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Protocol for Monitoring Gulf War Veterans with Imbedded Fragments of Depleted Uranium

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PROTOCOL FOR MONITORING GULF WAR VETERANS WITH IMBEDDED DEPLETED URANIUM FRAGMENTS

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March 1993

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The research requirements of this protocol will be approved by the appropriate DoD or VA Institutional Review Board for the Protection of Human Subjects.

Preface

The Army's Office of The Surgeon General (OTSG) initiated this effort to care for Desert Storm veterans with imbedded depleted uranium (DU) shrapnel. In February 1992, OTSG requested that the Armed Forces Radiobiology Research Institute (AFRRI) conduct a review of the potential health hazards (radiological and toxicological) of allowing DU shrapnel to remain imbedded throughout the lifetime of the soldier. Specifically, OTSG wanted to know if there was any reason to change the current surgical practice for fragment removal. No compelling evidence was found in the literature review[1] to change current surgical criteria for fragment removal. There were, however, significant uncertainties about the impact of DU fragments on the health of these patients that warranted long-term follow-up.

OTSG concurred with this finding and initiated action to implement this follow-up in the Army. The Department of Veterans Affairs (DVA) agreed to perform the follow-up for personnel discharged from the service. Both the DVA and OTSG requested AFRRI's assistance in drafting the protocol to be used in the follow-up effort.

A group of DoD physicians and scientists met at AFRRI to draft the protocol. At a subsequent meeting on 10 September 1992, a panel of experts reviewed and revised the draft protocol; representatives of the DVA and OTSG also attended this meeting. The protocol was once again reviewed and approved by the panel of experts.

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Protocol for Monitoring Gulf War Veterans With Imbedded Depleted Uranium Fragments

1. Objectives

This protocol will implement two separate but complementary efforts. The first is the clinical follow-up of Desert Storm patients with known or suspected imbedded depleted uranium (DU) fragments, DU contaminated wounds or significant amounts of inhaled DU. The second is the conduct of research into the toxicological and radiological effects of this unique exposure modality. Specifically, this protocol will provide the following:

a. Early detection of abnormalities related to the presence of DU so that prompt, efficacious treatment is effected if required. The study will also provide the scientific data required to fairly settle claims for compensation.

b. Treatment recommendations that will provide a firm clinical basis for fragment removal decisions and for decisions concerning the need for efforts to reduce the uranium in the body.

c. Quantification and documentation of the toxicological (heavy metal toxicity) and radiological (cancer and tissue necrosis) risks of imbedded uranium fragments by

(1) measuring and documenting uranium levels in each soldier using *in vivo* and *in vitro* measurement techniques,

(2) determining the parameters and models needed to translate uranium levels in the body into estimates of the increased cancer risk from this exposure,

(3) comparing the clinical course of the body's response to the DU fragments with that for other non-DU fragments to determine whether clinically significant differences exist due to either the chemical or radiological properties of depleted uranium, and

(4) determining the risk of chronic kidney toxicity due to the long-term chronic exposure to elevated levels of uranium.

2. Approach

The comparison of the clinical course of DU fragments with non-DU fragments will be made using a prospective study approach. The data from patients with internalized DU (the exposed population) will be compared to that from two unexposed populations: patients with fragments that are not DU and soldiers who were not wounded and not exposed to DU.

a. Exposed Population

Each crew member of the attacked vehicles is a candidate for inclusion in the exposed group. An initial check has revealed that there are approximately 22 soldiers whose records indicate that they have imbedded fragments that might be DU. There are an additional 13 soldiers who were wounded and hospitalized but were not specifically identified as having shrapnel. The remaining crew members (besides the 35 already discussed) were either not wounded during the incident or had minor wounds that were treated in the field. The latter two sets of soldiers might have inhaled uranium or experienced DU contamination of wounds or minor fragmentation wounds that were either not noticed or did not require extensive treatment.

The small size of the exposed population limits the study's ability to detect differences to only those effects where the differences between DU and non-DU imbedded fragments are large. For example, it is highly unlikely that definitive conclusions concerning cancer induction will be obtainable from the study. However, this approach will allow a direct comparison of differences that may exist in deterministic effects. Examples of such effects include differences in the body's propensity to encapsulate a DU fragment, the onset of local or whole-organ tissue necrosis, thorotrastoma-like growth induction, or the onset of chronic kidney toxicity. In addition, following a nonexposed group will provide information concerning nominal values for each metabolic value studied in protocol (e.g., normal concentrations of uranium in the body and body fluids as well as kidney function variations with age).

There are two criteria for including a soldier in the exposed group. First, the soldier must have been in or on the vehicle when the vehicle was struck by DU munitions. Second, the soldier must have internalized DU at levels that are high enough to cause the uranium in the urine either to exceed background levels of uranium excretion by a factor of four or to be detected by whole-body or partial-body counting. Uranium in urine measurements from the control group will establish the background levels for these two measurements. The exposed group has two subgroups.

(1) The first consists of those soldiers with internalized DU not from imbedded fragments. This group will consist of personnel who have DU from inhalation or through wound contamination. The data from this group will be used in both the metabolic modelling and chronic kidney toxicity studies.

(2) The second consists of soldiers with imbedded DU fragments. The data from this group will be used to compare the clinical course of DU fragments with non-DU shrapnel as well as to provide information for the metabolic modelling and kidney toxicity studies.

Determining the presence of DU shrapnel is not as straightforward as verification of the presence of internalized DU. The analysis is complicated because the penetration of an armored vehicle by a DU penetrator generates DU fragments, non-DU fragments, and fragments that are a mixture of DU and the other components of the vehicle. In addition, the size of these fragments will vary dramatically. In the two cases that have been studied so far, the fragment sizes ranged from just at the resolution limit of film radiography (approximately 0.5 mm) to 15 mm in diameter. Until more experience is gained, a patient is assumed to have DU shrapnel if shrapnel is detected radiographically and internalized DU is detected.

b. Special Study Group

A subset of the exposed group will be selected for inclusion in the special study group. This group will receive the more intensive testing required to determine uranium metabolism accurately, identify early signs of toxicity, monitor fragment dissolution rates, and determine how the uranium is partitioned in the body as a function of time. Evaluation of these variables will provide the information required to construct the metabolic models needed to assess the risks associated with internalized DU.

Criteria for selection include the presence of DU fragments in the body, uranium in urine levels that exceed 14 μg/d (10 μg/l[a]) and the soldier's availability for the intensive monitoring envisioned. Recognizing that participation in the special study group will require a significant commitment, soldiers will be selected who are highly motivated to participate and are located near testing facilities.

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[a]*All conversions were calculated based on an assumed urinary excretion rate of 1.4 l/d.*

c. Nonexposed Groups

The data from the exposed population will be compared with that from two unexposed populations, which will serve as control groups for the study. The first control group, patients with non-DU fragments, is needed to determine whether the body's response to DU fragments differs from the body's foreign body normal response to shrapnel. The second group, unwounded and nonexposed, is needed to compare normal changes in kidney function with changes that might be due to the presence of uranium. The need for the second control group is based upon the assumption that non-DU fragments might cause changes in the parameters being measured.

Members of the non-DU fragment control population (the first control population) will be selected from veterans wounded in incidents not involving DU munitions. This will eliminate the possibility of a control group member having a small undetected DU fragment. Members of the unwounded and nonexposed control group will be selected from any unwounded population that does not meet the criteria for inclusion in the exposed population. In each case, groups will be appropriately matched (age, sex, smoking habits, similar Desert Storm experiences, etc.) with the exposed population.

d. Study Duration

At this point, it is difficult to determine the study duration, but the long latent periods for some effects[1] require that the study last at least 5 years. The study could extend for the lifetime of the members of the study groups.

3. Program Management

The program management group will supervise the initiation and conduct of the measurements, analysis, and documentation required by this project. The group will exercise oversight of each phase of the study and will control its overall direction. The group will consist of four representatives, at most, from the Department of Veterans Affairs, the Department of the Army and/or the Armed Forces Radiobiology Research Institute (AFRRI). The group has the following responsibilities:

a. Fiscal Management

The group will establish yearly budgetary requirements and maintain the records required to track the expenditure of funds during the fiscal year.

b. Patient Management

The group will identify the patients in each study group and establish mechanisms for patient tracking.

c. Data Gathering

The group will serve as the central repository for the data gathered in all phases of this study, including selecting the laboratories that will perform the required tests and developing and supervising the quality assurance program for these laboratories.

d. Data Analysis

The results of each required test will be submitted to this group for analysis and study. This group will be responsible for calculating and documenting dose estimates for each patient as well as determining if clinically significant changes had occurred.

e. Protocol Changes

The group will direct any changes required to meet the objectives of this study.

f. Treatment Recommendations

The group will be responsible for evaluating the data received to determine if an alteration in treatment is required and will make its recommendations to the attending physician.

g. Research Recommendations

The group will make recommendations for further research based upon their findings as appropriate.

h. Subject Matter Experts

To ensure the availability of the expertise required for this effort, the program management group will be augmented by a panel of subject matter experts. This panel will consist of physicians and scientists with expertise in radiation injury, epidemiology, health physics, uranium toxicology, and the laboratory procedures required by this protocol.

4. Patient Briefing

This briefing will be in sufficient detail to meet the requirements for informed-consent for participation in a human research project. Since long-term patient participation is key to the success of this study, it is recommended that this briefing be given by someone who will be with the project for an extended period of time and who has experience with this type of long-term study. This briefing will include a discussion of

a. the scope of the program and how the data will be used;

b. the tests and the frequency of testing, along with the risks entailed with participation and nonparticipation in the program;

c. the benefits and requirements of participation in the U.S. Uranium Registry;

d. procedures to follow for fragment removal. Standard medical guidelines should be used for decisions concerning fragment removal.[1] Once the removal decision is made, surgeons should use the procedures listed in paragraph 6.d. below for the removal of DU and non-DU fragments.

5. Protocol Test Requirements

a. Tests Required

(1) Table 1 outlines the required tests and test frequencies for each of the study populations. The specifics for each of the tests are explained in paragraph 6.

(2) The increased frequency of testing for soldiers with uranium concentrations in their urine at levels greater than 14 μg/d (10 μg/l) of urine (see Table 2) is based on the clinical need to monitor for signs of long-term kidney toxicity.

b. Modifications of the Test Protocol

(1) The program management group (see paragraph 3) will make modifications to the protocol as a whole or for an individual patient based upon its analysis of the results received. This re-evaluation should take place at least annually.

(2) The presence of symptoms in a patient (e.g., indications of toxicity, unusual growths, or other abnormalities) will trigger an immediate re-evaluation of the required tests and their frequency, and the need for medical/surgical intervention.

Table 1. *Recommended Tests and Test Frequencies.*

TEST	Exposed Population Urinary Excretion <14 µg/d	Exposed Population Urinary Excretion ≥14 µg/d	Special Study Group	Control Groups
Uranium in Urine	Annually	Table 2	Twice Weekly	Annually
Urine Chemistry	Annually	Table 2	Table 2	Annually
Uranium in Feces[1]			As Needed	As Needed
Tissue Analysis[2]	As Needed	As Needed	As Needed	As Needed
Whole Body and Regional Counting[3]	Initially	Initially	Biennially	Initially
Uranium in the Skeleton			Annually	Annually
Uranium in Blood			Quarterly	Annually
Blood Chemistry	Annually	Table 2	Table 2	Annually
Clinical Evaluation	Annually	Annually	Quarterly	Annually
Diagnostic Imaging[4]	Annually	Annually	Annually	Annually

[1]*Fecal samples will be performed whenever inhalation exposure is suspected. Control group fecal analysis will be used to provide estimates of normal uranium levels in feces.*
[2]*Tissue analysis will be performed on tissue samples taken as a result of a fragment removal procedure for both DU and non-DU fragments.*
[3]*Repeat after fragment removal or as required by the program management group.*
[4]*Radiographs are only required for personnel with imbedded fragments. This is not required for exposed or control group patients who do not have fragments.*

6. Test Specifications

This section describes the purpose and specifications for each of the tests required in the protocol. The specifications are designed to provide minimum test standards required to meet the objectives of the protocol. Selection of the laboratories where these tests are done will be made by the program management group based upon the guidance in this section and an assessment of the site's capabilities. The laboratories must meet the quality assurance requirements in paragraph 7 below. It is highly recommended that the same laboratory be used for each test whenever possible.

References 2 and 3 contain a partial listing of commercial and government laboratories with the capability for whole-body counting and for radiobioassay. While DoD laboratories are not specifically listed, the Army (U.S. Army Environmental Hygiene Agency) and the Air Force (Armstrong Laboratory) have the technology required to perform some of the radiobioassay procedures listed.

Table 2. *Test Frequency for Selected Tests as a Function of Initial Urine Uranium Concentration.*

Uranium Excretion Rate in Urine (μg/d)	*Test Frequency*[*]	*Remarks*
14-50	*Quarterly*	
50-250	*Monthly*	*Potential for the onset of kidney toxicity.*
> 250	*At Least Weekly*	*Potential for kidney toxicity.*

[*] *Tests include uranium in urine, urine chemistry, and blood chemistry.*

a. Uranium Concentration in Urine

(1) Purpose. This test will provide a direct determination of the uranium excretion rate which will be used for metabolic model construction and risk assessment.

(2) Specifications

(a) While a 24-hour urine sample is desirable, timed urine samples are acceptable. For 24-hour urine samples, it is important that all voids be collected. For timed urine samples, accurate accounting of the time period is a requirement and time periods of not less than 12 hours are recommended.

(b) Urine samples must be processed in a laboratory where the uranium measurement methods have a minimum detection limit of 0.4 μg of uranium per liter of urine or better. The laboratory must meet the quality assurance requirements listed in paragraph 7.

(c) Detailed sample collection and preservation procedures will be established by the laboratory performing the analysis.

(d) The nonexposed group will provide urine samples that will be used to establish background urinary excretion levels for uranium.

b. Urine Chemistry

(1) Purpose. The primary purpose of this test is to monitor the urine for signs of kidney toxicity or other abnormal changes in kidney function.

(2) Specifications. Urine chemistry to include a quantitative analysis of gamma-glutamyltransferase, beta-2-microglobulinuria, protein, amino acids, creatinine, phosphorus, and urinalysis (specific gravity, albumin, glucose, and microscopic sediment analysis) is required. Serum creatinine and creatinine clearance studies are needed to assess glomerular function and tubular integrity. It should be noted that these tests might underestimate filtration rate if tubular injury is present.

c. Uranium in Feces

(1) Purpose. This test is designed to give an indirect assessment of the uranium content in the lung and to assist in establishing lung clearance rates for metabolic modeling. This test should be administered only if significant lung contamination is suspected.

(2) Specifications. The specifications for fecal samples will be determined based upon the requirements for each test. As a general rule, the minimum detection limits for laboratories should be less than 3 μg of uranium per sample (less than 1 pCi per sample). Preservation and shipment requirements will be determined by the laboratory doing the analysis.

d. Tissue Analysis

(1) Purpose. This series of tests will be performed on tissues removed from a patient as a result of the patient's decision to have a fragment removed. The purpose of these examinations will be to determine

(a) the uranium content of the tissue (information will be useful in both metabolic modelling and risk assessment) and

(b) whether significant changes have occurred in the tissues surrounding the fragment. Thorotrast data indicate that long-term exposure to low-dose-rate alpha emitters can cause tissue fibrosis and necrosis with latent periods in excess of 5 years.[1]

(2) Specifications

(a) Surgical Removal of the Fragment. In addition to standard procedures, the following steps should be accomplished.

- Photograph the procedure. Of particular interest is evidence of total or partial fibrotic encapsulation; local tissue necrosis; growing granuloma; or if there is evidence of a breakdown, a formed fibrotic capsule.

- If the fragment is encapsulated, remove and save the intact capsule (with the fragment still inside) if possible. If the fragment must be removed from the capsule or if the capsule breaks during removal, document the capsular fluid appearance and volume. The capsule, capsular fluid, and any other tissue removed should be saved for histopathology and radioassay. Take careful note of the physical characteristics of the fragment upon removal. Specifics include color, shape, and any evidence that the fragment is breaking up. Color photographs of the fragment with a means of measuring its size are desirable. Seal the fragment in a plastic bag. Contact the program management group for instructions concerning the disposition of the fragment.

(b) Histopathology. The objective of this series of experiments is to determine if there are any unusual changes in cell structure of the surrounding tissue.

(c) Uranium in Tissue and Fluids. The uranium in retained tissue or fluids should be determined using techniques with the capability of detecting uranium levels on the order of 0.2 μg (0.06) pCi per tissue sample submitted. It should be noted that there are ultrasensitive fission-track counting techniques that can be used to detect 10^{-14} grams of uranium. At this level, the same tissue samples could be used for both histopathology and uranium concentration determinations.

(d) Sample Preservation Techniques. The sample preservation techniques used will depend upon which of the two procedures will be performed. At this point, it is uncertain if the same tissue sample can be used for both uranium concentration and histopathologic procedures. Once notified that a fragment will be removed, the program management group will decide which of the two procedures will be performed.

e. Whole-Body Counting, Regional-Area Counting, and Skeletal Uranium Determination

(1) Purpose. The combination of whole-body and regional-area counting allows for the quantification of the total amount of uranium in the body and the amounts of uranium in key locations in the body, using external measurement techniques. This information will be used in conjunction with urine and feces uranium contents to determine the metabolic models for uranium retention. The *in vivo* skeletal counting is an attempt to track uranium deposition in the skeletal system.

(2) Specifications

(a) The systems used must be capable of performing both whole-body and regional-area counting of uranium. Current systems can provide minimum detectable activities[b] (MDA) for regional-area counting of the lung on the order of at least 2 nCi (6 mg of DU) of DU in the lung by measuring the ^{234}Th progeny of ^{238}U.[3]

(b) Regional-area counting is required for the lungs, kidneys, liver, all wound or burn sites (regardless of how minor the wound), and of all areas with suspected DU fragments.

(c) Radiographs will be used to determine fragment location(s) so that estimates of tissue absorption and self absorption corrections for each of the areas counted.

(d) The *in vivo* skeletal-counting systems used should have an MDA of 10 nCi (30 mg) with adequate procedures for discriminating sources originating in the bone from those originating in the remainder of the body. The skeletal counting system developed at New York University is a good example of an acceptable skeletal-counting system.[3]

f. Uranium Concentration in the Blood

(1) Purpose. The test will measure the concentration of uranium in the blood by measuring the uranium concentration in the serum and cellular components of the blood.

(2) Specifications. Typical minimum detection limits for systems designed to measure the uranium content of the blood are on the order of 1 nano-gram of uranium per ml of blood. The laboratory selected to perform this test should have comparable efficiencies.

g. Blood Chemistry Evaluation

(1) Purpose. These tests are aimed at determining whether or not heavy metal toxicity and/or bone-marrow suppression has occurred.

(2) Specifications. SMA -12/20 or equivalent with complete blood count with differentials and platelet count.

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[b]*The referenced work defined MDA as 4.65σ where σ is the standard deviation of the background count.*

h. Clinical Evaluation

(1) Purpose. Clinical evaluation will determine the presence of any abnormalities such as nodules or unknown growths in the vicinity of fragmentation wounds or a degradation in the viability of the tissues. Reference 1 contains a discussion of potential abnormalities and estimates of the latent periods associated with each.

(2) Specifications. Emphasis will be placed on organ/structure dysfunction related to the location of the fragment(s) and to the consequences of the potential radiological and chemical effects. Specific tests are determined by the location of the fragment(s). Particular attention will be given to detecting thorotrastoma-like growths at the site of fragment implantation. A thorotrastoma is a growth that appears at the sites of extravascular Thorotrast with a latent period of 5-35 years post injection.[4-8] In some instances, these granulomas grew to enveloped clinically significant blood vessels and nerves and, in some cases, proved fatal.

i. Diagnostic Imaging

(1) Purpose

(a) Determine the composition of the fragments in an attempt to differentiate between solid DU and aluminum DU mixtures.

(b) Determine the approximate size and anatomic location of the fragment(s) in the body with sufficient detail to make absorption and self absorption corrections for whole-body counting data.

(c) Detect or confirm the presence of the formation of the fibrous encapsulation or of a thorotrastoma-like growth.

(d) Determine if there have been any gross changes in the location or size of the fragment.

(2) Specifications

(a) Both magnetic resonance imaging (MRI) and radiographic imaging are required for patients with imbedded fragments. MRI will be used to detect soft tissue abnormalities (granulomas, thorotrastomas) in the tissues surrounding imbedded fragments. MRI will only be performed after determining that there are no ferromagnetic fragments or objects in the patient.

(b) Radiographic imaging will be used to determine the size and position of imbedded fragments with sufficient accuracy to detect changes in the location of the fragment and to make the tissue absorption and self-shielding corrections required for whole-body counting. It is anticipated that at least two projections will be required.

7. Quality Assurance

The long-term nature of this protocol mandates the implementation of a stringent quality assurance program to ensure the accuracy and precision of the data collected. The program management group will develop the details of the quality assurance program. The program must incorporate the following provisions:

a. The use of accredited laboratories when possible. The laboratory performing each of these tests must be accredited by an appropriate accrediting agency to perform the required test. The laboratory must have a viable quality assurance program that is in accordance with the guidance provided in References 9 and 10. The program management group will establish standards based upon the guidance in this protocol when such accreditation is not available.

b. The use of the same laboratory to perform each type of test when possible. Adoption of this strategy will ensure the consistency of the data and enhance the program management group's ability to monitor the quality of the data collected. When the same laboratory cannot be used, the program management group must develop procedures to ensure the comparability of the data generated.

c. The use of intercomparisons by the specific laboratories chosen. The quality assurance program must include either a program of intercomparisons with other laboratories or, ideally, comparisons with a national standard.

Standard records management quality control procedures will be implemented to ensure the accuracy of the records maintained by the program management group.

Glossary of Terms

Exposed population. There are two criteria for including a soldier in the exposed group. First, the soldier must have been in or on the vehicle when the vehicle was struck by DU munitions. Second, the soldier must have internalized DU at levels that are high enough to cause the uranium in the urine either to exceed background levels of uranium excretion by a factor of four or to be detected by whole-body or partial-body counting. Uranium in urine measurements from the control group will establish the background levels for these two measurements.

Nonexposed population. The nonexposed population is composed of two subgroups: The first subgroup includes those soldiers with fragment wounds that are known not to be DU. The second consists of those soldiers who were not wounded and do not have internalized DU. DU is considered not to be present in significant amounts if the uranium concentrations in the urine are less than four times the background level and the results of whole-body or partial-body counting are negative.

Minimum detectable amount (MDA). The smallest amount of a substance that can be detected with a probability β of nondetection (Type II error) while accepting a probability α of erroneously deciding that a positive (non-zero) quantity is present in an appropriate blank sample (Type I error).[9] For this protocol both α and β are set at 0.05.

Program management group. A multi-disciplinary team that will oversee the implementation of the protocol and evaluate the results and direct changes in the protocol as required.

Radiobioassay procedure. For the purposes of this protocol, a radiobioassay procedure is any procedure used to measure the uranium in the body (whole-body counting) or in biologic material excreted or removed from the body for the purposes of estimating the uranium content in the body.[9]

Special study group. A subset of the exposed group that will receive the more intensive testing required to accurately determine uranium metabolism, to identify early signs of toxicity, to monitor fragment dissolution rates, and to determine how the uranium is partitioned in the body as a function of time.

Thorotrastoma. A large growth that appeared at the sites of extravascular thorotrast in patients injected with thorotrast, a thorium containing radiographic contrast agent. The growth appeared with a latent period of 5-35 years postinjection. These granulomas grew to large sizes and some enveloped clinically significant blood vessels and nerves and, in some cases, proved fatal. Thorotrastomas are discussed in the references.

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