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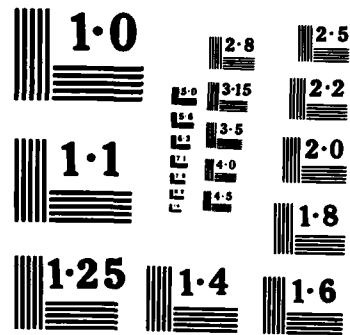
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Annual Research Report

AD-A157 717

Fiscal Year 1984

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Armed Forces Radiobiology Research Institute

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Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources, National Research Council.

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INTRODUCTION

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The Armed Forces Radiobiology Research Institute was established in 1961 as a subordinate command of the Defense Nuclear Agency. It is the primary Department of Defense facility for scientific research in the field of radiobiology and related matters. It conducts applied and basic research that is essential for the operational and medical support of the Department of Defense. The work is carried out by five scientific departments as listed below:

Behavioral Sciences: Effects of ionizing radiation, chemicals, and drugs on performance.

Biochemistry: Elucidation of mechanisms of injury, repair, and protection from the effects of ionizing radiation alone or in combination with other agents; development of improved methods to detect and quantify the severity of radiation injury.

Experimental Hematology: Investigation of radiation injury of bone marrow; development of therapy for damage from intermediate radiation doses; determination and treatment of injuries caused by combined effects of radiation, blast, and burns.

Physiology: Research on cellular, tissue, and whole-animal models to determine physiological and biophysical changes resulting from radiation either alone or in combination with drugs or other chemicals.

Radiation Sciences: Operation, maintenance, and quality control of all AFRRRI radiation sources; radiation dosimetry and estimation of tissue doses at various depths in different kinds of tissues; development and use of nuclear medicine and magnetic spectroscopic techniques for determining radiation damage in animals and model systems.

The results of this broad multidisciplinary program are summarized in this report. In addition, much of the work is published in the scientific literature, where it contributes significantly to the body of radiobiological knowledge, as well as in AFRRRI scientific and technical reports.



OVERALL BIOMEDICAL RESEARCH PROGRAM IN
THE DEFENSE NUCLEAR AGENCY

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The Armed Forces Radiobiology Research Institute (AFRRI) has a varied program concerning the biomedical effects of nuclear weapons. Mitigation of the medical effects of a nuclear detonation will maximize the effectiveness of combat troops on a nuclear battlefield. To achieve this objective, AFRRI research and DNA's Biomedical Effects contract research examine the responses of various biochemical, cellular, and whole-organism models to differing levels and qualities of ionizing radiation.

Measures to prevent, diagnose, and treat radiation injury are developed through the Combined Injury Program (CIP), which specifically addresses the impact of combined ionizing radiation and traumatic injury.

Estimates of individual radiation-induced combat performance decrement generated by the Intermediate Dose Program (IDP) are incorporated into the current revision of Army command guidance on the employment of tactical nuclear weapons (FM 101-31). Building on these results, crew effectiveness and unit effectiveness following radiation exposure are being estimated for insertion into Army algorithms for unit effectiveness (AURA). From this information, guidance on troop safety and casualty criteria are developed.

Research and technical guidance on neutron dosimetry is provided in direct support of the DoD Intrinsic Radiation (INRAD) Working Group.

The potential medical effect of long-term low-level radiation exposure due to fallout is also investigated. The Nuclear Test Personnel Review (NTPR) Program maintains a capability to identify participants and assign radiation exposure doses for an estimated 214,000 DoD personnel who were present at atmospheric nuclear weapons testing.

The medical management of casualties from a nuclear weapon detonation presents a unique medical problem. Therefore, the Surgeons General of the Military Services have directed that medical and operational personnel be updated on the Medical Effects of Nuclear Weapons (MENW) through the AFRRI education program.

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CATEGORIES OF RESEARCH EFFORT IN MILITARY RADIOBIOLOGY

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The major thrusts of research at the Armed Forces Radiobiology Research Institute are aimed at understanding the degradation of combat performance, the treatment of radiation effects, dosimetry, and the effects of fast neutrons and high-LET radiation.

DEGRADATION OF COMBAT PERFORMANCE

Effect of Ionizing Radiation on Combat Effectiveness

Military requirements exist for information on both individual and unit performance degradation due to the behavioral and physiological effects of exposure to ionizing radiation, as a function of radiation dose, quality, dose rate, and time after exposure. To meet those requirements, several disciplines and approaches must be integrated. Since human data on radiation effects are few and since animal experiments cannot be comprehensive models of human performance, confident predictions of radiation-induced combat ineffectiveness can be derived only by applying data on the degradation of specific functions to the actual task analyses of critical military tasks. Thus, the overall approach in meeting the requirements for information on radiation-induced performance decrement will be to

- carry out specific animal experiments to quantify radiation-produced degradation on the critical combat functions for which data do not exist;

- quantify the frequency and duration of prodromal radiation effects such as nausea and vomiting for midlethal to sublethal doses;

- combine these data with existing human data on similar radiation effects;

- establish descriptive models for radiation-induced performance decrement;

- define task analysis for critical combat tasks;

- apply the degradation data developed from the experiments to the task analyses and attempt to predict combat ineffectiveness;

- combine degradation analyses for crews in order to obtain information on unit ineffectiveness; and

- integrate this information with the Intermediate Dose Program (DNA contract program). Derivative programs will begin to answer specific Air Force and Navy problems.

Mechanisms of Performance Decrement and Incapacitation

Understanding the physiological basis for radiation-induced incapacitation and performance decrement is essential in order to provide protection against these radiation effects. It is necessary to verify the extrapolation of data from animals to man and to develop general models of radiation-produced performance decrement. Performance decrement postirradiation comprises a spectrum of responses from no effect, or malaise, to a variety of incapacitated states. To determine these mechanisms, the following factors will be assessed:

hypotension after irradiation, changes in membrane permeability and neurotransmitter release, changes in monosynaptic reflexes, measurements of alteration in neuronal and glial interactions, and mechanisms of damage produced by chemicals that simulate radiation-produced incapacitation (histamine, endorphins, prostaglandins);

regional cerebral blood flow (RCBF) measured by conventional invasive techniques with implanted cerebral electrodes; computer-analyzed evoked potentials;

RCBF measured by non-invasive techniques using radionuclides in combination with multiple arrayed detectors, and single photon emission computed tomography (SPECT);

Effect of Drugs on Combat Performance

The integrated battlefield poses a significant hazard not only because of the potential effects of chemical, nuclear, and biological agents but also because of the self-administration of a host of drugs: radioprotectants, antiemetics, chemical antidotes, vaccines, over-the-counter drugs, alcohol, and recreational drugs. The major therapeutic drugs will be evaluated for behavioral and physiological dysfunction pre- and postirradiation.

Combined Effects on Combat Performance

The interaction of nuclear weapons effects and chemical agents is of singular importance on the integrated battlefield. The effects of chemical and radiation insults will be evaluated by biochemical, electrophysiological, and radionuclide techniques. Attempts to mitigate these effects will also be studied, especially the possibility of reversible "opening" of the blood-brain barrier to chemical antidotes and radioprotectants.

TREATMENT OF RADIATION EFFECTS

Radioprotectants

The Walter Reed Army Institute of Research has devoted a tremendous amount of its research to the development of radioprotective drugs. Some of these drugs show minimum toxicity in humans, offer significant protection, and may be available for oral use within 5 years. The best radioprotective drug developed thus far is WR2721. AFRRI has initiated research to evaluate the efficacy of this and other drugs and different dietary adjuvants such as vitamins B₆, A, and E as possible radioprotectants. Multiple combinations of these radioprotectants will be assessed for different qualities of ionizing radiation.

Radiation-Induced Organ System Dysfunction

Rapidly proliferating tissues, such as bone marrow and gastrointestinal tract epithelium, are the most susceptible to radiation. Radiation-induced damage to these tissues leads to symptoms such as nausea, vomiting, diarrhea, anemia, bleeding, and infection. Therefore, means must be developed to (a) increase white

cell production, (b) devise techniques that can rapidly separate, type, and store white cells for infusion into irradiated personnel, and (c) devise methods to prevent the sequelae of gastrointestinal injury. Bone marrow transplantation and infusion of selected peripheral blood cell populations will be established in large-animal models for the rescue of lethally irradiated recipients. Reliable large-animal models for radiation injury, postirradiation sepsis, and combined injury will be established. A valid data base will be developed for the effects of these variables on the prognosis and treatment of combined radiation injuries on the nuclear battlefield. The efficacy of transplantation and transfusion procedures will also be determined in these models. Profound immunoparalysis is seen postirradiation; consequently, a comprehensive understanding of the immune system postirradiation is necessary to attempt to improve host defenses.

Medical and Surgical Treatment of Combined Effects

Blast and thermal energy in combination with radiation may be found in a future combat environment. Other factors, such as chemical and biological warfare agents and nonionizing radiation, are also very likely to be present. Therefore, it is important to determine the impact of these agents in combination with ionizing radiation on the overall response of personnel. Research will be conducted to

- evaluate blood-forming tissues and the immune system in the combined-injury individual;

- determine the effectiveness of radioprotectants and other interventions in increasing survival and in treating combined-injury personnel;

- evaluate medical and surgical procedures with noncontaminated wounds, contaminated wounds, and similar wounds after radiation;

- evaluate biologic response modifiers to augment host defenses to increase survival after combined injuries.

DOSIMETRY

Biologic Dosimetry

Development of improved dosimetric techniques that can be used in combat for the triage of military personnel are of utmost importance to field commanders and medical officers. Techniques for measuring biological indicators of radiation injury in physiological fluids have been the subject of extensive research at AFRRI. These techniques have been reassessed, and a systematic analysis of selected serum and urine components from irradiated animals is being made, using the techniques of greatest promise. The techniques developed for different qualities of radiation will then be validated, followed by automation of the developed assay techniques, for possible use in the battlefield. Electron paramagnetic resonance spectrometry has been used to detect the radiation-induced formation of free radicals in bone, teeth, and nails. A systematic study, begun at AFRRI, will continue to evaluate these non-invasive techniques as possible indicators of radiation injury. Fluorescence-activated cell sorting (FACS-II) has been shown to rapidly and reliably evaluate many physical and biochemical factors of peripheral blood cells using two lasers. It is hoped that rapid separation of stem cells will lead to useful dose-response relationships.

Physical Dosimetry

An improved dosimetric system will be developed to allow measurement of free-in-air dose, midline tissue dose, and bone marrow dose for different quantities and qualities of radiation. This system should be applicable to monoenergetic and polyenergetic neutron fields, gamma fields, and mixed neutron-gamma fields, as found in a combat environment. The reactor fields will be mapped in addition to the development of microdosimetric capability.

EFFECTS OF FAST NEUTRONS AND HIGH-LET RADIATION

The relative biological effectiveness (RBE) of neutrons has been a hotly contested scientific question, in large part because of the variable biological end point used in its determination. RBE varies, depending on neutron energy, dose rate, total dose, and the biologic system studied. The effects of 8-MeV neutrons on the gastrointestinal tract is being studied through the contract program. The potential neutron carcinogenesis will be assessed using a variety of systems and model systems through the contract program. AFRRI will continue its active participation in developing neutron dosimeters, and will actively collaborate with the USAF in understanding high-LET radiation effects.

STATUS OF IN-HOUSE RESEARCH AT AFRRI

The scientific work at AFRRI is conducted by five departments oriented toward the different disciplines necessary to achieve the product goals. These departments are Behavioral Sciences, Biochemistry, Experimental Hematology, Physiology, and Radiation Sciences.

Current research in each department is described on the following pages.



BEHAVIORAL SCIENCES DEPARTMENT

Group Title: Experimental Psychology Division

Objectives

To develop and validate animal models of human performance relevant to military missions.

To utilize animal models to characterize the effects of ionizing radiation on human performance in military situations.

To define and describe the magnitude, duration, and time course of radiogenic performance degradation and early transient incapacitation (ETI).

To develop and refine probabilistic models of performance degradation and ETI for use in computerized combat effectiveness models (e.g., AURA).

To evaluate the behavioral effects of radioprotectants.

Current Status

Experimental determination of the effects of ionizing radiation on monkey speed-stress visual discrimination task (SSVDT): 90% complete.

Incorporation of SSVDT into primate behavioral data base: 50% complete.

Analysis of emesis as a function of radiation quality: 20% complete.

Effects of radiation quality on rodent motor performance: 75% complete.

Effects of radioprotectants on motor performance: 10% complete.

Primate Data Base: 90% complete for 650 subjects, six radiation fields, and three behavioral tasks.

Future Goals and Directions

Neutron RBE for performance degradation and ETI

Effects of drugs and drug-radiation interaction on combat performance

Behavioral pharmacology of radioprotectants

Behavioral and psychophysiological analysis of the effects of ionizing radiation on sensory thresholds

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Accomplishments

It was determined that the ED₅₀ for ETI in monkeys on the speed-stress visual discrimination task is 900 rads at neutron:gamma of 3:1.

It was concluded that the RBE of high-energy electrons is greater than either bremsstrahlung or gamma radiation for producing ETI in rat motor (accelerod) performance.

Analysis of primate behavioral data base has been utilized in revisions of combat casualty criteria in the Army Field Manual FM 101-31-1 and NATO STANAG 2111 and 2083.

It was found that at therapeutic doses, radioprotectant WR-2721 produces significant decrements in rat motor performance, and does not protect against ETI under these circumstances.

Through a BHS-RSD collaborative effort, a rapid small-animal extractor is now operational in the TRIGA. This will greatly facilitate the analysis of immediate behavioral effects following acute exposure to ionizing radiation.

Analysis of a complex two-response task distinguished between the motor, sensory, and motivational aspects of performance degradation.

BEHAVIORAL SCIENCES DEPARTMENT

Group Title: Physiological Psychology Division

Objectives

To identify physiological mechanisms underlying performance degradation, ETI, conditioned taste aversions (CTA), and emesis.

To develop therapeutic approaches to prevent radiation-induced performance degradation, ETI, CTA, and emesis.

Current Status

Role of humoral factors in emetic response and conditioned taste aversions: 75% complete.

Role of neurotransmitters and neuromodulators (e.g., dopamine, endogenous opiates) in radiogenic performance decrements: 20% complete.

Role of stimulated Na^+ movement in neurons: 50% complete.

Combined behavioral effects of irradiation and anesthesia: 10% complete.

Future Goals and Directions

Assess the role of additional neurotransmitter systems (e.g., GABA, acetylcholine) underlying performance degradation and ETI.

Isolate and characterize blood-borne humoral factor(s) associated with radiation-induced emesis and conditioned taste aversions.

Accomplishments

It was found that basic neuronal excitatory processes are impaired after exposure to ionizing radiation.

We concluded that neurotransmitter activity (e.g., dopamine) is altered in a biphasic pattern, and correlates with the time course of ETI.

We found that a blood-borne factor probably mediates radiation-induced emesis through an interaction with a specific brain area (i.e., area postrema).

BIOCHEMISTRY DEPARTMENT

Group Title: Hematopoietic Stem Cell Isolation

Objectives

To isolate a pure population of functional hematopoietic stem cells that may be used in bone marrow transplants in irradiated individuals.

Current Status

AFRRI has available to its investigators a state-of-the-art fluorescein-activated cell sorter for isolating pure immune cell preparations. For instance, peripheral lymphocyte subpopulations (T-helper and T-suppressor cells) can be sorted with 99% purity and 98% viability.

The development of a rapid stem-cell isolation procedure would significantly enhance progress in the area of bone transplantation free of graft-versus-host disease.

Future Goals and Direction

With the development of a new set of fluorescent dyes, we are developing a three-marker cell sort for hematopoietic stem cells. The three-marker plus the size profile sorting capacity on the FACS II cell sorter will enable us to characterize and isolate "pure" populations of viable stem cells within a reasonable time.

Accomplishments

By a simple one-antigen marker cell sort on the FACS II, we have been able to purify viable rat stem cells greater than 100-fold in approximately 1-1/2 hours.



BIOCHEMISTRY DEPARTMENT

Group Title: Radiation Effects on Bone and Bone Marrow Development

Objectives

To study the effects of ionizing radiation on the function and development of bone and bone marrow.

To develop methodology for investigating the effects of spaceflight on bone and bone marrow development.

Current Status

We have developed a method of inducing bone and bone-marrow formation in young rats.

We are studying the effects of radiation on cellular targets in bone and the underlying mechanisms.

We are studying radiation effects on the interrelationship of bone and bone-marrow development.

Future Goals and Directions

Determine the RBE of the hematopoietic microenvironment, using the model for endochondral bone and bone-marrow development. Develop methods by which radiation damage may be prevented or repaired.

Isolate and characterize growth factors that may be responsible for bone and bone marrow self-renewal. To evaluate these factors in reversing the effects of radiation and combined injury on bone development, remodeling, and fracture healing.

Investigate the relationship of bone and bone marrow in conditions caused by spaceflight radiation.

Accomplishments

Effects of radiation on the critical stage of radiation-induced bone formation and mineralization were studied.

We found that sublethal irradiation delayed the differentiation of cartilage and bone by impairing progenitor cell proliferation.

We determined that the cells that comprise the microenvironment of the hematopoietic system are sensitive to ionizing radiation.

BIOCHEMISTRY DEPARTMENT

Group Title: Radiation and Combined Injury and Circulating Mediators

Objectives

To identify circulating factors and neurohormonal mediators that have causal roles in the sequelae of radiation and/or combined-injury performance decrement and incapacitation.

To determine the efficacy of mediator intervention by various means (anti-inflammatory drugs, radioprotectants, antiemetics, and anesthetics).

To determine the potential use of levels of mediators in urine, CSF, and plasma as indicators of radiation exposure.

Current Status

We are studying radiation alteration of prostaglandins and other mediators known to affect a variety of cellular functions.

We are establishing the role of vasoactive substances in radiation-induced damage.

We are looking for simple biochemical indicators of radiation exposure.

We are seeking information on how radioprotectors modulate chemical mediators and messengers. We are evaluating the possibility of interventions by various types of drugs to alleviate radiation-induced injury.

Future Goals and Directions

Evaluate a number of mediators and chemical messengers as potential indicators of radiation damage in relation to lethality and specific parameters of radiation injury (e.g., lung damage, GI damage).

Substances studied will be prostaglandin F₂, E₂, D₂, thromboxane B₂, cyclic AMP and GMP, ACTH, beta-endorphin, cortisol/corticosterone, and complement in biological fluids and tissues.

Mediators will be studied in relation to dose of gamma or enhanced neutron radiation in models of different species (monkey, dog, mouse, guinea pig). Inter-species differences will be evaluated in terms of potential extrapolation to man.

Combined-injury models (radiation plus burn/wound) will be evaluated.

Accomplishments

Dose-related increases in prostaglandin levels were found in parenchymal and airway lung tissues of guinea pigs exposed to radiation.

We concluded that alterations in several urinary constituents in mouse and guinea pig models appear to be related to subsequent mortality.

We found that the classical pathway of complement does not appear to play an important role in survival after radiation exposure.

We determined that the prostaglandins and thromboxane levels measured in the plasma of monkeys did not change after radiation exposure, but that prostaglandin levels in gastric juice were significantly altered 2 days postexposure.

BIOCHEMISTRY DEPARTMENT

Group Title: Mucosal Immune System and Radiation/Combined Injury

Objectives

To investigate the effect of radiation on the IgA immune system (Peyer's patches, mucosal immune system).

Investigate methods by which the IgA arm of the immune system may be manipulated and/or modulated in order to reestablish immune function in irradiated individuals with other severe injuries.

Current Status

The effects of radiation on the IgG arm of the immune system are well known.

There is little knowledge about the effects of radiation on the IgA arm of the immune system.

We are investigating the effect of radiation on the mucosal immune system in order to prevent opportunistic infections.

Future Goals and Directions

Radiation effects on Peyer's patches immune cells in other tissues.

Specific subpopulations of mucosal lymphocytes will be isolated from irradiated animals to determine which cells are functional after radiation exposure.

Procedures will be determined by which the immune competency of the mucosal immune systems may be restored in combined-injury victims.

Accomplishments

It has been concluded that after 150 roentgens of ionizing radiation, Peyer's patches lymphocytes from rats are damaged, and regeneration of these lymphocytes is extremely slow, compared to the IgG arm of the immune system.

It has been found that the spleen is not required for a functioning IgA system.

BIOCHEMISTRY DEPARTMENT

Group Title: Chemical Radioprotection

Objectives

To obtain more effective radioprotective agents than are now available.

To determine the mechanisms of action of potential radioprotective agents, with various structures, in order to provide for the more rational application of radioprotective measures.

To determine the effectiveness of combinations of radioprotective agents and new delivery systems of drugs against different qualities of radiation.

Current Status

WR-2721 is the most effective, but other factors to be considered are its toxicity and side effects (nausea, hypotension). It does not protect the central nervous system.

A study is in progress on the subcellular distribution and mechanism of action, so that more efficient drugs can be developed.

We need to associate radioprotectants with immunomodulating agents.

Future Goals and Directions

Study the radioprotective activity in mice of compounds with various structures in comparison and in combination with WR-2721 derivatives.

Study the efficacy of compounds, showing that the best protection when administered i.p. to mice can also be achieved after oral administration, and using newer drug delivery systems (e.g., liposomes).

Evaluate protection against GI, hematopoietic, and CNS damage, using various compounds.

Accomplishments

It has been determined that no chemical tested has provided more radioprotection than WR-2721, in terms of LD50/30.

We have studied the effects of potential radioprotectants and/or immunomodulators on cell-mediated immunity in irradiated mice; this was determined by measuring changes in delayed-type hypersensitivity.

We have determined the effects of radioprotective drugs, sensitizing drugs, and glutathione peroxidase activity. Radioprotectors have been found to cause an increase in enzyme activity in tissues.

BIOCHEMISTRY DEPARTMENT

Group Title: Naturally Occurring Radioprotectors

Objectives

To study radioprotective factor(s) from a naturally radioresistant organism, and to determine its efficacy in preventing radiation damage and mechanisms of action.

To investigate the interrelationship of dietary elements, especially those with anti-oxidant properties (vitamins E, A, C, selenium, and other minerals) with respect to radioprotective properties.

To determine the relative importance of endogenous protective enzyme systems (superoxide dismutase, glutathione peroxidase, catalase) and endogenous non-protein sulfhydryl compounds (reduced glutathione) in preventing radiation damage to cells and tissues.

Current Status

Organisms known to be naturally radioresistant have poorly understood factors that provide this protection. We are determining whether there are potential medical applications for these substances.

The effects of radiation on nutritional status and, conversely, the effects of specific dietary elements on radiosensitivity are being studied.

The role of enzymes (superoxide dismutase, glutathione peroxidase, catalase) in radioprotection is being investigated.

Future Goals and Directions

Evaluate in mice the radioprotective properties of substances isolated from radioresistant microorganisms.

Develop a dietary regimen that will increase tissue levels of endogenous protective enzymes and glutathione, to optimize radioprotection.

Evaluate the effect of drugs on endogenous protective enzyme systems.

Accomplishments

An extract from *D. radiodurans* has been resolved into a 1000-dalton fraction that provides radioprotection when added to cultured cells. This fraction contains unidentified sulfhydryl compounds (possibly coenzyme A or derivatives).

Methods have been developed by gas-chromatographic techniques for identifying the volatile products formed on the peroxidation of lipids in cell membranes. These will be applied to determine the role of endogenous protective systems in radioprotection.

Possible reasons for the radioprotection given by increased amounts of vitamins and minerals have been studied. Increased survival of irradiated mice fed a diet of high vitamin E and selenium may be due to increased levels of glutathione peroxidase in tissues.

EXPERIMENTAL HEMATOLOGY DEPARTMENT

Group Title: Radiation-Induced Hemopoietic and Immune Dysfunction

Objectives

To delineate the mechanisms involved in the regulation of the processes of proliferation and differentiation of the hemopoietic stem cell and its committed progeny.

Current Status

Reliable in vitro assays are being established for multipotent hemopoietic cells from murine and monkey tissue.

Separation techniques, based on physical and immunologic properties of hemopoietic cells, are being developed singularly and in combination. Techniques being used are rosetting with SRBC, and soybean agglutination in combination with density separation and counterflow elutriation. This effects the depletion of unwanted T-lymphocytes while concentrating the stem cells.

Future Goals and Directions

Establish reliable assays for hemopoietic stem cells in the canine and primate.

Use monoclonal antibodies and specific growth factors to delineate cellular relationships in murine and primate hemopoiesis in *normal and irradiated animals*.

Establish a long-term culture system for primate bone marrow.

Initiate use of monoclonal antibodies against cells of the murine, canine, and primate hemopoietic systems to remove specific undesirable cell types from the total population.

Use autologous bone-marrow transplant in the canine and primate, to identify a functional pluripotent stem cell capable of long-term reconstitution.

Accomplishments

An in vitro assay for a multipotent stem cell has been established in the primate system.

The presence of this cell type in various cell fractions following counterflow centrifugation-elutriation has correlated with those fractions that promote long-term survival.

Immunologic separation of primate bone-marrow cells using sheep-red-blood-cell and soybean-lectin receptors on T-lymphocyte populations has concentrated the populations of hemopoietic progenitor cells two- to fivefold.

A model of autologous bone-marrow transplantation has been established in the primate. Whole bone marrow and separated bone marrow have been transplanted, with good results in terms of survival engraftment and reconstitution of peripheral elements.



EXPERIMENTAL HEMATOLOGY DEPARTMENT

Group Title: Radiation-Induced Hemopoietic and Immune Dysfunction

Objective

To determine the relative biological effectiveness (RBE) of fast neutrons (1 MeV) for hemopoietic and gastrointestinal effects in a large-animal (canine) model.

Current Status

The LD50/30 for the canine after exposure to AFRRI TRIGA (1 MeV) neutrons was established at 1-25 Gy.

The RBE for hemopoietic death in the canine for 1-MeV neutrons relative to cobalt-60 gamma-irradiation is approximately 1.63.

This RBE is also reflected in the sensitivity of specific cell types in the target tissue, the bone marrow.

The canine GI system is also very sensitive to neutrons. The RBE for the GI system may be as high as 5.0, when using the LD50/30 as an index.

Future Goals and Directions

Determine depth-dose relationships and target organ dose in a canine neutron radiobiology model.

Determine the LD50/30 in the canine for unilateral and partial-body neutron irradiation.

Correlate the above with assays for functional hemopoietic cells in target organs.

Accomplishments

Canines have been unilaterally exposed to a neutron dose range of 1.50 to 2.50 Gy. LD50/30 values have been placed at 2.25 Gy, relative to approximately 1.25 Gy for bilateral whole-body exposure.

It has been found that early death of these animals indicate greater gastrointestinal involvement, in addition to marrow depletion.

We have determined that a bilateral neutron dose of 2.00 Gy is over 90% lethal. Autologous bone marrow transplant ensures only 50% survival, again indicating greater involvement of damage to the GI system with neutron irradiation

EXPERIMENTAL HEMATOLOGY DEPARTMENT

Group Title: Radiation-Induced Hemopoietic and Immune Dysfunction

Objective

To enhance postirradiation recovery in hemopoietic stem and progenitor cell populations.

Current Status

New hemopoietic stem cell assays are being tested for reliability. D_0 and recovery parameters are being determined.

Various immunomodulators are being tested for their ability to enhance the recovery of hemopoiesis following irradiation. These include glucan, detoxified endotoxin, and selected agents from the Biological Response Modifiers Program (NCI, Frederick, MD).

Glucan has proved to be very effective in stimulating hemopoiesis when given before and immediately after irradiation.

Glucan is being tested in combination with agents such as WR-2721, antibiotic regimens, and immunoglobulin therapy.

Future Goals and Direction

Determine the ability of the immunomodulator glucan to enhance hemopoiesis in the canine and primate.

Determine the ability of the immunomodulating capacity of glucan to (1) enhance survival in irradiated mice and dogs through hemopoietic stimulation, and (2) prevent infection by opportunistic pathogens.

Determine the efficacy of combining agents such as glucan, antibiotics, and immunoglobulins in the large-animal radiobiology and sepsis models.

Accomplishments

It has been found that both particulate and soluble glucan enhance hemopoietic repopulation in sublethally irradiated mice and significantly enhance survival in otherwise lethally irradiated mice.

Studies with particulate glucan indicate that survival is due to enhanced hemopoiesis and resistance to colonization by opportunistic pathogens.

Preliminary studies have indicated the dose range of glucan for maximal stimulation of hemopoiesis in the canine and primate.

EXPERIMENTAL HEMATOLOGY DEPARTMENT

Group Title: Radiation-Induced Hemopoietic and Immune Dysfunction

Objective

To prevent and treat radiation effects, including radiation-induced hemopoietic dysfunction, and the medical and surgical therapy of combined effects.

Current Status

Small-animal and large-animal (canine) models for sepsis have been established for investigating the mechanisms of cellular dysfunction following irradiation. Models of sepsis have been established.

The canine model for peritoneal sepsis has been established and characterized relative to lethality, hemopoietic and immune responses, and hemodynamic status.

Small-animal models are being used in combination with trauma models such as wounds and thermal injury.

Monoclonal antibodies to lymphocyte subpopulations are being used to decipher changes in specific subpopulations following irradiation and sepsis.

Specific mediators such as interferon, interleukin, plasminogen activator, and acute-phase reactants are being investigated relative to the cellular inflammatory response following infection in normal and irradiated animals.

Future Goals and Directions

Establish immunologic parameters to be measured in the various models of radiation, trauma, and combined injury. These include lymphocyte populations, macrophages, and mediators of inflammation.

Define the dynamics of microbial changes after radiation, trauma, and combined-injury regimens.

Explore the timing variable in the interval between exposure to radiation and trauma.

Evaluate "biological response modifiers" modulation of immune suppression following radiation and trauma.

Utilize the canine model of peritoneal sepsis for assessing avenues of therapy.

Accomplishments

The large-animal model of canine peritoneal sepsis has been established as a valid model of human sepsis.

We have determined that a nonlethal dose of E. coli bacteria can be administered within 4 hours or 6 days after a sublethal dose of radiation (1.50 Gy cobalt-60) without producing lethality. Fluid therapy is essential.

The dose of radiation (1.50 Gy cobalt-60) does not impair the ability of granulocytes to chemotax, phagocytose, or kill bacteria.

Collaborators have shown that the use of nonsteroidal anti-inflammatory agents (such as indomethacin and ibuprofen) restore normal hemodynamics following E. coli sepsis, probably by inhibiting prostaglandin synthesis.

PHYSIOLOGY DEPARTMENT

Group Title: Neurophysiology Division

Objectives

To study the cellular mechanisms of radiation injury and how radiation affects excitable membrane properties.

To study the effect of neurotoxic chemical warfare agents and how they modify susceptibility to radiation.

To determine the direct and indirect effects of radiation on hippocampal neurons of the central nervous system.

To study the mechanism of radiation-induced fatigue.

Current Status

A number of tissue-comprising cell lines and primary dissociated tissue cultures are being used.

Cultures of autonomic nervous system neurons are being used to study the effect of radiation on single neuronal units.

Several radiation-released compounds are being studied, and their effect on hippocampal neuronal integration is being determined using neuronal brain slices.

A computer-assisted system is currently in operation, assessing the synaptic quantal content of neurotransmitter release in irradiated and matched nonirradiated synaptic junctions.

Future Goals and Directions

Individual ionic mechanisms by which synaptic control is affected by radiation-released compounds will be followed.

The use of the neuromuscular junction of the mouse and rat will be pursued to evaluate the effects of radiation on prolonged fatigue and performance decrement.

Accomplishments

The patch voltage clamp system has been introduced, and is being used by several laboratory groups to evaluate single-channel conductances.

Seven different voltage- and time-dependent conductances have been evaluated at the single ionic channel level in sympathetic neurons. The possibility has been discovered that radiation-released toxic compounds produce ionic changes by modulating calcium currents and therefore synaptic mechanisms.



PHYSIOLOGY DEPARTMENT

Group Title: Cellular Physiology Division

Objectives

To determine if exposure of cultured endothelial cells to ionizing radiation results in increased vascular permeability or altered cellular synthetic mechanisms.

To evaluate the mechanisms by which radiation damage affects the cell function of a number of cell types, by means of alteration of the sodium-potassium ATPase mechanism.

To determine the effects of radiation on an animal's host-defense mechanisms, by evaluating the role of the macrophage in combating infections and how macrophage function is affected by radiation.

Current Status

Endothelial cells from bovine aortas are being grown in tissue culture.

The sodium-potassium transport mechanism in neurons and in kidney epithelial cells is being evaluated.

Cellular properties of the human peripheral blood-derived macrophage, the mouse peritoneal macrophage, the mouse spleen macrophage, and macrophage-like tissue-culture cell lines are being evaluated, using biochemical and electrophysiological techniques.

Future Goals and Direction

Endothelial cells grown from a number of sources will be evaluated as to their structure and function.

The sodium-potassium transport system dysfunction will be evaluated as to whether its source of damage is direct or indirect. The effect of the sodium-potassium transporter on the sodium-mediated amino acid and glucose transport will be evaluated.

Macrophages from a number of sources will be evaluated for their secretory, phagocytic, and chemotactic abilities following radiation.

Accomplishments

It has been determined that the sodium-potassium coupling ratio may vary under certain environmental stresses.

It has been determined that radiation may influence the sodium-mediated glucose transport mechanism in kidney epithelial cells.

Patch-clamp methodology has recently been introduced to study the membrane properties of the macrophage.

Functional studies have indicated that macrophage-like cells exposed to radiation increase their phagocytosis and superoxide release, and develop a more activated state.

PHYSIOLOGY DEPARTMENT

Group Title: Gastrointestinal Physiology Division

Objectives

Sublethal doses of radiation produce nausea, vomiting, and diarrhea, while supra-lethal doses result in loss of fluid, electrolyte loss, toxemia, and death.

To study the effects of ionizing radiation on intestinal electrolyte transport at the cellular level, in an effort to elucidate the mechanism of radiation-induced diarrhea.

To determine if part of the gastrointestinal syndrome is due to complications and alterations in gastrointestinal blood flow following radiation.

Current Status

Programs are established to evaluate isotope fluxes of sodium, chloride, and potassium across isolated gastrointestinal mucosa from both irradiated and non-irradiated animals in vitro.

Measurements of intestinal blood flow are being made, using hydrogen washout techniques in isolated loop of the ileum of dogs from both irradiated and sham-irradiated animals.

Future Goals and Directions

Isotope fluxes, short-circuit currents, and standard electrophysiological intracellular recording techniques will be used to evaluate alterations in cell membrane permeabilities and intracellular ionic activities.

The intracellular trigger that initiates the loss of fluid and electrolytes associated with diarrhea as a result of radiation will be evaluated.

Changes in blood flow in the gastrointestinal system will be evaluated in the presence of pharmacological agents, including antihistamines, certain radio-protectants, and radiosensitizing agents.

Accomplishments

It has been determined that cobalt-60 may cause significant alterations in intestinal electrolyte transport 24 to 72 hours postradiation, resulting in a decrease in responsiveness to both secretory and absorptive stimuli.

Preliminary studies indicate a role of calcium in regulating the various membrane conductances associated with these diarrheal states.

We have determined that histamine blockers alter the initial postradiation increase in intestinal blood flow and the postradiation change in hematocrit measured in the gastrointestinal vascular system.

PHYSIOLOGY DEPARTMENT

Group Title: Cardiovascular Physiology Division

Objectives

Acute ionizing radiation produces a transient hypotension followed by a complete cardiovascular failure similar to that seen in circulatory shock.

To evaluate the effect of radiation-induced vascular hypotension of visceral organs, using intestinal vasculature as a model system.

To evaluate the production of histamine and other toxic byproducts released by radiation, to determine if they induce a circulatory shock state.

To study the loss of cardiovascular reserve following radiation, which may lead to fatality.

Current Status

Model systems are being used to evaluate cardiovascular dysfunction in various visceral organ systems. These include isolated gastrointestinal systems in the rat and the dog.

Cerebral vascular studies are under way to evaluate the changes in blood flow of individual areas of the central nervous system following whole-body and localized radiation.

Circulating radiation-released toxic elements are being evaluated for their mechanisms of action.

Various blockers are being evaluated to determine their radioprotecting potential.

Future Goals and Directions

Ongoing research will continue to evaluate the effects of antihistamines on intestinal blood flow, in an attempt to evaluate the effect of histamine released as an indirect radiation insult.

Accomplishments

Findings indicate that radiation-induced hypotension in the beagle was accompanied by increased intestinal blood flow.

H₁ and H₂ histamine blockers temporarily prevented the postirradiation increased blood flow and hematocrit.

A decrease in plasma glucose following the first hour postirradiation was demonstrated in beagles.

RADIATION SCIENCES DEPARTMENT

Group Title: Nuclear Science

Objectives

To determine the effects of ionizing radiation on the morphology and functional changes in different organ systems that are of direct importance to the combat performance decrement in acute radiation exposure. This includes studies of structural and functional changes of the respiratory and cardiovascular system, gastrointestinal and hepatobiliary kinetics, and metabolic behavior of muscarinic receptors using NMR and nuclear scintigraphic techniques.

Current Status

Work involving the muscarinic receptor and cardiovascular studies is 10% complete.

Ionizing radiation (to 100 Gy) confined to the precordium does not produce immediate changes in the heart. However, impairment of function occurs at postirradiation intervals.

Investigations into the effects of irradiation on GI function are approximately 40% complete. The kinetics of pharmacological agents is being studied.

Future Goals and Directions

Continue work on radiation effects on the GI and hepatobiliary function as well as CNS functions.

Investigate the effects of ionizing radiation on the central nervous system, and the toxicological effects of transuranic elements.

Accomplishments

We have determined the effects of cobalt-60 irradiation on GI function. We have studied methods of reducing these effects by use of antiemetic agents.

The tissue distribution of gallium-67 in rats irradiated with photons and fission neutrons has been determined.

We have completed myocardial scintigraphy studies with technetium-99m in dogs after acute irradiation of the heart. These studies were conducted in reference to a direct military relevance addressing combat performance in the postirradiation syndrome.

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RADIATION SCIENCES DEPARTMENT

Group Title: Physical Dosimetry

Objectives

To address the major needs for research requirements of a measurement system used in mixed ionizing radiation fields to determine doses as found in a combat environment. Included are dosimetric extrapolation from monkey to man, development of hazard-evaluating systems, identification of mechanisms of biological radiation damage, and neutron monitoring of extremities.

Current Status

Program objectives are divided into two major areas. Dosimetry Technology Base includes efforts to develop extrapolation models and studies of mechanisms of radiation damage. Operational Radiation Dosimetry (DT-526) includes work to develop and improve dosimetry devices such as a neutron criticality dosimeter and microdosimetry techniques. Work in these areas is 10%-20% complete.

Future Goals and Directions

In addition to the preparation of monkey-to-man dosimetric extrapolation schemes, other models may be investigated, such as dog-to-man models or other species. By fiscal year 85/86, the improved dosimetry techniques and devices such as the microdosimetry models (used to determine RBE to man) and the ALBEDO dosimeters (for extremity neutron monitoring) should be implemented to permit determination of militarily relevant exposures.

Accomplishments

We have completed verification of AFRR's primary dosimetry systems.

We have confirmed response coefficients for ion chambers.

We have established intercomparisons for electron-photon fields and neutron dosimetry.

A neutron spectrum for a monkey phantom has been determined.

RADIATION SCIENCES DEPARTMENT

Group Title: Biological Dosimetry

Objectives

To develop noninvasive dosimetric techniques that can be used in combat for the triage of military personnel.

Current Status

Studies involving EPR spectroscopy of irradiated bone and tooth samples are approximately 20% complete. Dose-response characteristics of different qualities of ionizing radiation have been investigated. Investigation of the sensitivity of DNA to ionizing radiation using NMR and EPR techniques have started.

Future Goals and Directions

Improve techniques to measure radiation-induced signals to extend the lower limit of sensitivity, and to enable other forms of samples (such as aqueous samples) to be used as dosimeters.

These new techniques will also allow the measurement of radiation-induced signals in a person's finger.

Future research will include assessment of damage by ionizing radiation on solid films of DNA, as well as DNA interaction with drugs and proteins.

Accomplishments

We have studied the use of red blood cells as an indicator of radiation damage.

Radiation-induced muscular fatigue has been studied using NMR techniques.

We have investigated ionizing radiation damage to plasma membranes irradiated up to 1 Mrad, using fluorescence probe methods.

CONTRACT RESEARCH PROGRAM AT THE DEFENSE NUCLEAR AGENCY

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The Defense Nuclear Agency coordinates, integrates, and interprets contract research for inclusion in the AFRRI and Defense Nuclear Agency program. The research concerns methods to mitigate, delay, prevent, or enhance the biologic response to nuclear, biological, and chemical weapons. Contract research that is complementary to that of AFRRI is conducted on low-level radiation effects, prevention and treatment of radiation effects, neutron relative biological effectiveness, combined injuries, radiation dosimetry, performance decrement and incapacitation, radioprotectors, and chelators.

Contract research for FY 1984 is described in the following section.

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Hawkins/295-2128
13 Feb 84

Title: Emetic Mechanism in Acute Radiation Sickness

Contract #: DNA 001-83-C-0010

Task Code: U99QMXMK

Work Unit Code: 00039

Funding: \$133,000 (FY83: \$120,000; FY 85: \$174,000)

Performer: Dartmouth Medical College

CTM: LCDR Hawkins

Start Date: 9 Dec 82

Completion Date: 30 Dec 85

Objectives: To determine to what extent the chemoreceptor trigger zone in the brain and nerve pathways from the upper abdomen to the brain contribute to vomiting after irradiation, and from the results of these studies, develop treatment to alleviate radiation-induced vomiting.

Technical Approach: The role of the chemoreceptor trigger zone in acute radiation sickness will be determined by establishing the dose response relationship of vomiting to whole body X irradiation in normal cats. The effects of central nervous system lesions and/or nerve sectioning will then be evaluated to determine if partial or complete protection against radiation-induced emesis occurs. Based on the results of these studies, it is anticipated that specific therapeutic agents can be developed to treat against radiation-induced emesis.

Outside Agency Involvement: None

Principal Investigator:

H. L. Borison
Professor of Pharmacology
Institute of Brain Stem Studies
Department of Pharmacology and Toxicology
Dartmouth Medical School
Hanover, New Hampshire 03755
(603) 646-2627

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Hawkins/295-2128
6 Feb 84

Title: Physiological Mechanisms of Acute Intestinal Radiation Death

Contract #: DNA 001-83-C-0009

Task Code: U99QMXMK

Work Unit Code: 00040 and 00089

Funding: \$166,000 (FY83: \$110,000; FY 85: \$112,000)

Performer: University of Washington

CTM: LCDR Hawkins

Start Date: 27 Dec 82

Completion Date: 30 June 85

Objectives: To clarify the role of fluid and electrolyte loss, bile duct ligation, radiation-damaged intestinal mucosa, bacterial toxemia and their interrelationship on radiation-induced gastrointestinal death. The relative effects of gamma rays and neutrons on this mechanism will also be evaluated.

Technical Approach: Damage to intestinal mucosa after gamma and neutron irradiation in correlation with levels of bacteria present in the gastrointestinal tract will be determined. The effects of bile-duct ligation and antibiotic decontamination on survival time after neutron and gamma irradiation will then be determined. During the second year, the experiments to determine effects of specific bacteria known to cause diarrhea or sensitivity to acute intestinal radiation death will be conducted. After these experiments, changes in body fluid compartments in normal and antibiotically treated animals after irradiation will be determined. During the third year, the influence of bile-duct ligation on body fluid compartments after irradiation will also be conducted. Finally, the administration of antibiotics in saline into the GI tract and the effects on survival times after irradiation will conclude the series of experiments.

Outside Agency Involvement: None

Principal Investigators:

K. L. Jackson and J. P. Geraci
University of Washington
Seattle, Washington 98195
(206) 543-4043

Hawkins/295-2128
13 Feb 84

Title: Immune Alteration Studies in Irradiated Dogs

Contract #: DNA 001-83-C-0172

Task Code: U99QMXMK

Work Unit Code: 00053

Funding: \$237,000 (FY 83: \$251,000; FY 85: \$300,000)

Performer: Immuquest Laboratories (MICRO)

CTM: LCDR Hawkins

Start Date: 1 Aug 83

Completion Date: 30 Sep 86

Objectives: To study the recovery of the immune function, susceptibility to microbial infections and overall recovery after irradiation alone or in combination with grafts of whole or fractionated bone marrow in the dog model. The studies will be designed to answer questions of immune competence recovery when other insults of injury and sepsis are combined with gamma and neutron exposures.

Technical Approach: The contractor will perform a large variety of assays to evaluate the immune competence of dogs exposed to mixed gamma/neutron irradiation. These assays will include evaluation of T-lymphocyte, macrophage, and granulocyte activity after irradiation. Primary and secondary humoral immune responses will also be evaluated to correlate recovery of circulating immunoglobulin concentrations after irradiation. Susceptibility to infection, response in delayed hypersensitivity to antigens, allogeneic skin graft rejection, and leukocyte migration studies will also be conducted.

Outside Agency Involvement: None

Principal Investigator:

C. A. Bowles
Immuquest Laboratories, Inc.
11 Taft Court
Rockville, Maryland 20850
(301) 253-6521

Hawkins/295-2128
13 Feb 84

Title: Development of Plutonium Chelators

Contract #: DNA 001-83-C-0263

Task Code: U99QMXMK

Work Unit Code: 00061

Funding: \$130,000 (FY83: \$45,000; FY85: \$122,000)

Performer: University of Florida

CTM: LCDR Hawkins

Start Date: 10 Aug 83

Completion Date: 31 Oct 85

Objectives: To develop a chelating agent that will complex plutonium 239 and make it more susceptible to excretion and/or metabolism.

Technical Approach: The following experiments will be performed: (1) Identify the best octacoordinate chelator for plutonium. That is, the one that has the proper connection of chelating units providing optimum chelating property for plutonium. In these experiments 13 ligands will be considered. (2) Establish the toxicity of the optimum octacoordinate chelator by determining the LD50 in mice. (3) Evaluate the ability of the chelators to bind cerium-IV using column elution techniques. During FY 85-86, experiments will be performed at Rocky Flats to evaluate the ability of these octacoordinates identified as nontoxic to remove plutonium and americium from internally contaminated rats.

Outside Agency Involvement: None

Principal Investigator(s):

Dr. R. J. Bergeron
University of Florida
Department of Medical Chemistry
Box J-4 JHMHC
Gainesville, Florida 32610
(904) 392-5900

Dr. James Navratil
Manager, Chemical Research
Rockwell International
Rocky Flats Plant
P.O. Box 464
Golden, Colorado 80401
(303) 497-2906

Hawkins/295-2128
13 Feb 84

Title: Prevention of Canine Graft-Versus-Host Disease (GVHD)

Contract #: DNA 001-83-C-0294

Task Code: U99QMXMK

Work Unit Code: 00074

Funding: \$199,000

Performer: Fred Hutchinson Cancer Research Center

CTM: LCDR Hawkins

Start Date: 28 Jul 83

Completion Date: 31 Oct 84

Objectives: The objective of this proposal is to develop monoclonal antibodies against canine T-lymphocytes to be used in attempts to prevent graft-versus-host-disease (GVHD) in DLA-matched and mismatched bone-marrow transplant in dogs.

Technical Approach: Antibody complement or antibody and toxin conjugates will be used to lyse the lymphocytes in bone marrow that initiate GVHD. The treated marrow will then be infused into lethally irradiated recipients to determine whether one can transplant without histocompatibility matching. The second goal will be to treat animals that have established GVHD, by intravenous infusion of monoclonal anti-T cell antibodies. In vitro assays will be used to monitor T-lymphocyte depletion.

Outside Agency Involvement: None

Principal Investigator:

Rainer Storb, M.D.
Professor of Medicine
The Fred Hutchinson Cancer Research Center
1124 Columbia Street
Seattle, Washington 98104
(206) 292-2311

Hawkins/295-2128
20 Jan 84

Title: Proliferative Characteristics of Intestinal Stem Cells: Response and Protection from High Energy Neutrons, Fission Spectrum Neutrons, and Photons

Contract #: DNA 001-84-C-0061

Work Unit Code: 00079

Task Code: U99QMXMK

Funding: \$115,000 (FY85: \$23,000)

Performer: Rush-Presbyterian St. Luke's Medical Center

CTM: LCDR Hawkins

Start Date: 1 Nov 83

Completion Date: 30 Sep 84

Objectives: To measure the radioprotective effects of Cytosine Aribinoside (Ara-c), Walter Reed compound-2721, and the combination of both given to mice before whole-body neutron or gamma ray irradiation. To estimate the LD50/6 and LD50/30 for control mice, Ara-c-treated mice, WR-2721-treated mice, and combination of the two agents, given before neutron or gamma irradiation.

Technical Approach: Experiments will be designed to determine the radio-protection of crypt stem cells by Ara-c, WR-2721, and combination of the two agents, given optimally before irradiation with neutrons and gamma photons. Mice will be given Ara-c or WR-2721 alone or in combination at various times before neutron or gamma irradiation, and stem cell survival will be evaluated. A second phase of these experiments will be to determine the relationship of intestinal stem cell survival to animal survival, in the dose range leading to gastrointestinal syndrome. To this end, the optimally protective regimen of the combination of Ara-c and WR-2721 will be given to groups of mice that will be irradiated with increasing doses from two neutron sources and cesium-137 gamma photons to obtain an estimated LD50/6.

Outside Agency Involvement: None

Principal Investigator:

W. R. Hanson
Director, Research Section
Department of Therapeutic Biology
Rush-Presbyterian St. Luke's Medical Center
Chicago, Illinois 60612
(313) 942-5751

Hawkins/295-2128
20 Jan 84

Title: Mechanisms of Radiation-Induced Emesis in Dog

Contract #: DNA 001-84-C-0121

Work Unit Code: 00087

Task Code: U99QMXMK

Funding: \$123,000 (FY 85: \$110,000; FY 86: \$120,000)

Performer: New York State Department of Health

CTM: LCDR Hawkins

Start Date: 1 Dec 83

Completion Date: 31 Oct 86

Objective: To develop effective treatment against radiation-induced emesis by identifying the neural circuitry and humoral substances involved in radiation-induced emesis.

Technical Approach: Both physiological and anatomical techniques will be used to define the sites within the central nervous system and peripheral nerve tissues responsible for radiation-induced emesis. After identification, neurochemical techniques will be employed to determine the transmitter systems involved. Thereafter, appropriate chemicals will be applied to suspected sites to identify the transmitter systems involved and to identify anti-radiation emetic drugs.

Outside Agency Involvement: None

Principal Investigator:

David O. Carpenter
Center for Laboratories and Research
New York State Department of Health
Albany, New York 12201
(518) 474-4170

Hawkins/295-2128
13 Feb 84

Title: Laboratory Animal Research

MIPR #: 84-589

Task Code: U99QMXMK

Work Unit Code: 00088

Funding: \$6,000 (FY 83: \$5,000, continuous at \$5,000/yr in future)

Performer: U.S. Army Medical Research and Development Command

CTM: LCDR Hawkins

Start Date: 1 Mar 83

Completion Date: 30 Sep 83

Objective: To support programs of the Institute of Laboratory Animal Research (ILAR), National Research Council, National Academy of Sciences.

Technical Approach: The U.S. Army Medical Research and Development Command will serve as the administrator on behalf of the DoD components supporting the ILAR effort.

Outside Agency Involvement: ILAR is currently supported by the Army, Navy, and Air Force Service-level Medical Research and Development Headquarters Organizations.

Principal Investigator:

Ms. Vincent
Fort Detrick
Frederick, Maryland 21701
Autovon 343-7363

Hawkins/295-2128
17 Feb 84

Title: Isolation Natural Chelates for Radionuclides Decorporation

IACRO #: 84-838

Task Code: U99QMXMK

Work Unit Code: 00091

Funding: \$150,000 (FY 82: \$200,000; FY 83: \$211,000)

Performer: Brookhaven National Laboratory

CTM: LCDR Hawkins

Start Date: 18 Dec 81

Completion Date: 31 Oct 84

Objectives: To develop a chelating agent that will complex plutonium-239 and make it more susceptible to excretion and/or metabolism.

Technical Approach: Pseudomonas aeruginosa will be cultured. This organism can produce unique complexing agents for thorium and uranium. The optimal growth consideration for this organism will be determined. The complexing agent will be concentrated, fractionated, and chromatographed. Based on the yields, characterizations of individual components will be initiated.

Outside Agency Involvement: None

Principal Investigator:

E. Premuzic

Brookhaven National Laboratory

Upton, Long Island, New York 11973

(516) 282-2893

Hawkins/295-2128

19 Jan 84

Title: Radiation Injury to the Canine Thymus and Lymphohematopoietic Stem Cells: Correlation With Functional Immunological Deficits

Contract #: DNA 001-84-C-0158

Work Unit Code: 00092

Task Code: U99QMXMK

Funding: \$95,000 (FY85: \$67,000)

Performer: Colorado State University

CTM: LCDR Hawkins

Start Date: 1 Mar 84

Completion Date: 30 Sep 85

Objectives: To evaluate the nature of radiation injury to the immune system, with emphasis on the assessment and correlation between thymic epithelial damage, lymphoid and progenitor cell damage, and resultant immunological functional defects.

Technical Approach: Prenatal and early postnatal animals will be used to determine if significant radiation-induced injury to epithelial cells occurs when exposed either pre- or postnatally. The immune system will be evaluated functionally, and hematopoietic progenitor cells will be assayed for damage and correlated with thymic and functional disorders. The techniques employed will yield information that will determine the role of the thymus in immunodeficiency disease after irradiation.

Outside Agency Involvement: None

Principal Investigator:

James B. Nold
Collaborative Radiological Health Laboratory
College of Veterinary Medicine & Biomedical Sciences
Colorado State University
Fort Collins, Colorado 80523
(303) 491-8522

Hawkins/295-2128
19 Jan 84

Title: Radiation-Induced Germ Cell Mutations, Their Detection and Modification

Contract #: DNA 001-84-C-0170

Task Code: U99QMXMK

Work Unit Code: 00093

Funding: \$99,000 (FY85: \$242,000; FY86: \$289,000)

Performer: University of California, San Francisco

CTM: LCDR Hawkins

Start Date: 1 Mar 84

Completion Date: 31 Oct 86

Objectives: To evaluate the mutagenic hazards to male and female germ cells caused by densely ionizing radiation, gain insight into the mechanisms responsible for inducing mutation, and attempt to modify and minimize the hazards of mutagenesis in germ cells by applications of drugs and other dose-modifying procedures.

Technical Approach: An in vivo, in vitro rodent system has been developed to investigate the induction and transmission of germ cell damage in the form of chromosome aberrations. This assay will be used to determine the kinetics of induction and transmission of germ cell damage induced by two very effective forms of radiation: fission-spectrum neutrons and charged-particle radiation with a LET of 95 keV/um. The mechanisms involved will also be investigated by establishing the relationship of cell division rate and micronucleus formation to survival in the mutated zygote. Modification of the mutant rate by physical and chemical procedures will also be investigated.

Outside Agency Involvement: None

Principal Investigator:

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Department of Radiation Oncology
CED - 200
University of California
San Francisco, California 94143
(415) 666-2461

Hawkins/295-2128
19 Jan 84

Title: Human Hematopoietic Stem Cell and Its Growth Factor

Contract #: DNA 001-84-C-0165

Task Code: U99QMXMK

Work Unit Code: 00094

Funding: \$125,000 (FY85: \$135,000; FY86: \$146,000)

Performer: Oklahoma Medical Research Foundation

CTM: LCDR Hawkins

Start Date: 1 Mar 84

Completion Date: 31 Oct 86

Objectives: To utilize monoclonal antibody technology to generate antibodies that react preferentially with human pluripotential hematopoietic stem cells. This technique will be used to concentrate stem cells that will ultimately be used to determine if they can reconstitute bone marrow elements after irradiation.

Technical Approach: Stem cells will be detected using the in vitro mixed colony unit formation for granulocytes, erythroid monocytes, and megakaryocytes (CFU-GEMM). The less mature progenitor cells from bone marrow and peripheral blood will be enriched by utilizing either soybean agglutinin or by an immune rosetting method to deplete the more mature cells with monoclonal antibodies. Monoclonal antibody technology will then be applied to identify new types of stem cells that will, in turn, be evaluated for their ability to reconstitute bone marrow elements after irradiation.

Outside Agency Involvement: None

Principal Investigator:

Shu Man Fu
Cancer Research Program
Oklahoma Medical Research Foundation
825 N.E. 13th Street
Oklahoma City, Oklahoma 73104
(405) 271-6673

Hawkins/295-2128
20 Jan 84

Title: Genetic Markers of Host Resistance and/or Susceptibility to the Lethal Effects of Radiation and Combined Radiation-Burn Injuries

Contract #: DNA 001-84-C-0166

Task Code: U99QMXMK

Work Unit Code: 00095

Funding: \$94,000 (FY85: \$57,000)

Performer: State University of New York at Stony Brook

CTM: LCDR Hawkins

Start Date: 1 Mar 84

Completion Date: 31 Oct 85

Objectives: To identify and analyze possible genetic parameters involved in determining host resistance and/or susceptibility to ionizing radiation, utilizing a standard end point of mortality following dose- and time-controlled exposure to ionizing radiation.

Technical Approach: The possible influence of genetic factors in conditioning the host's natural resistance to the lethal effects of ionizing radiation will be assessed in two outbred and seven inbred strains of rats of fully defined genetic backgrounds. Previous studies have defined the parameters of response of the rat strains to controlled thermal injury, and the proposed studies will compare the mortality produced by standard doses of ionizing radiation in groups of animals from each strain. Outbred animals will be tested first, and the LD50/30 day dose range will be tested in the seven inbred strains of rats. Parallel groups of male and female rats of the inbred strains will be used to assess the role of sex-linked determinants in the observed results.

Outside Agency Involvement: None

Principal Investigator:

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Department of Surgery
State University of NY at Stony Brook
School of Medicine
Stony Brook, New York 11794
(516) 444-2209

INTERACTION OF AFRI AND THE NORTH ATLANTIC
TREATY ORGANIZATION

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DEFENSE NUCLEAR AGENCY
ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
BETHESDA, MARYLAND 20814

REPLY TO
ATTN OF: G.N. Catravas, BIC, 51337

25 April 1984

SUBJECT: Trip Report

TO: Director, AFRRI

1. DATE/PLACE: 10-13 April 1984, Sanitatsakademie, Munich, West Germany.
2. PURPOSE: To participate in the NATO meeting, RSG-5, Panel VIII.
3. ITINERARY:

A. Workshop

10 April 1984

Following an introduction by Dr. Schick (Germany) and opening remarks by Mr. Sentenac (France), the following presentations were given:

(1) Biological Evaluation of Lesions

- (a) Dr. Van Der Schans (The Netherlands), Battlefield dosimetry development of biological dosimeter.
- (b) Dr. Kaffenberg (Germany), Multivariate analysis of biological parameters for triage.
- (c) Dr. Bauchinger (Germany), Chromosome analysis—an approach for quantitative estimation of radiation exposure.
- (d) Dr. Schick (Germany), The role of amino acids in biological dosimetry. Serum levels in pigs after total-body irradiation.
- (e) Dr. Løvhaug (Norway), Can radiation-induced changes in the sedimentation properties of blood cells serve as a biological dosimeter?

11 April 1984

(2) Cellular Radiobiology

- (f) Dr. Maas (France), Evolution du tissu hematopoietique de la souris pendant et apres irradiation continue a faible debit de dose.
- (g) Dr. Tumbragel (Germany), Further testing of the cell kill model by inhomogenous irradiation of mice.

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(3) Physical Dosimetry

(h) Dr. Laugier (France), Compte rendu d'une experience de dosimetrie sur mannequins anthropomorphes en environnement nucleaire tactique simule a Aberdeen Proving Ground.

(i) Dr. Laugier (France), Distribution angulaire des neutrons dans l'air a 400 metres de la source de fission d'Aberdeen Proving Ground.

12 April 1984

(4) Clinical Evaluation of Lesions

(j) Dr. Court (France), Modifications neurovegetatives au cours du syndrome aigu de l-irradiation du primate soumis a une irradiation n,gamma (rapport n/gamma compris entre 1,3 et 12).

(k) Dr. Carmichael (England), Purely medical requirements for dosimetry in nuclear warfare.

(l) Dr. Ross (Canada), Mechanism of radiation-induced vomiting.

(m) Dr. Carmichael (England), The Royal Marsden Hospital project.

(n) Dr. Court (France), Apport de l'electroencephalogramme au diagnostic et pronostic des irradiations accidentelles.

(o) Dr. Maisin (Belgium), Life shortening and tumor induction after single and fractionated neutron or gamma irradiation.

(p) Dr. Ross (Canada), Radioprotective effect of dextran sulphate.

(q) Dr. Maisin (Belgium), The structure of the lungs and its change after radiation. Observation by transmission and scanning electron-microscopy.

B. RSG 5 - Meeting

13 April 1984

1. Examination of the report from the last meeting.
2. National orientation papers.
3. Exchange of views on the progress realized in our technical objectives.
4. Actual statement in common experimentations.

5. Future orientations of our studies.
6. On the opportunity to create a subgroup of a physical dosimetry intercomparison.
7. Varied questions.
8. Place and date of the next meeting.

14 April 1984

A special discussion took place between Dr. Court (France) and myself about the writing of the final report of the research conducted at AFRRI by the French team (Drs. Court, Gourmelon, and Mestries), in the Fall of 1982. Dr. Court gave me some additional material and promised to send me the remaining material as soon as he can.

4. DISCUSSION:

10 April 1984

Dr. Van Der Schans (The Netherlands) discussed the possibility of measuring radiation damage by immunochemically determining radiation damage in the DNA in white cells of possibly irradiated persons, and utilize it as a biologic dosimeter. A second approach is based on repair process in the cell measured, autoradiographically, by the incorporation of label nucleotides. Dr. Van Der Schans admitted that the proposed techniques are time consuming and that it is rather difficult to be utilized in cases of mass casualties.

Dr. Kaffenberg (Germany) discussed the possibility of assessing radiation damage to the organism by measuring up to 16 different hematologic and routine clinical parameters of experimental animals at different times postirradiation. He claimed that on the basis of his results he was able to sort individual animals into triage groups.

Dr. Bauchinger (Germany) utilized chromosome analysis as an approach for quantitative estimation of radiation exposure. Chromosome aberrations in T-lymphocytes are sensitive indicators of radiation exposures even at low levels of radiation. However, such a technique does not appear to be practical in cases of mass casualties.

Dr. Schick attempted to arrive at a definite assessment of the suitability of amino acids in the serum of irradiated animals, for biological dosimetry. He admitted that such an assessment is quite difficult, especially since other insults as burns, infections, administration of drugs and even the nutritional status of the individual can affect the composition and levels of serum amino acids.

Mr. Løvhaug (Norway) discussed experiments to explore the possibility of measuring radiation-induced damage to hematopoietic cells by observing their sedimentation characteristics in fluids of selected densities and osmolarities. At present, the doses needed to observe an effect are much higher than 500 rads.

11 April 1984

Dr. Maas (France) discussed experiments on the evolution of the hematopoietic tissue in mice exposed to continuous whole-body gamma radiation at daily doses of 10^{-1} to 2×10^{-1} Gy for approximately 3 months. The depopulation of the hematopoietic system appeared to stabilize within approximately 3 weeks, and 97 days after the end of irradiation, repopulation remains incomplete. Dr. Maas suggested that it would be interesting to further decrease the daily dose rate in order to determine whether there is a limit below which no changes occur in the components of the hematopoietic system under investigation, and also determine the dose rates and duration of irradiation following which a complete repopulation of the hematopoietic system takes place.

Dr. Tumbragel (Germany) discussed the effects of partial shielding of mice on survival following 14-MeV neutron irradiation. He observed that partial-body irradiated mice died in a shorter more concentrated time interval than whole-body irradiated mice. His results led to the suggestion that the lethality of heavily shielded mice must be caused by some other damage mechanism. The effectiveness of the shielding as described by Dr. Tumbragel was questioned in terms of neutron diffusion in the tissues of the animal and uniformity of irradiation.

Dr. Laugier (France) reported results of dosimetry experiments he carried out at the Aberdeen Proving Grounds in collaboration with AFRRI using anthropomorphic phantoms. Purpose of the experiments was to determine the absorbed doses in various organs and tissues of the human body. Measurements were carried out at 400 meters from the reactor. Although the study is incomplete and the data are still being analyzed, results thus far indicate that the effect of anisotropy (geometry of the source and dosimetry in the phantom) is not as large as it was originally thought. It is negligible for measurements of the dose in the brain and acceptable for measurements of dose in internal organs. Present results do not apply to the neutron spectrum, since the error increases with neutron dose.

12 April 1984

Dr. Court (France) presented results of research conducted at AFRRI by his team, in collaboration with BIC, in which the effects of intermediate doses of neutron-enriched radiation (neutron to gamma >10 to 1) in the form of a pulse on the subhuman primate. Among the effects were radiation-induced disturbances in the diurnal rhythms of cerebral blood flow and temperature.

Dr. Carmichael (UK) presented results of partial- or whole-body irradiation of cancer patients at the Royal Marsden Hospital, some of whom were also treated with cytotoxic drugs such as cyclophosphamide and melphalan. The patients were examined for fluid output, urea, and creatinine. No significant changes were observed in any of these three parameters. In partially irradiated patients, no differences were observed in terms of nausea and vomiting patterns whether the upper or lower body (above or below the iliac crest) was irradiated.

In a second communication Dr. Carmichael (UK) discussed the medical requirements for dosimetry in nuclear warfare. He then described the inherent inaccuracies of physical dosimeters including: dosimeter location, neutron quality factors, dose rate effects, critical organ of interest, age, sex, general health, etc. He stressed, however, the need for a dosimeter especially for mass casualties, because, in his view, the biological dosimeter is still too far in the future. In terms of LD50/60 in man, the consensus UK view is that it probably is about 400 to 450 cGy to bone marrow which equates to between 530 and 600 cGy midline tissue dose free in air.

Dr. Ross (Canada) discussed Dr. Harding's (Canada) work on the mechanisms of radiation-induced vomiting and the role of area postrema and chemoreceptor trigger zone.

In a second communication, Dr. Ross presented data on the radioprotective properties of dextran sulfate (DS). He used two different molecular weights: 10,000 (DS₁₀) and 500,000 (DS₅₀₀). DS₅₀₀, when given at 50 mg/kg, has better radioprotective properties than DS₁₀. However, it causes a transient anaphylactoid shock in all experimental animals (mice) within 15 min, but most recover with no ill effects. This shock is under investigation.

Finally, Dr. Maisin (Belgium) discussed results of research he conducted on radiation-induced damage to the microstructure of the lung of experimental animals using transmission and scanning electron microscopy.

5. CONCLUSIONS/RECOMMENDATIONS:

13 April 1984

Following examination and approval after certain modifications of the report from the last meeting, it was recommended and approved that the representative(s) of each member nation prepare an orientation paper on that nation's research activities which are pertinent to the aims of the Panel. These orientation papers should be sent to the Chairman of the Panel in time for inclusion in the next NATO RSG-5 (Panel VIII) meeting (1 April 1985).

It was recommended that (a) research be continued on the development of both physical and biologic dosimeters, especially for neutrons; (b) define the RBE of neutrons in a battlefield environment for LD50, emesis, and ETI; (c) determine doses causing these effects; and (d) create a subgroup of physical dosimetry intercomparison among the member nations.

It was agreed that the (30%) accuracy of the PIN diode (neutron) phosphate glass (gamma) dosimeter is sufficient to meet battlefield requirements. However, the UK and Germany have no funds to deploy it.

It was requested that Dr. Young make available to the Panel the oral presentation he made during the previous RSG-5 meeting.

Both Dr. Zeman and I were asked why AFRRI was not on the agenda to present progress on pertinent research since the last meeting.

It was approved that the next meeting will take place in Ottawa, Canada, in the autumn of 1985.

6. BENEFIT TO AFRRI/DNA:

Scientific information presented by member nations during the NATO RSG-5 (Panel VIII) meeting on physical and biologic dosimetry and on evaluation of radiation-induced lesions as well as discussions and recommendations that followed was of great interest and importance to mission-related research being conducted at AFRRI.

Attachments:

1. List of participants
2. Agenda
3. Text of oral presentations
4. UK views on LD50/60 in man
5. Canadian paper on dosimetry
intercomparison project
6. Canadian orientation paper

GEORGE N. CATRAVAS, D. Sc.
Chairman
Biochemistry Department

CF:
DD
SD
XO
Department Chairmen



DEFENSE NUCLEAR AGENCY
ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
BETHESDA, MARYLAND 20814

26 April 1984

REPLY TO

ATTN OF: RSD (CDR Zeman, 51047)

SUBJECT: NATO Research Study Group Five (RSG.5) Meeting in Munich, 10-13 Apr 84;
Trip Report of

TO: DIR

1. CDR G. Zeman (RSD) and Dr. G. Catravas (BIC) represented AFRRRI at subject meeting held at the German Federal Armed Forces Medical Academy (Akademie des Sanitats).

2. The following documents were distributed and are enclosed:

- a. List of participants
- b. Agenda
- c. Texts of oral presentations (except numbers 2, 9, 15, and 17)
- d. Discussion paper on Dosimetry Intercomparison (Canada)
- e. Canadian Orientation Paper
- f. U.K. Views on LD 50/60 in Man

3. Dr. Sentenac opened and closed the meeting by stating that he must report in October 84 to NATO Panel 8 on the program made on RSG.5 objectives since its inception in 1977. The question posed for the present meeting was to decide how much time is needed to reach the objectives.

4. RSG.5 Objectives are listed below:

- a. Define the RBE of neutrons in battlefield radiation environments for LD50, emesis, and ETI.
- b. Determine dose levels causing above effects.
- c. Prescribe physical and/or biological dosimeters to measure above doses.

5. The majority of the oral presentations addressed objective 3. It was apparent that biological dosimetry has a long way to go before being battlefield applicable. With regard to physical dosimetry:

a. The consensus opinion is that the PIN diode (neutron) phosphate glass (gamma) dosimeter of German, U.K., and U.S. Army has sufficient accuracy (30%) to meet battlefield needs, and will not be substantially improved on in the next 10 years.

b. The need for individual (versus group) dosimeters was recognized.

c. Further work is needed on technical questions such as orientation of wearer, importance of dose rate, organ (marrow) dose versus free in air, RBE of neutrons, dosimeter readout by medical or operational personnel, and partial-body irradiation.

d. The German representative (Schanzler) repeatedly emphasized that physical dosimetry problems and questions have been satisfactorily solved, that battlefield neutron/gamma radiation fields were well characterized (even for enhanced radiation weapons), and that present dosimetry hardware is ready for practical operational use.

e. Both U.K. and Germany lack funds to fully deploy the PIN diode phosphate glass dosimeter at present.

f. The work of Dr. Laugier (France, papers #8 and 9) at Aberdeen was well received. The need was recognized to repeat this work in tanks or other practical geometries.

g. The need for intercomparisons of battlefield dosimetry measurements was recognized. Dr. Ross (Canada) took the lead in this area; see attached discussion paper. CDR Zeman offered his support and assistance as may be needed to conduct the intercomparison.

6. Comments and questions referred to Dr. Catravas and myself were:

a. Why was AFRRI not on the formal agenda to present progress on the several efforts reported at the Oct 82 meeting in Bethesda? Response: We were unaware of our attendance until after the agenda had been drawn.

b. Why has U.S. not submitted a "national orientation paper" (overview of national efforts towards RSG.5 objectives)? Does U.S. support continuance of this communication vehicle between RSG.5 member nations? Will AFRRI representative prepare a national orientation paper covering all (not just AFRRI) efforts (due April 1984)? Response: We recognize the need for and support continuing this requirement.

c. Can you request of Dr. Young (AFRRI) that his Oct. 1982 oral presentation to RSG.5 be made available? Response: Yes (Catravas).

d. Is it possible to delete the "... statement made by a former AFRRI director" from pp. 349 of the Oct. 1982 proceedings, to wit "... as a surgeon I would ignore dosimetry"? Response: None. (Attendees of the Oct. 1982 meeting agreed that the somewhat out-of-context quote was indeed accurate, albeit out-of-taste and counterproductive.)

e. Dr. Laugier (France) informally expressed concern over the status of his proposed dosimetry experiments to be done in summer 1984 and Aberdeen at AFRRI under DNA funding. He had heard informally from Dr. Kazi (APRD) that CDR Devine (STBE) had obtained funding approval, but had received nothing in writing. Response: I raised this issue to CDR Devine on return. A letter had indeed been forwarded to the French months ago, and CDR Devine will ensure that it reaches Dr. Laugier.

7. Recommendations. From my experience at this meeting and in recognizing that RSG.5 objectives parallel those of AFRRI, I offer the following recommendations:

a. AFRRI should be committed to a balanced level of support to NATO RSG.5. The contrasting energetic level of 1982 and passive level of 1984 represent the extremes. A balanced level of support should consist of one overview and one or two scientific papers being presented at each meeting.

b. A civilian project officer to RSG.5 should be appointed from the AFRRI or DNA staff to coordinate U.S. involvement. Military officers rotate too fast for continuity in the 18-monthly meetings.

c. AFRRI should prepare and submit to RSG.5 the requested "national orientation paper," due by April 1, 1985. The paper should contain an overview of AFRRI and all U.S.A. efforts towards RSG.5 objectives.

d. AFRRI should consider using contracts to obtain scientific compilations by experts in the areas of RSG.5 objectives.

(1) The contract approach would be most useful in preparing the national orientation paper. The AFRRI RSG.5 project officer could act CTM.

(2) A contract approach would also be useful with regard to the still unresolved LD50/60 question; the one-day LD50 workshop in Delft in July 1983 identified data bases and scientific experts relevant to this question.

e. Present AFRRI/STBE contracts work in physical dosimetry should be made ready for presentation at the next RSG.5. In particular, include recently completed SAI work on tactical radiation environments, and the upcoming work on battlefield dosimetry. This information is vital to supplement the premature conclusions (drawn by the Germans and others) concerning physical dosimetry at the 1982 and 1984 meetings.

f. The work of Dr. Davidson and the intermediate dose panel should be formally presented to RSG.5. This work was mentioned only in passing with regard to RSG.5 objectives. It appears to be highly relevant.

g. If Dr. Laugier (France) is to use AFRRI radiation facilities and require RSDP support in calendar year 1984, then STBE (Devine) must begin at once to coordinate and schedule the experiments.

GARY H. ZEMAN
CDR, MSC, USN
Acting Chairman, RSD

Cy Furn
SD
DD
Dr. Catravas
CDR Devine
Dr. Young

MEMORANDA OF UNDERSTANDING

MEMORANDUM OF UNDERSTANDING AMONG
THE U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND,
THE U.S. AIR FORCE AEROSPACE MEDICAL DIVISION,
THE NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND, AND
THE ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
FOR THE RDTE OF HEMOPOIETIC FAILURE AND
COMBINED RADIATION AND CONVENTIONAL TRAUMA

1. PURPOSE. This memorandum establishes general policy and a framework for coordination and cooperation among the parties for RDTE efforts relative to the diagnosis and treatment of hemopoietic casualties, and combined radiation and trauma casualties.

2. RESPONSIBILITIES

a. The parties jointly agree that:

(1) Collaborative efforts should be entered into at every phase of these studies when considered feasible and practicable by the respective service program managers. The complexity of combined injuries requires a multidisciplinary approach in an effort to develop appropriate and effective treatment for these problems.

(2) Each of the parties' medical and research personnel shall participate in research and development by sharing scientific and clinical information and providing personnel for training or as staff in the programs.

(3) Each will share technology developed from in-house and contract studies on a continuing basis at bench scientist/division chief/research area manager level and at the yearly Joint Technology Coordinating Group (JTCCG) scientific review.

b. The Navy-managed in-house and contract programs shall concentrate on:

(1) Improved surgical and medical therapy of injuries from combined irradiation and trauma coordinated with, and complementary to, U.S. Armed Forces Radiobiology Research Institute (AFRRI) and Army studies.

(2) Development of methods for the isolation, purification, and concentration of stem cells and blood products from primates and humans devoid of immunocompetent cells.

(3) Isolation and characterization of stem cell growth factors for propagation of stem cells.

(4) This work will be performed in accordance with the provision of an existing Memorandum of Understanding between AFRRI and NMRDC dated 13 May 1982.

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(5) Reconstitution studies with cryopreserved blood in primates and humans, evaluating autologous, syngeneic, and allogeneic transplantation, including methods to diagnose and treat graft-versus-host disease.

c. The AFRRRI-managed in-house and contract programs shall concentrate on:

(1) Studies of the biological effects of radiation injury, using animal models, including effects on hemopoietic and gastrointestinal systems to include studies focused on:

(a) Growth and differentiation of stem cells.

(b) Development of methods to enhance stem cell renewal and differentiation into specific pathways in the radiation-compromised animal.

(2) Identification, collection, purification, and concentration of stem cells and blood products from animal models devoid of immunocompetent cells.

(3) Reconstitution studies with hemopoietic cell populations isolated and identified as in (2) above, animal models. Cell populations are to be derived from autologous and allogeneic sources.

(4) Improved surgical and medical therapy of injuries from combined irradiation and trauma coordinated with, and complementary to, studies by Army and Navy.

(5) This work will be performed in accordance with the provisions of an existing Memorandum of Understanding between AFRRRI and NMRDC dated 13 May 1982.

d. The Army-managed in-house and contract programs shall concentrate on studies in animal models of surgical and medical therapy of injuries from combined irradiation, and conventional trauma coordinated with, or complementary to, studies by AFRRRI and Navy.

e. The Air Force-managed in-house and contract programs shall generally utilize technology developed through the auspices of this memorandum.

3. ADMINISTRATION

a. Coordinating Group

(1) A coordinating group shall be established from representatives of the parties. Members will be the triservice JTCG representatives and AFRRRI representatives from research and clinical hematology/oncology-oriented programs. If appropriate, triservice representatives from clinical hematology/oncology-oriented research programs may also be included.

(2) This coordinating group shall be chaired by the party representative hosting the meeting and shall meet in conjunction with the JTCG Program Review in order to coordinate in-house and contract research programs.

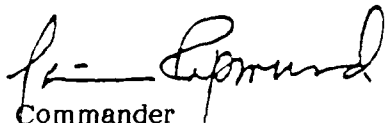
b. The parties jointly agree that each shall plan, program, and budget resources as required for that portion of the effort they manage.

c. Individual efforts fostered through this memorandum which require transfer of resources between the parties will be fully documented on Project Order or Interservice Support Agreement forms, as appropriate.

d. This memorandum shall become effective upon the date of last signature and shall remain in effect for six years.

(1) The memorandum will be reviewed no less often than biannually; however, it may be amended at any time by mutual agreement of the parties.

(2) Any and each of the parties may unilaterally withdraw from participation in the agreement by providing the other parties 120 days written notice of their intent to withdraw.



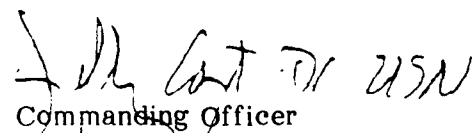
Commander
U.S. Army Medical Research and
Development Command

Date: 2 March 1984



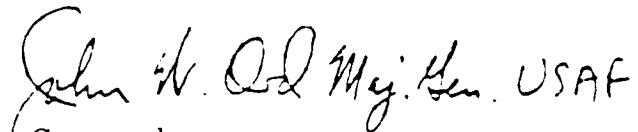
Director
U.S. Armed Forces Radiobiology
Research Institute

Date: 2 March 1984



Commanding Officer
Naval Medical Research and
Development Command

Date: 2 March 1984



Commander
U.S. Air Force Aerospace Medical
Division

Date: 2 March 1984



DEPARTMENT OF THE NAVY
NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
NATIONAL NAVAL MEDICAL CENTER
BETHESDA, MD 20814

IN REPLY REFER TO:
NMRDC-45:mr
3900
13 May 1982

From: Commanding Officer, Naval Medical Research and Development Command
To: Director, Armed Forces Radiobiology Research Institute, National Naval Medical Center, Bethesda, Maryland 20814

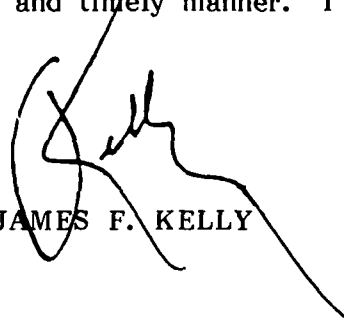
Subj: Memorandum of Understanding and Collaborative Research Agreement Between AFRRI and NMRDC for Research, Development, Test and Evaluation of Treatment Modalities for Radiation Induced Hemopoietic Failure

Ref: (a) Our meeting on 16 February 1982
(b) Our meeting on 2 April 1982
(c) JTCG/CCC Science Review 12-16 April 1982

Encl: (1) Proposed MOU and Collaborative Research Agreement Between AFRRI and NMRDC for Development, Test and Evaluation of Treatment Modalities for Radiation Induced Hemopoietic Failure

1. Enclosure (1) has been reviewed and in my opinion is consistent with our discussions (references (a) through (c)). It is forwarded for your review and approval.

2. It has become obvious through our discussion that the requirement to develop treatment modalities for CBR-induced hemopoietic failure has a very high priority. It is also apparent that by combining the Navy's resources with those of AFRRI the project can be brought to fruition in a more efficient and timely manner. I look forward to the initiation of these collaborative efforts.


JAMES F. KELLY

Copy to:
CNR
CND
CNO
ASBREM
CO, NMRI
BUMED-3111

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Proposed Basis for Memorandum of Understanding and
Collaborative Research Agreement Between AFRRI and
NMRDC for Research Development, Test, and Evaluation of Treatment
Modalities for Radiation-Induced Hemopoietic Failure

PURPOSE

This document provides general policy and establishes guidelines for coordination and cooperation between the Armed Forces Radiobiology Research Institute (AFRRI) and the Naval Medical Research and Development Command (NMRDC), Bethesda, Maryland, relative to the diagnosis and treatment of casualties with hemopoietic failure secondary to radiation exposure. The basis of this understanding lies in the recognition of AFRRI's charter as the principal radiobiological research laboratory for the Department of Defense (DoD). In exercising this charter, AFRRI's mission is to conduct research in the field of radiobiology and related matters that are essential to the operational and medical support of DoD and the military departments. In context, it is recognized that the AFRRI cannot conduct in-house, all relevant research pertaining to its mission. It is appreciated that radiobiological and associated expertise also resides at other Defense and civilian organizations. That expertise is considered valuable and essential to the total Defense radiobiological program. A significant principle of this memorandum is the recognition of the need for an integrated biomedical effects and casualty care research program to insure that research results at key facilities are shared and complementary. The mission of NMRDC is to manage the Navy Medical Department research, development, test and evaluation programs concerning the health, safety and performance of naval personnel. In recognition of the technology gap to deliver definitive care procedures to treat massive numbers of chemical, biological or radiation combat casualties, NMRDC has begun a major increase of its efforts in the transplantation of blood-forming cells. It is therefore both timely and pertinent to enter into a collaborative research agreement as well as memorandum of understanding between AFRRI and NMRDC relative to our individual missions and research potentialities.

ORGANIZATION

A joint working group shall be established consisting of designated representatives from Navy and AFRRI. This committee shall bi-annually review the status of the MOU and shall coordinate the efforts of basic research and clinical direction including in-house and contract programs.

GENERAL PROCEDURES

1. AFRRI in-house and contract programs:
 - a. Biological effects of radiation injury using animal models, including effects on hemopoietic and gastrointestinal systems to include studies focused on:
 - (1) stem cell physiology—growth and differentiation
 - (2) enhance stem cell renewal and differentiation into specific pathways in the radiation-compromised animal.
 - b. Identification, collection and purification, concentration of stem cells and blood products from dogs and primates devoid of immunocompetent cells.

c. Reconstitution studies with hematopoietic cell populations isolated and identified as in b) above in dogs and primates. Cell populations are to be derived from autologous and allogeneic sources.

d. Studies on surgical and medical therapy of injuries from combined irradiation and trauma. Models are being used in cellular, humoral and hormonal effects.

2. The Navy in-house and contract program:

a. Clinical evaluations of stem cell and bone marrow transplants.

b. Development of new techniques for cryopreservation and effects of long-term storage on stem cells and blood products.

c. Isolation and characterization of stem cell growth factors for propagation of stem cells.

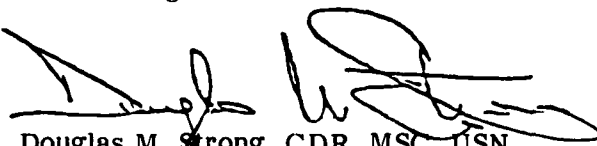
d. Isolation, purification and concentration of stem cells and blood products from primates and humans devoid of immunocompetent cells.

3. Joint AFRRI and Navy efforts:

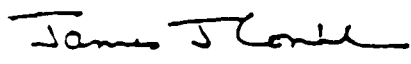
a. Collaborative efforts should be entered into at every phase of these studies. The complexity of each objective requires a multidisciplinary approach in an effort to maximize results and progress toward the objective.

b. AFRRI medical and research personnel shall participate in the Navy basic research and clinical programs by sharing scientific information, providing medical and/or research personnel for training and/or as staff in the clinical bone marrow transplant program.

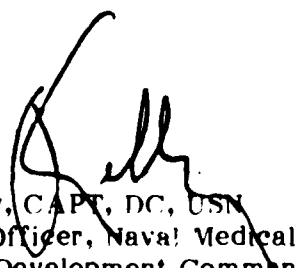
c. AFRRI-Navy will share technology developed from in-house and contract studies including both basic research and clinical studies.

By: 
Douglas M. Strong, CDR, MSC, USN
Program Coordinator
Naval Medical Research and
Development Command

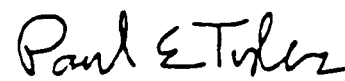
Date: 14 May 1982

By: 
James Conklin, Lt Col, USAF, MC
Armed Forces Radiobiology
Research Institute

Date: 17 May 1982

Approved: 
James F. Kelly, CAPT, DC, USN
Commanding Officer, Naval Medical
Research and Development Command

Date: 14 May 1982


Paul E. Tyler, CAPT, MC, USN
Director, Armed Forces Radiobiology
Research Institute

Date: 17 May 1982

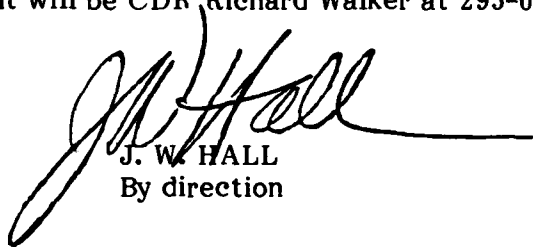


DEPARTMENT OF THE NAVY
NAVAL MEDICAL RESEARCH INSTITUTE
NATIONAL NAVAL MEDICAL CENTER
BETHESDA, MD 20814

In Reply Refer To
NMRI: FSO:JWH:jes
5751
3 August 1982

From: Commanding Officer
To: Director, Armed Forces Radiobiology Research Institute, Bethesda, MD 20814
Subj: Memorandum of understanding and collaborative research agreement between NMRI and AFRRI.
Encl: (1) Original memorandum of understanding and collaborative research agreement between NMRI and AFRRI

Enclosure (1) has been endorsed and is hereby returned. Primary point of contact for NMRI with regard to this agreement will be CDR Richard Walker at 295-0755.


J. W. HALL
By direction

Copy to: Director, CCPC
Director, IDPC
CDR Walker
Agreement file
Chron file



DEFENSE NUCLEAR AGENCY
ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
BETHESDA, MARYLAND 20814

EXH

29 July 1982

SUBJECT: Proposed Memorandum of Understanding and Collaborative Research Agreement Between AFRRRI and NMRI for Research, Development, Test and Evaluation of Medical and Surgical Treatment Modalities for Infectious Complication of Combined Injuries

CAPT James Vorosmarti
Commanding Officer
Naval Medical Research Institute
Bethesda, Maryland 20814

1. The Proposed Memorandum of Understanding and Collaborative Research Agreement between the Armed Forces Radiobiology Research Institute and the Naval Medical Research Institute for Research, Development, Test and Evaluation of Medical and Surgical Treatment Modalities for Infectious Complication of Combined Injuries (Encl 1) has been reviewed and, in my opinion, is consistent with the recognized need for an integrated biomedical effects and casualty care research program to insure that research results at key facilities are shared and complementary.

2. I look forward to the initiation of these collaborative efforts.

Encl:
as stated


BOBBY R. ADCOCK
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Proposed Basis for Memorandum of Understanding and
Collaborative Research Agreement Between AFRRI and NMRI
for Research, Development, Test and Evaluation of Treatment
Modalities for Infectious Complications of Combined Injuries

PURPOSE

This document provides general policy and establishes guidelines for coordination and cooperation between the Armed Forces Radiobiology Research Institute (AFRRI) and the Naval Medical Research Institute (NMRI), Bethesda, Maryland, relative to the study of and development of treatments for post-trauma complications. The basis of this understanding lies in the recognition of AFRRI's charter as the principal radiobiological research laboratory for the Department of Defense (DoD). In exercising this charter, AFRRI's mission is to conduct research in the field of radiobiology and related matters that are essential to the operational and medical support of DoD and the military departments. In context, it is recognized that the AFRRI cannot conduct in-house, all relevant research pertaining to its mission. It is appreciated that radiobiological and associated expertise also resides at other Defense and civilian organizations. That expertise is considered valuable and essential to the total DoD radiobiological program. A significant principle of this memorandum is the recognition of the need for an integrated biomedical effects and casualty care research program to insure that research results at key facilities are shared and complimentary. The mission of NMRI is to conduct research, development, test and evaluation programs concerning health, safety and performance of naval personnel. In recognition of the technology gap to deliver definitive care procedures to treat massive numbers of personnel with combined injuries, including radiation, it is both timely and pertinent to enter into a collaborative research agreement as well as a Memorandum of Understanding (MOU) between AFRRI and NMRI relative to our individual missions and research potentialities.

ORGANIZATION

A joint working group shall be established consisting of designated representatives from NMRI and AFRRI. This committee shall bi-annually review the status of the MOU and shall coordinate the efforts of research and development including in-house and contract programs.

GENERAL PROCEDURES

1. AFRRI in-house and contract programs:

- a. Determine effectiveness and mechanism of immunomodulation in promoting recovery of injuries and protection from sepsis.
- b. Study in animal models of biological effects of radiation injury, including hemopoietic, gastrointestinal, immunologic and biochemical effects.
- c. Studies on surgical and medical therapy of injuries from combined irradiation and trauma.

2. NMRI program:

- a. Development of a vaccine against Pseudomonas aeruginosa.

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b. Determination of role and mechanisms of host cell surface changes in bacterial colonization after trauma.

c. Develop combined antimicrobial approaches to treatment of infection in compromised hosts.

d. Perform surgical manipulations to compromise resistance of experimental animals, monitor physiological responses to injury and sepsis, and test treatment modalities against sepsis.

3. Joint AFRRRI and NMRI efforts:

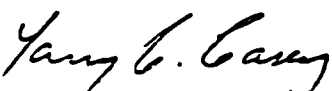
a. Collaborative efforts should be entered into at every phase of these studies. The complexity of each objective requires a multidisciplinary approach in an effort to maximize results and progress toward the objective.

b. AFRRRI research personnel shall participate in the NMRI basic research and development program by sharing scientific information and/or providing research personnel for training.

c. AFRRRI-NMRI will share technology developed from in-house and contract studies including both basic research and clinical studies.

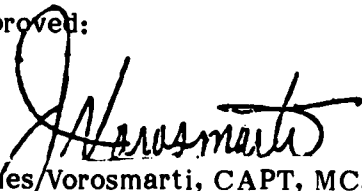
By: 
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Date: 30 July 1982

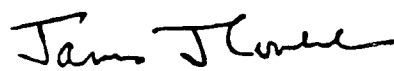
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Date: 2 August 1982

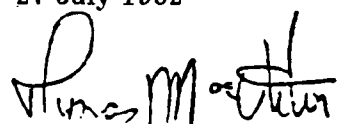
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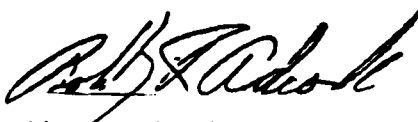
Date: 3 August 1982

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