
**REPORT TO THE SENATE ARMED SERVICES
COMMITTEE AND THE HOUSE OF REPRESENTATIVES
NATIONAL SECURITY COMMITTEE**

on

**Department of Defense
Animal Care and Use Programs 1995**

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LIST OF ACRONYMS

AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care International
AALAS	American Association of Laboratory Animal Science
ACLAM	American College of Laboratory Animal Medicine
APHIS	Animal and Plant Health Inspection Service
ASBREM	Armed Services Biomedical Research Evaluation and Management
AWA	Animal Welfare Act
AWIC	Animal Welfare Information Center
BRD	Biomedical Research Database
CRISP	Computer Retrieval Information of Scientific Projects
DDR&E	Director, Defense Research and Engineering
DoD	Department of Defense
DTIC	Defense Technical Information Center
ELISA	Enzyme Linked Immunosorbent Assay
FEDRIP	Federal Research in Progress
FY	Fiscal Year
IACUC	Institutional Animal Care and Use Committee
IG	Inspector General
ILAR	Institute of Laboratory Animal Resources
JDL	Joint Directors of Laboratories
JTCG	Joint Technology Coordinating Groups
LAM	Laboratory Animal Medicine
MATRIS	Manpower and Training Research Information Services
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NTP	National Toxicology Program
OPRR	Office for the Protection from Research Risks
OSD	Office of the Secretary of Defense
PADPRP	Poly (ADP-ribose) Polymerase
PCR	Polymerase Chain Reaction
PHS	Public Health Service
RDT&E	Research, Development, Test, and Evaluation
S&T	Science and Technology
SEB	Staphylococcus Enterotoxin B
STO	Science and Technology Objective
TAPSTEM	Training and Personnel Systems Science and Technology Evaluation and Management
USAMRMC	United States Army Medical Research and Materiel Command
USDA	United States Department of Agriculture
WRAIR	Walter Reed Army Institute of Research

SECTION I

INTRODUCTION/OVERVIEW

This is the Fiscal Year (FY) 1995 Report to Congress on Department of Defense Animal Care and Use Programs. In addition to a general overview, this report provides a detailed accounting of Department of Defense (DoD) animal use; to include its publicly accessible database, animal care and use oversight procedures, Institutional Animal Care and Use Committees (IACUC), alternatives to animal use programs, Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) status, and animal use.

The report covers animal research conducted by the DoD including education, training, and testing both in DoD laboratories and by extramural projects funded by the Department for FY95. This report does not include information on animals used by the DoD solely for the purpose of food preparation for human or animal consumption, ceremonial activities, recreation, or the training, care, and use of military working animals.

I.1 REQUIREMENTS FOR USE OF ANIMALS IN THE DoD

Department of Defense use of animals in research, development, education, and training is critical to sustained technological superiority in military operations in defense of our national interests. The DoD's biomedical research, development, test, & evaluation (RDT&E) and training programs that are dependent on animal use ultimately translate into improved military readiness as well as reduction in morbidity and mortality associated with military operations. These programs contribute directly to ensuring that service men and women maximize their capabilities to survive the numerous and various hazards they face around the world. Additionally, many examples of the humanitarian benefits of the DoD investment in animal research that are shared on an international basis improve the quality of life of both humans and animals. Several prime examples of the humanitarian benefits of DoD research efforts

are: the Junin vaccine that has provided critical protection for over 120 thousand individuals in endemic areas of Argentina against the ravages of Argentinean Hemorrhagic Fever; DoD-developed Venezuelan Equine Encephalitis (VEE), Eastern Equine Encephalitis (EEE), and Western Equine Encephalitis (WEE) vaccines that have been used to limit and control epidemics of VEE in Venezuela and Colombia in 1995, and to protect occupational workers in vaccine production plants around the world. In addition to being important public health tools, the equine encephalitides vaccines are obviously critical adjuncts to animal health programs around the world.

Biomedical research has benefited greatly from animal use alternatives such as non-living systems, cell and tissue culture, and computer technology. However, complex human organ systems interactions, in addition to environmental factors and confounding variables, necessitate the continued judicious use of animal models in DoD programs. Although many innovative animal use alternatives have been developed and are in use by Department scientists, situations remain in which there are no acceptable non-animal alternatives available. As new advances, technologies and breakthroughs in animal use alternatives occur, the DoD will embrace them whenever possible. The chapter on alternatives in this report gives a full accounting of the aggressive programs and numerous animal use alternatives implemented in DoD laboratories.

Disease remains a major cause of death and disability in military operations and conflicts. During Operations Desert Storm and Restore Hope, outbreaks of respiratory diseases, diarrheal diseases such as shigellosis, and parasitic diseases such as leishmaniasis and malaria, threatened the health and well-being of our troops. Indeed, the DoD is still assessing and addressing concerns over the long-term effects of various environmental, physical, and medical factors associated with the Persian Gulf Conflict. It is obvious that the health

and well-being of military personnel extend far beyond the immediate scope of the battlefield. We have an irrefutable moral obligation to our soldiers, sailors, airmen, and marines to provide the maximum protection and care possible. DoD researchers are committed to accomplishing this goal, and in many cases, animal-based research is the critical underpinning for the fulfillment of that obligation.

The DoD must develop the materiel and technological means to best protect and sustain the health and well-being of service men and women against all threats, and provide the best medical treatment possible to those who become casualties. This responsibility underlies the need for the DoD to conduct research, and to train and educate military health-care providers in the most effective medical management of battlefield casualties. Battlefield health care must very often be provided in an austere, harsh and hostile environment, hours away from a definitive care hospital, unlike medical counterparts found in civilian emergency medicine and trauma management. A domestic, low velocity projectile gunshot patient in a modern civilian shock and trauma center will be supported and resuscitated by a full complement of medical staff with a plentiful supply of oxygen, fluids, medications, surgical intervention and nursing. The combat casualty may be supported by only a single aidman and the medical supplies, experience, and expertise he can carry.

One of the most critical areas requiring DoD animal use is the compelling need to develop vaccines, drugs, and therapies to protect, sustain and treat service men and women during military operations. These research programs are strongly focused on a myriad of militarily relevant diseases and threats, many of which can result in potentially fatal diseases or conditions that have no known treatments, therapies, or cures. Consequently, there are numerous instances, including medical chemical and biowarfare defense, where animal-based studies are particularly critical. Ethical concerns, as well as regulatory requirements of the Food and Drug Administration, necessitate that candidate vaccines and drugs be safe and efficacious in laboratory animal models prior to initiation of human use protocols whenever possible. The rationale for this is to prevent the fielding and use of ineffective or dangerous treatments. Indeed, during the final stages of

vaccine and drug development, large-scale safety and efficacy testing is usually conducted using human volunteers. However, in the search for understanding and developing protection against many highly lethal agents, human use protocols are simply not possible. Consequently, carefully regulated animal use is absolutely vital to the success of Department biomedical research programs. The ultimate goal is to maximize the survivability of our troops in all situations.

I.2 DoD POLICY GOVERNING ANIMAL RESEARCH

The Department of Defense is committed to full ethical and regulatory compliance for its animal-based biomedical research programs. We have been proactive in increasing the fixed infrastructure and span of control necessary to ensure lawful and efficient execution of programs and maximize oversight of diverse and varied missions. The Department has aggressively implemented focused programs and working documents that optimize standardization of animal care and use at the user level. This enhanced standardization and oversight have improved a historically good system, and made it outstanding.

In 1995 the DoD developed and implemented a new directive dealing specifically with animal care and use (DoD Directive 3216.1, "The Use of Animals in DoD Programs," 1995) (Appendix A). This directive strengthens and clarifies requirements for nonaffiliated membership on IACUCs and directs all DoD animal use facilities that maintain animals for research, testing and training to apply for AAALAC accreditation.

The DoD also implemented a Policy Memorandum entitled "Department of Defense (DoD) Policy for Compliance with Federal Regulations and DoD Directives for the Care and Use of Laboratory Animals in DoD-Sponsored Programs" (Appendix B). This 1995 policy letter specifies training requirements for nonaffiliated DoD IACUC members and implements a standard format for animal use protocols (Appendix C), a standard checklist for IACUC inspections (Appendix D), and a standard reporting requirement for all animal use research to support a publicly accessible database (Section II).

All animal research must conform to requirements of the 1966 Animal Welfare Act (P.L. 89-544) as amended in 1976 (P.L. 94-279) and 1985 (P.L. 99-198), as well as the National Institutes of Health (NIH) *Guide for the Care and Use of Laboratory Animals*, (fifth edition, 1985, NIH 86-23) and the requirements of the applicable regulations of the United States Department of Agriculture (USDA).

Although the Animal Welfare Act currently exempts mice and rats in the genus *Mus* and *Rattus*, the DoD has long afforded them, along with all other vertebrates, the same consideration given non-exempt species under the Animal Welfare Act. At the same time, DoD biomedical researchers have aggressively developed novel procedures to replace, reduce, and refine the use of animals during experimentation.

I.3 SCOPE OF REPORT

This report provides a comprehensive accounting of DoD biomedical research and animal care and use programs. There are sections that include in-depth discussions of:

- a. Publicly accessible information on Department research (Section II),
- b. Policies and procedures for oversight of Department animal care and use programs (Section III),
- c. AAALAC accreditation for Department animal care and use programs (Section IV),
- d. Service and DoD animal use by research categories (Section V), and
- e. DoD initiatives to promote alternative methods that replace, reduce, or refine animal use (Section VI).

I.3.1 Publicly Accessible Information on Animal Use in the DoD

On October 1, 1995, the Department of Defense implemented a publicly accessible database analogous to the NIH Computer Retrieval Information of Scientific Projects System. The DoD Biomedical Research Database is available online

to the public, and is composed of succinct summaries of Department research projects, allowing interested individuals easy access to Department research information. The cost of FY95 animal-based research is presented by work unit summary in the BRD. In order to prevent duplication this information is not presented in this report. More information on accessing the database is presented in Section II.

I.3.2 Oversight of DoD Animal Care and Use Programs

DoD animal use oversight is reviewed in Section III. In general, internal and external oversight provisions for animal research conducted by the DoD are at least as stringent as those for research in any other department of the federal government, and in many ways exceed the standards. As a matter of policy, the DoD abides by the applicable federal regulations pertaining to animal care and use, including provisions for oversight. All DoD facilities and extramural institutions sponsored by the DoD must submit proposals for animal use to an IACUC. The IACUCs review proposed animal protocols to ensure compliance with the Animal Welfare Act, and address concerns of the community. The revised DoD Directive 3216.1 (1995) continues to specify that DoD IACUCs exceed the provisions of the Animal Welfare Act. Each IACUC serves as an independent decision-making body for the institution and establishes policy for the care and use of animals at that facility in accordance with applicable DoD directives, federal law and regulations.

The DoD has developed and implemented a standardized protocol format for use by all of its units (Appendix C). It includes requirements for search of Federal Research in Progress database or an equivalent database to prevent duplication of ongoing federally funded research. The principal investigator must justify the use of animals, including consideration of alternatives, justify the choice of species and the number of subjects, and include a literature search and assurance that the work does not needlessly duplicate prior experimentation. The protocol must specify procedures to be used with animals, methods to avoid or minimize pain, include a literature search for possible alternatives, qualifications of the

individuals conducting procedures with animals, and disposition of animals at the termination of the work.

The IACUC ensures that personnel involved in animal-based studies are properly trained and, if necessary, establishes a training program to support the staff. The IACUC inspects facilities and animal care programs at least twice annually, and prepares a written report including a plan to address deficiencies. It enforces compliance with procedures specified in the protocols by conducting inspections, evaluating and, if necessary, investigating reports of deviation from approved procedures. The IACUC of each facility performs semiannual program reviews of all animal use areas. The DoD 1995 Policy Letter strengthens that process by establishing a standardized semiannual review checklist that outlines the areas required for IACUC review. This guidance is consistent with the recommendations of the DoD Inspector General (IG) report of February 1994 (Appendix E). A formal report of inspection shall be prepared twice annually, noting the use of the checklist, and indicating all major and minor deficiencies, a plan for correction of deficiencies, signatures of IACUC members conducting the inspection, and a statement indicating whether there are or are not minority opinions. Finally, the IACUC serves as an impartial investigator of reports of violations of good animal practices and is empowered to suspend the use of animals for protocols not conducted in accordance with the Animal Welfare Act or institutional policy.

The revised DoD Directive 3216.1 (1995) clarifies composition, membership, and training requirements of the IACUC. The changes address the House Armed Services Committee's request to improve community representation and to appoint animal advocates to the Department's IACUCs, consistent with a recommendation of the IG Report of February 1994. The revised Directive (1995) increases the minimum membership of all DoD IACUCs from three to five. In addition, it specifies that

"there shall be at least one non-scientific member on the IACUC. In addition, there shall be at least one member representing the general community interest who is

nonaffiliated with the research facility. The nonaffiliated member and the non-scientific membership can be filled by the same person. To ensure community representation at each meeting and inspection, an alternate to the nonaffiliated member shall be designated for all IACUCs having a single nonaffiliated membership."

Each DoD IACUC has increased their membership to comply with this Directive.

This Directive exceeds the requirements of the Animal Welfare Act and is further strengthened by the DoD 1995 Policy Letter which requires a minimum of 8 hours of training for new non-affiliated members. In support of this training, the DoD developed a program consisting of a set of topics and recommended resources that may be used by individual IACUCs.

Responsibility for oversight of the Department's science and technology programs rests with the Director, Defense Research and Engineering (DDR&E). Her staff, in conjunction with representatives from the Services, annually review the science and technology efforts to ensure they are fully coordinated and without unnecessary duplication of effort. The preponderance of animal use within the Department occurs in biomedical programs. These activities receive specific oversight from the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee, which was created by congressional direction in 1981. The ASBREM Committee is chaired by the DDR&E and co-chaired by the Assistant Secretary of Defense (Health Affairs). The overall biomedical effort is carefully integrated and reviewed to eliminate unjustified duplication of effort by seven subordinate Joint Technology Coordinating Groups reporting to the co-chairpersons.

I.3.3 Accreditation of DoD Laboratories by AAALAC

Animal use programs in the DoD strive to meet all the requirements of AAALAC. AAALAC accreditation is recognized as the "Gold Standard" for animal care and use programs. DoD Directive 3216.1 (1995) states that all DoD laboratories that maintain animals for use in research, testing or

training shall apply for AAALAC accreditation. Currently there are 37 DoD animal facilities worldwide, of these 33 (89%) are accredited, a record that far exceeds the approximately 46% accreditation rate for civilian research laboratories registered with the USDA. All other DoD facilities have applied for accreditation.

AAALAC's philosophy of accreditation is steadily evolving from an emphasis on physical facilities (engineering standards) to a more comprehensive evaluation of the total laboratory animal care and use program (performance standards). Consequently, research units that were previously regarded as unaccreditable until major facility renovations or upgrades were completed have now been accredited by AAALAC. The Inspector General's "Review of the Use of Animals in the Department of Defense Medical Research Facilities" confirmed the effectiveness of animal husbandry programs in DoD facilities and concluded that although not all facilities were AAALAC accredited, animals in DoD facilities were maintained in healthy environments and treated humanely. As stated in the report, "The inspection teams were completely satisfied with the health and welfare of the animals in DoD research facilities.... All the personnel assigned the care of the animals were competent, interested, and committed to the humane care of the animals."

I.3.4 DoD Animal Use Profiles by Research Category

A profile of DoD animal use is provided in Section V. In this report, a detailed system was adopted for classifying animal use that includes 8 categories with 23 subcategories: 8 medical research, 4 non-medical research, 3 clinical research, 2 training, and 6 other categories of studies and use. Detailed charts and graphs are included in Section V.

In 1995, the DoD used 431,879 animals which is a 28% decrease from FY94. Of these, 28,245 (7%) were USDA reportable species as defined in the Animal Welfare Act of 1985. Table I-1 summarizes the major animal use statistics for DoD research. In addition, it should be noted that no animals were used for development or testing of offensive weapons.

Table I-1 Summary of DoD Animal Use Statistics

Total Animal Use by Species	% of Total
Rodents, fish, amphibians and birds	96.51
Rabbits	0.92
Farm animals (i.e., sheep, pigs, cows, horses)	1.55
Dogs, cats, nonhuman primates, marine mammals	0.66
Other	0.36

Percentages may not add up to 100% due to rounding of calculations.

Total Animal Use by Category	% of Use
Medical RDT&E	84.9
Non-Medical RDT&E	4.2
Clinical Investigation	4.9
Adjuncts/Alternatives	3.9
Training & Instructional	1.8
Breeding Stock	< 1
Classified Secret or Above	< 1
Offensive Weapons Development	0

Percentages may not add up to 100% due to rounding of calculations.

I.3.5 DoD Initiatives to Promote Alternative Methods that Replace, Reduce, and Refine the Use of Animals

Congress requested that the DoD establish aggressive programs to replace, reduce, and refine current uses of animals. Approximately 170 examples of DoD efforts to replace, reduce, and refine the use of animals in research are reviewed in Section VI. Animal research is an essential part of the scientific process, but it is only initiated after due consideration of alternatives. The DoD uses a Standard Protocol Format that specifically requires each investigator to consider alternatives to the use of animals and to justify the animal model selected. In addition, all protocols that involve unrelieved pain or discomfort require consultation with a veterinarian, and a specific database search for

scientifically acceptable alternatives to the proposed method. Each protocol that involves animals in research or training must explain the need for the animal research and defend the choice of species as the most scientifically valid model. Often, economies of time and resources are gained when scientifically valid alternatives to animal use are available. Our review of current animal research reveals that scientists in the DoD have developed or adopted many alternative methods based on ethical considerations and other inherent benefits. The U.S. Army Medical Research and Materiel Command has established a major objective to develop replacement, reduction, and refinement strategies for the use of animals in research. In addition, the Department sponsors conferences and workshops to promote alternatives to animal research. The DoD sponsors a 5-year grant with the Institute of Laboratory Animal Resources of the National Research Council to develop institutional training materials, education, and publications in support of DoD laboratory animal care and use programs. The Institutional Animal Care and Use Committee process also includes a strong emphasis on consideration of alternatives in all new protocols. Table I-2 describes several examples of new Department initiatives that replace, reduce and refine the use of animals.

In conclusion, it is the policy of the DoD that animal utilization will be conducted in full compliance with the Animal Welfare Act and that

Table I-2 Examples of DoD Initiatives for Replacement, Reduction, and Refinement of the Animals Used in Research

Replace nonhuman primates with rats for Hepatitis E Virus (HEV) bioassay.
Use of guinea pigs will preclude the requirement for nonhuman primates in all but the most critical pathogenesis and protective efficacy studies.
Cell cultures used to replace mice and rats to test inhibitors of cAMP degradation.
Reduction in numbers of swine and goats by conducting power analysis to determine minimal numbers of animals to use in surgical studies.
Reduction in numbers of mice through use of computer modeling of potential peptide antigens to determine if conformation sequence is analogous to native protein.
Use of a slow release subcutaneously placed estrogen capsule avoids the need for daily intramuscular injections in rats.
Development of fish (rainbow trout, zebra danio fish and medaka) as predictive models for epigenetic carcinogens has reduced mammalian animal use in carcinogenesis studies.

animals are used in research only when scientifically acceptable alternatives are not available. At the same time, the use of animals in research is essential to protect the health and lives of military personnel; therefore, the DoD will be engaged in biomedical research that involves the use of animals for the foreseeable future.

SECTION II

PUBLICLY ACCESSIBLE INFORMATION ON ANIMAL USE IN THE DoD

II.1 CONGRESSIONAL REQUEST INFORMATION

House Armed Services Committee Report 4301 (1995) requested the Secretary of Defense to "develop a mechanism for providing Congress and interested constituents with timely information... about [DoD] animal use programs, projects and activities, both intramural and extramural." In response to this request, and to serve the interest of both the scientific community and general public, the Department has implemented a publicly accessible database called the Department of Defense Biomedical Research Database (BRD). The BRD is a database containing succinct summaries of the Department's research projects involving the use of animals. This database is analogous to the National Institutes of Health (NIH) Computer Retrieval of Information of Scientific Projects (CRISP) System. The CRISP System is a biomedical database containing information on research projects supported by the United States Public Health Service, as well as information on intramural research programs of the NIH and the Food and Drug Administration. The BRD became accessible to the public through Internet on October 1, 1995. It is located on the Manpower and Training Research Information Services (MATRIS) home page.

II.2 THE FY94 BIOMEDICAL RESEARCH DATABASE

The data in the FY94 BRD were developed from the current work unit summary system of the Defense Technical Information Center (DTIC). DoD organizations performing research, development, test and evaluation (RDT&E) projects are currently mandated to provide annual reports of research to the DTIC. The DTIC maintains these work unit summaries in a database. While the majority of DoD animal use occurs in RDT&E projects, some work is performed in clinical investigations programs that are not mandated to provide work unit summaries to DTIC. Therefore, the DoD

directed that these non-RDT&E DoD animal research projects develop summaries to be entered into the BRD. The areas of research, testing and training in the FY94 BRD include, but are not limited to, the following: infectious diseases, biological hazards, toxicology, medical chemical defense, medical biological defense, clinical medicine, clinical surgery, physical protection, training, graduate medical education and instruction.

Military activities that house, care, or use animals provided a work unit summary for any animal-based research. The FY94 BRD contained 790 summaries and was made accessible to the public on October 1, 1995. A work unit summary may refer to a single protocol or a series of protocols that are performed in a given category of animal use. The summaries include the following information:

Accession Number: Identification number given by the database.

POC/Author: Primary contact for the work unit is usually the Public Affairs Office.

POC Address: The complete mailing address of the POC.

Title: Title of the work unit.

Funding Fiscal Year: The funding for the entire work for a given fiscal year. The funding includes civilian salaries, cost of animals, cost of materials, cost of human-based research, cost of non-animal based research, etc. – all costs related to the work unit except military salaries.

Performing Organization: The name of the activity where the work is performed.

Objective and Approach: This section is a narrative on the objectives and the approach of the work unit. This narrative provides a general summary of the work.

Indexing Terms (Descriptors): A list of indexing terms or keywords. The keywords

contain "animals" and the term for any animal types which may be used in the work unit (i.e., guinea pigs, rats).

These summaries were compiled into the BRD and organized into a presentation format for the Internet.

II.3 ACCESS AND USE OF THE BIOMEDICAL RESEARCH DATABASE

The BRD can be accessed through the MATRIS home page at:

<http://dticam.dtic.mil/www/welcome.html>

or directly at:

<http://dticam.dtic.mil/www/dodbr/dodbrfrm.html>

The BRD home page shown in Figure II-1 is a searchable database. To perform a search, enter a specific search topic in the search window and click on Do Search or press Enter. The results of the search will produce a hypertext list of titles (Figure II-2). To access a particular summary, click on the specific title and a summary will appear (Figure II-3). In addition, a list of all the summaries can be accessed by selecting [View all titles](#).

II.4 FY95 UPDATE OF THE BIOMEDICAL RESEARCH DATABASE

The DoD will make all FY95 work unit summaries of animal use in research, testing, education, and training available to the public this year. All military activities that house, care, and/or use animals have provided summary information on any animal research, testing, education, or

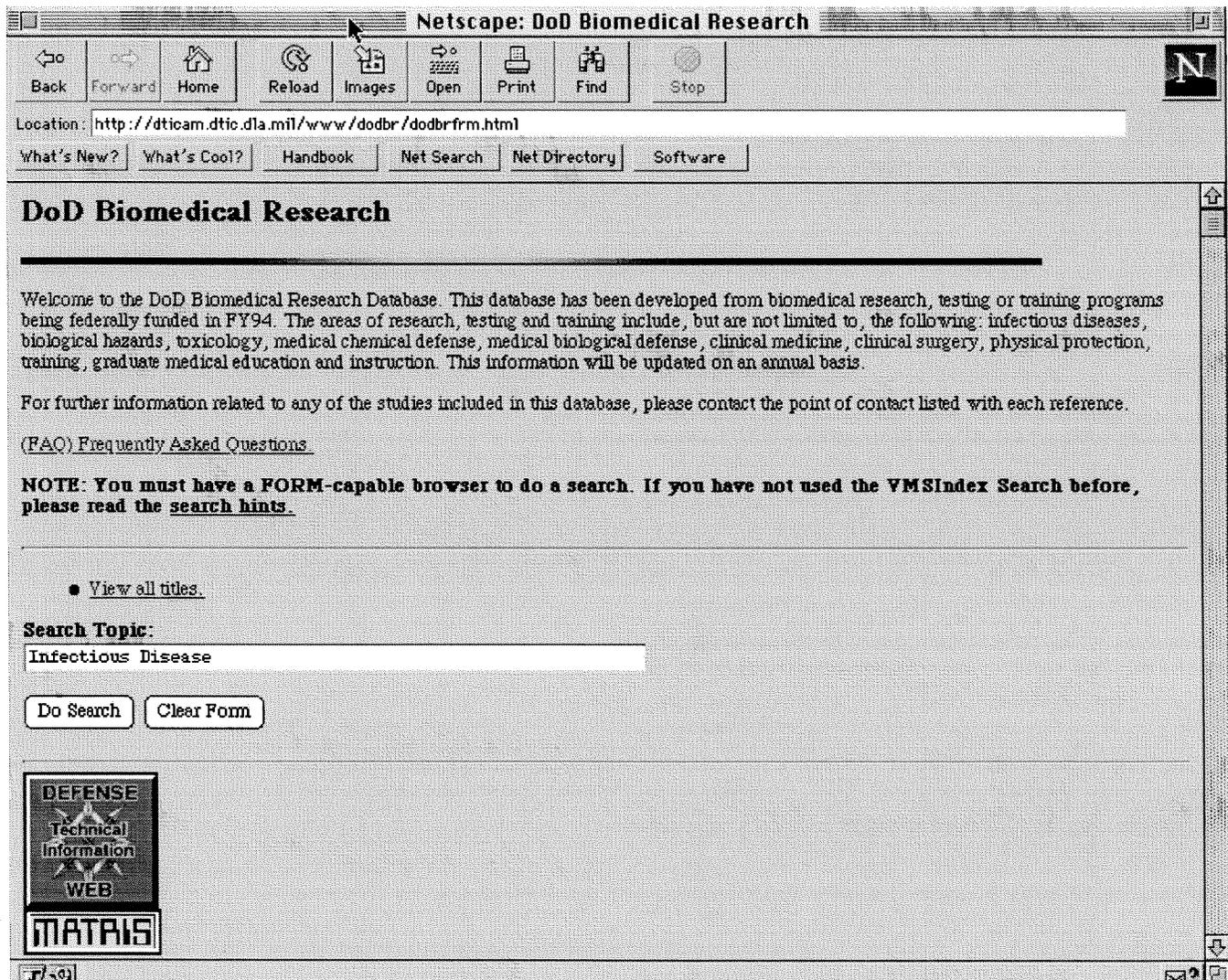


Figure II-1 DoD Biomedical Research Home Page

training work for the FY95 BRD. The cost of FY95 animal-based research is presented by work unit summary in the BRD. In order to prevent

duplication, this information is not presented in this report. These data will become available to the public on October 1, 1996.

Netscape: Search all dodbr html files on MATRIS

Location: <http://dticam.dtic.dla.mil/htbin/dodbrquery>

What's New? What's Cool? Handbook Net Search Net Directory Software

infectious disease

There are 24 items found:

1. [Identification and Control of Insect Vectors of Infectious Diseases](#)
2. [Animal-Facilitated Clinical Medicine Studies in Support of Graduate Medical Education](#)
3. [Prophylactic and Therapeutic Measures Against Infectious Diseases of Military Importance Endemic to Southeast Asia](#)
4. [Evaluation of the Potential Threat of Arboviral and Other Infectious Diseases to Deployed Military Troops in the Amazon Basin Region of Peru](#)
5. [Purification and Characterization of the Soluble Toxin and Immunosuppressive Factor\(s\) of Mycobacterium Ulcerans](#)
6. [Pathogenesis of a Newly Isolated Viruslike Infectious Agent in Experimental Animals](#)
7. [Risk Assessment and Establishment of the Murine Model for Brucellosis](#)
8. [Role of Macrophages in VEE Pathogenesis - A Molecular Approach](#)
9. [Regulation of B Cell Maturation](#)
10. [Burn Injuries](#)
11. [Prepare Field Sites for Evaluating Malaria Vaccines](#)
12. [Improve Isolation and Identification of Malaria](#)
13. [Characterize the Biochemical, Physical, Antigenic, and Molecular Structure of Leishmanial Macromolecules](#)
14. [Investigate the Genetics and Physiology of Yersinia Pestis](#)
15. [Design, Characterize, and Evaluate Medical Countermeasures \(i.e., Vaccines, Immune Serum\)](#)
16. [Evaluate Genetically Engineered VEE Vaccines](#)
17. [Evaluate Insect Populations and Subpopulation Diseases](#)
18. [Vaccines Vectored - Korean HF Vaccine](#)
19. [Characterize, Design, and Evaluate Methodology for Improved Diagnosis and Cultivation of Viruses of Military Importance](#)
20. [Dengue Recombinant Subunit Vaccine Development](#)
21. [Rift Valley Fever and Other Arboviral Infections](#)
22. [Vaccine Induced Enhancement of Equine Infectious Anemivirus \(EIAV\) Application and Disease](#)
23. [Production of Cytokine-Specific Monoclonal Antibodies that Modulate Immune and Inflammatory Processes](#)
24. [Vaccine-induced Enhancement of EIAV Replication and Disease](#)

Figure II-2 Search Results on Infectious Disease from the BRD

Title: Treatment and Prevention of Sepsis and Septic Shock

FY94 Funding: \$444,500

Primary Contact: Public Affairs Office

Organization: Naval Medical Research Institute

Address: 8901 Wisconsin Avenue

City: Bethesda

State: MD

Zip: 20889-5607

Performing Organization: Naval Medical Research Institute

Address: 8901 Wisconsin Avenue

City: Bethesda

State: MD

Zip: 20889-5607

Objective and Approach:

Objective: The objective of this work is to evaluate candidate therapies to lessen the morbidity and mortality in septic shock in combat casualties. Sepsis and septic shock are the result of a profound host response to bacterial infection. In sepsis, high concentrations of powerful mediators induce the adhesion and activation of inflammatory cells and consequent widespread tissue damage. To date therapies directed at ablating this inflammatory sequence have been shown to be promising in animal models but have proven ineffective in clinical trials. This proposal is directed at evaluating treatments to specifically modulate the inflammatory response and prevent the unwanted, promiscuous adhesion and activation of inflammatory cells. The goal is to prevent inflammation-induced damage to tissues in areas remote to the infection yet retain the bactericidal benefits at the site of infection. Specifically, the aim of this proposal is to evaluate the efficacy of antisense oligonucleotide agents directed at preventing the expression of specific molecules on the surface of cells thus preventing the adhesion of inflammatory leukocytes. A second aim is to evaluate the efficacy of carbohydrate-based agents to inhibit the binding of adhesion molecules to their carbohydrate receptors, thereby preventing the adhesion of inflammatory leukocytes. Both of these therapies offer the potential of being directed at highly specific targets and only in specific tissues. In addition, the regulation of lipopolysaccharide-induced genes during sepsis will be studied to develop new targets to prevent sepsis.

Approach: Antisense oligonucleotides complementary to target sequences in the mRNA and pre-mRNA or various cell adhesion molecules will be tested in cell culture assays in another work unit. The most active oligonucleotides will be evaluated for their ability to prevent neutrophil adhesion in the lungs of lipopolysaccharide stimulated mice. In addition, the oligonucleotides will be tested for their ability to enhance survival in a galactosamine-sensitized low-dose lipopolysaccharide lethality model and for their ability to prevent sepsis in animals. Various delivery systems will also be evaluated for the potential to enhance the specificity and to improve morbidity and mortality. The adhesion of leukocytes to sites in the vascular bed depends on the specific binding of pairs of cell surface bound adhesion molecules. In this binding, the adhesion molecules recognize and bind to specific carbohydrates on the complementary cell. In this proposal, various carbohydrate-based inhibitors will be used to disrupt the adhesion of leukocytes. They will be evaluated in the same animal models for the ability to prevent leukocyte adhesion and lessen morbidity and mortality in sepsis. Heparin analogues proven to be effective in improving microvascular patency in hemorrhagic shock will be evaluated in these models as well.

Indexing Terms:

antisense
oligonucleotides
inflammation
cell adhesion
sepsis
septic shock
carbohydrate
heparin
leukocytes
gene expression
animals
mice
LPS

Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to the use of animals in research and was reviewed and approved by the Institute's Animal Care and Use Committee.

Figure II-3 Sample of Publicly Accessible Information in the BRD

SECTION III

OVERSIGHT OF DoD ANIMAL CARE AND USE PROGRAMS

This section of the Department of Defense (DoD) Report to Congress provides a detailed overview of the formal mechanisms and strategies for providing adequate oversight to the Department's numerous animal care and use programs. For the purposes of this report, research is defined as those congressionally authorized science- and technology- (S&T) based activities - Title II, Research, Development, Test and Evaluation - of the Military Departments, and for which funds are appropriated, within program elements 6.1 (Basic Research), 6.2 (Exploratory Development) and 6.3 (Advanced Development).

The mechanisms detailed here show a clear and long-standing commitment by the DoD to manage its biomedical research and clinical programs in a systematic, comprehensive, and effective manner. Individual programs are driven by specific mission requirements, and are subjected to a thorough, stratified review and analysis prior to commitment of funds. The DoD uses animals only when necessary to complete its mission, and in a way that is in full compliance with applicable laws, regulations, and guidelines.

III.1 DETERMINATION OF DoD NEEDS FOR ANIMAL RESEARCH

Determining research needs and research plans is a comprehensive process integrated into DoD's planning, programming and budgeting processes. Integral elements of these processes are the Department's Research and Development Descriptive Summaries submitted to Congress in justification of the annual budget request. These summaries provide the Office of the Secretary of Defense, the Office of Management and Budget, and the Congress with significant detail of every research project's past accomplishments, planned accomplishments and future plans.

Each DoD research laboratory tailors its organization, staffing, and related infrastructure within available resources to best meet its science

and technology mission and to support each Commander's accountability, responsibility and authority. In October 1995, the Department implemented the use of a comprehensive DoD Standard Protocol Format as a basis to justify and document all proposed animal use (Appendix C). The Standard Protocol Format solicits specific information that ensures a complete and thorough Institutional Animal Care and Use Committee (IACUC) review for all animal use proposals. Although the specific procedural elements and processes of individual protocol review may differ in minor ways from facility to facility, the general submission, review and approval processes are summarized as follows.

An investigator develops a research protocol in support of departmental S&T guidance and other supplementing instructions developed within the chain-of-command, both external and internal to the laboratory. Augmenting the formal S&T coordination and review process is a literature search to verify non-duplication of previous or ongoing research. Previously, this search was performed only on the Defense Technical Information Center (DTIC) database. DTIC maintains a database of ongoing and completed DoD research at the work unit level of detail. The Standard Protocol Format requires that "a search of Federal Research in Progress (FEDRIP) and DTIC databases or their equivalent is required for DoD-funded research. An additional search of the scientific literature (MEDLINE, GRATEFUL MED, MEDLARS, AWIC, etc.) is highly recommended." Review and certification that this requirement has been met are integral elements of the review and approval process prior to initiation of a research project. If animal use is planned for the intended research, the principal investigator must prepare an animal protocol request for the local IACUC. In addition to the DTIC and FEDRIP search, the Standard Protocol Format requires detailed information regarding results and dates of other on-line database searches (e.g., AWIC, AGRICOLA, CAAT, MEDLINE) that deal with alternatives to painful procedures. Additional pertinent know-

ledge and information on the proposed study are gained through review of the scientific literature and participation in scientific meetings, symposia, and workshops detailing other ongoing or completed research.

Since protocols require the utilization of Defense resources, individual protocols are reviewed for factors such as military relevancy, necessity, scientific merit, and relative research priority. Such reviews are normally conducted within the laboratory's command-and-control structure and are routinely characterized by the features of peer review systems.

DoD IACUCs carefully review research proposals involving the care and use of animals for numerous factors, including but not limited to (a) the study is based on sound scientific principles; (b) the number of animals used is the minimum required to achieve the purpose; (c) the phylogenetically lowest species of animal is selected as the appropriate model; (d) there is appropriate use of analgesics and anesthetics, or if required, there is adequate scientific justification if not used; (e) the research is not unnecessarily duplicative; (f) the personnel conducting the research are qualified by training and experience to conduct the research; and (g) the scientific question to be answered is of sufficient importance to warrant the use of animals. Additionally, detailed information regarding methodology, techniques, schedules, etc., is required, greatly facilitating a comprehensive and thorough review by IACUCs.

III.2 OVERSIGHT OF ANIMAL CARE AND USE PROGRAMS AND FACILITIES

There are three principal vehicles for oversight of animal care and use programs at DoD research facilities: Major DoD Activities and Service Command Staff, the local IACUC, and the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

III.2.1 Military Departments

Each Military Department has a component or components responsible for oversight and review of its research facilities and animal care and use programs. Periodic reviews, site visits, and

inspections are conducted formally, and reports are prepared as required.

The Army's ultimate oversight responsibility is divided between two major commands: the U.S. Army Medical Command, and the U.S. Army Materiel Command. In the U.S. Army Medical Command, programmatic guidance and site visits are performed by specialty trained laboratory animal medicine (LAM) veterinarians in the Headquarters, U.S. Army Medical Research and Materiel Command, and the U.S. Army Medical Department Center and School (Veterinary Programs Manager). In the U.S. Army Materiel Command, oversight is provided by a specialty trained LAM veterinarian assigned to the U.S. Army Chemical and Biological Defense Command. Ultimate responsibility for laboratory animal care and use programs in the Navy resides in the Office of the Surgeon General of the Navy. Oversight is accomplished by a specialty trained LAM veterinarian assigned to the Naval Medical Research and Development Command, who also serves the Health Services Education and Training Command (Clinical Investigations), and the Inspector General at the Naval Bureau of Medicine and Surgery. Air Force oversight responsibility rests with a specialty trained LAM veterinarian assigned to the HQ, Air Force Medical Operations Agency, Clinical Investigations & Life Sciences Division, Office of the Air Force Surgeon General, and with the Office of the Director of Medical Inspection, Air Force Inspection Agency.

III.2.2 IACUC

The backbone of the review procedures for all DoD animal-based research is the IACUC review of the research proposal or protocol. DoD Directive 3216.1 requires all DoD facilities using animals in research to comply with the Animal Welfare Act (AWA). The AWA requires the Chief Executive Officer to appoint an IACUC, qualified through the experience and expertise of its members, to assess the research facility's animal program, facilities, and procedures. The AWA requires that IACUCs have a minimum of three members: an appropriately qualified chairman; at least one member not affiliated with the institution in any way other than as a member of the Committee; and a veterinarian with training or experience in laboratory animal medicine and science. Each DoD IACUC is

currently chaired by an individual with credentials and experience appropriate to the post, typically a senior physician, scientist, or veterinarian. The DoD Directive 3216.1 (1995) (Appendix A) clarifies the composition, membership, and training requirements of the IACUC. The revised Directive (1995) increases the minimum size of all DoD IACUCs from three to five, which is in concert with the National Institutes of Health (NIH) Office for Protection from Research Risks (OPRR) model. In addition, it specifies that:

“...there shall be at least one non-scientific member on the IACUC. In addition, there shall be at least one member representing the general community interest who is nonaffiliated with the research facility. The nonaffiliated member and the non-scientific membership can be filled by the same person. To ensure community representation at each meeting and inspection, an alternate to the nonaffiliated member shall be designated for all IACUCs having a single nonaffiliated membership.”

The diverse backgrounds/professions of the nonaffiliated and alternate nonaffiliated IACUC members are provided in Appendix F. Currently, 28% of the nonaffiliated members are private sector civilians, 49% are civilians employed by the federal government, and 23% are military. In accordance with the Directive, these members represent the community and are not affiliated with the research facility. Full compliance with the new Directive has resulted in an increase in the overall number of DoD IACUC members.

This Directive exceeds the requirements of the AWA and is further strengthened by the DoD 1995 Policy Letter (Appendix B) that directs a minimum of 8 hours of training for the new nonaffiliated members. DoD IACUCs implemented these requirements on October 1, 1995.

Each IACUC has at least one Doctor of Veterinary Medicine with training or experience in laboratory animal science and medicine, who serves as an animal advocate. The U.S. Army Veterinary Corp's formal postgraduate training program in laboratory animal medicine provides didactic training in IACUC composition, function, and

regulatory requirements. This training also prepares them to serve as animal advocates.

It is a proactive Department policy that nonaffiliated members are encouraged to perform unannounced site visits of animal care facilities in addition to full participation in all discussions and votes on all research proposals. At least 20 unannounced visits to Department animal facilities by nonaffiliated members of DoD IACUCs were reported in FY95.

The IACUC has statutory responsibility for reviewing the facility's animal care and use program and inspecting the animal facilities on a semiannual basis. Consequently, at least once every 6 months, each IACUC performs an in-depth review of the animal care and use program and inspects the animal facilities. To facilitate these inspections, the DoD has developed and implemented a standardized semiannual program review checklist that details the requirements of the review. Each DoD IACUC is currently using the new standardized checklist during their semiannual program reviews. The IACUC prepares written reports of its evaluations and submits them to the Institutional Official, usually the facility commander. Reports specifically address compliance with the AWA, and identify any departures from the Act to include an explanation for the departure. The report must distinguish between significant and minor deficiencies and provide a schedule for resolution of deficiencies.

All DoD IACUCs document their meetings and activities, including the results of inspections, complaints, actions, and training. They are empowered to review and investigate concerns involving the care and use of animals at the research facility resulting from complaints received from the public or in-house workers, or from reports of noncompliance received from laboratory personnel. To facilitate the reporting and resolution of complaints or concerns, facilities commonly place signs or notices in high-traffic areas and in animal study areas advising both the public and personnel who work with animals how to contact members of the IACUC, facility commanders, and/or the Inspector General (IG) whenever questions concerning humane care and treatment of animals arise. DoD facilities have developed a wide variety of proactive and innovative mechanisms to both

inform the public on how to contact responsible individuals as well as programs to ensure that those who work with animals are fully apprised of the requirement to provide humane and ethical care (Appendix G). Additionally, IACUCs make recommendations to the Institutional Official regarding any aspect of the research facility's animal program, facility, or personnel training; review and approve, require modification to, or withhold approval of new research protocols involving the use of animals; review and approve, require modification to, or withhold approval of proposed significant changes regarding the care and use of animals in ongoing research protocols; and suspend an activity involving animals when they determine that the activity is not being conducted in accordance with the approved protocol.

III.2.3 AAALAC

AAALAC is a nonprofit organization chartered to promote high quality standards of animal care, use, and welfare through the accreditation process. The AAALAC accreditation process provides scientists and administrators with an independent, rigorous assessment of the organization's animal care and use program. To increase accountability and tracking, a centralized DoD point of contact and database for AAALAC information have been established to enhance monitoring, reporting, and facilitation of the AAALAC accreditation process. An in-depth discussion of the AAALAC accreditation process and a profile of DoD's participation are provided in Section IV.

III.2.4 Training

The DoD provides extensive veterinary and animal care services for DoD facilities. Veterinarians with specialty training in LAM direct programs for animal care and use throughout the Department. They serve as a valuable resource to the research staff and the IACUC to ensure that all research methods and maintenance procedures are consistent with the latest principles of animal medicine, and current interpretations and implementing regulations of the AWA. The DoD sponsors formal post-doctoral training programs for veterinarians in LAM, including a nationally recognized in-house 4-year residency program culminating in specialty board eligibility for

certification in the American College of Laboratory Animal Medicine. Some DoD veterinarians attend various university post-graduate LAM training programs resulting in a masters degree or Ph.D. It is significant that approximately 25% of the current membership of American College of Laboratory Animal Medicine, the veterinary specialty most closely associated with animal welfare and laboratory animal care and use, received either all or part of their training in DoD-sponsored LAM training programs. In August 1995, the DoD began a formal post-graduate Masters of Public Health in Laboratory Animal Medicine at the Uniformed Services University of the Health Sciences. This outstanding new program will provide the Department with a new source of laboratory animal medicine experts who will significantly enhance animal welfare in our research laboratories.

In addition to veterinarians, the DoD trains animal care specialists (Military Occupation Specialty 91T) to assist in the daily management, care and treatment of laboratory animals. Over the last 28 years, the DoD has trained over 3,250 animal care specialists. Additionally, DoD research institutions send appropriate staff to a variety of seminars and workshops sponsored by the National Institutes of Health, other federal agencies, and private institutions dedicated to the proper care and use of research animals - The Annual Public Responsibility in Medicine and Research meeting is an outstanding example of this type of training.

The DoD provides detailed informational and instructional material to all members of the IACUC, including nonaffiliated members, to ensure that each is fully cognizant of the numerous responsibilities of IACUC members under the provisions of the AWA. The DoD Directive 3216.1, "The Use of Animals in DoD Programs," requires new nonaffiliated IACUC members to receive an initial 8 hours of training and continued training for IACUC members, investigators and technicians. This requirement went into effect on October 1, 1995. Although training is an individual institute's responsibility, the DoD has developed a program consisting of a set of topics and recommended resources to support the training requirement (Appendix H). The topics are meant to be general and allow for tailoring of the training to meet the institute's specific needs. The recommended resources are readily available

commercially. Formal training on animal care and use issues is provided to all appropriate personnel in Department research laboratories in accordance with the provisions of the AWA. Examples of training or materials currently provided to IACUC members are detailed in Appendix H.

III.2.5 Community Visits

Individuals or groups wishing to visit Department facilities need to comply with certain procedural guidelines. All DoD facilities are served by a public affairs office, either at the facility, post, or base. Visits by the public or the press are arranged and coordinated through the appropriate public affairs office. DoD facilities are visited by various special interest groups including community and civic groups; animal welfare or animal advocates, groups or individuals; dignitaries, academics and teachers; local, state, and national politicians; congressional members and staff; elementary to post-doctoral students; print and electronic journalists and authors, etc. Consequently, a greatly diversified range of individuals are constantly visiting and observing the quality of Department facilities.

III.2.6 Office for Protection from Research Risk Oversight

A number of DoD research laboratories participate in the NIH grants process. Institutional compliance with The Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) is a prerequisite for granting or continuation of NIH intramural and extramural funding. The formal vehicle for compliance with the PHS policy is an "Animal Welfare Assurance" negotiated between individual institutions and the OPRR. The principal references for the negotiation of an OPRR "assurance" are the Health Research Extension Act of 1985 (Public Law 99-158, November 20, 1985, "Animals in Research"), the Animal Welfare Act, and NIH's *Guide for the Care and Use of Laboratory Animals*. Consequently, OPRR provides additional oversight to those laboratories that have negotiated OPRR assurances.

III.2.7 Additional Oversight

Within the DoD, individuals may raise animal welfare concerns. This may be with the IACUC,

facility commanders, the IG, or the attending veterinarian. Other means of compliance or concern may be voiced through "Waste, Fraud and Abuse Hotlines," or the formal chain of command. Procedures to enhance and facilitate these mechanisms have been implemented in DoD facilities.

The function of the IACUC and the role of an ombudsman is augmented by the Department's IG. An ombudsman is defined by Webster's dictionary as a government official charged with investigating citizens' complaints against the government. The Humane Society of the United States, a witness at the April 7, 1992 hearing on The Use of Animals in Research by the Department of Defense before the House Armed Services Committee, offered the ombudsman program at the Massachusetts Institute of Technology as an example of a model program. This program consists of an ombudsman assigned to the university president's office to hear complaints regardless of the nature. These include, but are not limited to, personnel complaints, sexual harassment, animal welfare, etc. The DoD assigns this responsibility to its IG and respective Inspectors General of the Military Departments. In addition, military bases and large organizations on military bases have their own Inspectors General who fulfill this function. Significantly, IG complaints can be made anonymously, with no requirement to identify oneself in the registering of a complaint. Also of note is the fact that IG investigations are conducted with complete autonomy, and are completely insulated and immune to pressure from the chain of command.

Oversight of extramural (contract) animal-based research is provided for in the revised DoD Directive 3216.1 (1995). It states that

- a. "all extramural research proposals using live animals shall be administratively reviewed by a DoD veterinarian trained or experienced in laboratory animal science and medicine before grant or contract award."
- b. "the most recent USDA inspection reports are provided or obtained for the facility under consideration for a research contract

or grant using animals, and that during the term of the award, the most recent USDA inspection reports be reviewed on an annual basis."

- c. "a DoD veterinarian trained or experienced in laboratory animal science and medicine shall conduct an initial site visit to evaluate animal care and use programs at contract facilities conducting DoD-sponsored research using nonhuman primates, marine mammals, dogs, cats, or proposals deemed to warrant review. The initial site visit shall occur within 6 months of when the facility has taken delivery of the animals under DoD contract or grant award. Any facility receiving a DoD-funded grant or contract for animal-based research shall notify the DoD component sponsor and shall have a site inspection within 30 days of notification of loss of AAALAC accreditation for cause, or notification that the facility is under USDA investigation. Site inspections for cause shall evaluate and ensure the adequacy of animal care and use in DoD-sponsored programs, and provide recommendations to the sponsoring DoD component about continued funding support of the research."

As directed by DoD Directive 3216.1, all nonhuman primate protocols receive an additional centralized review external to the research facility.

III.3 CHAIN OF COMMAND OVER ANIMAL CARE AND USE PROGRAMS

The chain of command is designed to resolve problems at the lowest possible level. It provides control and communication between various components of organizations. Each link in the chain of command is a level of responsibility and authority that extends from the President of the United States, as Commander in Chief, down to the lowest supervisory level. Different levels within the chain have different responsibilities and authority. Each level in the chain is responsible for a lower level and accountable to a higher one. Every individual in the military is part of the chain of command and is accountable to it.

III.4 AVOIDANCE OF UNINTENDED DUPLICATION OF RESEARCH

Both the DoD and the Congress have a long history of concern about the potential for unintended duplication of Defense research. Within the past decade, the Department has initiated significant improvements in its mechanisms for coordination, joint planning and review of its research programs.

In 1981, Congress expressed concerns about the potential for unnecessary duplication of biomedical research among the Military Departments (H.R. 96-1317). This resulted in the DoD proposing an Armed Services Biomedical Research Evaluation and Management Committee to coordinate biomedical research planning and the conduct of biomedical research among the Military Departments. Congress fully endorsed and built upon this proposal by establishing DoD Lead Agencies for major elements of the biomedical research programs for which there were either no, or very few, service-unique requirements (H.R. 97-332). For example, the Army was designated the DoD Lead Agency for military infectious disease and combat maxillofacial research while the Navy was designated DoD Lead Agency for preventive and emergency dentistry research. The ASBREM Committee established Joint Technology Coordinating Groups (JTCCGs), consisting of directors of biomedical research programs and representatives of biomedical research laboratories, to coordinate all DoD biomedical research planning and execution. The ASBREM Committee process has proven to be highly effective at eliminating unnecessary duplication of biomedical research.

The ASBREM Committee process became the model for joint DoD coordination initiatives. Responsibility for joint coordination, planning, execution and review of the Department's S&T programs was assigned to joint oversight bodies: the Joint Directors of Laboratories (JDL), the ASBREM Committee, the Training and Personnel Systems Science and Technology Evaluation and Management (TAPSTEM) Committee, and the Joint Engineers. The resulting technology area responsibilities are shown in Figure III-1. Joint S&T oversight bodies are assisted in execution of their responsibilities by subordinate S&T coordinating groups that are focused on coordination of specific

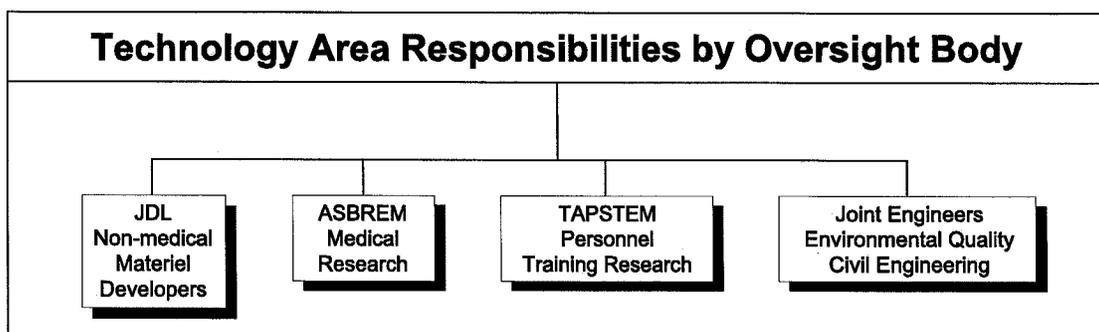


Figure III-1 DoD Technology Area Responsibilities

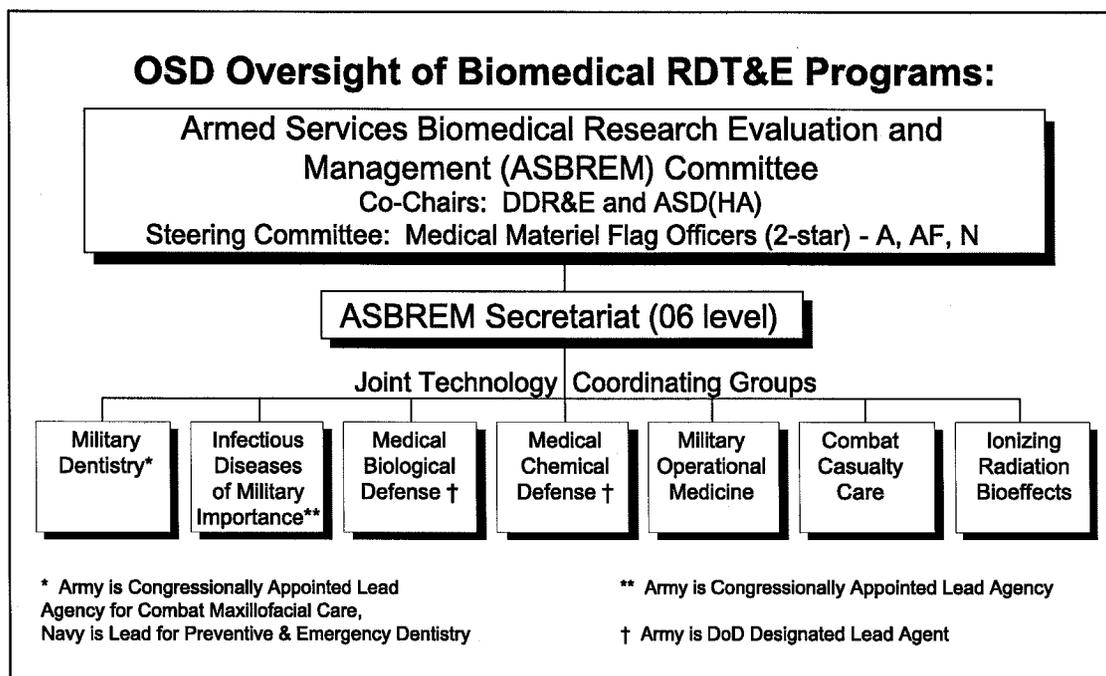


Figure III-2 Structure of Armed Services Biomedical Research Evaluation and Management Committee

technology areas. For example, the ASBREM Committee is supported by the JTCGs (Figure III-2) and the JDL is supported by separate technology panels.

In addition to these formal coordination and review processes to eliminate unintended duplication of research, there are a number of less formal mechanisms that provide significant disincentives for research duplication. Competition, both in-house and extramural, for research support is a prominent feature of S&T; each year large numbers of scientifically meritorious research proposals cannot be funded due to shrinking resources and funding shortages. In most cases the professional stature of individual scientists or engineers among their peers is measured in proportion to their individual and original

contributions to the scientific literature. There is little if any reward for unnecessarily duplicating the work of others; such actions often have significant negative impacts on how the scientist or engineer is viewed by peers and on the ability to secure research support. Additionally, within the DoD civilian personnel system, scientists' and engineers' pay grades are determined in part by the level of individual scientific and technological contributions. One outcome of research is publication of a manuscript in a professional journal or presentation to a professional meeting (Appendix I). Peer-reviewed journals critique the research during the review process leading to an overall enhancement of the research process as well as validating the scientific merit and necessity of the research. These less formal, relatively unquantifiable, disincentives substantially augment

and buttress the Department's formal mechanisms for regulating and avoiding unnecessary research duplication within its S&T programs.

III.5 AVOIDANCE OF UNNECESSARY RESEARCH

The same factors that effectively prevent unwarranted duplication of research are also applied to prevent unnecessary research. Additionally, through Cooperative Research and Development Agreements, the Department has increased its emphasis on leveraging and exploiting for Defense needs, S&T investments from other federal agencies, U.S. industry, and academic institutions, as well as from the international scientific community. Past descriptions of Defense S&T "spin off" have been supplanted by programs intended to "spin-on" accomplishments by others as well as to optimize the dual-use potential of the Defense S&T investment. The foundation of Defense S&T strategy is the application of S&T accomplishments to sustain Defense technological superiority through efficient and responsive modernization of our warfighting capabilities.

III.6 SUMMARY

Biomedical research using animals is highly structured and regulated in the United States, being governed by numerous laws, regulations, and

policies. Consequently, the DoD has a number of stratified formal and informal mechanisms for reviewing, regulating, and executing its biomedical research mission and animal care and use programs. Research performed by the DoD is carefully reviewed by various offices, committees, and program managers before it is funded or implemented. These reviews serve to determine the necessity to the mission, provide oversight of animal care and use, and avoid unnecessary or unintended duplication of research. Over the past decade, the DoD in concert with the Congress has streamlined and greatly improved coordination of its S&T activities to avoid unnecessary duplication and provide a focused program of research responsive to the DoD's unique and wide-ranging needs. Individual IACUCs provide oversight of animal care and use programs and research. Additionally, IACUCs provide training and information about animal care and use, and ensure the humane use of animals in research. Each DoD facility's IG is an effective means for investigation of concerns about the necessity of animal use, as well as the ethical treatment and humane care of animals used in DoD research. When viewed in its totality, the Department's significant progress and investment in administration, infrastructure, standardization, training, and oversight of animal use are indeed impressive, and can serve as useful models for the rest of the biomedical research community.

SECTION IV

AAALAC ACCREDITATION OF DoD LABORATORIES

The Department of Defense (DoD) recognizes the benefits of the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) accreditation. With the publication of the Joint Regulation on the Use of Animals in DoD programs, June 1, 1984 (AR 70-18), the DoD implemented more stringent animal care and use requirements than those required by statute. The Joint Regulation established uniform procedures, policies and responsibilities for the use of animals in the DoD. The DoD has elevated the requirement with the current DoD Directive 3216.1 (1995), which states that "all DoD laboratories that maintain animals for use in research, testing or training shall apply for AAALAC accreditation." The Joint Service Regulation also cites the National Institutes of Health (NIH) publication, *Guide for the Care and Use of Laboratory Animals*, which is the principal document used by AAALAC in its accreditation process. The animal care and husbandry standards and requirements contained in the Guide are designed to provide an environment that ensures proper care and humane treatment are given to all animals used in research, testing, and training. This care requires scientific and professional judgment based on knowledge of the husbandry needs of each species, as well as the special requirements of the research program.

IV.1 AAALAC ACCREDITATION

AAALAC accreditation is widely accepted by the scientific community, and viewed as an extremely desirable feature of the Department's animal care and use programs. The Association is highly respected as an independent organization that evaluates the quality of laboratory animal care and use. Accreditation covers all aspects of animal care to include institutional policies; laboratory animal husbandry; veterinary care; facility physical plant; support facilities; and special areas of breeding colony operations and animal research

involving hazardous agents such as radioactive substances, infectious agents, or toxic chemicals.

The independent and external peer review that is fundamental to continuing AAALAC accreditation is valuable to any program. AAALAC findings highlight program strengths and identify potential weaknesses. Laboratories maintaining accreditation demonstrate a high degree of accountability and program excellence. AAALAC standards stress the appropriate appointment, composition, and empowerment of an Institutional Animal Care and Use Committee (IACUC). This Committee is responsible for monitoring and evaluating all aspects of the institution's program that uses animals for teaching and/or research purposes. IACUC functions are addressed in Section III of this report.

IV.2 DoD PROGRAM REVIEWS

The DoD utilizes external peer review for the evaluation of many of its programs, such as drug screening laboratories, and review of military medical facilities by the Joint Commission for Accreditation of Health Organizations. At the same time, the DoD recognizes the diversity of mission operations and global reach of the military mission. There are situations where external peer reviews are not cost effective due to the remote locale, limited scope of operations, or host nation sovereignty. In these cases, equivalency standards can apply and be effectively monitored. The Joint Service Regulation and Service-conducted inspections of facilities implement the requirements of the Animal Welfare Act and the NIH *Guide for the Care and Use of Laboratory Animals*.

The DoD is committed to continuing its full participation in the AAALAC accreditation process as the external peer review evaluation method for assessing program compliance with regulations, guidance and ethical responsibility.

IV.3 DoD AAALAC ACCREDITED PROGRAMS

The number of DoD AAALAC accredited programs that maintain animals for research testing and training has significantly increased over the past 3 years (Figure IV-1). There are 37 DoD animal facilities worldwide that use animals; of these, 33 (89%) are AAALAC accredited. This increase reflects DoD's commitment to accrediting all of its animal care and use programs.

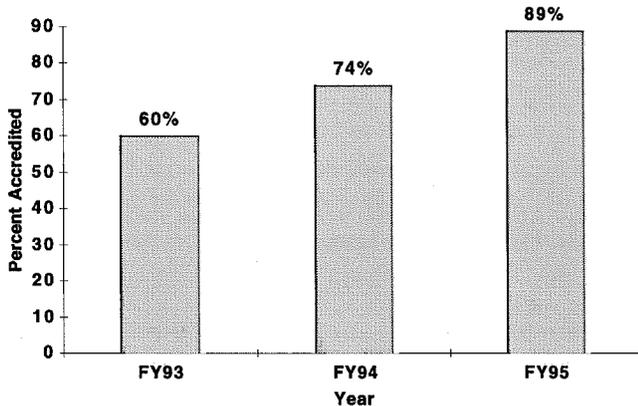


Figure IV-1 DoD AAALAC Accreditation FY93 - FY95

IV.4 AAALAC ACCREDITATION STATUS FOR U.S. DoD PROGRAMS

There are 33 programs in the U.S. that maintain animals for research, testing, or training for the DoD. Table IV-1 shows that of the 33 DoD programs in the U.S., 91% are accredited by AAALAC. This compares very favorably with the accreditation rate for the 1,324 United States Department of Agriculture registered and active animal facilities; 604, or 46%, are accredited by AAALAC. The three remaining DoD programs in the U.S. that are not yet accredited have applied for accreditation. In addition, there are four DoD animal use programs that share DoD AAALAC accredited facilities. These programs are small detachments that are assigned to DoD bases and therefore share their animal care and use facilities. Appendix J provides additional information on AAALAC accreditation by program.

The AAALAC philosophy of accreditation is steadily evolving from an emphasis on physical

Table IV-1 DoD FY95 AAALAC Accreditation Status

AAALAC Status	U.S. DoD Programs	Overseas DoD Programs
Accredited	30	3
Application Submitted	3	1
Total	33	4

facilities (engineering standards) to a more comprehensive evaluation of the total laboratory animal care and use program (performance standards). Facilities are still an important consideration in the accreditation process, but are no longer the paramount element. Consequently, research units that were previously regarded as unaccreditable until major facility renovations or upgrades were completed are now actively pursuing AAALAC accreditation on the basis of comprehensive, high quality laboratory animal care and use programs. The lack of accreditation does not imply that animals are exposed to unhealthy conditions.

IV.5 AAALAC ACCREDITATION STATUS FOR DoD OVERSEAS PROGRAMS

There are four DoD programs using animals outside the United States. In foreign countries, the accreditation process is often complicated by issues of sovereignty; local governments have their own regulations and policies that must be considered. Renegotiation of various agreements may be involved in construction or renovation projects. Despite these and various other impediments, the DoD has raised the standard of excellence in its animal care and use programs by receiving full accreditation in three (75%) of its four overseas laboratories. The Naval Medical Research Detachment in Lima, Peru, is the first laboratory in South America, to receive AAALAC accreditation. The Naval Medical Research Unit #2 in Jakarta, Indonesia, is the first DoD laboratory in Southeast Asia to be accredited, and the Naval Medical Research Unit #3 in Cairo, Egypt, is the first laboratory in Africa to be accredited.