THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D C 20301-1200

HEALTH AFFAIRS

SEP 20 2004

The Honorable Saxby Chambliss
Chairman, Subcommittee on Personnel
Committee on Armed Services
United States Senate
Washington, DC 20510-6050

Dear Mr Chairman:

Senate Report 108-46, which accompanies the National Defense Authorization Act for Fiscal Year 2004, requests that the Secretary of Defense submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident

The Senate Report identified five specific issues to be addressed in the response, including analyses of 1) the adequacy of the AFRRI's staff, resources and facilities in responding to incidents involving nuclear or radiological attacks; 2) the organizational relationships linking AFRRI expertise to DOD homeland defense activities; 3) the DOD and AFRRI research and development goals for improving national response capabilities, 4) the impact of zero funding authorization in the 2003 fiscal year budget, and 5) the lessons learned from the U.S Army Medical Research Institute of Infectious Diseases response during the terrorist anthrax attack of 2001 as it relates to the AFRRI's mission

I am pleased to forward the enclosed report fulfilling this requirement Thank you for your continued support of the Military Health System

Sincerely,

William Winkenwerder, Jr , MD

cc:
Senator Ben Nelson

Enclosure·
As stated

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D C 20301-1200

HEALTH AFFAIRS

SEP 20 2004

The Honorable John McHugh
Chairman, Subcommittee on Total Force
Committee on Armed Services
U S. House of Representatives
Washington, DC 20515-6035

Dear Mr. Chairman·

Senate Report 108-46, which accompanies the National Defense Authorization Act for Fiscal Year 2004, requests that the Secretary of Defense submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident.

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Sincerely,

William Winkenwerder, Jr , MD

cc
Representative Vic Snyder

Enclosure:
As stated

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D C 20301-1200

HEALTH AFFAIRS

SEP 20 2004

The Honorable Jerry Lewis
Chairman, Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515-6018

Dear Mr Chairman.

Senate Report 108-46, which accompanies the National Defense Authorization Act for Fiscal Year 2004, requests that the Secretary of Defense submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident.

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Sincerely,

William Winkenwerder Jr.

William Winkenwerder, Jr., MD

cc:
Representative John P Murtha

Enclosure.
As stated

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D C 20301-1200

HEALTH AFFAIRS

SEP 20 2004

The Honorable Ted Stevens
Chairman, Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510-6028

Dear Mr Chairman

Senate Report 108-46, which accompanies the National Defense Authorization Act for Fiscal Year 2004, requests that the Secretary of Defense submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident.

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Sincerely,

William Winkenwerder Jr.

William Winkenwerder, Jr , MD

cc:
Senator Daniel K Inouye

Enclosure:
As stated

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D C 20301-1200

HEALTH AFFAIRS

SEP 20 2004

The Honorable John W. Warner
Chairman, Committee on Armed Services
United States Senate
Washington, D.C. 20510-6050

Dear Mr Chairman·

Senate Report 108-46, which accompanies the National Defense Authorization Act for Fiscal Year 2004, requests that the Secretary of Defense submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident

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William Winkenwerder Jr.

William Winkenwerder, Jr , MD

cc
Senator Carl Levin

Enclosure·
As stated

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D C 20301-1200

HEALTH AFFAIRS

SEP 20 2004

The Honorable Duncan Hunter
Chairman, Committee on Armed Services
U.S House of Representatives
Washington, DC 20515-6035

Dear Mr. Chairman:

Senate Report 108-46, which accompanies the National Defense Authorization Act for Fiscal Year 2004, requests that the Secretary of Defense submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident.

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Sincerely,

William Winkenwerder, Jr.

William Winkenwerder, Jr., MD

cc:
Representative Ike Skelton

Enclosure
As stated

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D C 20301-1200

HEALTH AFFAIRS

SEP 20 2004

The Honorable C.W Bill Young
Chairman, Committee on Appropriations
U S House of Representatives
Washington, DC 20515-6015

Dear Mr. Chairman

Senate Report 108-46, which accompanies the National Defense Authorization Act for Fiscal Year 2004, requests that the Secretary of Defense submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident.

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Sincerely,

William Winkenwerder Jr.

William Winkenwerder, Jr , MD

cc:
Representative David R Obey

Enclosure
As stated

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D C 20301-1200

HEALTH AFFAIRS

The Honorable Ted Stevens
Chairman, Committee on Appropriations
United States Senate
Washington, DC 20510-6025

SEP 20 2004

Dear Mr. Chairman

Senate Report 108-46, which accompanies the National Defense Authorization Act for Fiscal Year 2004, requests that the Secretary of Defense submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident.

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Sincerely,

William Winkenwerder Jr.

William Winkenwerder, Jr , MD

cc:
Senator Robert C Byrd

Enclosure:
As stated

Report to Congress

Armed Forces Radiobiology Research Institute (AFRRI)

Plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident.

The Senate Report 108-46, which accompanied the National Defense Authorization Act of Fiscal Year 2004, directed the Secretary of Defense to submit a report at the time of submission of the Fiscal Year 2005 budget request detailing plans for the role of the AFRRI in responding to a terrorist nuclear incident. The Assistant Secretary of Defense for Health Affairs notified Congress that the report on AFRRI would be delayed.

Senate Report 108-46 identified five specific issues to be addressed in the report. The issues and relevant information on each follows:

1. The adequacy of AFRRI's staff, resources and facilities in responding to incidents involving nuclear or radiological attacks.

The AFRRI mission is to conduct relevant applied radiobiological research in support of the military medical mission. AFRRI also has the potential, under DoD's program of support to civil authorities, to support responses to accidental or premeditated events involving conventional or improvised nuclear weapons, nuclear reactors, radiological dispersal devices, or any other incident that involves nuclear or radiological materials. AFRRI is a Tri-Service organization located in a 173,242 square foot complex built in the early 1960s on the campus of the National Naval Medical Center (NNMC) in Bethesda, Maryland.

The facility consists of a 1 Megawatt TRIGA nuclear reactor, a cobalt-60 irradiator licensed for up to 500,000 Curies, a 54 Mev linear accelerator, a 100 Curie cobalt-60 irradiator for studies of low-dose/low-dose-rate chronic exposures to radiation, a full-service veterinary facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International, and a full complement of laboratory and administrative spaces. Particularly unique features of the TRIGA nuclear reactor are its ability to simulate the high prompt doses of gamma and neutron radiation from the detonation of a nuclear weapon, and its two exposure rooms that can accommodate experimental work involving large-animal models and other large irradiation studies.

Governance. On September 22, 1992, the Deputy Secretary of Defense approved a program decision memorandum and transferred the management of AFRRI from the Defense Nuclear Agency (DNA) to the Uniformed Services University of the Health Sciences (USU); the Director of AFRRI reports directly to

the President of USU An Administrative Plan for program execution and administrative support for the integration of AFRRI as an Institute within USU was approved in October of 2000. The Office of the Director, Defense Research and Engineering (DDR&E) directly funded AFRRI's programs and provided management oversight of its research programs through the Director, Bio Systems

In January of 2002, the DoD Comptroller approved Program Budget Decision (PBD) 203C that was to transfer funding and management responsibility for the AFRRI programs to the National Institutes of Health (NIH); AFRRI was to remain a DoD asset and NIH was to continue funding its programs on a reimbursable basis. However, the transfer of AFRRI funding to NIH was disapproved during the Health and Human Services' Fiscal Year 2003 Appropriations process As a result, in November of 2002, PBD 630, *Congressional Adjustments to Investment Appropriations*, was issued placing funding authority for the AFRRI programs back with the DoD. At that time, it was too late in the DoD appropriations process to restore funding for AFRRI in Fiscal Year 2003. Thus, funding for the AFRRI programs during Fiscal Year 2003 required Prior Approval Reprogramming Authority; and, AFRRI was funded at its previously programmed amount During Fiscal Year 2004, AFRRI funding was placed in the Defense Health Program by DDR&E and transferred to AFRRI through USU

Current human resources consist of 154 professional, technical and administrative personnel, 97 of whom are DoD or contract civilian employees. Officer and enlisted personnel from the Army, Navy and Air Force comprise the remaining 57 personnel Of all assigned personnel, approximately 31% are scientists and technicians performing research, 44% provide direct technical support to the research programs; and, the remaining 25% of personnel provide administrative and indirect support

Between 1993 and 1999, a 40% budget reduction precipitated two reductions in force and has led to a deteriorating facility infrastructure Also, the objectives of AFRRI's scientific program were reoriented to narrowly focus on product development opportunities, in some cases through leveraged collaborations with corporate partners and academic laboratories The approach centered on channeling diminishing resources to projects that represented a balance between the greatest needs and the best probabilities for success, with the goal of achieving at least partial solutions to technology gaps within reasonable timeframes In facility maintenance, budget challenges forced indefinite delays of major renovation projects and routine maintenance; patchwork repairs were completed as needed to maintain minimum functionality of mechanical and structural systems in order to meet the essential components of the AFRRI mission, as further discussed in Issues 2 and 3.

The AFRRI budget was leveled off in Fiscal Year 2000; and the falling trend reversed direction in Fiscal Year 2001 Recognizing the critical state of the facility infrastructure and an opportunity to support the advancement of a promising new radioprotective drug that had been under development, $3M of additional funding was reprogrammed by OSD into the AFRRI budget for each of Fiscal Years 2003 and 2004 to supplement its $11 3M annual budget Of the $6M total over two years, $4M was identified to finance a portion of the most critically needed infrastructure upgrades, and, $2M was ear-marked to support AFRRI's development of the radioprotective drug 5-androstenediol (HE-2100) in collaboration with its corporate partner Hollis Eden Pharmaceuticals In Fiscal Year 2005 and beyond, AFRRI's budget returns to its pre-Fiscal Year 2003 baseline of $11.3M

Discounting the need for major facility upgrades, currently projected budgets will allow the continuation of a limited effort at developing a targeted few of the existing opportunities for filling major gaps in medical countermeasures against ionizing radiation injury. With its current staffing level, its existing infrastructure, and the absence of medical countermeasures licensed for preventing, diagnosing and treating radiological injuries, with current funding levels, AFRRI is capable of responding primarily in an advisory capacity to incidents of radiological attack, if such an attack were limited in scope Beyond a strict advisory role, AFRRI's biological dosimetry laboratory can provide a limited throughput volume of radiation dose assessments if called upon during a nuclear or radiological incident A large-scale radiological attack, or the detonation of a nuclear device in an urban area, would require a National response far in excess of AFRRI's existing capability

Maintaining AFRRI's current readiness posture remains in a delicate balance with the continuing problems of the physical infrastructure Deteriorating mechanical and structural systems will eventually exceed the ability of patchwork repairs to maintain functional integrity.

<u>One-Time Property Renovation Costs</u>. AFRRI's urgent requirements for real property maintenance and repair and/or renovation projects were not addressed until late in 2003 due to AFRRI's consistent budget reductions, which began in 1993. The Facilities Divisions of USU and AFRRI coordinated to provide an estimated total cost for addressing these concerns The estimated one-time cost for renovations and/or repairs totaled four million dollars These real property maintenance and renovation projects were urgently required for the continued use of AFRRI's 173,000 square foot complex; the costs were discussed with the Office of the Director of Defense Research and Engineering The projects included: the building of firewalls, the renovation of the heating, ventilation, and air conditioning systems; major

laboratory upgrades; and, the renovation of elevators. All of the projects were five to ten years beyond the recommended timeframes for implementation

The four million dollars for the above mentioned renovation projects was scheduled for receipt by AFRRI over two years, during Fiscal Years 2003 and 2004 The Fiscal Year 2003 installment of two million dollars was not received until late 2003 because of reprogramming delays for funding AFRRI's entire program To date, the initial funding allotment has been concentrated on major upgrades to the veterinary facility Cage Washing System, the Heating/Ventilation/Air Conditioning Systems, and the Steam Supply System. Plans are in place to allocate the remainder of the funding scheduled for receipt during 2004; however, costs for upgrades to the veterinary facility have been greater than anticipated, which will impact the implementation of the remaining renovation projects.

2. The organizational relationships linking AFRRI's expertise to Department of Defense homeland defense activities.

The AFRRI's principal operational link to DoD homeland defense activities is through its Medical Radiological Advisory Team (MRAT). AFRRI's military physicians, health physicists and enlisted technicians staff the MRAT, they train and deploy with the Defense Threat Reduction Agency Combat Support Emergency Management Division (DTRA-CSE) Consequent Management Advisory Team (CMAT) The CMAT, along with the AFRRI contingent, supports multiple requirements including the United States Northern Command's Joint Task Force Civil Support (JTF-CS) Joint Technical Augmentation Cell (JTAC), the Joint Nuclear Accident/Incident Response Team (JNAIRT), the National Military Command Center, and certain classified DTRA special missions. The AFRRI MRAT military personnel train, organize and equip to assemble and deploy within a Combatant Commander's area of responsibility against a spectrum of contingency, operational, and response plans.

Under a memorandum of understanding (MOU) with the Office of the Deputy Assistant to the Secretary of Defense (Nuclear and Chemical and Biological Programs) for Nuclear Matters (OATSD(NCB)/NM), AFRRI provides radiological and health physics support required by the OATSD(NCB)/NM in the form of staff advice in the event of a nuclear weapon or radiological accident or incident During such incidents, AFRRI provides on-site subject matter experts at J-4 Medical, Joint Chiefs of Staff, Pentagon, who are able to advise, or obtain advice, on biological effects of ionizing radiation, medical aspects of the nuclear environment, and medical treatment of nuclear and nuclear-related injuries The MOU also requires that AFRRI personnel participate during readiness/preparedness exercises for nuclear or radiological accidents or incidents

Selected examples of AFRRI activities related to homeland defense and security are provided·

Support to the National Pharmaceutical Stockpile Program - May 2003. The AFRRI participated in a Radiological/Nuclear Threat Countermeasures Working Group, initiated in May of 2003 The Working Group was co-chaired by the Director of AFRRI and the AFRRI Scientific Director, with the participation of other AFRRI scientists The Working Group was successfully able to· 1) define national requirements for therapeutics/protectants and diagnostics; 2) develop acquisition plans for the Strategic National Stockpile purchase of therapeutics/protectants and diagnostics, and, 3) develop a coherent radiological/nuclear threat countermeasures research and development agenda The working group consisted of representatives from a broad range of Federal agencies and included a few key individuals from the private sector. Some of the agencies represented included: Health and Human Services; the Department of Defense; multiple representatives from the National Institutes of Health; the Centers for Disease Control; the Food and Drug Administration; the Department of Homeland Security (Strategic National Stockpile); the Department of Veterans Affairs; the National Aeronautics and Space Administration; and, the Department of Energy. The Director of AFRRI also serves as a voting member on the Intragovernmental Committee for the Composition of the Strategic National Stockpile.

Support for the Presidential Office of Science and Technology Policy (OSTP). During 2003, The Director of AFRRI and the AFRRI Scientific Director and the Medical Advisor for OSTP co-chaired a Federal-level working group under the direction of the President's Office of Science and Technology Policy to assess radiological/nuclear threat countermeasures A product of the working group included a prioritized listing of research needed to enhance medical radiological defense capability. An AFRRI senior scientist Co-Chaired the Biodosimetry Subgroup to the Working Group

Support for the Department of Homeland Security. In 2003, an AFRRI-developed software application to support medical recording following a radiation accident, *The Biodosimetry Assessment Tool*, was recommended for use during a CDC webcast and also in a document prepared by the Department of Homeland Security Working Group on Radiological Dispersal Device Preparedness.

Support to the Centers for Disease Control and Prevention. On July 18, 2002, AFRRI staff gave presentations to senior representatives from the Centers for Disease Control and Prevention (CDC) covering the threats posed by radiological dispersal devices, surreptitious planting of radiation sources, improvised nuclear weapons, and sabotage of nuclear power reactors The presentations included discussions on the appropriate use of potassium iodide to mitigate risks of thyroid

cancer from exposure to radioactive iodine and an overview of AFRRI's role in emergency response, medical training, and research and development.

Support to the President's Science Advisor and the Office of Science and Technology Policy. On March 12, 2002, the AFRRI Director and the head of AFRRI's Military Medical Operations Department briefed the Radiological, Nuclear and Conventional Threats Detection and Response R&D Working Group of the Office of Science and Technology Policy (OSTP) on the capabilities of AFRRI's Medical Radiological Advisory Team.

Training for National Guard Civil Support Teams. A Presidential Directive following the incidents of September 11, 2001, established National Guard Civil Support Teams to provide State Governors with cadres of first responders specifically trained and equipped to deal with terrorist incidents involving chemical, biological, radiological, nuclear or explosive (CBRNE) incidents. In March of 2002, AFRRI's Medical Radiological Advisory Team (MRAT) hosted a two-week conference to train personnel assigned as first responders to the newly established civil support teams. The training included lectures on operational health physics, Federal/DoD regulations, risk analysis, radiological instrumentation, DoD and non-DoD radiological assets, and design characteristics of nuclear power plants, radiological dispersal devices and nuclear weapons. Learning objectives focused on decision-making during the crucial first 12 hours following a nuclear/radiological event The conference was highly successful. As a consequence, the National Guard Bureau of Washington, D.C has requested the AFRRI MRAT to provide training on an annual basis

Support to the Vice President of the United States. On February 7, 2002, the AFRRI Director and other AFRRI staff briefed the Vice President's Senior Advisor for Medicine and Public Health and the Senior Advisor for Biodefense on the medical consequences of terrorist use of improvised nuclear weapons and radiological dispersal devices

Support to United States Forces Command. On February 12, 2002, the AFRRI Director briefed the principal flag officer staff and Command Surgeon of the United States Forces Command (USFORSCOM) on the radiological risks from potential attacks on, sabotage of, or accidents involving nuclear power plants in areas of operation The briefing included a review of the Food and Drug Administration (FDA) and DoD policies on the stockpiling and use of potassium iodide for the emergency treatment of personnel exposed to radioactive iodine, which can be released during events involving nuclear power reactors.

Support to the President of the United States. On November 19, 2001, members of AFRRI's Military Medical Operations Department spent the morning at

the White House training the President's medical unit personnel on the medical effects of ionizing radiation and the latest preventive, assessment and treatment measures that can be applied to mitigate radiation-induced injury.

3. The DoD and AFRRI research and development goals for improving national response capabilities.

The Defense Science and Technology Advisory Group (DSTAG) has identified six Defense Technology Objectives (DTOs) representing the highest priority initiatives of DoD's Medical Radiological Defense Research Program within the Defense Technology Area Plan. Each DTO identifies a specific technology advancement to be developed or demonstrated within a projected timeframe and specifies one or more metrics that will be met if successful All six DTOs support the Quadrennial Defense Review (QDR) transformation operational goal of Project and Sustain United States Forces The six DTOs are summarized as follows:

Pharmacologic Prevention of Ionizing Radiation Injury. This DTO will develop advanced medical strategies for the prevention of radiation injuries. Pharmacologic interventions based on 5-androstene steroids (5-androstenediol and analogs), a novel class of radioprotectants, will be designed and tested in preclinical model systems. Results will define the decision point for possible transition to clinical testing of preventive treatments designed to maximize protection of personnel against early arising radiation syndromes (i e , performance decrement and lethality) Effective mitigation of health consequences and performance-degrading effects will: 1) reduce the casualty load at medical treatment facilities, 2) sustain a more effective operational force after a radiation exposure event; 3) allow commanders to conduct operations in radiation field environments with reduced risk of decremented performance due to acute tissue injury; and, 4) reduce the negative psychological impact on personnel tasked to operate in contaminated environments Significant reductions in acute casualty rates are expected based on recent studies

Cytogenetic-Based Diagnostic Biodosimetry System. This DTO will develop a biodosimetry assay system, based on chromosomal aberrations, that permits a rapid, high-throughput capability to assess ionizing radiation exposure for large numbers of casualties Symptomatology and physical dosimeters, even when available, do not provide adequate diagnostic information to treat life-threatening radiation injuries. The objective assay system will provide physicians with the ability to definitively triage radiation victims, make appropriate treatment decisions, reduce the uncertainties associated with the variability of individual response to radiation exposure, and discriminate between cases of whole, versus partial, body exposures

Toxicity of Embedded Depleted Uranium. The objective of this DTO is to determine the long-term health effects of exposure to depleted uranium (DU) fragments by characterizing multiple biological indices indicative of carcinogenicity using experimental model systems. Friendly fire incidents during the Gulf War produced DU shrapnel-type injuries among United States soldiers The success of this new class of munitions guarantees its large-scale deployment by future adversaries, greatly increasing the number of casualties with DU fragment injuries Little is known of the health risks from chronic exposure to embedded DU fragments due in part to DU's unique combination of radiological and toxicological properties Current treatment strategies are in the most basic stage of development, and conventional diagnostic capabilities do not differentiate DU from other high-velocity metal injuries This technology effort will define the pathologic consequences of chronic exposure to tissue-embedded DU fragments using generally accepted *in vitro* and *in vivo* experimental systems, and develop rapid assessment tools to identify personnel wounded with DU. Data will provide risk analyzers and managers with the information needed to develop policies addressing the health hazards of DU, and to establish safe and effective treatment strategies to minimize the long-term health risks from DU fragments The DTO will be completed during 2004.

Medical Countermeasures Against Bacterial Sepsis after Irradiation. This DTO will develop combined treatment modalities against lethal or incapacitating radiation-induced bacterial sepsis. Polymicrobial sepsis is the leading cause of death following acute, whole-body irradiation. Ionizing radiation depresses immunity and damages intestinal epithelium, both of which promote microbial translocation from the intestines and sepsis Effective medical countermeasures for battlefield-sustained radiation mass casualties will require a radically different approach than what is commonly used to manage cancer patients receiving chemotherapy or fractionated radiation therapy under highly controlled conditions Appropriate antimicrobial therapy is critical, especially in cases of radiation-induced intestinal injury in which the wrong antibiotic can exacerbates the injury Therapy must target the endogenous and exogenous bacteria causing sepsis and not the normal anaerobic bacteria of the gastrointestinal tract that are beneficial. This effort will examine antibiotics in a rodent model to enhance treatment strategies for radiation-induced infections. Findings can be transitioned to preclinical studies to secure an FDA indication for antimicrobials in irradiated personnel to enhance survival in military operational environments. Successfully achieving the objective will provide a treatment strategy for radiation-induced bacterial sepsis that. 1) effectively reduces morbidity and mortality; 2) reduces casualty loads at medical treatment facilities, 3) shortens therapeutic intervention and accelerates return to duty, 4) reduces the requirement for prolonged antibiotic therapy, thereby lessening the likelihood of inducing antimicrobial resistance; and, 5) helps to sustain a robust fighting force in nuclear or radiological environments

Molecular Biomarkers-Based Diagnostic Biodosimetry System. This DTO will develop a biodosimetry assay system based on radiation dose-dependent alterations in gene expression and their encoded proteins. The system will measure changes in the relative concentrations of cellular messenger RNA and blood proteins (molecular biomarkers) and will provide for early, forward field-based radiation exposure assessment. Successful efforts will produce the following results 1) molecular biomarkers can be measured rapidly (within hours) with the same hand-held and field-laboratory analytic systems used to identify biological weapons agents, 2) the assay system will provide the ability to distinguish individuals not exposed, including the worried well, from exposed individuals (>10 cGy) and to determine individual exposure doses before the onset of symptoms to aid decision-making for medical triage; and, 3) assessment of a radiation dose early after exposure enhances the operational commander's situational awareness of the radiation exposure status of deployed forces and increases the prospect of reduced morbidity and mortality through early medical intervention

Prevention of Ionizing Radiation Injury by Isoflavones. This DTO will develop advanced medical strategies for the prevention of radiation injuries Preliminary findings on the isoflavones, genistein and daidzein, demonstrate promising radioprotective efficacy with a single subcutaneous injection or multiple oral doses in a rodent model The soybean and clover isoflavones, genistein and daidzein, will be evaluated in a preclinical animal model for radiation protection Results will define the decision point for possible transition to clinical testing of preventive treatments designed to maximize protection of personnel against early arising radiation syndromes that result in mortality. Products of this effort will give the warfighter a level of protection against radiation-induced injury. Desirable characteristics of the products will include: 1) the provision of additional options for radioprotective therapies that can be used alone or in combination with other agents (i.e., 5-AED). Additive or even synergistic effects may be realized with combinations of drugs; 2) increased survivability and decreased morbidity; 3) reduced casualty loads at medical treatment facilities; 4) ability of commanders to conduct operations in radiation field environments with reduced risk, and, 5) reduced psychological impact on personnel tasked to operate in radiation environments

In support of these DTOs and other efforts of the Medical Radiological Defense Research Program, AFRRI research addresses prevention, assessment and treatment of radiological injury, a description follows·

Radiation Casualty Management. Radioprotective and therapeutic drugs are under development that can potentially reduce radiation injury and save lives A number of compounds are currently under investigation.

- **5-Androstenediol** – A nonandrogenic steroid that upregulates components of the innate immune system and blood platelets, protecting the irradiated service member from life-threatening sequelae such as infection and bleeding following exposure to lethal doses of radiation Preclinical studies are under way in partnership with the civilian pharmaceutical industry More information on this product is provided below.

- **Ex-RAD, ON 01210** – A synthetic compound that is easy to produce, stable for long-term storage, and provides radioprotection in mice. Studies are in progress to explore the cellular and molecular mechanism by which *ON 01210 exerts its radioprotective effects and to evaluate the toxicity,* pharmacology, and efficacy of the drug in rodents.

- **Isoflavones and vitamins** – Nutrients with beneficial medical effects, such as soy-based isoflavones and vitamin E analogs, that show promise as radioprotectants. Preliminary findings on the isoflavone genistein show, in the *mouse, radioprotective efficacy with multiple oral doses and with a single* subcutaneous injection. Vitamin E analogs have greater radioprotective efficacy than the parent compound and act by scavenging highly reactive cytotoxic free *radicals generated in the body upon deposition of ionizing radiation*

- **Other radioprotectants** – Compounds that are proposed as *radioprotectants by biomedical researchers or pharmaceutical companies and are* evaluated on a regular basis. AFRRI receives frequent inquiries from scientists in academia, government, and industry with suggestions for new radioprotectants and therapeutics. The AFRRI staff evaluates these agents and tests those that are most promising in an effort to develop the most effective agents.

Expanding on the development of 5-androstenediol (5-AED), AFRRI investigators have demonstrated significant radioprotective qualities associated with this non-androgenic steroid. The drug has no measurable toxicity at the doses being used to achieve protection On-going research includes attempts to deliver similar protective efficacy by the oral route of administration and should lead to a product that can be more easily managed logistically and used by deployed military troops In October of 2001, AFRRI investigators and representatives from a corporate partner presented preliminary data and a research plan for clinical trials of 5-AED at a pre-investigational new drug meeting before the FDA. The plan was favorably received, and, the FDA provided valuable guidance on how to proceed with pre-clinical trials toward an IND application

During the past 18 months, the 5-AED Project has progressed considerably and is on track for potential submission of an investigational new drug (IND) application to the FDA by the end of Calendar Year 2005 The 5-AED corporate

partner of AFRRI completed two pilot studies in nonhuman primates during 2003, demonstrating efficacy when 5-AED is administered both pre- and immediately post-exposure to gamma photons. The AFRRI has also established a contract to carry out the pre-clinical safety and toxicity studies under current good laboratory practices (cGLP) conditions that are required prior to an IND application

- 'RRI has made important technical

achievements, which significantly advance the science and medical application of cytogenetic-based methods of radiation dose assessment. The purpose of this research is to develop rapid assays to measure radiation exposure to casualties, to enhance both triage and medical management capabilities, and to distinguish psychological casualties from those with radiation injury The primary thrusts are·

- **Semiautomated dicentric analytical platform** – Automated sample processing and image analysis that increase the throughput rate of the "gold standard" cytogenetic method for radiation dose assessment Efforts are under way to increase efficiency at various steps in sample processing, preparation, analysis, and reporting.

- **Premature chromosome condensation assay** – A novel cytogenetic assay for assessing chromosome fragmentation in interphase cells The assay correlates to actual radiation dose over a broad range, is highly amenable to automation, and accelerates the assessment compared to the "gold standard" dicentric assay The new procedure will allow testing of larger sample numbers within a single day's time instead of the usual three days Further enhancing this development, the team, in collaboration with private industry under a cooperative research and development agreement, has developed an automated microscopic imaging system that will facilitate the processing of even larger numbers of samples with higher precision and accuracy. This new procedure, known as The Premature Chromosome Condensation (PCC) Assay, may potentially supplant the current gold standard dicentric assay for cytogenetic-based biodosimetry. A patent application for the PCC assay was recently accepted, and it is expected to transition within the next three to five years. A recently published report on the procedure and abstract presentations at several national and international conferences have drawn considerable attention from around the world to AFRRI's Biological Dosimetry effort.

- **Molecular biodosimetry markers** – Development of biological dosimetry assessment based on radiation dose-dependent alterations in gene expression and their encoded proteins. Molecular biomarkers can be measured rapidly (within hours), and preliminary studies show that radiation causes quantifiable changes over a broad dose range Success in this area will, for

the first time, allow use of radiation dose assessment and diagnostic techniques to aid triage and medical management decisions during field operations.

Treatment of radiological casualties. This effort focuses on the problem of understanding and developing medical countermeasures against the radiation-induced translocation of intestinal bacteria into the bloodstream, and other naturally occurring infectious *sequelae* that accompany higher doses of ionizing radiation. The primary areas of focus are:

- **Antibiotic regimen** – Assessment of new-generation antibiotics to treat polymicrobial sepsis, which is the leading cause of death following acute, whole-body irradiation Currently no antimicrobials have an approved indication for use in treating radiation-induced infections Studies are ongoing to evaluate the pharmacokinetics and efficacy of antibiotics in treating infections following exposure to ionizing radiation During 2003, initial studies were completed in a small animal model demonstrating the efficacy of new-generation antibiotics for treating opportunistic infections following sublethal irradiation The team initiated preparations for more definitive studies in a large animal model, with a long-term goal of obtaining FDA approval for re-labeling currently licensed antibiotics for use in treating radiation-induced sepsis

- **Biological response modifiers** – Compounds that enhance outcomes by improving the body's innate response to infection and disease, including beta-glucan, cytokines, and growth factors Beta-glucan enhances recovery from radiation injury and might be useful alone or in combination with other treatments. Filgrastim (G-CSF) and oprelvekin (IL-11), two cytokines that are approved by the Food and Drug Administration (FDA) for other indications, have been shown to be of synergistic benefit in treating hematopoietic injuries from exposures to lethal doses of ionizing radiation. Keratinocyte growth factor (KGF) shows promise for treatment of the gastrointestinal syndrome that follows radiation exposure.

Depleted Uranium. In response to concerns over Gulf War Illness, AFRRI organized a team of scientists to study the biological consequences and potential health risks from chronic exposure to tissue-embedded depleted uranium (DU) The team's research findings have resulted in a recent change to medical doctrine, which calls for a more aggressive removal of DU shrapnel fragments The AFRRI team also works closely with the Office of the Special Assistant for Gulf War Illness as subject matter experts and consultants on DU issues, and has collaborated with the Department of Veterans Affairs in its program to medically follow Gulf War veterans wounded by DU shrapnel AFRRI scientists have been called upon on several occasions to give testimony before Congress in this regard The development and refinement of an inductively coupled mass spectrometry procedure, which can

differentiate DU from natural uranium in biological samples, has become an integral part of this collaborative study and has contributed to AFRRI's being recognized as a center of excellence in DU studies The development of a simple chemical assay for DU, which can be configured into a compact, rapid field test to aid triage and medical management decisions, is another achievement of the DU team Together, these accomplishments and their validation in peer-reviewed publications have made the AFRRI a focal point of recognized expertise frequently consulted by DoD and other United States and NATO government policy-makers The Rapid Field-Based DU Detection Assay has been patented and is expected to transition within the next two to three years. Work on toxicity of depleted uranium will be completed in the near future. Extramural funding will continue to support open questions regarding 1) the transmission of genetic damage to offspring of a parent exposed to DU; 2) DU associated carcinogenesis, and, 3) possible toxicity to the immune system. Expertise and resources will be re-directed toward assessment of internal contamination with radioisotopes.

4. The impact of zero funding authorization in the 2003 fiscal year budget.

As noted above, funding for the AFRRI programs during Fiscal Year 2003 required Prior Approval Reprogramming Authority; and, AFRRI was funded at its previously programmed amount. During this time, research, training and consultative activities continued as described in Issues 2 and 3.

5. Lessons learned from the U.S. Army Medical Research Institute of Infectious Diseases' (USAMRIID) response during the terrorist anthrax attack of 2001.

Many of the lessons learned from USAMRIID's response to the terrorist anthrax attacks of 2001 apply to what might be anticipated in a nuclear or radiological event, and some are related to the response provided for Issue #1 regarding AFRRI's ability to respond. Four lessons would apply directly to AFRRI

The capacity of AFRRI's biodosimetry laboratory in trained personnel, equipment and reagents is not sufficient to manage the testing of the large number of clinical samples that would be expected in a moderate, to large scale, nuclear or radiological terrorist attack Such an attack in a populated area would generate a large number of potential radiation-exposed individuals The first challenge would be to differentiate between exposed and non-exposed individuals to reduce the impact of the population of psychological casualties ("worried well") on the medical treatment system and consequence management operations The second challenge would be to effectively triage the radiation-exposed population to identify the level of medical care required at the individual level In both cases, an effective biological dosimetry testing capability would be required with the

capacity to manage the patient load. Although AFRRI's biodosimetry laboratory is the only national laboratory with the expertise and capability to conduct biodosimetric analyses, it is not adequately funded, equipped or staffed with the capacity to respond to anything more than a small-scale event.

Widely understood uniform standards for collecting and handling biological samples for radiation dose assessment do not exist For a biological dosimetry test to be valid, the clinical sample must be collected in an appropriate container and properly packaged for shipment to the testing laboratory; to arrive within a specified time following collection. Unlike routine clinical laboratory tests run in hospitals and reference labs, biodosimetry tests are rarely done, and standards are thus not widely known Communicating advice and guidance to on-scene responders and medical staff for sample collection during an incident would pose serious difficulties.

Related to the above paragraph, communication, in general, with on-scene personnel is expected to be difficult. Drawing upon AFRRI's expertise during a crisis would require an effective communication link between on-scene personnel and any number of experts standing by at the AFRRI facility Depending on the scale of the incident, the AFRRI is not staffed to deploy the spectrum of experts that might be needed at the site of a large-scale incident A reach-back capability via a secure and reliable communication link is critical to an effective response, which would include advice and guidance from trained medical professionals, health physicists, biological dosimstrists, or radiobiologists

Managing data flow and analysis during, and immediately following, an incident is critically important to generate accurate information on which to base decisions that can mitigate the consequences of an event In a nuclear or radiological attack, a large volume of factual information including physical, biological, and certain demographic parameters will have to be collected, collated and analyzed in real time to assess the precise nature of environmental radiation contamination, and individual and population exposure levels Such an analysis is needed to channel the right amount and type of limited resources to where they can be most effectively employed. Again, depending upon the scale of the incident, AFRRI is not staffed or equipped to adequately manage the data flow, analysis or generation of information

SUMMARY

Senate Report 108-46 that accompanied the National Defense Authorization Act for Fiscal Year 2004 (S 1050) requested the Secretary of Defense to submit a report detailing plans for the role of the Armed Forces Radiobiology Research Institute (AFRRI) in responding to a terrorist nuclear incident.

The Senate Report identified five specific issues to be addressed in the response, including analyses of 1) the adequacy of the AFRRI's staff, resources and facilities in responding to incidents involving nuclear or radiological attacks, 2) the organizational relationships linking AFRRI expertise to DOD homeland defense activities; 3) the DOD and AFRRI research and development goals for improving national response capabilities; 4) the impact of zero funding authorization in the 2003 fiscal year budget, and 5) the lessons learned from the U.S. Army Medical Research Institute of Infectious Diseases response during the terrorist anthrax attack of 2001 as it relates to the AFRRI's mission.

The AFRRI is capable of responding in a limited advisory role to incidents of radiological attack A decade of declining budgets, attempts to eliminate the program and reductions in force have decremented staffing levels and physical infrastructure, and led to curtailed research and development activities for producing licensed medical countermeasures A large-scale radiological attack, or the detonation of a nuclear device in an urban area, would require a National response well in excess of AFRRI's existing capability.

The AFRRI's principal operational link to DoD homeland defense activities is through its Medical Radiological Advisory Team (MRAT) AFRRI's military physicians, health physicists and enlisted technicians staff the MRAT; they train and deploy with the Defense Threat Reduction Agency Combat Support Emergency Management Division (DTRA-CSE) Consequent Management Advisory Team (CMAT) The CMAT-AFRRI supports multiple requirements including the United States Northern Command's Joint Task Force Civil Support (JTF-CS) Joint Technical Augmentation Cell (JTAC), the Joint Nuclear Accident/Incident Response Team (JNAIRT), the National Military Command Center, and certain classified DTRA special missions

The Defense Science and Technology Advisory Group (DSTAG) has identified six Defense Technology Objectives (DTOs) as the highest priority initiatives of DoD's Medical Radiological Defense Research Program, All six DTOs support the Quadrennial Defense Review (QDR) transformation operational

goal of Project and Sustain United States Forces, and they account for approximately 50% of the AFRRI's total research effort. The DTOs and the remainder of AFRRI's program focus on applied and developmental research leading to licensed medical products for preventing, assessing and treating radiological injuries that can be employed across all echelons of an operational environment.

The zero funding authorization for Fiscal Year 2003 only resulted in delays in executing the year's planned activities Prior Approval Reprogramming Authority was used to fund the program at its originally budgeted amount.

Lessons learned from USAMRIID's response to the terrorist anthrax attacks relate to what might be anticipated in a nuclear or radiological event Four lessons that apply directly to AFRRI are 1) the capacity of AFRRI's biodosimetry laboratory in trained personnel, equipment, and reagents is not sufficient to manage the large number of clinical samples that would be expected in a nuclear or radiological terrorist attack, 2) widely understood uniform standards for collecting, handling and transporting biological samples for radiation dose assessment do not exist; 3) communication with on-scene personnel is expected to be difficult, and a significant element of AFRRI's capability to respond to a crises would depend on a secure and reliable communications link between on-scene personnel and experts standing by at the AFRRI facility; and 4) managing data flow and analysis is critically important to generate accurate and timely information on which to base decisions that can mitigate the consequences of an event