant Visas are acceptable to the Research Council. If an awardee chooses to apply for an Exchange Visitor Visa, sponsorship must be by the National Research Council. If he or she chooses to apply for an Immigrant Visa, the Research Council will not be involved in the procedure.

Education and Experience

Awardees must hold the PhD, ScD, or other earned research doctoral degree recognized in US academic circles as equivalent to the PhD or must present acceptable evidence of having completed all the formal academic requirements for one of these degrees before tenure may begin. Applicants must have demonstrated superior ability for creative research.

An applicant's training and research experience may be in any appropriate discipline or combination of disciplines required for the proposed research.

Opportunities for Research at the US Army Medical Research and Materiel Command (AMRMC)

This booklet contains abstracts, or opportunities for research, that describe areas of research in which Associateships may be awarded at the US Army Medical Research and Materiel Command (AMRMC), which includes the following laboratories:

Walter Reed Army Institute of Research (WRAIR)
- US Army Dental Research Detachment-WRAIR
- US Army Medical Research Detachment-WRAIR
- US Army Medical Research Unit-Brazil
- US Army Medical Research Unit-Kenya
- Armed Forces Research Institute for Medical Sciences
  Bangkok, Thailand

US Army Medical Research Institute of Infectious Diseases

US Army Medical Research Institute of Chemical Defense

US Army Research Institute of Environmental Medicine
US Army Institute of Surgical Research

AMRMC provides the funds for this program and furnishes all necessary support services, facilities, and equipment for the approved research program of each Associate.

While every effort has been made by AMRMC to provide opportunities of ample scope and relevance, the publication of any opportunity in this booklet does not guarantee that it will be available at the time awards are offered. Changes and/or deletions may occur following publication because of temporary lack of equipment, laboratory renovation, staffing already sufficient to meet research goals, or a lack of funding.

Research Adviser and Laboratory Program Representative

Shown with each opportunity for research are the names of one or more Research Advisers who conduct or direct the work described in the opportunity.

An Adviser is a scientist or engineer at an AMRMC laboratory with whom a Postdoctoral Research Associate works most closely. An Adviser acts as a surrogate of the Research Council in monitoring an Associate, and all matters relating to an Associate's research program fall under his or her purview.

For a Senior Research Associate, an Adviser functions in a more collegial relationship and assists as needed in securing technical support and resources.

The Laboratory Program Representative is a professional staff member at an AMRMC laboratory who is responsible for managing its Research Associateship program and for assisting an Associate with all administrative aspects of tenure:

Dr Sara Rothman*
Director, Office of Research Management
Building 40, Room 1074
WALTER REED ARMY INSTITUTE OF RESEARCH
Washington, DC 20307-5100
Telephone: (202) 782-3061 FAX: (202) 782-0602
E-Mail: Rothman@wrair-emhl.army.mil

*Sara Rothman is also the Laboratory Program Representative for the Bangkok, Kenya, and Brazil labs listed below. Applicants may also contact the labs directly:

Bangkok:

Thomas K. Brewer, Col, MC
USA Med Comp
ARMED FORCES RESEARCH INSTITUTE OF
MEDICAL SCIENCES
Bangkok, APO AP 96546-5000
Telephone: 0-11-66-2-245-7284 FAX: 0-11-66-2-247-6030
E-Mail: brewert@wrair-emh1.army.mil

Kenya:

LTC Lawrence K Lightner
Commander
US ARMY MEDICAL RESEARCH UNIT KENYA
Unit 64109, Box 401
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APO AE 09831-4109
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FAX: 0-11-254-2-340838 or 0-11-254-2-714592
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Dr Cleon W Goodwin
Colonel, MC
Chief,Laboratory Division
US ARMY INSTITUTE OF SURGICAL RESEARCH
3400 Rawley E. Chambers Avenue
Fort Sam Houston, Texas 78234-6315
Telephone: (210) 916-4832 FAX: (210) 916-1851

Research Proposal

Each applicant must submit a research proposal that relates to a specific opportunity for research at AMRMC. A proposal must be the original work of an applicant and be approved by an Adviser listed with the opportunity.

Before writing a proposal, however, an applicant is advised to communicate directly with the Adviser, who can provide more specific information on current research and available technical facilities and offer scientific support of proposal development.

Laboratory/Center Review

Each applicant's proposal must be approved by one of the Advisers listed in this booklet and endorsed by the Program Committee of AMRMC to be eligible for an award.

The endorsement affirms that the proposal is compatible with AMRMC's interests and that adequate programmatic support will be available if an award is offered.

AMRMC's action on the proposal, together with a copy of the Adviser's comments, will be provided directly to the applicant by the Program Representative.

No applicant will be eligible for further consideration until the Associateship Programs office has been advised by AMRMC that his or her proposal has been approved by an Adviser and endorsed by the Program Committee. Otherwise, the Associateship Programs office will assume that the proposal is not of sufficient current interest to AMRMC or that support facilities cannot be made available.

Since the final review of applications is conducted by special panels appointed by the Research Council, all applicants should note that endorsement by an Adviser or laboratory, while essential to the application process, does not imply or guarantee an award by the Research Council.

The Panel Review

The Associateship Programs office receives all application materials and supporting documents and conducts the competitive evaluations of applications.

Evaluations for AMRMC Associateships are conducted in February, June, and October by special panels convened for this purpose. Panelists are chosen to review applications on the basis of their stature and experience in the fields of science and engineering, and their evaluations become the basis from which awards are made on behalf of AMRMC.

Applicants are recommended for awards only after this open, national competition, in which the panels rank candidates on the basis of quality alone.

Final ranking in order of quality and the recommendation of applicants for awards are the exclusive prerogatives of the panels, and only notification by the Associateship Programs office of an applicant's status in the competition is authoritative.

Stipend

An Associate receives a stipend from the Research Council while carrying out his or her proposed research. The current annual stipend for a Postdoctoral Research Associate is as follows:

Walter Reed Army Institute of Research (WRAIR)	$33,700
US Army Dental Research Detachment-WRAIR	$33,700
US Army Medical Research Detachment-WRAIR	$33,700
US Army Medical Research Unit-Brazil	$33,700
US Army Medical Research Unit-Kenya	$33,700
Armed Forces Research Institute for Medical Sciences Bangkok, Thailand	$33,700
US Army Medical Research Institute of Infectious Diseases	$35,045
US Army Medical Research Institute of Chemical Defense	$30,000

US Army Research Institute of Environmental Medicine	$32,400
US Army Institute of Surgical Research	$27,750

An appropriately higher stipend will be offered to Senior Research Associates.

This stipend is subject to adjustments from time to time in accordance with general national guidelines pertaining to scientists and engineers.

The Research Council is required by the US Tax Code to withhold an amount from the stipends of non-resident aliens who hold Exchange Visitor (J-1) Visas. Exchange Visitors are advised that approximately 30% per month will be withheld from stipends and reported to the US Internal Revenue Service annually.

Applicants are cautioned against entering into any agreement or understanding with individual Advisers or other laboratory personnel concerning additional funding or other remuneration for work as an Associate.

Stipends for Associates are limited to the amounts and by the conditions set forth above, and any other arrangement, formal or informal, between an applicant and laboratory personnel for additional monies or other considerations is strictly prohibited by the Research Council.

Initiation of Tenure

Sufficient time must be allowed between the offer of an award and the beginning of tenure to enable the Associateship Programs office and AMRMC to complete all necessary administrative procedures.

The date on which tenure may begin is negotiated on an individual basis, normally within six months of the award. The starting date may be delayed by mutual agreement of AMRMC, the Associate, and the Associateship Programs office but cannot be later than 12 months from the date on which the award was originally offered.

If this condition cannot be met, a new application, including a newly approved research proposal, must be submitted to the Associateship Programs office and will be judged without prejudice in the next competition.

Prior Affiliation with the Laboratory

A primary objective of the Associateship Programs is to provide a mechanism for new ideas and sources of stimulation to be brought to the sponsoring laboratory. Thus persons with recent prior affiliation with a specific laboratory may not be eligible to apply for an Associateship there.

Prior affiliation includes direct employment relationships either with the laboratory or with a contractor whose work is performed there. A long-term consulting relationship usually makes an applicant ineligible.

Research contracts with universities that provide support for graduate students or faculty who perform research on campus are not ordinarily considered to be disqualifying.

Reapplication

Persons who have previously held an Associateship may apply for another award only if a period of at least two years will have elapsed between termination of the first award and the proposed tenure of a second.

Persons who have previously applied for an Associateship, but who were not recommended for an award by the panels, may reapply after one year.

Candidates who were recommended for an award by the panels, but who were not offered an award because of funding or other limitations, may reapply at any time without a mandatory waiting period.

Taxes and Insurance

As a guest investigator, an Associate is self-employed. All arrangements for payment of income taxes are the responsibility of the individual Associate, who is advised to become familiar with the relevant sections of the current tax codes.

The Research Council is required by the US Tax Code to withhold an amount from the stipends of non-resident aliens who hold Exchange Visitor (J-1) Visas. Exchange Visitors are advised that approximately 30% per month will be withheld from stipends and reported to the US Internal Revenue Service annually.

Job-related injury or death is covered by insurance (workmen's-compensation type). A group health-insurance program is required for Associates and is optional for dependents.

Relocation and Travel

A suitable relocation reimbursement is determined for each awardee. Funds are also available for limited professional travel during tenure, provided such travel is approved in advance by the Associate's Adviser, the AMRMC Program Representative, and the Associateship Programs office. Details are provided at the time of an award.

Publication

Since an Associate's later scientific and technical career will be judged by others, publication in the accepted open technical literature is highly encouraged.

Publications should include a statement indicating that the research was conducted while the author held a National Research Council Research Associateship.

Application Procedure

Detailed information on procedures and all necessary application materials and supporting documents are available on request from the

Associateship Programs
TJ 2114
National Research Council
2101 Constitution Avenue NW
Washington, DC 20418

E-Mail: rap@nas.edu
WWW (Internet): http://www.nas.edu/rap
Gopher: nas.edu/rap

All deadlines for receipt of application materials are strictly observed by AMRMC and the Associateship Programs office. No allowances or exceptions are made for late submissions.

Application materials from previous competitions may not be used.

Panel Review Schedule

Although applications for AMRMC Research Associateships are accepted throughout the year, they are evaluated by the panels only in February, June, and October.

February Review

To be eligible for review in February, completed application materials must be postmarked no later than January 15, 1997, and received by the Associateship Programs office no later than January 25, 1997 Supporting documents must be received by February 15, 1997.

June Review

To be eligible for review in June, completed application materials must be postmarked no later than April 15, 1997, and received by the Associateship Programs office no later than April 25, 1997. Supporting documents must be received by June 1, 1997.

October Review

To be eligible for review in October, completed application materials must be postmarked no later than August 15, 1997, and received by the Associateship Programs office no later than August 25, 1997. Supporting documents must be received by October 1, 1997.

Application Materials

Submit the following to the Associateship Programs office:

Signed Application
Questionnaire Sheet
Research Proposal (1 Copy)
Previous and Current Research

Supporting Documents

Have the following sent directly to the Associateship Programs office:

For Postdoctoral Research Associateship Applicants

Official transcripts of all graduate and undergraduate credits.

Four Reference Reports from the respondents listed on the Application. Only official Reference Reports may be used.

For Senior Research Associateship Applicants

Transcripts are not required of Senior Research Associateship applicants.

Letters of reference are accepted in lieu of Reference Reports. Senior Research Associateship applicants should endeavor to include some letters of reference from individuals who are not co-employees.

Laboratory/Center Documents

Submit the following directly to the Laboratory/Center Research Adviser:

Research Proposal (1 Copy)
Laboratory/Center Review (1 Set)

The Adviser will review the proposal and forward it to the Program Committee for review.

Notification of Awards

Awards are made only by the National Research Council. The endorsement of an application and research proposal by AMRMC, while essential to the application and review processes, does not constitute an agreement or obligation to confer an award.

A review board, drawn from members of the Research Council panels, determines a cutoff score. Applicants who score below this score cannot be considered further for an award and are so notified within two to four weeks.

Applicants who score above the cutoff score are recommended for awards by the board. These applicants are notified of the board's action as early as possible and are offered awards or alternate status to the extent of available facilities and funding by AMRMC.

Acceptances and declinations must be made directly to the Associateship Programs office of the National Research Council.

Opportunities for Research

WALTER REED ARMY INSTITUTE OF RESEARCH
Washington, DC

Division of Biochemistry

Biological Chemistry

PK Chiang AD Wolfe 97.15.25.01

Research areas of interest include (1) molecular biology of gene expression, transcription factors, cellular differentiation, HIV virology, antivirals, and apoptosis; (2) biochemistry, molecular biology, and pharmacology of cholinergic receptors and nitric oxide; (3) neurotransmitters and enzymes involved in neurotransmission, peptide biology, membrane biology, and computer modeling; and (4) development of novel pharmacological agents by chemical and enzymatic synthesis.

Biochemistry of Peptides and Toxins

RK Gordon 97.15.25.02

Research is conducted to understand the biochemical actions of chemical agents, toxins, and peptides on enzymes and cellular receptors. The objective of this research is to use peptides and other pharmacologically active compounds as prophylactic or therapeutic substances for toxic agents. Primary or tissue culture cells are used for investigating the biochemical relationship between receptor stimulation and toxin or peptide perturbation of signal transduction processes such as calcium fluxes and phosphatidyl inositol metabolism. Additionally, quantitative-structure activity relationships between biochemical data and molecular parameters are used to enhance predictive avenues toward greater potency and efficacy. The following techniques are employed for this research: receptor-ligand assays, fluorescent laser-dye

spectroscopy, inline-radioactive detection, high-performance liquid chromatography, peptide synthesis, and computer-aided modeling.

Biological Chemistry

BP Doctor A Saxena 97.15.25.03

The use of macromolecules and synthetic peptides as bioscavengers of toxic substances is explored. Our main objective is to develop antidotal therapy that focuses on using cholinesterases in the presence of nucleophilic oximes to detoxify organophosphate inhibitors. Current projects include developing bioscavengers for toxic chemicals, biological toxins, and pesticides. The following techniques are used for this research: enzyme assays, computer modeling, rational molecular design, peptide synthesis and purification, protein sequencing, antibody production and characterization, and enzyme-linked immunosorbent assays.

References

Caranto GR, et al: Biochemical Pharmacology 47: 347, 1993

Saxena A, et al: Biochemical and Biophysical Research Communications 197: 343, 1993

Structure-Function Studies on Macromolecules

A Saxena BP Doctor 97.15.25.04

Research focuses on understanding the role of specific amino acid residues in cholinesterases in conferring selectivity for various inhibitors. Current research topics include (1) studying cholinesterase, organophosphate anhydrases, and other esterases; (2) establishing structure-activity correlations using enzyme kinetics, site-specific mutagenesis, physicochemical modification, and molecular modeling; and (3) elucidating the mechanism of action of various inhibitors such as organophosphates, peptide neurotoxins, and monoclonal antibodies and nucleophilic reactivators. The following techniques are used for this research: enzyme assays, computer modeling, rational molecular design, peptide synthesis and purification, protein sequencing, and enzyme-linked immunosorbent assays.

References

Segau Y, et al: Biochemistry 32: 13441, 1993

Saxena A, et al: Protein Science 3: 1770, 1995

Membrane Biochemistry

CR Alving 97.15.25.05

This program features research on liposomes as drug carriers and carriers of vaccines, the immunology of lipids, and lipid metabolism of cultured cells. Areas of research include (1) development of antiparasitic and antiviral vaccines; (2) development of liposomes as carriers of vaccines for malaria, AIDS, and Gram-negative bacterial sepsis; (3) studies on biological and biochemical effects of adjuvants and immunomodulators; (4) studies on chemistry, immunology, and biology of endotoxin and lipid A; (5) development of liposomes as carriers of antiparasitic drugs; (6) biology, immunology, and chemistry of prostanoids; (7) intracellular fate of liposomes and liposomal antigens; and (8) mechanisms of immunologic presentation of liposomal antigens.

References

Alving CR, et al: Immunology Review 145: 5, 1995

Rao M, et al: Infection and Immunity 63: 2396, 1995

Division of Communicable Diseases and Immunology

Bacterial Diseases

WD Zollinger AK Bhattacharjee DL Hoover 97.15.10.01

Basic studies are concerned with pathogenesis and immunology of bacterial diseases with special emphasis on meningococcal disease (Dr. Zollinger) and gram negative sepsis (Dr. Bhattacharjee). Research opportunities include the characterization, purification, and chemical characterization of bacterial antigens, especially cell-surface antigens (polysaccharides, proteins, and lipopolysaccharides), and the analysis of host-immunological responses to these antigens. Biochemical and molecular biology techniques will include protein and DNA sequencing, the development of mouse and human monoclonal antibodies, high-performance liquid chromatography, synthesis of peptides and conjugates, sugar and amino acid analysis, Western blotting, enzyme-linked immunosorbent assay, and innovative research techniques. There are also opportunities to study the mechanisms of immune enhancement, using both active and passive immunization, in a wide variety of animal models. The role

of cytokines in these diseases and the effects of modulating these cytokine responses are also under investigation (Dr. Hoover).

Brucella Host-Parasite Interactions

RL Warren DL Hoover 97.15.10.02

We use genetic and immunochemical approaches to study the pathogenesis of *Brucella* and to define antigens that elicit protective immunity. Attenuated strains of *Brucella sp.* are constructed by making specific deletion mutants. Interactions of *Brucella* with human and murine phagocytic cells are studied *in vitro*. These studies include mechanisms of uptake and killing, and induction of cytokines by virulent and attenuated strains. We also examine immunopathogenesis of *Brucella* infection in a murine model using intranasal inoculation. Research focuses on cytokine regulatory networks in *Brucella*-infected animals immunized with live, attenuated, or subcellular component vaccines.

Reference

Drazek ES, et al: Infection and Immunity 63: 3297, 1995

Enteric Bacterial Pathogenesis, Vaccines, and Diagnosis

TL Hale MM Venkatesan 97.15.10.03
EV Oaks AB Hartman

Genetic and immunochemical approaches are used to study the pathogenic mechanisms of enteroinvasive *Shigella* species. Research programs use bacterial genetics techniques to dissect the molecular basis of pathogenesis. Tissue culture and animal models are also used to assess the effects of genetic manipulation on the following stages of *Shigella* infection: (1) endocytosis of the bacteria by mammalian cells, (2) degradation of endosomal vacuoles, (3) intracellular bacterial multiplication, and (4) intercellular bacterial spread. Basic mechanisms of cellular and humoral immunity elicited by natural *Shigella* infections or by vaccination are also evaluated in animal models and in humans. Applied studies employ genetic engineering techniques for construction of attenuated, living vaccine candidates and for the development

of DNA probes or primers for diagnostic use. Nonliving subunit vaccines are also developed and tested in animals and in humans.

References
Venkatesan MM, et al: Journal of Bacteriology 174: 1990, 1992
Turbyfill KR, et al: Infection and Immunity 63: 3927, 1995
Hartman AB, et al: Infection and Immunity 62: 412, 1994

Vector Physiology and Competence

RA Wirtz CF Golenda 97.15.10.04
R Rosenberg SK Martin

We are interested in (1) the interaction between protozoal parasites and their arthropod vectors, especially at the biochemical, molecular, or ultrastructural level; and (2) the aspects of vector physiology that may indirectly affect disease transmission such as the biochemistry of host attraction. The Entomology Department maintains colonies of anopheline mosquitoes and phlebotomine sand flies, as well as infective human and rodent malaria parasites and leishmania. We are studying induced nitric oxide synthase transcription in mosquitoes, factors in the mosquito gut necessary for *Plasmodium* fertilization, and the role of lipophosphoglycans in *Leishmania* survival in the sand fly.

References
Pimenta PFP, et al: Science 256: 1812, 1992
Rosenberg R, et al: Molecular and Biochemical Parasitology 53: 129, 1992

Insect/Arthropod Repellents

RK Gupta RA Wirtz 97.15.10.05

The goal of this program is to extend the insect/arthropod repellent science base and to develop new or advanced technology with emphasis on repellents for application to the skin, clothing, or outdoor areas. Current and future research areas include characteristics and efficacy of combination repellents with multiplicative and additive effects; modes of action of repellents, with emphasis on olfactory/contact repellents; comparative sensitivity of infective and noninfective vectors to repellents in current use; physiology of man/vector/repellent interactions; and innovative sustained-release mechanisms for topical repellents. Climate-controlled insectaries are available for rearing insects used in repellent studies. In addition, a variety of *in vivo* animal and human volunteer test systems have been developed and validated for testing

repellent compounds and formulations against insects. Field studies are also conducted, as required for verification of laboratory results.

References

Rutledge LC, et al: Journal of the American Mosquito Control Association 10: 565, 1994
Gupta RK, et al: American Journal of Tropical Medicine and Hygiene 50 (Suppl): 82, 1994

Molecular Systematics and Diagnostics

RC Wilkerson 97.15.10.06

Research is conducted on the molecular systematics and diagnostics of malaria vectors. Molecular techniques are employed to distinguish potential *Anopheles* vectors of malaria parasites. These studies will provide molecular diagnostics tools for use in epidemiological, control, and population genetics studies. Emphasis is placed on defining genetic markers by using genetic sequences derived from genomic and mitochondrial DNA, and using random primers. Diagnostic tools are based on polymerase chain reaction primers (PCR) and on PCR using fluorogenic probes.

Reference

Wilkerson RC, et al: Journal of Medical Entomology 32: 697, 1995

Immunology-Leishmaniasis

AJ Magill 97.15.10.07

Research focuses on developing improved methods for the diagnosis of leishmaniasis. Emphasis is placed on the detection of *Leishmania* specific immune responses. Methods include (1) identification of amastigote dominant antigens, whole promastigote lysates, secretory antigens, and cell surface membrane proteins for use in various different test systems, including a skin test to elicit a delayed type hypersensitivity response; (2) *in vitro* measures of cell mediated immunity including proliferation and cytokine production; (3) serodiagnosis using ELISA methodologies; and (4) antigen detection systems. A wide variety of animal models are available for study, and human clinical trials of candidate diagnostics are planned. Antigens identified through this program may be useful in immunotherapy or in vaccines for human disease.

Malaria

WR Ballou DM Gordon DE Lanar 97.15.10.08
JD Haynes JA Lyon U Krzych

Malaria antigens and the immune response to malaria are studied. Emphasis is on protective immunity and approaches to the development of vaccines against erythrocytic and pre-erythrocytic stages of malaria parasites. Included are studies of *in vitro* correlates of immunity mediated through both humoral and cellular mechanisms, immunochemical studies on antigens, and studies on clones of the genes coding for these antigens. Human pathogens are used in preference to model parasites whenever feasible.

Immunology — Malaria

U Krzych JA Lyon DE Lanar 97.15.10.09

Research involves (1) analysis of immune reactivities (mainly mediated by T cells) in response to malaria vaccine candidates and (2) elucidation of cellular mechanisms involved in mediating anti-malaria protective immunity in human and murine model systems induced by immunization with radiation-attenuated Plasmodia sporozoites.

Anti-malaria vaccines comprise components of pre-erythrocytic and erythrocytic-stage antigens that are expressed in a variety of systems, including vaccinia and "naked DNA", or are delivered in several adjuvants, including liposomes. We analyze immune responses to the vaccines in murine, simian, and human systems. Our primary goal is to elucidate protective mechanisms involving T-cell subsets that secrete lymphokines or mediate cytolytic effector functions.

An irradiated sporozoite model of protective immunity facilitates carefully planned approaches to investigating regulatory T cells. Emphasis is placed on studying immune mechanisms that involve the participation of specific T-cell subsets as effectors in the elimination of malaria parasites. We are also investigating pathways of antigen presentation, MHC involvement, and mechanisms of cell recognition of exo-erythrocytic and erythrocytic malaria antigens.

References

Link H, White K, Krzych U: European Journal of Immunology 23: 2263, 1993
Krzych U, et al: Vaccine 11: 1341, 1993

Gene Regulation Induced by Host-Parasite Interaction

LE Lindler 97.15.10.10

Basic research focuses on regulating genes involved in the virulence determinants of *Enterobacteriaceae*, with emphasis on *Salmonella* and *Brucella*, as well as other Gram negative pathogens. We will use molecular biology, biochemistry, immunology, genetics, and pathology to identify genes which are regulated in response to the host environment. In addition, we will characterize genetic determinants involved in the host-pathogen relationship at the molecular level, and determine their precise role in virulence of the organism. Animal models and *in vitro* cell culture are used to characterize events during infection, including immune response by the host. Current studies focus on developing molecular gene fusions to study the stress response induced by *Salmonella* or *Brucella* associated with antigen presenting cells (macrophages). The results of these studies will be applied to immunization using live attenuated bacteria.

Virus Diseases

CH Hoke, Jr BL Innis 97.15.10.11

JR Putnak LN Binn

The Department of Virus Diseases mission is to devise strategies for protecting soldiers against viral threats to military operations. In the past, we have made substantial contributions to the development, testing, and licensure of adenovirus, Japanese encephalitis, and hepatitis A vaccines. We are currently developing vaccines to prevent dengue fever and hepatitis A. Possible future candidates may include Norwalk, and other unidentified agents. Our full range of studies include clinical, microbiological, laboratory, genetic engineering, and epidemiological. We are also developing live attenuated, formalin inactivated, genetically engineered subunit, and vectored vaccines.

Research opportunities include (1) identification of appropriate immunogens; (2) biochemical studies of protective epitopes; (3) animal studies to evaluate the efficacy of whole virus or subunit constructs; (4) analysis of specimens collected in human studies; (5) basic studies of pathogenesis and replication; (6) novel strategies for developing immunogens through analysis

of mechanisms of attenuation; and (7) application of modern molecular technology to rapid, sensitive viral detection techniques.

References
Innis BL, et al: Journal of the American Medical Association 271: 1328, 1994
Hoke CH, et al: Journal of Infectious Disease 171 (Suppl 1): S53, 1995

Vaccine Production

KH Eckels 97.15.10.12

Human vaccine research, development, production, and testing is performed under this program. Viral vaccines being investigated include dengue, Japanese encephalitis, HIV, and hepatitis; bacterial vaccines include those to prevent diarrheal diseases, meningitis, and sepsis; and malaria vaccines. We produce these vaccines using conventional methodology or by recombinant technology, with emphasis placed on processes required to move products to full-scale production. This research includes optimizing culture conditions for eucaryotic and procaryotic cells in bioreactors and fermentors; optimizing expression of recombinant proteins in culture; perfecting down-stream processing and purification of immunogens; formulating and freeze-drying experimental vaccines; and developing assays to test purity, efficacy, and safety of candidate vaccines.

Host Resistance to Infectious Agents

DL Hoover 97.15.10.13

This program focuses on defining the role of nonspecific immunity in host resistance to infectious disease.

Current research projects include the following: (1) activation of mononuclear phagocytes or macrophages for microbicidal activity against viral, rickettsial, or parasitic targets. This is an integrated program in both human- and animal-model systems that identifies and defines the role of endogenous (e.g., interferon) and exogenous (e.g., bacterial cell-wall components) stimuli, the mononuclear phagocyte response to such stimuli, and the effect of intercurrent infection on these interactions. Suppressive mechanisms initiated by the infectious agent that subverts the activation reaction are also examined. (2) We also characterize nonantibody humoral factors that modify host resistance—i.e., components of the classical and alternate complement pathways, clotting factors, and cell mediators derived from lymphoid and nonlymphoid sources. Special emphasis is placed on identification of

nonspecific immune reactions that can be manipulated in the long or short term for prophylaxis and therapy of infectious disease or adjuvant action in specific vaccine programs.

Division of Medicine

Cell Signaling

JG Kiang GC Tsokos 97.15.40.01

Our program involves the study of cell signaling process as it relates to the delivery of a death message and its reversal. Cultured lymphocytes, pituitary, thyroid, epithelial, and mammary gland cells are used in these studies.

The following approaches are in progress: (1) understanding of the mechanism of cross-talk between T-cell receptors and APO-1 (programmed cell death antigen) mediated cell signaling—both the physiologic and the pathophysiologic relevance of this cross-talk are under investigation; (2) delineation of the isoforms of protein kinase C (PKC) that are involved in the signaling in normal and pathologic cells—emphasis is placed on the identification of isoform-specific inhibitors that may alter certain PKC-mediated cell functions; (3) characterization of the isoforms of inositol-triphosphate receptors that are involved in cell signaling in various cell types; and (4) exploitation of the role of heat shock proteins in the modification of the function of molecules that are involved in cell signaling. We are studying the effect of HSP-72 in the function of kinases that are associated with the T-cell receptor signaling and in the function of thyroid receptor.

References

Kiang JG: European Journal of Pharmacology 291: 107, 1995
Kovacs B, Tsokos GC: Journal of Immunology 155: 5543, 1995

Heat Shock Proteins

JG Kiang GC Tsokos 97.15.40.02

Heat shock proteins (HSP) are induced under a variety of stressful conditions, and have been shown to induce thermotolerance and cross tolerance at cellular and organ levels.

In our studies, HSP are induced using physical or chemical modalities along with vectors that contain the genes encoding for HSP or the heat shock factor (HSF). Emphasis is placed on identifying a combination of modalities

that induce HSP at optimal levels for a controlled period of time. A main effort of this program is to identify proper vectors for cell and organ transfection. Our goal is to learn more about the mechanisms that are involved in the display of the cytoprotective effect. For example, overexpressed HSF in HSF gene-transfected cells requires phosphorylation at serine and threonine sites prior to its translocation to the nucleus and its binding to the promoter region of the HSP gene.

We are also studying contrivances in the HSP-mediated protection of various organs such as the gut and lung.

References

Kiang JG, et al: Journal of Investigative Medicine 44: 53, 1996
Stodjadinovic A, et al: Gastroenterology 109: 505, 1995

Complement in B Lymphocyte Function and Cell Injury

GC Tsokos 97.15.40.03

Basic studies are conducted to characterize the regulation of the expression of complement receptors (CR) in human B cells. CR are important in the regulation of B-cell function.

Biochemical and molecular biology technology is applied to identify nuclear proteins that regulate the expression of CR. We are characterizing a newly identified protein that displays CREB features.

A novel approach in designing vaccines is also in progress. Dominant pathogen-defined antigens are conjugated to complement receptor ligands. Then, their effect on antibody production is tested.

Reference

Tolnay M, et al: Arthritis and Rheumatology 38: 5157, 1995

Gastrointestinal Diseases

YH Tai CE McQueen JE Van Hamont MK Wolf FJ Cassels 97.15.40.04

Basic studies are being conducted to establish specific and effective means for prevention and treatment of enteric diseases of military importance caused by micro-organisms. Research is directed toward development of optimal mucosal immune responses to vaccine candidate validation of antibiotic regimens, and testing of antidiarrheal agents for prophylaxis and/or treatment of these diseases.

Specific research areas being pursued include (1) molecular genetic studies of determinants involved in the adherence of pathogenic *Escherichia coli* to the intestinal epithelial cells, (2) development of oral vaccines against enterotoxigenic *E. coli* based on colonization factor antigens as isolated preparations in novel delivery systems (e.g., microspheres, or expressed on live attenuated organisms), (3) development of synthetic peptide oral vaccines against enterotoxigenic *E. coli* using peptide analogs to enhance immunogenicity as determined by *in vitro* assays using gut-associated T cells and B cells, (4) isolation and characterization of *E. coli* intestinal glycoconjugate receptors, and (5) studies to elucidate the *in vivo* and *in vitro* fluid and electrolyte movement across intestinal tissue in response to bacterial toxins and studies focusing on the ability of therapeutic agents to prevent or reverse fluid and electrolyte movement.

References

McQueen CE, Boedeker EC, et al: Vaccine 11: 201, 1993
Tai YH, Feisk J, et al: Journal of Membrane Biology 149: 71, 1996

Renal Physiology

JL Atkins 97.15.40.05

Studies are conducted on the pathophysiology of acute renal failure with emphasis on nephrotoxins, including humoral mediators of renal blood flow and membrane transport, metabolic effects of renal ischemia, and toxin effects on renal epithelia in tissue culture. Emphasis is also placed on measuring oxygen tensions in local regions of the kidney in acute renal failure and in changes in renal levels and distributions of epidermal growth factor and its membrane associated precursor. Techniques include intact renal physiology, protein purification, gel electrophoresis, epithelial membrane transport, tissue culture, electrophysiology including patch clamp and noise analysis, isolated perfused tubules, tissue oxygen measurement by porphyrin phosphorescence half life, radioimmunoassay, membrane biochemistry, and high-performance liquid chromatography.

Cell Membranes/Electrophysiology

RS Fisher 97.15.40.06

The environment outside of living cells varies tremendously from one cell type to another, and the ionic and osmotic constraints imposed on cells by their environments are unique for each different cell type. Plasma membrane, salt,

and water transport processes are important for maintaining cell steady-state morphological and functional characteristics. Research focuses on (1) the mechanisms of plasma membrane ion transport by epithelial tissues, with emphasis on electrophysiological approaches to describe these fundamental cells processes; (2) basic mechanisms of ion movements across the plasma membrane and their modulation by inhibitors and hormones; and (3) the influence of biological toxins on these ion transport processes of cell membranes. Techniques include macroscopic electrical, isotopic flux, and volume measurements; and single channel measurements using patch clamp, noise analysis, and planar lipid bilayers.

Reference

Sariban-Soharaby S, Abramow M, Fisher RS: American Journal of Physiology 263: C1111, 1992

The Regulation of Hemostasis

C Krishnamurti 97.15.40.07

Research in the Coagulation Laboratory focuses on those factors that regulate hemostasis, using both animal models and *in vitro* experiments. The laboratory focuses on therapies that can improve hemostasis under conditions of trauma and sepsis, including studies on the effect of stroma-free hemoglobin on hemostasis and the regulation of thrombosis by endogenous inhibitors of thrombin. These experiments require knowledge of protein biochemistry and cell biology.

Reference

Krishnamurti C, et al: Blood 82: 3631, 1993

Phagocytic Cell Biology

J Nath 97.15.40.08

This research, which addresses the cellular mechanisms of inflammatory responses of blood phagocytes (neutrophils and monocytes), is carried out with normal human blood cells. Specific areas include neutrophil functions in acute inflammatory responses, signal-transduction mechanisms involved in neutrophil activation, neutrophil cytoskeleton roles in inflammatory responses, and neutrophil secretory product influences on specific immune-recognition events. A major focus is on neutrophil-endothelial cell interactions during

inflammation; and the role of oxygen, hemoglobin, and nitric oxide in neutrophil-mediated tissue injury.

References
Nath J, et al: Journal of Immunology 149: 1370, 1994
Rothwell SR, Nath J, Wright DG: Journal of Cellular Physiology 154: 582, 1993

Pathophysiologic and Biochemical Evaluation of Acute Lung Injury

AJ Januszkiewicz NM Elsayed 97.15.40.09

The mission of the Department of Respiratory Research is to understand injury, assess risk, and develop pharmacological approaches for combat-related injury to the cardiopulmonary system. Emphasis is primarily placed on inhalation and mechanical injury. Whole animal, isolated organ system (lung), and cell culture models are used to evaluate pathophysiologic, biochemical, and cellular status before and after insult. A large animal incremental-exercise, performance-decrement model incorporates standard physiologic and biochemical variables to gauge cardiorespiratory fitness and incapacitation following insult. The effects of toxicants on performance are evaluated, as are the effects of exercise on the expression of toxicant-induced injury.

Both small and large animal experimental models are used to study injury and treatment. Before and after a controlled level of insult is delivered, respiration, pulmonary mechanics, and hemodynamics are measured. Bronchoalveolar lavage fluid is taken and examined for cellular changes. Then it is assessed for appearance of endogenous chemical mediators of inflammation. Bodily fluids and tissues are examined using both routine and specialized biochemical analyses, with emphasis placed on oxidative stress. Comprehensive histopathologic evaluations are also performed. Along with the exercise model, this approach yields a toxicologic profile which relates the insult to specific tissue damage, and concomitant vital function and integrated heart and lung function derangement. Knowledge of biochemical and physicochemical interactions helps in understanding injury mechanisms and new avenues of prophylaxis or treatment.

Primary research areas include inhalation injury by nitrogen dioxide and mechanical injury by impulse noise (blast overpressure). Nitrogen dioxide is an environmental toxin found in high concentration in confined crew compartment fires. In nitrogen dioxide studies, nose-only and lung-only exposures are conducted, and insult to both upper and lower airways are addressed. Emphasis is placed on the impact of respiratory pattern on

dosimetry. Blast overpressure is inherent with denotation. In impulse noise experiments, sonomicrometry is used to assess cardiac function, and biochemical mechanisms of contusion injury are examined. Computer technology has enabled modeling the relationship between impulse noise and pathological injury. This model is being transitioned to an incapacitation model. A similar computer model for combined gas injury is being developed in order to simulate injury from exposure to a complex mixture of gases, typically found in fire scenarios. Other studies address performance-impairing effects of potentially fielded anti-cyanide agents, and evaluations of suitability of various analgesic and anesthetic regimens for cardiopulmonary studies.

References

Januszkiewicz AJ, Mayorga MA: Toxicology 89: 279, 1994
Elsayed NM: Toxicology 89: 161, 1994

Oxidative Stress and Molecular Mechanisms of Injury and Repair

NM Elsayed 97.15.40.10

Free radical-mediated oxidative stress resulting from exposure to blast overpressure (high-energy impact noise) or toxic gases (nitrogen dioxide, halides), smoke, particulates, ischemia/reprefusion, and Adult Respiratory Distress Syndrome (ARDS) or ARDS-like conditions can cause injury manifested in structural and/or functional alterations of cells, tissues, organs, or death. Basic and applied research opportunities exist to investigate mechanisms of free radical-mediated oxidative stress and antioxidant defenses, targets of damage, and techniques for assessing injury and repair. Our major objective is to understand the molecular mechanism and the pathophysiological significance of the observed alterations, with emphasis on isolated perfused organ (lung or heart) systems; electron spin resonance; other analytical techniques for free radical measurements, lipid peroxidation, and protein oxidation; and the interaction between various nutritional or exogenous antioxidants to inhibit or reverse the injury process. We would apply these findings to the design of useful intervention strategies. Associates may collaborate with investigators in universities and in other research institutes.

References

Elsayed NM, Nakashima JM, Postlethwait EM: Archives of Biochemistry and Biophysics 302: 228, 1993
Elsayed NM (ed): Toxicology 89(3): 161, 1994

Division of Neuropsychiatry

Human Performance in Complex Operational Systems

GL Belenky 97.15.50.01

We conduct studies in human performance in complex operational systems, as well as research in sleep, sleep deprivation, and continuous operations. Our goals are to develop a sleep management system which will include (1) the technology to measure sleep in operational settings; (2) a model to predict performance on the basis of prior sleep; (3) a stimulant to sustain performance when no sleep is possible; (4) a sleep-induction/rapid-reawakening drug combination to promote recuperative sleep; (5) an on-line, real-time alertness/performance monitor to predict lapses and errors prior to their occurrence; and (6) integration of the above into the soldier computer. We also study stress and performance in operational deployments. These studies include measurement of solider well-being, performance, horizontal and vertical cohesion, and other organizational climate issues during operational deployments, and the development of statistical tools to evaluate the degree to which individual responses represent group characteristics. Our staff consists of physicians, psychologists, physiologists, and biochemical engineers.

Division of Neurosciences

Neuroanatomy/Neurotoxicology

JM Petras 97.15.51.01

Opportunities are available for neuroanatomical, neurocytological, neuropathological, and neurotoxicological studies of the mammalian brain and spinal cord. Current interest focuses on the cytopathology and systems neuropathology of blast overpressure induced injury. The neurological implications are considered following an analysis of the systems neuropathology. Our laboratory is equipped for experimental (1) anterograde and retrograde "suppressive" silver impregnation and histochemical techniques, (2) immunohistochemical, (3) histofluorescent, and (4) autoradiographic

methods. Morphometric data analysis is performed using computer-based image analysis systems.

References

Petras JM: Journal of Experimental and Analytical Behavior 61(2): 319, 1994
Petras JM, et al: American Journal of Tropical Medicine and Hygiene 51(3): 100, 1995

Neuropharmacology and Central Nervous System Injury

JB Long 97.15.51.02

Research efforts focus on the characterization and pharmacological management of the degenerative and regenerative mechanisms associated with head and spinal cord injury. Investigative approaches include complementary assessments of the interplay among pathophysiological mediators using neurological, neuroanatomical, electrophysiological, biochemical, and blood flow measurements *in vivo* and cell culture techniques *in vitro*. Related research in neuropeptide pharmacology focuses on peptide effects on the central nervous system vasculature and the mechanisms that underlie neuropeptide-mediated neurological dysfunction and neuronal injury. Additional studies address the interactive effects of selective ligands for multiple opioid receptors (μ, δ, and κ) on brain and spinal cord opioid receptor binding, G-protein coupling systems, and adenylate cyclase activity, with specific emphasis placed on their relevance to mechanisms of opioid tolerance and dependence.

References

Long JB, et al: Journal of Pharmacology and Experimental Therapeutics 269: 358, 1994
Long JB, et al: Journal of Neurotrauma 13: 149, 1996

Neurobiology of the Stress Response

JL Meyerhoff GA Saviolakis 97.15.51.03

This goal of this research is to identify and ameliorate the adverse effects of chronic stress on performance. Studies examine hormonal, autonomic, and psychological indices of the stress response in humans; and the central peptidergic regulation of behavioral, pituitary, and adrenal responses in animals exposed to stressors, including acute and chronic social defeat. Conducted by an interdisciplinary team in both field and laboratory settings, human pyschoendocrine studies employ ambulatory physiological and biochemical measures, and psychometric testing for designing behavioral interventions to counteract the adverse effects of stress on performance. Research on rodents

utilizes stimulation or lesioning of central pathways, remote monitoring of cardiovascular function, pharmacological stimulation or blockade, and examination of molecular mechanisms of defensive behavior by brain regional *in situ* hybridization. Particular emphasis is placed on the role of stress-related peptides in stress-induced immunosuppression, gastric ulcer formation, adaptation to chronic stress, and on pharmacological measures to prevent stress-induced pathology. Biochemical studies of response mechanisms to stress *in vivo* are complemented by *in vitro* studies of peptide-stimulated cyclic nucleotide metabolism, phosphotidylinositol hydrolysis, calcium mobilization, and protein kinase activity. Biochemical assays are available for interleukins, ACTH, dynorphin, beta-endorphin, beta-lipotrophic hormone, neuropeptide Y, met-enkephalin, cortisol, corticosterone, growth hormone, prolactin, catecholamines, and cyclic nucleotides.

References

Potegal M, et al: Journal of Behavioral and Neural Biology 60(2): 93, 1993
Glass CR, et al: Journal of Counseling Psychology 42(1): 47, 1995

Neurochemical and Pharmacological Studies of Seizures

JL Meyerhoff DL Yourick ML Koenig 97.15.51.04

In this vertically integrated program, projects range from *in vitro* studies in brain slices or cultured neurons, to brain regional neurochemical and *in vivo* pharmacological experiments in rats, to clinical studies of biochemical changes in epileptic foci in brain tissue taken from humans undergoing temporal lobectomy for intractable epilepsy. As a model of post-traumatic epilepsy, the program utilizes the electrical kindling technique for inducing permanently increased seizure susceptibility in rats. In examining neurochemical mechanisms of seizure development, we have reported increases in the thyrotropin-releasing hormone and in the excitatory dipeptide N-acetyl-aspartyl glutamic acid (NAAG) in specific brain regions. We have recently shown that TRA or GABA inhibit glutamatergically stimulated calcium influx, while NAAG directly stimulates influx of calcium into cultured neurons. In addition to its direct effects, NAAG may also indirectly affect excitability by its enzymatic hydrolysis to glutamic acid. We are (1) studying the effect of seizures on agonist-stimulated changes in calcium flux, phospholipid metabolism, and cyclic nucleotide metabolism; (2) examining molecular indices of the neuronal plasticity involved in epileptogenesis, using brain regional *in situ* hybridization; and (3) exploring novel pharmacologic

approaches to blockade of kindling, such as ion channel openers and blockers, and antagonists at various sites on the NMDA receptor complex. Equipment is available for stereotaxic surgery and chronic recording of EEG from freely moving rats, as well as histochemical and biochemical preparation and analyses of brain tissue. In addition, we use interactive confocal laser cytometry (including both the ACAS 570C and InSight Plus systems), which permits intracellular imaging of changing pH, membrane potential, and/or ion distribution and studies of receptor binding, as well as intercellular communication.

References

Meyerhoff JL, et al: Brain Research 593: 140, 1992
Koenig ML, et al: NeuroReport 5(9): 1063, 1994

Neurochemistry and Neuroendocrinology

GJ Kant 97.15.51.05

Research focuses on characterizing physiological and behavioral responses to acute and sustained stress, and on elucidating the neurochemical mechanisms that underlie these stress-induced alterations. Specifically examined are neurotransmitter dynamics, plasma hormones, and neurotransmitter and hormone receptors. The neurochemical and behavioral effects of neuropeptides and other physiologically active compounds is also an area of study. Studies are usually conducted in rodents. A well-equipped biochemical laboratory and behavior apparatus are available. Radioimmunoassay, radioenzymatic, receptor binding assays, and other methodologies are used. Collaboration with other neuroscientists is encouraged within this interdisciplinary department.

References

Kant GJ, et al: Physiology and Behavior 54: 499, 1993
Kant GJ, et al: Physiology and Behavior 57: 1187, 1995

Stress-Induced Changes in Central Nervous System Function

SM Anderson 97.15.51.06

The primary goal of research opportunities in this area is to clarify the relationship between stress-induced brain alteration and disruption of performance, attention, sleep, and normal behavior. Although we are primarily interested in long-term chronic stress, we use acute, repeated, and continuous stress models to examine various aspects of the stress response. Our previous work focused on determining stress-induced changes in neurotransmitter,

neuromodulator, and neuroendocrine factor receptors measured in membrane preparations from the brains and pituitaries of stressed rats. Ongoing studies are on finer neuroanatomical resolution of stress responsive brain regions using *in situ* autoradiographic measurement of brain and pituitary receptors. A newly emerging emphasis of this project concerns gender and other individual differences in stress responses. In addition to the neurochemical and histological aspects of the project, this interdisciplinary research program requires behavioral and neurogenic stress studies, including kindled seizures, RIA plasma hormone assays, and pharmacological studies. Consequently, most research involves collaborating with behavioral psychologists, endocrinologists, molecular biologists, and pharmacologists in the division, as well as others outside the WRAIR.

Reference

Anderson SM, et al: Pharmacology, Biochemistry, and Behavior 44: 755, 1993

Physiology and Behavior

GJ Kant RA Bauman 97.15.51.07

The Department of Neurobehavioral Assessment conducts research on the physiological, pharmacological, neuroanatomical, and neurochemical determinants of behavior. Emphasis is placed on variables affecting performance, such as stress and fatigue, disease, trauma, environmental hazards, or drugs used as antidotes, and prophylactics to protect against biological and chemical threat agents. Animal models are utilized to study basic mechanisms that influence behavior; these multidisciplinary approaches include operant conditioning, behavioral pharmacology, and neuropharmacological and neurophysiological techniques. Opportunities exist for collaborations with investigators representing subdisciplines within the neurosciences field.

References

Kant GJ: Pharmacology, Biochemistry, and Behavior 53: 385, 1996
Bauman RA, Kant GJ: Physiology and Behavior 57: 1187, 1995

Behavioral and Physiological Toxicology

RA Bauman 97.15.51.08

Our principal objective is to characterize the disruption of exercise performance, respiratory gas exchange, and food and fluid intakes in rats by a wide range of pharmacological, physiological, and environmental insults

including chronic stress, anticonvulsant compounds, acellular hemoglobin substitutes for human whole blood, traumatic brain injury, and blast overpressure. A multitask, multiuser computer system is used to monitor and control rodent exercise performance and caloric regulation within successive 24-hour time periods, while a PC-controlled indirect calorimetry system is used to quantify correlated changes in O_2 consumption, CO_2 production, and energy metabolism. This protocol has been used to characterize the disruption of exercise performance and food intake by oxygen-carrying blood substitutes, drugs that oxidize hemoglobin, and blast overpressure. It was most recently used to characterize disruptions of respiratory gas exchange and energy metabolism caused by traumatic brain injury.

Performance Assessment and Chemical Evaluation

RF Genovese 97.15.51.09

We assess behavioral and cognitive performance in rodents using operant behavior, maze performance, passive avoidance, and spontaneous motor activity. Performance models are used to develop and evaluate novel pharmacological treatments for potentially adverse conditions of interest to the military. Research focuses on characterizing experimental drugs and on a multidisciplinary approach to investigate pharmacological and biochemical correlates of memory and performance. Collaboration with Institute pharmacologists and biochemists is essential. Current interest areas include prophylaxis therapy for organophosphorus toxicity, behavioral toxicity of antimalarial compounds, and treatment of fluid percussion injury.

References

Genovese RF, Doctor BP: Pharmacology Biochemistry and Behavior 51: 647, 1995

Genovese RF, et al: Annals of Tropical Medicine and Parasitology 89: 447, 1995

Electrophysiology/Neuropharmacology

FC Tortella 97.15.51.10

Several areas of neuropharmacology research, with a primary emphasis on receptor function, are encouraged. These include studies of the neuropharmacology/neurophysiology of seizure disorders, stroke, and other neurodegenerative diseases of the central nervous system (CNS). Interest is maintained in the determination of psychotomimetic properties of neuroactive compounds, particularly centrally acting analgesics, neuroprotectant, and anticonvulsant drugs. *In vivo* and *in vitro* approaches identifying functional

receptor interactions and ionic/molecular mechanisms have been established. Studies are typically carried out in rodents. Techniques include spontaneous cortical and depth electroencephalogram (EEG) recording, computerized frequency analysis of EEG, chemical and electrical models of experimental seizure activity, *in vivo* and neuronal culture models of CNS injury, laser-Doppler velocimetry of blood flow, and quantitative image analysis.

Particular emphasis is placed on using basic principles of receptor pharmacology to study the actions of novel drugs on CNS function from the molecular level to the whole organism.

References

Tortella FC, et al: Neuroscience Letters 198: 79, 1995
Clapp LE, et al: Brain Research 693: 101, 1995

Response Differentiation and Behavioral Pharmacology

G Galbicka 97.15.51.11

Operant conditioning techniques are utilized to model the variables that contribute to the local control of response characteristics. On-line manipulation of response criteria allows experimental control of local reinforcement parameters independent of changes in molar ones. Both appetitive and aversive control techniques are employed. In addition to being used as performance models, these procedures are also employed as behavorial baselines from which to study the effects of pharmacological interventions. These procedures not only allow characterization of a drug's behavioral effects, they can also elucidate any environmental modulation of a drug's effects as a function of changes in either local or overall reinforcement parameters. Current emphasis is on acutely delivered serotonergic compounds, both agonists and antagonists. Some work also attempts to examine the environmental modulation of tolerance development as a function of drug-induced reinforcement loss.

References

Galbicka G, et al: Journal of the Experimental Analysis of Behavior 60: 171, 1993
Galbicka G, et al: Pharmacology, Biochemistry, and Behavior 49: 943, 1994

Role of Immediate-Early Genes in Central Nervous System Injury and Recovery

JR Dave 97.15.51.12

The primary goal of our research is to understand the role of a variety of immediate-early genes (e.g., proto-oncogenes and stress protein genes) in

central nervous system (CNS) injury. A number of oncogenes are considered to be neuroprotective genes, while others are neurotoxic genes. Knowledge of the mechanisms of expression of these genes could provide a valuable tool for treatment strategies following CNS injury. *In vivo* rat and mouse brain injury models are utilized to understand the region-specific expression of *c-fos*, *c-jun*, beta-actin, heat-shock protein 70, and *bcl-2* genes. Studies are also in progress using primary neuronal cultures obtained from fetal rat cerebellum, hippocampus, and cerebral cortex to understand the expression of these genes following glutamate/NMDA-mediated neurotoxicity or toxicity associated with hypoxia. The ultimate goal is to develop a multigene therapy approach for human CNS injury in which expression of neuroprotective genes would be elevated and those of neurotoxic genes would be temporarily suppressed.

References

Dave JR, Tortella FC: Pharmacology Communications 1: 319, 1992

Dave JR, Tortella FC: NeuroReport 5: 1645, 1994

Division of Experimental Therapeutics

Medicinal Chemistry

AJ Lin NA Roth JP Scovill 97.15.30.01

Research focuses on the design, synthesis, and isolation from natural sources of potential drugs against malaria and other parasitic diseases. In addition, antidotes to chemical and biological threat agents such as vesicants and biological toxins are also prepared. Chemical structure modification is based on the evaluation of biological screening data. Further guidance is obtained by studying quantitative structure-activity relationships and molecular modeling. Specialization has been in synthesizing organic nitrogen and sulfur compounds, as well as in terpene chemistry. Many of the new compounds obtained are also screened for antibacterial, anticancer, and antiviral activity by collaborating institutions. Laboratory investigations are aided by the availability of such instrumentation as Fourier-transform infrared, ultraviolet, and nuclear magnetic resonance spectrometers; gas and high-performance liquid chromatographic; and gas chromatograph/mass spectrometers.

Parasitic Diseases

JE Jackson EO Nuzum 97.15.30.02

JD Berman DE Kyle

Research is conducted on the chemotherapy and chemoprophylaxis of parasitic diseases, with emphasis on malaria and leishmaniasis. Research opportunities include parasite biochemistry and molecular biology related to mechanisms of action of experimental antiparasitic drugs, identification of potential biochemical and molecular targets for drug action, elucidation of molecular and biochemical mechanisms of drug resistance, and the pathobiology of acute infection syndromes. Ongoing research projects include development of culture methods and animal models for studies of new or potential chemotherapeutic drugs, the use of these models to develop and characterize new chemical classes of antiparasitic drugs, and the development of rapid diagnostic techniques for differentiating resistant and susceptible parasites.

Pharmacology

MH Heiffer H Chung JM Karle 97.15.30.03

The basis for this research effort is to develop drugs for human use for malaria, other parasitic diseases, and as antidotes against chemical and biological threat agents.

Basic and applied research opportunities exist in the following broad areas: (1) computer-aided drug design; (2) characterization and regulation of receptors; (3) biochemical pharmacology studies—including *in vitro* microsomal, isolated hepatocyte, and isolated perfused liver drug metabolism studies; *in vivo* drug disposition, and metabolite(s) identification and quantitation; (4) alteration of hepatic drug metabolism in disease states and quantitative liver function studies; (5) mechanisms of hepatic drug toxicity; (6) mechanisms of methemoglobin formation and its role in hemolysis; (7) bioavailability and pharmacokinetics in animals and man; (8) development of mathematical models and computer programs that relate to pharmacokinetics; (9) analytical methodology for estimating drug and metabolite(s) concentrations in blood, urine, bile, and other biological fluids; (10) drug interactions; (11) mechanisms of action of drugs; (12) *in vitro* toxicology studies; and (13) single crystal x-ray crystallography.

Drug Intervention of *falciparum* Malaria: Targeting the Parasite's Membrane Systems

TH Hudson 97.15.30.04

Malaria is a leading cause of morbidity and mortality in many developing countries, with an estimated 100 to 300 million infections per year worldwide and 1 to 2 million deaths. *Plasmodium falciparum* malaria is considered to be the most important malaria parasite because of its high morbidity and mortality, particularly in Africa, Southeast Asia, and the tropical zones of the Americas.

The proper functioning of various membrane systems in both parasite and host cells is central to the infection process. At various times in the infection cycle, the parasite must recognize, bind, and invade specific and diverse host cells. The parasitic utilization of erythrocyte haemoglobin and sequestering of toxic iron byproducts requires the interaction of a number of membranous organelles. The sequestering of *Plasmodium falciparum* infected erythrocytes within the brain microvasculature involves the transport and localization of parasite encoded molecules into the red cell membrane. Resistance of parasites to multiple therapeutic drugs involves a membrane protein which is capable of transporting the drugs out of the cell against a concentration gradient. This laboratory elucidates the cellular and molecular basis for membrane dynamics during *Plasmodium falciparum* infection. Our goal is to identify targets for drugs which might disrupt membrane functioning.

Reference

Pasloske BL, Howard RJ: Annual Review of Medicine 45: 283, 1994

Cytotoxic Mechanisms

P Ray 97.15.30.05

Biochemical and pharmacological mechanisms of actions of toxic chemical and biological compounds are investigated using *in vitro* cell culture models. Specialized research areas include basic cell biology, cell death, membrane biochemistry and biophysics, receptor functions, calcium metabolism, enzymology, and molecular biology. Research focuses on mechanism-based intervention of cytotoxicity.

References

Ray P, et al: The Journal of Biological Chemistry 268: 11057, 1993
Ray P, et al: Neurochemical Research 19: 57, 1994

Division of Pathology

Pathogenesis of Infectious Microbial Agents and their Toxins

M Jett 97.15.20.01

We study the pathogenesis of tissue injury induced by microbial agents and their toxins. Research focuses on pathologic changes evaluated by histopathology, electron microscopy, immunochemistry, *in situ* hybridization, polymerase chain reaction, and other emerging technologies. Our goal is to determine and test potential medical countermeasures against microbial agents and toxins of military importance.

Immunopathology of Toxins

J Tseng J Komisar 97.15.20.02

Research is under way to determine the mechanism of immunological and pathological responses in mucosal tissues to biological toxins and infectious agents. Current investigations focus on (1) antigenicity and superantigenicity of toxins, (2) mucosal immunity, (3) cellular mechanisms of toxicosis and toxic shock, (4) mucosal lymphoid and epithelial cell migration, and (5) cytokines and mediators involved in toxicosis and infections.

Approaches involve using modern technologies of immunology, biochemistry, molecular biology, and cell biology; with the goal of obtaining basic information for developing polyvalent vaccines against biological toxins and infectious agents.

Molecular Biology of Toxins

M Jett RJ Neill 97.15.20.03

Protein toxins, such as staphylococcal enterotoxins, and other related virulent factors from microbes, are investigated to provide fundamental information at the molecular, biochemical, and cellular levels. The mode of action of toxins, their structure-function relationships, their genetic control, and their toxic effects on animals and cell culture models are being studied with a multifaceted approach, using concepts and technologies related to cell biology, biochemistry, immunology, molecular biology, microbiology, and recombinant DNA. The goal of this research is to achieve sufficient understanding of these toxins to prevent the toxemia and disease.

Division of Preventive Medicine

Epidemiology

PW Kelley 97.15.41.01

The objectives of the preventive medicine program are to assess infectious disease risks of military importance and to apply epidemiologic methods to produce evidence to support the making of medical standards for military personnel. We also evaluate vaccines and chemoprophylactic drugs.

Reference

Broadhurst LE, Erickson RL, Kelley PW: Journal of the American Medical Association 269: 227, 1993

Retrovirology

DL Birx DL Mayers 97.15.41.02

JG McNeil MT Vahey

The objective of the retrovirus program is to minimize the impact of human immunodeficiency virus (HIV-1) on military populations. As a direct consequence of its aggressive retrovirus HIV testing programs and standardized medical evaluations, the military has the unique ability to rigorously evaluate new preventive interventions. Advances in the basic sciences are rapidly translated into improvements in medicine because WRAIR is the lead agency for the Department of Defense retrovirus research program, which is to be closely linked to operational health care delivery. The major emphasis of this research program is to develop and test HIV-1 preventive vaccines.

References

Louwagie J, et al: Journal of Virology 69(1): 263, 1995

Mascola JR, McNeil JG, Burke DS: Journal of the American Medical Association 272(6): 488, 1994

Trauma, Shock, and Organ Failure

FJ Pearce 97.15.41.03

The Division of Surgery conducts research into the mechanisms of hemorrhagic and endotoxic shock, with particular emphasis on the role of oxygen-free radicals, iron, cytokines, and cyclo-oxygenase products on cell and organ function. The purpose of this research is to (1) understand the mechanisms involved in the onset of vascular decompensation during hemorrhagic shock in order to develop treatment strategies for preventing or

reversing this currently irreversible phase of shock, and to (2) identify and test potential therapeutic maneuvers capable of mitigating organ damage following resuscitation from hypotensive episodes of various severity and duration. We perform experiments in animal models of shock, which involve physiological monitoring and measurements of organ blood flow and function combined with studies of cellular energetics that emphasize the lung, liver, gut, and kidneys. Current interests focus on (1) the role of endothelin and nitric oxide on vascular smooth muscle function and organ blood flow following shock, (2) the role of endotoxin in the etiology of vascular decompensation in shock, (3) the development of metabolic resuscitation and support strategies, (4) development of noninvasive physiologic monitoring capabilities for the battlefield, and (5) development of servo-controlled ventilatory and fluid support algorithms for resuscitation of hemorrhagic shock.

US Army Dental Research Detachment

Polymer Chemistry

JE Van Hamont 97.15.55.01

This laboratory offers unique opportunities for a polymer chemist interested in developing new controlled release drug delivery systems applicable to combat casualty care. Innovative novel drug delivery systems enable better use of established drugs for numerous clinical applications. The systems of interest will sustain release anesthetics, antimicrobial agents, and/or growth factors. *In vivo* models and procedures to evaluate the efficacy of the developed drug delivery system(s) are validated and in use. Therefore, we will incorporate the selected drug(s) or bioactive agent(s) into biodegradable polymeric microspheres, macrobeads, or other systems of predesigned geometric format, so that we may achieve a predetermined *in vivo* release of the active agent. Experts will help us determine the specifications of the delivery system(s) that are most likely to be biologically successful. For many applications, we anticipate that the formulation of targeted drug delivery system(s) capable of appropriate sustained drug release over time will provide more effective therapeutic benefits with fewer side effects than systemic, comparatively higher doses. Research facilities include a polymer chemistry laboratory.

US Army Medical Research Detachment
Blood Research - Maryland

Blood Preservation

JR Hess SJ McFaul 97.15.80.01

This program is designed to develop new red-blood-cell preservation systems for military and civilian use. The goals are to increase the quality of red cells during storage and to extend the shelf life of stored red cells. Blood storage at various temperatures (frozen, 4°C, and ambient temperature) is being compared with respect to the maintenance of functional integrity. Improved methods are developed to deglycerolize frozen-thawed red cells and provide a post-thaw storage capacity for such cells. This research includes studies of the metabolism of red cells in the presence of various nutrient additives, the evaluation of changes in membrane stability during preservation, and attempts to understand the signal transduction of RBC membrane microvesiculation during storage. The techniques of statistical design and mathematical modeling are used to maximize experimental results. Autologous clinical trials are done to evaluate the *in vivo* survivability of red cells stored in experimental solutions.

Reference

Moore GL, Hess JR, Ledford ME: Transfusion 33: 709, 1993

Mechanisms of Red Cell O_2 Transport

VW MacDonald 97.15.80.02

The purpose of this research project is to understand the critical properties of intravascular O_2 transport necessary for optimal tissue oxygenation by oxygen-carrying blood substitutes. Although many details of the functional properties of individual oxygen carriers, such as hemoglobin in solution are known, detail is lacking in understanding the complex interactions of these materials with one another, with red blood cells, or with humoral mechanisms that control blood flow distribution. Experimental materials for these studies include normal human and animal red blood cells, cell-free hemoglobin and other acellular blood substitute candidates, microencapsulated hemoglobin, and red blood cells preserved in various media. *In vitro* measurements of both equilibrium and kinetic behavior of ligand (O_2 and CO_2) binding are carried out, and correlations are made with *in vivo* measurements of physiological

function in whole animal and isolated perfused organ models. The results will be used to refine computer models of tissue O_2 delivery and to design optimal properties of blood substitutes, red blood cells, and stored blood.

Reference
MacDonald VW, Winslow RM: Journal of Applied Physiology 72(2): 476, 1992

Stability of Chemically Modified Hemoglobin

VW MacDonald 97.15.80.03

The purpose of this research is to delineate how the chemical modification of hemoglobin alters susceptibility to oxidation and protein degradation. Correlations are sought between molecular structure, ligand (O_2) binding properties, and/or oxidation and protein stability. Experimental materials include native and chemically modified human and animal hemoglobin being developed as potential oxygen carrying blood substitutes. Rapid scanning spectrophotometric techniques and complex numerical analysis are utilized to identify chemical intermediates and products, and to define their reaction kinetics during drug-, anion-, and nitric oxide-induced oxidation of the heme moieties. Structural determinants are sought for heme oxidation potential and porphyrin stability within the heme pocket. Measurements are also made of heme exchange with target proteins and heme/membrane interactions. The results will be used to optimize design of cell-free hemoglobin-based blood substitutes.

Physiology of Administered Hemoglobin Solutions

JR Hess SJ McFaul 97.15.80.04

The purpose of this research is to study the physiologic effects of administering resuscitation quantities of hemoglobin-based red blood cell substitutes. Hemoglobin solutions transport oxygen and sustain life at lethally low concentrations of red cells; however, their development as resuscitation fluids has been slow, since their safety is in question. A number of chemical and physiological mechanisms of potential toxicity have been identified including (1) hemoglobin interaction with EDRF, (2) hemoglobin mediated lipid peroxidation, (3) altered blood viscosity, (4) short intervascular persistence, and and (5) white blood cell activation. Biochemical, cell culture,

cell sorting, isolated organ perfusion, and whole animal oxygen transport models are used to study model hemoglobin solutions.

References

Hess JR: Journal of Applied Physiology 74: 1769, 1993
McFaul SJ, et al: Blood 84: 3175, 1994

Structure and Function of Hemoglobin-Based Blood Substitutes

VW MacDonald JR Hess 97.15.80.05

The goals of this research are to determine the functional properties of modified hemoglobins, both free in solution and encapsulated, which are being developed as blood substitute products. Studies include (1) measuring the kinetics and equilibria of ligand binding to hemoglobin, (2) determining the structural stability of modified hemoglobins, (3) correlating the mechanisms of toxicity *in vitro* and *in vivo* with the molecular function of modified hemoglobins, and (4) delineating the effects of new modified hemoglobins designed to combine optimal *in vivo* oxygen transport properties with minimal toxicity.

Data from functional measurements are applied to mathematical models of oxygen transport and to molecular models of hemoglobin structure. Rapid kinetic measurements are accomplished using high-speed, spectral scanning, stopped-flow and flash photolysis, while steady-state equilibrium measurements are made using spectral and manometric analyses of hemoglobin saturation as a function of dissolved oxygen content. New technologies are being developed and refined for both kinetic and equilibrium measurements, and new mathematical techniques are being exploited for analyses and modeling of large data matrices.

Reference

MacDonald VW: Methods in Enzymology 231: 480, 1994

Laser Research - Texas

Laser Bioeffects and Vision

H Zwick 97.15.90.01

This research centers on evaluating acute or repeated laser retinal exposure on visual function. Opportunities exist to measure spatial and chromatic visual

mechanism alteration in response to coherent laser exposure in animal models. Emphasis is placed on correlating various light damage endpoints including retinal morphology, physiology, psychophysics, and visual performance. Parallel human study opportunities are available to assess human macula accidental photic injury with simulation techniques that involve optical artificial scotoma generation and their effects on complex visual function and performance measures. Available technology includes scanning laser ophthalmoscopy (SLO) imaging and visual function testing, computer image processing, head and eye tracking modalities, oculomotor servo artificial scotoma control, and SLO morphological and functional comparison of photic maculopathy and nonphotic human maculopathies. The latter projects focus on long-term development of more sensitive human diagnostic tools for laser retinal injury and the establishment of permissible laser eye exposure limits.

ARMY MEDICAL RESEARCH UNIT BRAZIL
Rio de Janeiro, Brazil

Molecular Biology and Biochemistry of Parasites

M Grogl 97.15.91.01

The US Army Medical Research Unit in Brazil supports AMRMC efforts to develop drugs and vaccines against tropical diseases of military importance. Current molecular research opportunities include (1) studies on the genetic basis of tropism in *Leishmania* using a cosmid library/functional complementation based approach, (2) studies on the basis of drug resistance (Pentostam and paromomycin) in leishmaniasis using a transfection/over-expression based approach, and (3) studies correlating mutations in pfmdr1 with clinical drug resistance in malaria. Biochemical research opportunities include studies on the mechanisms of action of antimony against *Leishmania* and identification of antigens differentiating *L. brasillensis* strains which are strictly cutaneous, and *L. brasillensis* strains which eventually cause mucosal disease. Parasitology research opportunities include (1) development of improved models for the study of tropism in *Leishmania*, (2) surveillance of *Leishmania* and malaria for drug resistance, (3) development of new drug screening models for testing selected potential anti-leishmanials, and (4) development and testing of new diagnostic assays for *Leishmania* and malaria.

The Unit is fully equipped to support molecular and biochemical research; it also has extensive parasite culture facilities. There is ready access to clinical specimens and untapped potential for natural product drug discovery through field sites and Brazilian collaborators.

Applied Clinical and Epidemiologic Research in Tropical Diseases

JL Sanchez LW Pang M Grogl 97.15.91.02

The clinical research department of the US Army Medical Research Unit in Brazil collaborates with a variety of Brazilian institutions to conduct field and hospital-based studies. Applied research involves phase 2 and 3 studies designed to evaluate potential drugs, vaccines, and diagnostic tests against tropical diseases such as malaria, leishmaniasis, dengue, leptospirosis, emerging pathogens (e.g., hantaviruses and rickettsial agents), and diarrheal

enteropathogens. Baseline epidemiologic studies for these diseases are also supported as a necessary preceding step in defining their incidence, seasonality, and risk factors prior to the conduct of vaccine or chemoprophylactic studies.

Clinical research opportunities include (1) evaluation of chemotherapeutic agents for uncomplicated *P. falciparum* malaria; (2) evaluation of chemoprophylactic agents for *P. falciparum* and *P. vivax* malaria; (3) evaluation of new treatment drugs for cutaneous and visceral leishmaniasis; and (4) early diagnosis of malaria, leptospirosis, and dengue. Epidemiologic research opportunities include (1) seroepidemiologic studies of hantaviruses, hepatitis E, and rickettsial infections in the Amazon river basin; (2) community-based, clinico-epidemiologic studies of dengue and fevers of unknown origin among urban populations in Southeast Brazil; and (3) community-based, clinico-epidemiologic studies of bacterial enteropathogens in urban populations of Rio de Janeiro.

USAMRU-B has developed field sites at four separate locations in Brazil (Southern Amazon, Northern Amazon, Southeast Brazil, and Rio de Janeiro). There is ready access to modern parasite and bacterial culture and serum processing facilities at an outlying laboratory in Vitórla (Federal University of Espirito Santo), and three main laboratories in Rio (USAMRU-B, Federal University of Rio de Janeiro, and FIOCRUZ).

US ARMY MEDICAL RESEARCH UNIT KENYA
Nairobi, Kenya

The United States Army Medical Research Unit in Kenya (USAMRU-K) is an overseas foreign activity of Walter Reed Army Institute of Research in Washington, DC. Its mission is to field test drugs and vaccines against infectious diseases of interest to the US military.

Malaria Field Studies

PE Duffy 97.15.46.01

The parasitology and cellular immunology laboratory in Kisumu, western Kenya supports epidemiology, immunology, vaccine intervention, and drug intervention studies, which are conducted at the nearby field site of Saradidi. Access to samples in an area where malaria incidence is greater than 90% allows us to investigate an array of questions regarding the pathogenesis, prevention, and cure of the disease. Current research areas include the genetic basis for disease resistance, use of transmission-blocking vaccines, role of cytoadherence in disease, and the cell-mediated basis of protection with blood stage vaccines.

Immunology and Pathology of Leishmaniasis and Malaria

FW Klotz 97.15.46.02

In association with the Kenya Medical Research Institute, USAMRU-Kenya investigates the immunity and pathogenesis of human malaria and leishmaniasis. Laboratory research focuses on analyses of nitric oxide or nitric oxide synthase in human diseases, including spectrophotometric, immunochemical, cytochemical, and polymerase chain reaction analyses of nitric oxide byproducts in human tissues. We will also correlate cellular immune functions and cytokine analyses with nitric oxide levels. Research opportunities involve (1) evaluating nitric oxide as an indicator of immunity in individuals receiving various malaria vaccines, including Spf 66, sporozoite antigens, blood stage, and gametocyte antigens and (2) evaluating malaria diagnostic tests and malaria serology.

Antimalarial Drugs

GD Shanks 97.15.46.03

The primary emphasis of the malaria chemotherapy group is phase II/III field trials of new antimalarial drugs for chemoprophylaxis and treatment of falciparum malaria. Research is conducted in the field, away from the main laboratory in Nairobi. Drugs expected to be tested within the next few years include halofantrine, azithromycin, WR 238605, and new antifolate compounds. Opportunities exist for projects in clinical pharmacology, practical aspects of drug resistance, public health aspects of malaria control, new forms of rapid malaria diagnosis, and applied aspects of clinical medicine. Research focuses on producing compounds for international registration as new antimalarial agents. Physicians, clinical pharmacologists, or epidemiologists are invited to express their interests and ideas to USAMRU-K.

ARMED FORCES RESEARCH INSTITUTE OF MEDICAL SCIENCES
Bangkok, Thailand

The research opportunities offered at the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand, are provided as an extension of the Associateship program of the Walter Reed Army Institute of Research. Awardees must be in residence at AFRIMS for the duration of the award period.

Dependents may accompany Associates to Thailand, with reimbursement of relocation under the same regulations applied to persons coming to the US for tenure. While in Thailand, they may attend school and participate in community activities at the Associate's expense. As a visiting scientist, the Associate and dependents will be under the jurisdiction of AFRIMS. Associates, however, are not US government employees. The US Embassy, Bangkok cannot provide administrative support privileges (e.g., duty-free privileges and APO mail) that are available to US government employees. Associates must apply to the Thai Embassy/Consulate in their respective countries for the appropriate visa prior to arrival in Thailand.

Enteric Diseases

PD Echeverria L Bodhiditta 97.45.15.01

Studies focus mainly on the diagnosis, pathogenesis, epidemiology, and therapy of enteric infections. Primary interest is in the practical application of DNA or RNA probes to the identification of different enteric pathogens in the field. Also of interest is the development of methods of detecting and characterizing enteric pathogens with nonradioactive probes.

Medical Entomology

KJ Linthicum SW Gordon 97.45.15.02

The Entomology Department studies all aspects of the transmission of vector-borne diseases, particularly those of malaria, dengue, and scrub typhus. Aside from a modern research facility and insectaries in Bangkok, it maintains two field stations. There is a staff of more than thirty technicians and researchers who are experienced in collection and dissection techniques, blood examination, taxonomy, and biochemical and immunological assay. Current

research includes longitudinal studies of malaria and dengue transmission; molecular biology of heterologous malaria antigens; taxonomy and bionomics of the *Anopheles dirus* group; epidemiology of scrub typhus transmission; development of immunological assays for dengue and Rickettsia; and quantification of malaria and dengue survival in their mosquito hosts. The department also collaborates with local scientists on *Anopheles* genetics research. Proposed research need not fit precisely into current work.

References

Suwanabun N, et al: American Journal of Tropical Medicine and Hygiene 50: 460, 1994
Sattabongkot J, et al: Journal of Infectious Diseases 169: 464, 1994

Immunology and Parasitology

DG Heppner, Jr K Pavanand 97.45.15.03
C Wongsrichanalai S Pichyangkul

The Department of Immunology and Parasitology in Bangkok develops vaccines and drugs against human malaria. Current immunology research opportunities include (1) preclinical characterization of cellular and humoral responses to malaria vaccines; (2) study of the immune response in clinical trials of pre-erythrocytic, blood stage, and transmission-blocking malaria vaccines; and (3) investigation of the cellular mechanisms of immune depression in malaria. Parasitology research opportunities include studies of (1) novel antimalarial compounds, (2) *in vitro* cultivation of *Plasmodium vivax*, (3) mechanisms of drug resistance, (4) cytoadherence/rosetting, and (5) cultivation of exoerythrocytic stages of *P. falciparum*.

The Department is fully equipped to support research using flow cytometry/sorting, polymerase chain reaction, ELISA, molecular probes, and bioassay of anti-malarial compounds. Departmental field sites and institutional affiliations provide ready access to clinical specimens.

References

Wongsrichanalai C, et al: American Journal of Tropical Medicine and Hygiene 47: 112, 1992
Kyle DE, et al: American Journal of Tropical Medicine and Hygiene 48: 126, 1993

Malaria and Scrub Typhus Studies

G Watt 97.45.15.04

The Department of Medicine provides access to clinical material and populations for controlled clinical trials on all aspects of malaria and scrub typhus. Our department recently discovered a focus of drug-resistant *Rickettsia*

tsutsugamushi infection in Northern Thailand, which has enabled us to study the mechanism(s), epidemiology, prevention, and treatment of the first naturally occurring drug-resistant infections reported for the genus *Rickettsia.* The department's field sites offer the opportunity to correlate *in vitro* and *in vivo* data for the application of new technologies.

This Department also has a full-time laboratory facility devoted to the study of the biology and treatment of the liver stages of the two principal human malarias: *Plasmodium falciparum* and *P. vivax.*

Viral Studies

DW Vaughn 97.45.15.05

Studies concern viral diseases and viruses of local medical importance: dengue viruses, Japanese encephalitis virus, other arboviruses, hepatitis A virus, and hepatitis E virus (HEV). Field, clinical, and basic science research are combined to exploit the opportunity to study acutely ill patients, predictable epidemic disease activity, and an extensive collection of virus isolates and patient sera.

Research opportunities include (1) studies of the pathophysiology of plasma leakage and hemorrhage in dengue hemorrhagic fever; (2) the humoral and cellular immune response to the flaviviruses and hepatitis viruses; and (3) the epidemiology, improved diagnosis, therapy, and immunoprophylaxis of these diseases. Molecular virologic techniques, including cDNA cloning, polymerase chain reaction, sequencing, and *in situ* hybridization are available. Areas of recent active interest are (1) the characterization of HEV, (2) animal models of hepatitis and dengue infections, and (3) the definition of viral determinants of virulence for all these agents.

US ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES
Frederick, Maryland

Bacteriology Division
AM Friedlander, Chief

Bacterial Diseases and Immunology

SL Welkos PL Worsham 97.20.10.01

We are interested in mechanisms of microbial pathogenesis and host resistance to infection with *Yersinia pestis* and *Bacillus anthracis*. Recent research with them has included (1) pathogenesis and host response to infection; (2) mechanisms of immune protection against anthrax and plague; and (3) cloning and analysis of DNA encoding the toxins, capsule, and other virulence factors/antigens. With *B. anthracis*, we used a mouse model to characterize the genetic differences of host susceptibility, determined mechanisms of innate resistance to lethal infection, and characterized the plasmid-associated virulence of nontoxigenic *B. anthracis*. We identified and characterized the plasmid-encoded gene for a positive trans-activator of capsule synthesis. We also helped develop recombinant *B. subtilis* and attenuated *B. anthracis* live vaccine strains. Current research involves using *Y. pestis* to (1) study the roles in virulence and immunity of antigens encoded on the three major plasmids, (2) identify mechanisms of innate and acquired immunity to infection, and (3) develop optimal synthetic or live vaccines for protective immunity to the plague.

References

Vietri N, et al: Gene 152: 1, 1995

Welkos S. et al: Contributions to Microbiology and Immunology 13: 229, 1995

Genetics and Physiology of Bacterial Pathogens

PL Worsham 97.20.10.02

Our laboratory focuses on mechanisms of bacterial pathogenesis, with emphasis placed on *Yersinia pestis* and *Bacillus anthracis*. Current work centers on evaluating the role of plasmid and chromosomal antigens of *Y. pestis* in virulence and immunity, including the genetic characterization of *Y. pestis* variants isolated from immunized animals. Recent studies with *B.*

anthracis have involved the isolation and characterization of an asporogenic vaccine production strain. Our goal is to use these results to improve vaccines and diagnostics.

References

Worsham PL, Stein MP, Welkos SW: Contributions to Microbiology and Immunology 13: 325, 1995

Friedlander AM, et al: Clinical Infectious Diseases 21(2): S178, 1995

Pathogenesis and Immunology

BE Ivins 97.20.10.03

Basic and applied research is being conducted on *Bacillus anthracis* and on experimental anthrax in guinea pigs, with research opportunities available in the following areas: (1) mechanisms of nonspecific resistance and specific immunity and (2) development and evaluation of experimental vaccines.

The ultimate goals of this research are to develop improved prophylaxis against anthrax and to define those host factors responsible for nonspecific and specific immunity to anthrax.

Reference

Ivins BE, et al: Infection and Immunity 60: 662, 1992

Live Bacterial Vaccine Vectors

TA Hoover 97.20.10.04

A research opportunity exists to develop bacterial antigen delivery systems. Various live, attenuated bacteria harboring foreign antigen genes are being evaluated as vaccine vectors. Research efforts will include cloning and optimizing the expression of antigen genes in a particular bacterial host that utilizes recombinant-DNA techniques, evaluating the safety and efficacy of candidate bacterial vaccines in animal models, developing attenuated bacteria by specific mutagenesis, or determining genetic lesions that effect attenuation in strains currently under consideration for use as vaccine vectors.

References

Hoover TA, Vodkin MH: Cloning and expression of *Coxiella burnetti* DNA, in O fever: The biology of *Coxiella burnetti*. Edited by Williams JC, Thompson HA. Boca Raton: CRC Press, 1991

Hoover TA, Vodkin MH, Williams JC: Journal of Bacteriology 174(17): 5540, 1992

Immunology and Vaccine Development

GW Anderson, Jr 97.20.10.05

Current research focuses on determining critical immunogens for vaccine development, testing the efficacy of immunogens in animal models, and developing *in vitro* correlates that demonstrate protective immunity against Yersinia pestis. Opportunities also exist to investigate host mediated immune responses to bacterial antigens, the relative role of immunogens for vaccine development, and assays which can demonstrate protective immunity.

Protein Biochemistry

J Farchaus 97.20.10.06

Current research focuses on investigating the structure/function relationships for prokaryotic toxins and surface array proteins. Our objectives are to improve basic science and apply that information to the identification and production of immunogens for vaccine applications. Specific research areas involve cloning and expression of recombinant proteins using *Bacillus* expression systems, purification and biochemical characterization of proteins, site-directed mutagenesis, and biochemical characterization of *in vitro* assembled multisubunit toxins.

Pathogenesis, Immunology, and Vaccine Development

AM Friedlander 97.20.10.07

Work in this laboratory focuses on the cellular aspects of natural and immune resistance to diseases caused by extracellular and facultative intracellular bacteria, including anthrax and plague. We carry out pathogenic studies of infections using both *in vitro* and *in vivo* models, with particular emphasis on interactions of pathogens with phagocytic and epithelial/mucosal cells. Specific interest areas include (1) cellular and molecular mechanisms of interference with host resistance by microbial virulence factors; (2) the study of endosome, phagosome, and lysosome function; (3) intracellular processing of organisms, antigens, and toxins by macrophages; (4) identification of target antigens and mechanisms of protective immunity; and (5) evaluation of recombinant expression proteins as candidates for vaccine development.

References

Bhatnagar R, Friedlander AM: Infection and Immunity 62: 2958, 1994

Friedlander AM, et al: Infection and Immunity 61: 245, 1993

Diagnostics Systems Division
EA Henchal, Chief

Molecular Virology

EA Henchal 97.20.26.01

Research opportunities are available for basic and applied research to characterize the gene function of arthropod-borne viruses, particularly the flaviviruses; and to understand factors contributing to virus attenuation. Approaches include characterizing virus variants using automated DNA sequencing, molecular cloning, expression of viral genes in prokaryotic and eukaryotic vectors, protein purification, and immunological evaluation using monoclonal antibodies. We collaborate with other divisions, departments, and research teams developing viral vaccines and diagnostic products.

Respiratory and Mucosal Immunology

AO Anderson 97.20.26.02

Work in this laboratory focuses on the cellular and molecular mechanisms required *in vivo* for effective immunity against pathogens or toxins, which may be encountered in aerosols or ingested material. Both mucosal and systemic immunity are required to produce this kind of protection. The induction mechanisms of both forms of immunity involve complex interactions among cells, and with cytokines in the presence of integrins and extracellular matrix proteoglycans. Therefore, analysis of the host conditions should reveal materials that will be useful for designing second generation vaccines for effective immune induction.

The laboratory supports investigators interested in (1) cloning and expressing chimeric recombinant vaccine candidates that have the desired targeted activity, and testing for efficacy in animals; (2) analyzing the effects of priming with candidate antigens or adjuvants on compartmentalization and traffic of immune cells in the tissues responsible for initiating the immune response using *in situ* hybridization and immunohistochemistry; and (3) using polymerase chain reaction amplification and DNA cloning of immune cells, recovered from tissues by micromanipulation, to analyze antigen receptor gene

expression and somatic mutation events required for high affinity immune responses.

References

Weinstein PD, Anderson AO, Mage RG: Immunity 1: 647, 1994
Elson CO, et al: Journal of Immunology 154: 1032, 1995

Medical Entomology

MJ Turell 97.20.26.03

Basic research is conducted on the interactions of arthropod-borne viral pathogens and their invertebrate and vertebrate hosts. Current research includes *in vitro* and *in vivo* laboratory studies under simulated environmental conditions and in the field. These studies involve physiology, genetics, biology, and ecology as they relate to mechanisms of overwintering, vector competence, and vector and reservoir incrimination. Investigators are designing and evaluating methodologies for the rapid detection and identification of arthropod-borne pathogens from field-collected specimens. Research opportunities are enhanced by excellent arthropod-rearing facilities, environmental-simulation capabilities, and containment facilities for both exotic vectors and arbovirus pathogens.

Reference

Turell MJ, et al: Journal of Medical Entomology 29: 62, 1992

Molecular Diagnostics

MS Ibrahim 97.20.26.04

The goal of this research is to develop diagnostic procedures for a variety of viral and bacterial pathogens, including immunological and molecular biological techniques to develop highly sensitive and specific assays for detecting disease pathogens in vertebrate hosts and arthropod vectors. Research areas consist of optimization of reverse transcriptase-polymerase chain reaction (RT-PCR), immuno-PCR, cloning, antibody and nucleic acid screening, sequencing, and protein expression and purification. Facilities for laboratory research, development, and field testing include containment facilities, insectaries, automated sequencing, oligonucleotide synthesis, high-performance liquid chromatography, and a variety of detection devices and equipment.

Toxinology Division
CL Wilhelmsen, Chief

Microbial and Animal Toxins

LA Smith 97.20.35.01

Investigations are conducted to understand the genes involved in toxin production and the mechanisms by which bacterial and animal toxins poison eucaryotic cells. Research objectives include studies on structure-activity relationships of toxins and designing pharmacological measures for the prevention, diagnosis, and treatment of bacterial plant and animal toxicoses. Toxins currently being studied include botulinum toxin, ricin, and various snake and scorpion toxins.

Research areas include the purification and chemical characterization of toxins; study of the biologic and/or enzymatic activities of toxins; immunological characterization of toxins; molecular organization and regulation of toxin genes; expression of toxin genes using mammalian, viral, yeast, and bacterial expression systems; and site-directed mutagenesis of toxin genes. Expression of toxin genes in heterologous host systems, gene regulation, and evolution of toxin genes are the primary emphasis of this laboratory.

Pathophysiology of Toxemias to Plant, Animal, and Microbial Toxins

RW Wannemacher 97.20.35.02

Studies involve evaluating the pathological alterations and metabolic excretion patterns after the intoxication of laboratory animals with ricin and saxitoxin. Research opportunities consist of metabolic alterations, measurements of distribution and excretion patterns of toxins, prophylaxis, drug therapy, and/or comparative toxicity. These studies employ the following techniques: gas-liquid chromatography, high-performance liquid chromatography, mass spectrometry, cell biology, and pathophysiology in laboratory animals. One of the objectives of this program will be to develop effective therapeutic agents for prophylaxis and/or treatment of individuals exposed to these toxins.

Detection, Prophylaxis, and Therapy of Plant, Animal, and Microbial Toxins

JF Hewetson 97.20.35.03

Studies are in progress to develop innovative immunodetection and diagnostic techniques for plant, animal, and microbial toxins in biological matrices. Nonradioactive assays that maximize sensitivity and selectivity for these toxins are stressed, as well as research on toxins such as ricin, saxitoxin, staphylococcal enterotoxins, and botulinum toxin. Also under investigation is passive antibody therapy, which includes monoclonal and polyclonal antibody fragments, and vaccination studies to protect against oral, aerosol, or parenteral exposure. In addition, opportunities exist to study the modulating effect of toxins on cellular and humoral function, host survival, and susceptibility to pathogenic agents. Support services such as cell culture and hybridoma laboratories are available for all research.

Analytical Toxicology

HB Hines 97.20.35.04

Research centers on developing and applying innovative analytical techniques to identify and quantify biological toxins and/or their metabolites at trace and ultratrace levels in complex matrices, and also to provide structural information about these compounds and possible derivatives. To attain these goals, original research employs the following instrumentation: (1) chromatographic, including gas and liquid chromatographs; (2) capillary electrophoresis; and (3) mass spectrometric, including one medium-resolution hybrid instrument, and one triple quadruple instrument—each with a range of accessories that include gas chromatography, liquid chromatography (thermospray), DCI, FAB, and electrospray. Other techniques may be used as necessary.

References

Hines HB: Biological Mass Spectrometry 22: 243, 1993

Hines HB, Brueggeman EE: Journal of Chromatography A, 670: 199, 1994

Signal Transduction and the Molecular Basis of Toxin Action

RB Wellner 97.20.35.05

This laboratory focuses on the molecular mechanisms by which toxins express their cytotoxic effects in animal cells. Mechanistic studies concern binding such toxins to cellular components, transporting them to the action site, and expressing enzymatic or nonenzymatic activities. Emphasis is placed on second

messenger pathways (e.g., cAMP, Ca^{2+}, inositol phosphates, G-proteins, protein kinases, and phosphatases), and their role in the expression of toxin effects. Toxins of interest include (but are not limited to) botulinum, ricin, and maitotoxin. A wide variety of biochemical and somatic cell genetic techniques are utilized in our studies. In addition, fluorimetry (including imaging) is available for measuring changes in intracellular free [Ca^{2+}], pH, membrane potential, and other parameters associated with signal transduction and toxin action.

Detection, Pathophysiology, and Therapy of Marine Toxins

MA Poli 97.20.35.06

A primary research goal is to purify and isolate toxin metabolites from *in vivo* and *in vitro* mammalian systems. These studies utilize novel high-performance liquid chromatography methods and other separation technologies, stressing separations from biological matrices and cell culture systems. Other projects target (1) the development of immunoassays for marine toxins, as well as immunotherapy and immunoprophylaxis protocols and (2) the pathophysiology of intoxication in whole animal and cell culture models. Toxins of interest include dinoflagellate toxins (e.g., saxitoxin, brevetoxins, ciguatoxin, maitoxin) and palytoxin. Opportunities also exist to study protein toxins, including ricin.

Reference

Poli MA, et al: in Marine Toxins: Origin, Structure, and Molecular Pharmacology. Edited by Hall S, Strichartz G. Washington DC: American Chemical Society, 1990: 176

Pathophysiology and Treatment

CT Liu 97.20.35.07

The main objectives of this laboratory are (1) to understand the physiological and biochemical mechanisms of pathogenesis of selected toxemias; (2) to search for physiological and/or pharmacological means to reverse or inhibit processes of lethal, toxemic diseases; and (3) to develop new techniques for physiological studies.

Current research activities emphasize mainly dynamic functional changes and systematically integrated relationships during certain toxemias. Toxicokinetics are also studied. Laboratories are well designed and equipped with modern devices for studying cardiovascular, renal, cerebral, gastrointestinal, respiratory, and hepatic functions; fluid compartmental analysis; and metabolism of water, electrolytes, carbohydrates, lipids and lipid

mediators in monkeys, guinea pigs, rabbits, and other animals. Effects of postural changes (head-up and head-down tilts) on cardiopulmonary functions, and physiological changes in isolated and perfused organs of control and toxemic animals are also stressed. Excellent computer facilities are available for data processing and statistical analysis.

References

Guo ZM, et al: Laboratory Animal Science 43: 569, 1993
Qian C, et al: Laboratory Animal Science 44: 600, 1994

Pharmacological Intervention in Neurointoxination

RD Crosland 97.20.35.08

Research in this laboratory focuses on developing nonimmunological therapies for the prevention, treatment, and cure of neurotoxin poisoning. Past efforts have included *in vivo* testing of selected drugs for their efficacy in providing protection from the effects of snake venoms and their constitutive neurotoxins. Experiments are also under way to elucidate the mechanism of action of various presynaptic neurotoxins with the hope that understanding a toxin's mechanism of action will facilitate the development of therapeutic strategies to counteract the toxin's effects. These experiments should provide insight into the normal mechanism of release of neurotransmitters. Current studies explore the effects of neurotoxins on the following processes in synaptosomes and neuronal cells lines: (1) uptake, level and release of neurotransmitters; (2) flux and level of ions and second messengers; and (3) membrane potential. The factors that affect binding of neurotoxins are also being determined, while electrophysiological and chemical techniques are being utilized to investigate the effects of toxins on transmission at the mammalian neuromuscular junction. Further research will not be limited to these areas of investigation; thus, the Associate may suggest alternative approaches that contribute to the objective of the laboratory. Moreover, collaboration with other members of the Institute who have expertise in this field is encouraged.

Molecular Immunology of Antigen Recognition

RG Ulrich 97.20.35.09

Our research concerns the mechanisms by which bacterial and viral antigens are recognized by specific receptors of the immune system. Contemporary techniques of molecular biology, biochemistry, and cell biology are emphasized. The two major receptors are T-lymphocyte antigen receptors and

the peptide-binding glycoproteins known as MHC (Major Histocompatibility Complex)-class II molecules. Protein antigens, which are either produced by cells of the immune system or taken up from the extracellular environment, are usually broken down into peptides ("antigen processing") and brought into contact with antigen receptors of the MHC. Furthermore, T lymphocytes can recognize and respond to antigens only if they are bound to MHC molecules. By mass spectroscopy and other microanalysis methods, we can identify naturally processed antigenic peptides. This information is being used to develop more effective vaccines. We also study immune recognition of super antigens produced by strains of the bacterium *Staphylococcus aureus*. In an unprocessed form, these toxins exhibit a high-binding affinity for MHC-class II molecules. This class II/toxin complex is recognized by T lymphocytes expressing antigen receptors of specific Vβ subclasses. Site-specific mutagenesis and other recombinant-DNA techniques are used to alter the products of both toxin and receptor genes, allowing us to directly assess the role of protein structure in the function of each component of the immune and toxin response. Other ongoing projects related to vaccine research include expression of heterologous proteins in mammalian and alternative (non-Saccharomyces) yeast cell systems.

Immunology of Protein Toxins

BG Stiles 97.20.35.10

Our goal is to define neutralizing epitopes on protein toxins employing such techniques as epitope mapping with the Geysen "peptide on pins" procedure using polyclonal/monoclonal antibodies, nonradioactive receptor assays to detect protective monoclonal/polyclonal antibodies against postsynaptic neurotoxins, polyacrylaminde gel electrophoresis, immunoelectrophoresis, Western blotting, ELISA, and affinity chromatography. Although our research has involved snake venom toxins and the staphylococcal enterotoxins, other protein toxins may be studied using the same techniques. We also encourage the use of different techniques to solve goal-oriented research; freedom to do multiple, focused projects; and collaborations with other scientists inside or outside the institute.

Characterization of Antibody Products for Therapy in Botulinum Type A Intoxication

LA Smith 97.20.35.11

The current inventory of potential antibody therapeutics for Botulinum type A intoxication is limited. A polyclonal equine $F(ab)_2$ product, characterized in mice and nonhuman primates, is the standard against which alternatives must be compared. An avian antibody product represents one alternative. We have studied the advantages of a chicken product (over an equine alternative) for North American crotalid invenomation. Monoclonal antibodies would be a more optimal solution since a human product could be developed. Single monoclonal antibodies, as well as combinations of two and three will need to be considered. We will use the Pharmacia BIAcore as the instrument to assess monoclonal antibody pair-wise binding and affinity, and will make comparisons between monoclonals and one polyclonal, or between the two polyclonal antibody preparations. Western blot, ELISA, and BIAcore analysis of the Botulinum holotoxin; and its subunits and peptides will be conducted. Correlations with *in vivo* protection (in mice) should elucidate the mechanisms of protection/neutralization, while an improved therapeutic antibody can be characterized. Our goal would be to understand passive immune prophylaxis and therapy at the molecular level.

Reference

Carroll SB, et al: Toxicon 30(9): 1017, 1992

Mucosal Immunization Using Cholera Toxin as a Vaccine Adjuvant

MT Dertzbaugh 97.20.35.12

Our laboratory is interested in developing vaccines to agents of military relevance that can be mucosally administered and/or that elicit mucosal immunity. Particular emphasis is placed on using cholera toxin and its B subunit as vaccine adjuvants. Unlike most proteins administered orally, cholera toxin is able to induce a potent immune response to itself and induce immunity to antigens that are normally poor immunogens when administered orally. We have developed plasmid vectors for genetically fusing antigens to cholera toxin and are currently using these vectors to make fusion proteins for incorporation into subunit vaccines. These fusion proteins are purified and then evaluated for their immunogenicity and protective efficacy. We are also using cholera toxin to probe the mucosal immune system so we can understand the properties that make it such an effective mucosal immunogen. Using site-directed

mutagenesis, our goal is to correlate changes in the structure of cholera toxin with changes in its immunogenicity. In addition, we are exploring alternate routes of mucosal immunization (e.g., intranasal or inhalation) in order to determine how different routes affect the potency and distribution of the immune response.

References

Dertzbaugh MT, Elson CO: Infection and Immunity 61: 48, 1993
Dertzbaugh MT, Elson CO: Infection and Immunity 61: 384, 1993

Aerobiology

MLM Pitt 97.20.35.13

Research focuses on preclinical efficacy studies of candidate vaccines to protect against aerosol challenges with both infectious agents and biological toxins. Studies include generation and characterization of biological aerosols; development of appropriate animal models for evaluating candidate vaccines; research on the pathogenesis and immune mechanisms involved in the disease/intoxication processes; and design and performance of efficacy studies to determine route, dose, schedule, and formulation of candidate vaccines.

Inhalation Toxicology

DA Creasia 97.20.35.14

This laboratory conducts research to evaluate toxicity from the inhalation of plant, animal, and microbial toxins. Emphasis is placed on studies that involve alterations in pulmonary and cardiorespiratory parameters in laboratory animals following intoxication from inhaled toxins. Research opportunities exist in the following areas: (1) toxin aerosol deposition and clearance, (2) alteration in pulmonary mechanics resulting from inhaled toxins, (3) pulmonary physiology including respiratory immunology, (4) macrophage function, and (5) evaluation of therapeutic intervention for preventing toxicosis after the inhalation of toxin aerosols. In addition, the laboratory offers opportunities to collaborate with experts in the areas of metabolism, cardiac function, and immunology.

Targeted Delivery of Vaccines for Micro-organisms and Toxins, and Amplification of Their Efficacy with Immune Response Enhancers

M Kende 97.20.35.15

Research focuses on (1) targeting devices made of polymeric microcapsules, nanoparticles, liposomes, and other delivery systems in conjunction with

immunoadjuvants or cytokines for prolonged release, continued stimulation of the biological responses, and enhancement of the immunity; and (2) delivery systems suitable for oral or aerosol delivery of the immunogen, and methods for time-dependent stimulation of the immune response. The biological activity of the carrier system(s) and formulations of the synthetic adjuvant(s), which elicit both the humoral (systemic and/or mucosal) and the cellular immune response by targeting the antigen into antigen-processing cells will be characterized by cytokine markers and markers of lymphocyte subsets. The ability of the synthetic immunomodulator to enhance MHC class I and II expression on the surface of respective cells will be studied as an indication of the enhanced immune response, in conjunction with microbial immunogen delivered in a carrier.

Reference

Kende M, Tice RD, Yan C: Carrier-mediated antiviral therapy, in Liposomes in Biomedical Applications, Drug Targeting and Delivery. Edited by Shek PN. Amsterdam: Harwood Academic Publishers, 1995: 147

Immune Responses to Infectious Agents and Biotoxins

T Krakauer 97.20.35.16

Current research explores *in vitro* systems to study the interaction of bacteria (*Yersinia pestis*, *Francisella tularensis*) and biotoxins (bacterial endotoxin, *Staphylococcal* enterotoxins, ricin) with human lymphoid cells. Research focuses on (1) the ability of macrophages to phagocytose foreign substances, process and present antigens to T lymphocytes, and produce and release soluble mediators (cytokines) in the inductive phase of an effective immune response; (2) the induction of macrophage antimicrobial activity against extra- and intracellular pathogens; and on (3) cellular receptors for migration of lymphocytes to sites of antigenic stimulation. Animal models will also be developed for these infectious agents to study the cellular and humoral immune response.

References

Krakauer T: Journal of Leukocyte Biology 56: 458, 1994

Krakauer T, Oppenheim JJ: Journal of Immunology 150: 1205, 1993

Directed Subversion of the Immune Responses through Antigen Processing and Presentation

S Bavari 97.20.35.17

Diverse mechanisms are used to capture protein antigens by antigen presenting cells. Internalized antigens are transferred to the acidic compartments where degradation occurs. The resulting antigenic peptides reach a specialized major histocompatibility complex class II compartment, in which class II molecules encounter peptides. Peptide-loaded class II complexes are then transported to the cell surface for sampling by T helper cells. The internalization and routing of antigens play a decisive role in their processing and presentation of T lymphocytes, which ultimately determine the effectiveness of the immune response.

Research focuses on understanding the antigen processing and presentation pathways of protein toxins and on studying the molecular mechanisms of T-cell anergy caused by bacterial superantigens and other disease states. Broad and complex investigations require advanced knowledge of theory and methodology in many areas of biological science. Emphasis is placed on cellular biology, cellular and molecular immunology, and molecular biology. Research centers on understanding molecular and cellular mechanisms of action of protein toxins, and on developing new and innovative methods for evaluation and construction of new and improved vaccines against biological protein toxins.

Virology Division
GB Jennings, Chief

Viral Immunology

AL Schmaljohn 97.20.25.01

Principal research interests are antigenic and immunogenic properties of viruses and viral subunits, with particular emphasis on identifying and testing epitopes relevant to new vaccines. Efforts include explorations of viral antigenic structure, mechanisms of immune-mediated resistance, fundamental bases of immunogenicity, and related topics. A wide variety of experimental approaches are used—ranging from classical techniques in virology, immunochemistry, and cellular immunology—to the exploitation of molecular

biology for expression of viral proteins and subunits. Principal emphasis has been placed on humoral immunity; however, appropriate initiatives in cellular immunology are also encouraged. Current emphasis is placed on filoviruses, especially marburg virus; other agents studied include vaccinia virus, hantaviruses, and alphaviruses.

Immune Responses to Viruses and Viral Vaccines

MK Hart 97.20.25.02

Basic and applied research opportunities are available to study the immune responses to viruses. This program focuses on understanding the mechanisms by which specific immune responses are activated. These studies complement and support concurrent efforts to develop new or improved viral vaccines for human use. Specific research areas include the induction of helper T-cell subsets and particular antibody isotypes following immunization with different viral immunogens, with emphasis on the induction of protective immune responses at mucosal surfaces. We also use synthetic peptide technology to identify viral sequences that serve as T- or B-cell epitopes and to distinguish the epitopes that induce protective responses from those inducing responses that limit vaccine efficacy. A unique HLA data base allows us to study the genetic restriction of antigen presentation. Facilities include suites for studying viruses requiring high levels of biocontainment, in-house peptide synthesis, and tissue culture support for hybridoma production.

Pathogenesis of Viral Infections

PB Jahrling 97.20.25.03

Basic and applied research opportunities exist for investigating several important human pathogens with particular emphasis on viruses causing hemorrhagic fever and encephalitis. Many studies are carried out in animal models using viruses not pathogenic for humans, but unique facilities also exist to permit work with high-hazard viruses as well. A major focus of research is the role of cellular and humoral immune responses in protection, recovery, and pathogenesis of these diseases. There is a strong interest in genetic determinants of host resistance or susceptibility and the determinants of viral virulence. Mechanisms underlying the action of experimental vaccines, immunotherapy, and chemotherapy are under active investigation. Human vaccines against togaviruses, bunyaviruses, and arenaviruses are under

development and testing. Activities are coordinated with those of other divisions and departments.

Characterization and Chemotherapy of Filovirus Infections

JW Huggins 97.20.25.04

Research centers on defining approaches for therapy of viral hemorrhagic fevers, especially those caused by filovirus; and on developing and characterizing improved animal models. Unique facilities are available for work with the high-hazed filovirus viruses, Ebola and Marburg, which cause the most severe viral hemorrhagic fevers. We encourage the following studies: (1) elucidating molecular targets for or mechanisms of drug action, both *in vitro* and *in vivo*; (2) developing specific methods and compounds that inhibit these functions; and (3) developing appropriate *in vivo* and *in vitro* models to test antiviral approaches. This laboratory has extensive experience, including clinical trials, in developing drugs active against viral hemorrhagic fevers. A key enzyme in regulating methylation reactions (S-adenosylhomocysteine hydrolase) has been identified as a molecular target for Ebola chemotherapy, presumably by inhibition of viral cap methylation, a required step in viral replication. Several inhibitors of S-adenosylhomocysteine hydrolase are under investigation and have shown protection in animal models.

Virology

JF Smith 97.20.25.05

Research opportunities are available for basic or applied research in molecular arbovirology. This program primarily focuses on biochemical studies of viral replication mechanisms and viral components, with emphasis placed on identifying the molecular determinants responsible for virulence, attenuation, and induction of protective immune responses. Current research involves (1) developing live-attenuated vaccines for alphaviruses by site-directed mutagenesis of infectious molecular clones, (2) developing nonreplicating vaccines for alphaviruses and hemorrhagic fever viruses by microencapsulation of viral immunogens obtained from eukaryotic expression systems, and (3) determining the safety and efficacy of candidate vaccines in animal models. Opportunities also exist to study viruses which require high levels of biocontainment.

Viral Biology and Micro Ecology

GV Ludwig 97.20.25.06

Basic and applied research opportunities exist to study potential human viral pathogens, with emphasis placed on members of the alphavirus genus. The current program focuses on (1) the study of the initial events of virus infection of cells as they relate to maintaining natural disease cycles—particular emphasis is placed on the isolation, identification, and characterization of receptors responsible for attaching viruses to cells, and for determining the relationships between the presence or absence of specific receptors in vertebrate and invertebrate hosts with the natural ecology of these viruses; (2) the use of monoclonal antibodies and other modern techniques to define the antigenic structure and function of virion proteins; (3) and the development and refinement of microencapsulation techniques for the production of a new generation of inactivated alphavirus vaccines. Facilities include high biocontainment level laboratories, access to mainframe and supercomputers, statistics support, and cell culture and hybridoma core support.

Reference

Ludwig GV, et al: Microbiology Pathology 11: 411, 1992

Molecular Virology

CS Schmaljohn K Anderson 97.20.25.07

The basic structure and function of viral genes and gene products are investigated using such molecular techniques as recombinant-DNA cloning, expression by eucaryotic vectors, protein purification, and monoclonal antibody production. Of particular interest are studies which lead to an understanding of mechanisms of replication, antigenic structure, or virulence properties of human pathogens. Opportunities for research are available on a variety of RNA viruses, including bunyaviruses, filoviruses, alphaviruses, and flaviviruses. Oligonucleotide and peptide synthesizers, containment facilities, and support services such as cell culture and hybridoma laboratories are readily accessible.

References

Li D, et al: Virology 206: 973, 1995

Schmaljohn CS: Reviews in Medical Virology 4: 185, 1994

Virus Research Related to Vaccine Development

GB Jennings 97.20.25.08

Research is conducted on several different pathogenic viruses to identify and characterize important epitopes and antigenic determinants that are potentially useful in protecting against human disease. Although we emphasize approaches employing recombinant-DNA technology and foreign gene expression systems, we also utilize classical vaccine development. Examples of future vaccine candidates include recombinant poxviruses, as well as chimeric alpha- and flaviviruses derived from "infectious cDNA clones". The goals of this laboratory are to develop genetically engineered polyvalent vaccines that protect against a variety of virus and nonviral threats, and to develop experimental animal models and study pathogenesis in order to evaluate the protection provided by experimental immunogens. Opportunities are available to investigate several different virus models and potential vaccines in facilities designed for containment and/or certified production of biological products. A modern biotechnology laboratory is also available for the more molecular aspects of the research. This program emphasizes the basic virology/immunology research that is required to design and develop new and improved human vaccines of the future.

References

London SD, et al: Proceedings of the National Academy of Sciences of the United States of America 89: 207, 1992

Schmaljohn CS, et al: Vaccine 10: 10, 1992

Vaccine Development

MD Parker 97.20.25.09

The goals of this laboratory are to develop and characterize vaccines that protect against a variety of viral diseases by combining elements of recombinant-DNA methodology and conventional vaccine development. Directed mutagenesis of infectious alphavirus cDNA clones provides a starting point for the analysis of virulence, attenuation, and pathogenesis. We are also utilizing intertypic reassortment of genomic RNA segments to characterize the virulence determinant of the Bunyaviridae and to develop and characterize vaccine candidates. Collaborations with clinical investigators facilitate the transition of vaccine candidates from basic research facilities to safety and

efficacy testing in primates and human volunteers. Opportunities are available to study other virus models that require higher levels of biocontainment.

US ARMY MEDICAL RESEARCH INSTITUTE OF CHEMICAL DEFENSE
Aberdeen Proving Ground, Maryland

Drug Assessment Divison

Basic Assessment Branch: Biochemical Mechanisms of Vesication and Inflammation

HL Meier 97.25.01.01

The biochemical mechanism of vesication induced by DNA-alkylating compounds and involvement of inflammatory mediators in the development of vesicating lesions are studied. The biochemistry of both metabolic changes induced by alkylating compounds and involvement of inflammatory mediators in vesication will be investigated in relevant human tissue. The development of a drug discovery program to determine the ability of a candidate to prevent vesicant-induced damage using (1) individual cell cultures of human lymphocytes and/or keratinocytes that will be analyzed to determine what effect alkylating compounds have on viability, energy production, and DNA repair mechanisms; (3) human mixed leukocytes and keratinocytes that will be examined to determine the effect of alkylating compounds and/or organophosphate esterase inhibitors on secretion of proteolytic enzymes and inflammatory mediators; and (3) skin organ cultures that will be investigated to determine the effect of alkylating compounds on morphology, mediator release, and lesion repair.

Therapeutic intervention will be designed from these studies on the biochemistry of lesion development. Potential candidate compounds will be investigated to determine their effects on the development of the lesion.

Neurobehavioral Assessment of Safety/Efficacy of Prophylactic/Treatment Compounds for Chemical Warfare Agents

JA Romano, Jr 97.25.01.02

This research program investigates the development of new methodologies to assess potential neurotoxicity of candidate compounds, as well as methodologies to assess the efficacy of candidate compounds in preventing or reversing the neurobehavioral effects of chemical warfare agents. Approaches used in this research include Serial Probe Recognition and one- or two-way

avoidance measures, to encompass conditioned discrimination avoidance or measures of place learning. A variety of species are also used, with the goal of understanding neurotoxic or myopathic actions of various chemical warfare agents and of selecting lead compounds for development based on successful safety and efficacy studies.

Characterization of Magnetic Biotechnology Spectroscopy to Address Biochemical Perturbations Induced by Chemical Warfare Agents

CM Arroyo 97.25.01.03

Research focuses on the application of sensitive spectroscopic techniques to study molecular mechanisms in cell systems, tissues, and organs. Spectroscopic techniques include magnetic resonance (electron paramagnetic resonance [EPR], electron nuclear double resonance, and nuclear magnetic resonance [NMR]) and fluorescence spectroscopy (time dependent, anisotropy, and polarization). Free radical research techniques are used to measure radicals and radical-mediated damage in chemical systems, cells, and tissues under the following headings: (1) determination of radical damage to DNA and RNA, (2) detection of protein structural modifications induced by free radicals, (3) lipid peroxidation, (4) antioxidant consumption, (5) indirect radical assays, and (6) transition metal complexes as sources of radicals. We have also employed similar approaches in order to characterize the optimal conditions for applying future *in vitro* and *in vivo* toxicology measurements using EPR/spin trapping/spin labeling and ^{31}P-NMR techniques to elucidate toxicity mechanism(s) induced by chemical agents.

We are also developing analytical methods to demonstrate safety and efficacy of reactive components for a topical skin protectant that will provide equivalent protection against penetration and will detoxify both vesicant and nerve chemical warfare agents.

Pathophysiology Division

Comparative Pathology Branch: Ultrastructural Correlates of Threat Agent-Induced Toxicity

JP Petrali 97.25.15.01

Research is being conducted to detect morphologic correlates of acute, chronic, and delayed effects of toxic compounds. Tissues from animal and cell

model systems exposed to lethal and sublethal doses of chemical-biological toxins are being gathered for morphologic, histochemical, cytochemical, and immunocytochemical analyses with emphasis placed on the neuromuscular, integumentary, endocrine, immune, nervous, and respiratory systems, as well as on blood-brain barrier function. Technology in ultrastructural disciplines, including transmission electron microscopy, scanning electron microscopy, and x-ray energy dispersive microanalysis, is available for use.

The goal of our research effort is to provide an ultrastructural pathology and morphocytochemical data base of threat agent-induced toxicity that will contribute anatomical considerations to the design of effective prophylactic and antidotal regimens.

Neurotoxicology: Electrophysiology

M Adler 97.25.15.02

The primary goal of the Membrane Biophysics Laboratory is to elucidate the mechanism of action of neurotoxic agents on central and peripheral voltage- and neurotransmitter-activated ion channels. We use voltage-clamp, iontophoresis, pressure-ejection, and single-channel patch clamp techniques. Research includes (1) evaluating the efficacy of metalloprotease inhibitors on botulinum toxin-induced muscle paralysis using capillary electrophoresis to monitor the cleavage of presynaptic peptides expressed by recombinant-DNA techniques, (2) assessing the actions of potential botulinum toxin treatment compounds on mouse phrenic nerve-hemidiaphragm preparations and on cultured spinal cord neurons, (3) determining the role of channel formation in the internalization of botulinum toxin using artificial lipid bilayers in conjunction with the patch-clamp technique, (4) using molecular modeling techniques to elucidate the three-dimensional structure of neurotoxin active sites. We have five electrophysiological recording units and a fully equipped cell/culture facility.

Neurotoxicology: Electrophysiology and Neuropharmacology

MG Filbert 97.25.15.03

Research focuses on (1) potential antidotes to botulinum toxins using electrophysiological techniques such as voltage clamp, iontophoresis, and intraneuronal micropressure-injections to examine the effects of toxins on synaptic transmission in the nervous system of the *Aplysia californica*; and on

(2) neuroprotective mechanisms for threat agent-induced, seizure-related brain damage.

Physiological Mechanisms of Biological Toxin Effects in the Nervous System

RE Sheridan 97.25.15.04

This research program investigates the physiological changes in nerve and/or muscle function that follow exposure to toxins of biological origin. Our approaches rely heavily on electophysiological measurements of nerve and muscle activity using patch-clamp, intracellular and extracellular techniques, as well as other functional assays of synaptic activity. These measurements are supplemented with molecular, biochemical, and ultrastructural examinations of the affected tissue as well as theoretical modeling of toxic interactions. A variety of preparations have been used, including isolated organs, brain slices, and single tissue-cultured cells. Our goal is to understand the neurotoxic actions of biological toxins and to select promising directions for therapeutic and prophylactic treatments.

References

Sheridan RE: Brain Research Bulletin 30: 577, 1993
Sheridan RE, Deshpande SS: Toxicon 33: 539, 1995

Research on Sulfur Mustard

ME Martens 97.25.15.05

Current research focuses on elucidating the basic biochemical mechanisms that underlie skin lesions (i.e., blister formation) induced by the chemical warfare agent, sulfur mustard, with emphasis on designing effective antidotes to this potent alkylating agent. This research considers questions which directly impact our understanding of the wider issues of skin toxicology and the mechanism of cell death. Primary emphasis is placed on cellular energy metabolism as a key component in sulfur mustard-induced cell injury. The goals of this project are to define (1) the effects of sulfur mustard on the major pathways of energy metabolism, (2) the mechanism(s) by which sulfur mustard alters cellular energy metabolism, and (3) the role of metabolic injury in the events leading from the initial alkylation event to blister formation. *In vitro* models used in this research are cultured human epidermal keratinocytes and artificial skin systems. We combine biochemistry, cell biology, and toxicology

to generate a picture of the energy state of the cell as it relates to cell structure and function.

Pharmacology Division

Biochemical Pharmacology

CA Broomfield 97.25.05.01

We are generally interested in protein structure, mechanisms of enzyme action, and in physiologically active peptides. Our diversified laboratory has protocols for a variety of research including studies of (1) drug binding to acetylcholine receptors, (2) the role of intrinsic peptides in the inflammatory response after mustard injury, (3) the effect of organophosphorus anticholinesterases on neuropeptide metabolism, and (4) the design and production of specific monoclonal antibodies to scavenge and hydrolyze organophosphorus compound (OP) cholinesterase inhibitors. In addition, research continues on two OP-acid anhydride hydrolases, which includes isolation, characterization, amino acid sequencing, and gene isolation. We have also recently initiated computer-modeling studies to design sited-directed mutants of cholinesterases that will efficiently hydrolyze OP anticholionesterases.

This laboratory is equipped for these studies with the following technology: high-performance liquid chromatography; fast protein, peptide, and polynucelotide chromatography; ultracentrifuges; spectrophotometers; spectrofluorometers; electron spin resonance spectrometers; Beckman Sequenator; spectropolarimeters; all other ancillary equpment; and recently installed computer molecular modeling equipment and software. Almost any protein chemistry protocol can be supported (even site-directed mutagenesis) if it is related to the mission of MRICD.

Reference

Broomfield CA, et al: in Enzymes Hydrolyzing Organophosphorus Compounds. Edited by Reiner R, Aldrich WN, Hoskin FCG. Chichester (England): Ellis Horwood, 1989: 79

Biochemical Pharmacology: Biochemistry of Antibodies and Enzymes

DE Lenz 97.25.05.02

Research focuses on identifying the structure and function of the specific site(s) on macromolecules (enzymes and antibodies) that are responsible for binding small molecules (e.g., inhibitors or haptens). The overall goal is to

design macromolecules which would function as biological "scavengers" *in vivo* and would provide prophylactic protection against selected toxic substances. Projects include (1) developing and using highly specific monoclonal antibodies that are capable of binding toxic substances *in vivo*, which would alter the pharmacokinetics of the toxicant so that it is rendered nontoxic; (2) using computer-aided molecular modeling of transition-state analogues to aid in the design of immunogens, which would result in the production of catalytic antibodies; (3) using molecular biological techniques to produce catalytic antobodies; and (4) using recombinant-DNA techniques or point mutation of gene products to alter the binding and kinetic properties of selected enzymes. Among the requisite equipment available to support this research are tissue culture facilities for hybridoma production, electrophoretic equipment, high-performance liquid chromatography, and spectrophotometric instrumentation. Furthermore, there are two Evans and Sutherland PS-390 graphics terminals available with supporting software on the VAX cluster, to carry out molecular modeling studies.

Biochemical Pharmacology: Toxicity as a Result of Disturbed Calcium Homeostasis and Neurotoxins

R Ray 97.25.05.03

Major research areas include (1) studies on calcium-mediated toxicity as a result of alkylating agents (e.g., sulfur mustard) and (2) pharmacological and molecular biological approaches in preventing neurotoxicity that results from botulinum toxins and sodium channel toxins. These studies are usually performed using cultured primary or clonal cell models. Experimental techniques involve (1) measurement of membrane transport of proteins and ions; (2) ligand-receptor interactions; (3) fluorometric determinations of cytotoxicity, ion concentrations, and enzyme functions; and (4) neurotransmitter metabolism and release.

Basic Pharmacology: Brain Neurotransmitters

TMA Shih 97.25.05.04

Current research explores the following subjects: (1) the mechanisms by which toxic compounds acutely or chronically affect central putative neurotransmitter systems with regard to neurotransmitter levels, release, uptake, or turnover rates; enzyme activity; receptor binding; interaction between neurotransmitter systems in various brain areas; and the effects of antidotal or pretreatment

compounds on these parameters and (2) the mechanisms of action of anticonvulsants and/or antiseizure compounds in convulsions and seizure activity induced after chemical toxicity. Among the chemical toxicants of interest are anticholinesterases, cyanide, and agents of biological origins (neurotoxins).

These projects involve electrophysiological and neuropharmacological studies on central neurotransmission using EEG analysis procedures, as well as automated gas chromatograph/mass spectrometry, high-performance liquid chromatography with electrochemical detection, and colorimetric and radioenzymatic techniques.

Cardiovascular Pharmacology: Biochemical Mechanisms

SI Baskin 97.25.05.05

Organophosphates and saxitoxin are known to exhibit effects such as cardiac arrhythmias and cardiac failure. The toxic actions of both of these classes of compounds include atrial changes, cardiac nodal shut down, and life-threatening ventricular or conductive tissue dysfunction. Mechanisms responsible for organophosphates may include alterations in cardiac cholinergic subpopulations, detoxification enzymes for acetylcholine and second messengers for cholinergic function, and possibly transport of cholinergic precursors. Specific chemical tools and/or known agents that affect excitable cell action could be utilized to probe and identify sites and mechanisms of the cardiac injury by this poison group. Development of specific antagonists could lead to new treatments against the cardiac toxicity caused by organophosphates, while agents that affect sodium channel and transporters, and tools that modify guanidino activity could be used to explore cardiac atrial-ventricular nodal function that regulate cardiac excitatory and pump effects of the heart. Antiarrhythmic drugs may be beneficial to the harmful effects of these types of poisons.

Further research is needed on elucidating the toxicological sites and treating with potential antidotes. We anticipate that new, more cardiac specific drugs will provide rational specific therapies for the future.

Molecular Pharmacology and Toxicology

JJ Schlager 97.25.05.06

Our primary research effort has centered on the production of catalytically active antibody binding fragments from mouse IgG and a Fab mRNA

combination of cDNA (cloned DNA) library using gene amplification, expression, and analysis techniques. These techniques include production of cDNA libraries, polymerase chain reaction, ELISA, and novel cloning and analysis procedures. Investigations focus on producing a combination of heavy and light chain mouse IgG cDNA libraries, which exhibit catalytic hydrolysis activity toward the organophosphonate soman and the screening of human synthetic Fab libraries for catalysis and binding. New research centers on the mechanistic analysis of cell toxicity produced by specific and nonspecific alkylating chemicals. Our goal is to identify new therapeutic intervention for human protection. We use molecular biological approaches to characterize toxic mechanisms of chemical warfare agents. Research topics include analysis of cell-cycle dependent proteins, protein phosphorylation events, cytoskeletal protein regulation, and the effects on cellular RNA after cell exposure to sulfur mustard alkylation. Laboratory equipment consists of automated DNA sequencing and synthesizing capabilities, thermal cyclers, FPLC, capillary electrophoresis, microtiter plate readers, spectrophotometers, and bacterial and eucaryotic cell growth facilities.

Biochemical Pharmacology

CA Broomfield 97.25.05.07

We are interested in protein structure-function relationships, mechanisms of enzyme action, and enzyme engineering. Current research involves developing novel enzymatic activity by site-directed mutagenesis of selected enzyme genes, using computer-aided molecular modeling to design the desired mutants. Recent work includes developing organophosphorus anticholinesterase hydrolyzing activity in human butyrylcholinesterase, while retaining butyrylcholine hydrolyzing activity. This success verifies the approach and begs for refinement and expansion of the basic idea to develop useful products.

Our laboratory is well equipped with DNA synthesizers, a DNA sequencer, thermocyclers, an amino acid analyzer, a peptide sequencer, a peptide synthesizer, high-performance liquid chromatography, FPLC, ion chromatography, analytical and preparative ultracentrifuges, capillary

electrophoresis, cell culture facilities, laminar flow hoods, and a silicon graphics Iris workstation with several modeling software packages.

References

Millard CB, Broomfield CA: Biochemical and Biophysical Research Communication: 1280, 1992
Broomfield CA, et al: in Enzymes of the Cholinesterase Family. Edited by Balasubramanian AS, et al. New York: Plenum Press, 1995

US ARMY RESEARCH INSTITUTE OF ENVIRONMENTAL MEDICINE
Natick, Massachusetts

The US Army Research Institute of Environmental Medicine (USARIEM) is a subordinate laboratory of the US Army Medical Research and Materiel Command. Our mission is to conduct basic and applied research to determine how exposure to extreme heat, severe cold, high terrestrial altitude, occupational tasks, physical training, and deployment operations affect the health and performance of military personnel.

Our principal goal is to elucidate complex interactions of environmental stress and the body's defense mechanisms. From such information, we can determine the techniques, equipment, and procedures that are most effective in ensuring our soldiers are operationally effective. Other goals include developing biomedical techniques to sustain health and enhance performance through advances in physical fitness; and exploiting nutritional strategies, pharmacological interventions, ergonomic aids, and other novel biotechnological approaches. The Institute also conducts physiological assessments of medical defense measures developed to protect against chemical battlefield threats.

Occupational Physiology

JF Patton, III 97.30.00.01

This program encompasses the basic and applied aspects of physical fitness requirements for occupational performance, physical performance capacity, and physical training. Emphasis is placed on identifying and quantifying the physiological, biochemical, biomechanical, and body compositional determinants of physically demanding occupational tasks such as repetitive lifting and load carriage. Also studied is the methodology of body composition, and its endocrine control and role in physical performance. This program investigates factors and training programs related to the performance of high-intensity (anaerobic) exercise and determines methods of assessing the various components of physical fitness.

Heat

RP Francesconi 97.30.00.02

Models of human heat/exercise-injury have been developed and utilized extensively by investigators of the Comparative Physiology Division. These models have been useful in identifying and quantitating the effects of factors that predispose to human heat/exercise syndromes, such as electrolye imbalance, low-grade fever, obesity, phenothiazine drugs, alcohol consumption, anticholinergics and anticholinesterases, and hypohydration. Extension in the use of a rat model is sought to study how the physiological cost of work in the heat can be reduced and human heat/exercise injury can be more effectively identified, prevented, and treated. In addition, rabbit and porcine models of the cardiovascular, neurological, and clinical sequelae of heat injury have recently been developed.

Further studies will assess models for RES competence and immunotherapy, along with other forms of supportive therapy.

Thermal Biophysics

RR Gonzalez 97.30.00.03

Experimental studies and related analytical investigations are conducted to provide a characterization of human interaction with the thermal environment. Emphasis is placed on the thermal biophysics of such problems as heat and moisture transport, thermal modeling, environmental stressors affecting clothing properties, and human reaction to such stressors. More applied ergonomic fields include heat exchange with chemical-protective clothing, upper-body versus lower-body heat transfer, water-immersion problems of heat transfer, infrared thermography, and intracellular dynamics. General investigative areas involve assessment of clothing, air motion and vapor transmission with dew-point sensors, regional heated copper hand-and-foot models, static mannequins, and an articulated movable mannequin.

Reference

Gonzalez RR: in Human performance physiology and environmental medicine at terrestrial extremes. Edited by Pandolf KB, Sawka MN, Gonzalez RR. Indianapolis: Benchmark, 1988: 45

Computer Prediction Modeling

KB Pandolf 97.30.00.04

Over the last two decades, our laboratory has established the data base and developed a series of predictive equations for deep-body temperature, heart

rate, and sweat loss responses of clothed soldiers who perform physical work in hot environments. We have developed a comprehensive model which is programmed on a Hewlett-Packard 41 CV hand-held calculator. The primary physiological inputs are deep-body (rectal) temperature and sweat loss; while the predicted outputs are the expected physical work/rest cycle, the maximal single physical work-time (if appropriate), and the associated water requirements. Preliminary attempts have been made to develop a prediction model for soldier performance in the cold, with the primary focus on water or air temperature, physical work level, clothing worn, and body morphology. However, this model needs further refinement before it can develop into an operational model similar to that employed for hot environments.

Altitude-Induced Illnesses and Pathophysiology

A Cymerman 97.30.00.05

Studies of acute and chronic altitude exposure are conducted to provide a basis for developing prophylaxis and treatment of altitude-induced illnesses, such as acute mountain sickness, pulmonary edema, and cerebral edema. A human program focuses on discerning altitude-sensitive individuals, effective pharmacological interventions, and basic physiological and biochemical mechanisms operative during acute exposure and acclimatization. In-depth research is directed toward studies of ventilatory control mechanisms, energy expenditure, and physical exercise. Recent areas of investigation include effects of simulated and real altitude exposure on fluid requirements and balance, nutrition, and dietary considerations; elucidation of factors predisposing to illness, such as exercise and ventilatory sensitivities to hypoxia and hypercapnia; and the role of the menstrual cycle in acclimatization of women to altitude. These effects are studied in an in-house, man-rated hypobaric facility capable of sleeping 8-10 individuals, at a field laboratory situated on the summit of Pikes Peak, Colorado, and in actual field conditions in mountainous areas of the world.

Human Environmental Physiology

AJ Young 97.30.00.06

Current research focuses on elucidating physiological mechanisms for alterations in human physical performance that occur during exposure to extreme climates. Recent investigations have studied the effects of heat and cold stress on skeletal muscle metabolism during exercise, and the effects of

muscle glycogen depletion on shivering and thermal balance during cold water immersion. Studies currently examine effects of hypohydration on shivering and vasoconstrictor responses during cold exposure, and examine thermoregulatory adjustments experienced by humans during the process of cold acclimatization. We are also investigating how human thermoregulatory, metabolic, and cardiovascular responses to cold exposure are affected when the additional stress of hypoxia is superimposed and are developing physiological tests to identify individuals susceptible to cold injury.

Reference

Young AJ, et al: Journal of Applied Physiology 75: 49, 1993

Thermal Physiology and Medicine

MN Sawka 97.30.00.07

Research opportunities exist to (1) define basic mechanisms and systemic physiological issues related to human thermoregulation; (2) delineate human tolerance limits and work performance capabilities in hot and cold climates; (3) enhance human climatic tolerance and work capabilities by acclimation, training, and biological interventions; (4) evaluate clothing and pharmaceutical products that potentially alter thermal strain; and (5) perform epidemiological studies to identify predisposition factors to thermal injuries/illnesses. Research is conducted in climatic chambers (-57° to +74°C), a water immersion laboratory (+5° to +45°C) pool, and temperature-controlled hypobaric (-35° to +43°C, 9000 meters) chambers. We also have the capability to perform almost any physiological or biochemical measurement employed by environmental or exercise scientists.

Neuroscience, Environmental Stress, and Nutrition

HR Lieberman 97.30.00.08

Research opportunities are available in the areas of neurochemistry, neuroanatomy, nutrition, and behavior. Brain mechanisms regulating behavioral functions such as arousal, memory, and responsiveness to stress are examined using a variety of methods. The effects of environmental stress on the brain are assessed, and treatments to mitigate such effects are developed. Central neurotransmitter systems are manipulated with drugs, nutrients, and environmental stress (e.g., heat, cold, hypoxia). A key objective is to elucidate the relationships between neurotransmitter systems and behavior. Both animal and human studies are conducted.

Brain neurochemistry is studied *in vivo* by performing microdialysis in freely moving animals and assaying samples with high-performance liquid chromatography. Histological and histochemical techniques utilized include receptor autoradiography, *in situ* hybridization, and computerized image analysis. Electrophysiologic capabilities include auditory and visual evoked potentials. Learning, memory, and operant behavior are assessed. Unique facilities consist of environmental chambers suitable for studies of heat, cold, and hypoxia in animals and humans.

References

Shukitt-Hale B, et al: Brain Research 621: 291, 1993
Stillman MJ, et al: Brain Research 32: 385, 1993

US ARMY INSTITUTE OF SURGICAL RESEARCH
Fort Sam Houston, Texas

Microbiology/Host Resistance Epidemiology/Wound Healing

AT McManus 97.40.00.01

Research focuses on various aspects of the interactions between host defenses (modified by burn injury) and opportunistic pathogens, including adaptation of molecular approaches to identifying specific microbial virulence factors and targeted host defects. This research is coordinated with a burn patient, dedicated clinical microbiology laboratory, which processes more than 10,000 specimens per year as well as a cumulative microbiology/infection data base (>150,000 records). We also investigate basic and applied aspects of wound protection and healing (topical agents/devices).

References

McManus AT, et al: Archives of Surgery 129: 1306, 1994
Chu CS, et al: Journal of Trauma 40: 738, 1996

Studies of Neuroendocrine Abnormalities and Thyroid Hormones in Burn Pathophysiology

GM Vaughan 97.40.00.02

The primary interest of this laboratory is neuroendocrinology with a major focus on burn-injured subjects as models of nonthyroidal illness. Current studies involve pituitary, gonadal, and adrenal function with an emphasis on thyroid and pineal function, utilizing measurement of hormones from these and other glands and assessment of morphologic and tissue-enzyme responses in the brain. A new ultrasensitive assay for melatonin has just been developed, and assays for circulating cytokines are being assessed. We are also developing convolutional and other models for assessing hormone kinetics.

References

Vaughan GM, Pruitt BA Jr: Seminars in Nephrology 13(4): 359, 1993
Vaughan MK, Vaughan GM: Metabolic and thyroidal consequences of melatonin administration in mammals, in Melatonin: Biosynthesis, Physiological Effects, and Clinical Applications. Edited by Hing-Sing Y, Russel JR. Boca Raton: CRC, 1993: 311

The Cell and Molecular Biology of Tissue Injury and Repair

PD Bowman 97.40.00.03

This program focuses on the cell and molecular biology of traumatic tissue injury and repair after hemorrhage or burn. Our goal is to understand the cellular mechanisms involved and to develop methods of mitigating damage after injury and accelerating repair. Basic and applied research opportunities are available to study the involvement of cytokines in mediating trauma and tissue repair, to develop novel approaches (e.g., neutralizing antibodies or antisense oligonucleotides) to controlling their effects, and to study the application of tissue engineering approaches to tissue repair. Studies usually begin with human cell culture models followed by validation in animal models. They also involve testing the response of human neutrophils, keratinocytes, endothelial cells, and osteoblasts to several types of injury.

Pathobiology of Hemorrhage and Trauma

MA Dubick 97.40.00.04

This is a multifaceted program evaluating the efficacy of resuscitation fluids and other pharmacological interventions in the treatment of trauma and hypovolemia resulting from hemorrhage. Research includes (1) studies of mechanisms associated with the hemodynamic, biochemical, hormonal, and immunological alterations associated with trauma and/or hemorrhage; (2) the influence of factors such as central nervous system trauma, dehydration, and oxygen radicals on the response to trauma, hemorrhage, and resuscitation efforts; and (3) the role of cytokines and growth factors, and proteolytic enzymes in mechanisms associated with tissue injury and repair. *In vivo* studies employ a range of surgical, biochemical, and physiological techniques, while *in vitro* studies utilize organ culture techniques.

References

Dubick MA, et al: Annals of Emergency Medicine 21: 498, 1992

Dubick MA, et al: Drug Development Research 25: 29, 1992

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Index of Research Categories

1997 Research Associateship Programs

Albany Research Center
Armed Forces Radiobiology Research Institute
Center for Devices and Radiological Health
Federal Highway Administration/Turner-Fairbank Highway Research Center
Morgantown Energy Technology Center
NASA Ames Research Center
NASA Dryden Flight Research Center
NASA Goddard Space Flight Center
NASA Jet Propulsion Laboratory
NASA Lyndon B Johnson Space Center
NASA John F Kennedy Space Center
NASA Langley Research Center
NASA Lewis Research Center
NASA George C Marshall Space Flight Center
NASA John C Stennis Space Center
National Biological Service
National Institute for Occupational Safety and Health
National Institute of Standards and Technology
National Institutes of Health
National Oceanic and Atmospheric Administration
Naval Command, Control, Ocean Surveillance Center/Research, Development, Test, and Evaluation Division
Naval Medical Research and Development Command
Naval Postgraduate School
Naval Research Laboratory
The Aerospace Corporation
US Air Force Laboratory
US Army Armament Research, Development, and Engineering Center
US Army Edgewood Research, Development, and Engineering Center
US Army Medical Research and Materiel Command
US Army Missile Command
US Army Natick Research, Development, and Engineering Center
US Army Research Laboratories
US Army Research Office
USDA Forest Service
US Environmental Protection Agency
US Geological Survey
Waterways Experiment Station

Research opportunity booklets and application documents for all programs may be obtained by contacting the

Associateship Programs — TJ 2114
National Research Council
2101 Constitution Avenue
Washington, DC 20418
(202) 334-2760

National Research Council
1997 Research Associateship Programs
Alphabetical by Acronym

Organization	*Accepts the Following Applicants*			
	Postdoctoral	Senior	Foreign	Application Deadlines
AERO THE AEROSPACE CORPORATION	Yes	Yes	No	Jan 15/Apr 15/Aug 15
AFRRI ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE	Yes	Yes	Yes	Jan 15/Apr 15/Aug 15
ALRC ALBANY RESEARCH CENTER	Yes	Yes (Limited Number)	In special cases, where additional support is available	Jan 15/Apr 15/Aug 15
AMRMC US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND	Yes	Yes	Yes	Jan 15/Apr 15/Aug 15
US Army Medical Research Institute of Chemical Defense	Yes	Yes	No	
ARDEC US ARMY ARMAMENT RESEARCH, DEVELOPMENT, AND ENGINEERING CENTER	Yes	Yes	No	Jan 15/Apr 15/Aug 15
ARL US ARMY RESEARCH LABORATORY	Yes	Yes	No	Jan 15/Apr 15/Aug 15

Organization	*Accepts the Following Applicants*			
	Postdoctoral	Senior	Foreign	Application Deadlines
ARO US ARMY RESEARCH OFFICE	Yes	Yes	Yes	Jan 15/Apr 15/Aug 15
CDRH CENTER FOR DEVICES AND RADIOLOGICAL HEALTH	Yes	Yes	Yes	Jan 15/Apr 15/Aug 15
EPA US ENVIRONMENTAL PROTECTION AGENCY	Yes	Yes	Yes	Jan 15/Apr 15/Aug 15
ERDEC US ARMY EDGEWOOD RESEARCH, DEVELOPMENT, AND ENGINEERING CENTER	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
FHWA FEDERAL HIGHWAY ADMINISTRATION	Yes	Yes	Yes	Jan 15/Apr 15/Aug 15
METC MORGANTOWN ENERGY TECHNOLOGY CENTER	Yes	Yes	No	Jan 15/Apr 15/Aug 15
MICOM US ARMY MISSILE COMMAND	Yes	Yes	Legal Permanent Residents Only	Jan 15/Apr 15/Aug 15

Organization	*Accepts the Following Applicants*			
	Postdoctoral	Senior	Foreign	Application Deadlines
NASA — NATIONAL AERONAUTICS AND SPACE ADMINISTRATION				
ARC — AMES RESEARCH CENTER	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
DFRC — DRYDEN FLIGHT RESEARCH CENTER	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
GSFC — GODDARD SPACE FLIGHT CENTER Goddard Institute for Space Studies Wallops Flight Facility	Yes	Yes	In Basic Science Areas	Jan 15/Apr 15/Aug 15
JPL — JET PROPULSION LABORATORY	Yes	Yes	In Basic Science Areas	Jan 15/Apr 15/Aug 15
JSC — LYNDON B. JOHNSON SPACE CENTER	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
KSC — JOHN F. KENNEDY SPACE CENTER	Yes	Yes	In Basic Science Areas	Jan 15/Apr 15/Aug 15
LaRC — LANGLEY RESEARCH CENTER	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
LeRC — LEWIS RESEARCH CENTER	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
MSFC — GEORGE C. MARSHALL SPACE FLIGHT CENTER	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
SSC — JOHN C. STENNIS SPACE CENTER	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
NBS NATIONAL BIOLOGICAL SERVICE	Yes	Yes	No	Jan 15/Apr 15/Aug 15
NIH NATIONAL INSTITUTES OF HEALTH	Yes	Yes	Seniors only; Otherwise, Legal Permanent Residents	Jan 15/Apr 15/Aug 15

Organization	*Accepts the Following Applicants*			
	Postdoctoral	Senior	Foreign	Application Deadlines
NIOSH NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH	Yes	Yes (Limited Number)	Yes	Jan 15/Apr 15/Aug 15
NIST NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY	Yes	No	No	Jan 15
NMRDC NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND	Yes	Yes	Yes	Jan 15/Apr 15/Aug 15
NOAA NATIONAL OCEANIC AND ATMOSPHERIC ADMINISTRATION	Yes	Yes	Yes	Jan 15
NPS NAVAL POSTGRADUATE SCHOOL	Yes	Yes	In Selected Areas	Jan 15/Apr 15/Aug 15
NRaD NAVAL COMMAND, CONTROL, AND OCEAN SURVEILLANCE CENTER; RESEARCH, DEVELOPMENT, TEST, AND EVALUATION DIVISION	Yes	Yes	No	Jan 15/Apr 15/Aug 15
NRDEC US ARMY NATICK RESEARCH, DEVELOPMENT, AND ENGINEERING CENTER	Yes	Yes	Yes	Jan 15/Apr 15/Aug 15
NRL NAVAL RESEARCH LABORATORY	Yes	No	No	Jan 15/Apr 15

Organization	*Accepts the Following Applicants*			
	Postdoctoral	Senior	Foreign	Application Deadlines
USAF US AIR FORCE LABORATORIES				
Armstrong Laboratory	Yes	Yes	Regular: No	Jan 15/Apr 15/Aug 15
Phillips Laboratory	Yes	Yes	(except in	Jan 15/Apr 15/Aug 15
Rome Laboratory	Yes	Yes	special cases)	Jan 15/Apr 15/Aug 15
Wright Laboratory	Yes	Yes	Senior: Yes	Jan 15/Apr 15/Aug 15
USDA/FS USDA FOREST SERVICE	Yes	No	No	Jan 15/Apr 15/Aug 15
USGS US GEOLOGICAL SURVEY	Yes	No	No	Jan 15
WES WATERWAYS EXPERIMENT STATION	Yes	Yes	In certain cases, with approval by director	Jan 15/Apr 15/Aug 15