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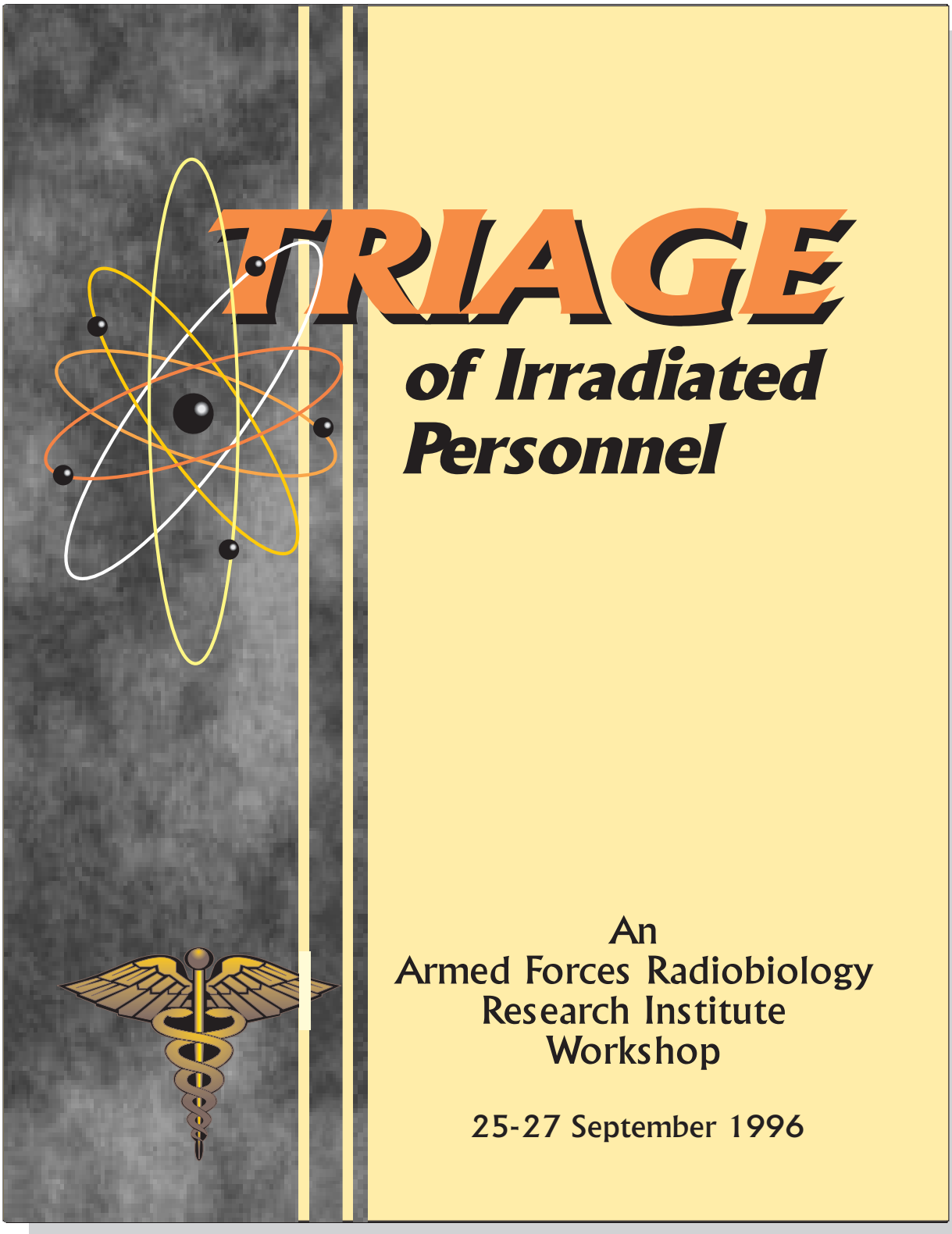

TRIAGE of Irradiated Personnel

An
Armed Forces Radiobiology
Research Institute
Workshop

25-27 September 1996

Proceedings

TRIAGE
of Irradiated Personnel

Edited by:

Glen I. Reeves, M.D.
David G. Jarrett, M.D.
Thomas M. Seed, Ph.D.
Gregory L. King, Ph.D.
William F. Blakely, Ph.D.

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Preface

The workshop, "Triage of Irradiated Personnel," sponsored by the U.S. Army Office of the Surgeon General, was conducted at the Armed Forces Radiobiology Research Institute (AFRRI) on September 25–27, 1996. This workshop focused on a reassessment of the radiation medicine section of Chapter 4, *Medical Aspects of Nuclear, Biological and Chemical Warfare, of Army Field Manual 8-10-7: Health Service Support in a Nuclear, Biological and Chemical Environment.* Sixty-five speakers and guests from the United States, Germany, Netherlands, Canada, United Kingdom, and France addressed the three issues: (1) operational effectiveness of exposed personnel with and without other injuries who receive medical care in Army echelon I and echelon II medical facilities, (2) operational effectiveness of personnel with multiple exposures (assuming a previous total dose of <1.5 Gy), and (3) methods for estimating exposure in personnel who receive antiemetics before or shortly after exposure.

Over the course of the 3-day workshop the following four sessions were conducted:

Session I. Background. An overview of doctrine and laboratory capabilities in a forward medical field environment and an assessment of the future operational capabilities of forward-deployed medical units and supporting laboratories.

Session II. Estimation of Exposure Using Blood Markers and Clinical Indicators. Assessment of the accuracy, sensitivity, and reliability of monitoring blood-cell responses and other clinical indicators, particularly if nausea and vomiting have been reduced or eliminated by the administration of antiemetics.

Session III. Predicting the Effects of Multiple Radiation Exposures. Assessment of the accuracy, reliability, and validity of animal and human data that have been used to predict the outcome of exposure scenarios.

Session IV. Forward-Field Bioindicators for Dose Assessment: Possible Alternatives. Evaluation of the status of several possible alternatives to peripheral blood counts and prodromal symptoms for field-dose assessment. Selected candidate assays were evaluated; characteristics included (1) negligible post-sampling incubation, (2) rapid processing suitable for a high degree of automation and high throughput, (3) low-threshold and broad dose-range capability, (4) relatively noninvasive sample collection, and (5) equipment hardware for which components are or soon will be available.

At the conclusion of each session a panel of invited speakers and AFRRI subject-matter experts discussed the presentations and session findings. Audience participation generated several questions and comments. The final morning summary session addressed the issues and highlighted the workshop conclusions as well as the remaining uncertainties.

The findings of this workshop are intended for use by U.S. Army medical planners, particularly those involved in the configuration, deployment, and logistics of forward-field medical facilities (echelon I and II). These Summaries do not necessarily reflect either current or future Army doctrine. It must be emphasized that triage is a dynamic process that includes prioritization at each iteration. The initial categorization and treatment delivered to the patient will require and receive reevaluation as the patient's clinical course develops and as echelons of available care and resources change. Physicians at each echelon of care will determine appropriate management based primarily on their clinical impression of the patient's condition and what means of intervention appear best suited to favorably influence the course of disease. Laboratory studies, including physical dosimetry—no matter how accurate—are used to support clinical judgment, not substitute for it. One final point: triage is NOT a decision based on military utility to "treat or not treat." It is a decision on how

best to use both personnel and materiel resources to maximize treatment for *every* patient and to achieve favorable clinical outcomes for as many patients as possible. Although the concept of triage is generally cited in a military medical context, it is a *de facto* practice in every busy emergency room and in every major disaster, civilian or military.

The success of this workshop is directly attributable to the excellence and expertise of the participants. In addition, each session chairman deserves praise for the formidable amount of preparation and knowledge—without which this workshop could not have succeeded. COL David G. Jarrett, M.D., USA, Session I Chairman; Dr. Thomas M. Seed, Session II Chairman; Dr. Gregory L. King, Session III Chairman; and Dr. William F. Blakely, Session IV Chairman, deserve high praise for the success of this endeavor.

This project was funded by the Department of the Army Surgeon General, Directorate of Health Care Operations.

GLEN I. REEVES
Col, USAF, MC, SFS
Workshop Coordinator

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Summary of Session I

Background

David G. Jarrett, COL, MC, USA
Chairman

Armed Forces Radiobiology Research Institute, Bethesda, MD

- Operational Capabilities of Army Forward Medical Facilities
  Gary C. Norris, LTC, MSC, USA
  Directorate of Combat and Doctrine Development
  Army Medical Department (AMEDD) Center and School
  Fort Sam Houston, TX

- Overview of Current Operational Policy
  Robert Mosebar, COL, MC, USA (ret)
  Directorate of Combat and Doctrine Development
  AMEDD Center and School
  Fort Sam Houston, TX

- Field Laboratory Capabilities
  Samuel J.P. Livingstone, Maj, MSC, USAF
  Wilford Hall Air Force Medical Center
  Andrews Air Force Base, MD

- Status and Limitations of Physical Dosimetry in the Field Environment
  David A. Schauer, LCDR, MSC, USN
  Naval Dosimetry Center
  Navy Environmental Health Center Detachment
  Bethesda, MD

- NATO Policy and Guidance on Antiemetic Usage
  Robert Kehlet
  Defense Special Weapons Agency
  Alexandria, VA

- Review of Potential Biomarkers of Radiation Exposure
  Dr. Clive L. Greenstock
  Radiation Protection Branch
  Atomic Energy Commission Limited, Chalk River Laboratories
  Chalk River, Ontario, Canada

Overview

The goal of Session I was to provide background information and a starting point for the many physicians and researchers who are not acquainted with the capabilities and limitations of providing medical care away from a permanent medical facility. The current and near-future deployable medical units were discussed and an overview of potential radiation biomarkers was presented.

Introduction

The United States Army must be prepared to effectively use soldiers in a radiologically contaminated environment during small-scale operations that include accidents and terrorist activity and in the event of a nuclear conflict. Current doctrine is based on scenarios of cold war transition to nuclear war and the resultant mass-casualty medical requirements. Early return to combat duty would be practiced for all soldiers who are nominally performance capable. Significant morbidity and mortality of radiation casualties would not occur until after the arrival of reinforcements. Isolated radiation injury does not necessarily cause significant immediate disability; and truly effective therapy for radiologically injured soldiers is considered improbable in a total nuclear war scenario. However, low- to mid-range radiation injury presents a unique problem as acute symptoms can be debilitating but are preventable with adequate prophylaxis. If left untreated, the hematologic intermediate-term (i.e., 2 to 6 weeks) effects of this same radiation injury would become devastating.

In view of the significant advances in the treatment of hematologic injury as well as changes in military operational requirements, a review of current doctrine is mandatory. The purpose of this section was to present to scientists the medical capabilities of deployable units to ensure that recommendations for implementing triage mechanisms will be practical.

Military Medical Care at Far-Forward Echelons

Military medical care is designed to be delivered as far forward as is practical. This doctrine maximizes the return to duty of individuals with minor injuries and makes a positive impact on battle outcome. The early evacuation of casualties requiring prolonged treatment concomitantly minimizes the individual casualty's morbidity and frees forward-medical resources to concentrate on short-term care. No current method is available to rapidly assess an individual's degree of radiologic injury, and as radiation is not likely to result in immediate mortality, triage is primarily based on other criteria. Those soldiers in whom radiation injury is suspected would require evacuation to the hospital level for evaluation.

Initial treatment may be provided by the combat lifesaver, a combat soldier trained in advanced first aid techniques. The first medical treatment (echelon I) is provided by the combat medic and his supervising battalion aid station (BAS), which has a physician and a physician's assistant. No laboratory or radiologic equipment is available at the BAS. The two basic choices are either treatment to allow return of the casualty to duty or stabilization for evacuation to echelon II or III. At echelon II (the medical company), rudimentary laboratory services and x-ray capability are available as are holding beds for patients who are expected to return to duty within a well-defined short time frame. Interventional surgery can be placed at this level as an augmentation module when additional forward capability is deemed practical. Echelon III is the first hospital facility and has the capabilities for true blood-cell counting and limited chemistry. Most patients who are evacuated to this level will proceed up the evacuation chain and will not return to duty soon. The next echelon of evacuation will be to a theater-level medical facility, a fixed-base facility, or a continental U.S. (CONUS) hospital. See Fig. 1 for possible routes of medical evacuation from the far-forward field.

The Theater Army Medical Laboratory (TAML) is an independent field laboratory capable of providing regional support that includes clinical laboratory reference testing for biochemical, toxicological, bacteriological, mycological, and parasitological agents. It is also capable of gross and microscopic pathology support. Its medical defense tactical applications include confirmation of endemic disease and suspected radiological, chemical, and biological warfare agents. Future plans include replacement of the TAML with an Area Medical Laboratory (AML),

which is smaller and requires less logistical support (diminished footprint); the rapid diagnostic and chemistry test capabilities will be relocated to echelon II medical companies. The AML will then be focused directly on battlefield health-hazard assessment.

Current Operational Policy

Symptoms of radiation injury will usually not be manifest at acute doses of less than 100 cGy but will be progressively more intense and more rapid in onset with higher radiation doses. Most soldiers who receive low to midrange radiation doses (100–300 cGy) will have symptoms of nausea and vomiting within several hours of exposure and are consequently less tactically effective. They are then significantly more prone to further traumatic injury as they can less proficiently operate weapon systems, defend themselves, and press the attack. Primary clinical guidance for triage of radiation casualties with unknown dose is based on symptoms during the prodromal period. This is the interval between time of exposure and cessation of nausea and vomiting. Radiation exposure dose is estimated based on the time interval between exposure, symptom onset, and symptom severity. To diminish the individual soldier's morbidity and performance degradation, the development of a safe prophylactic drug for the nausea and emesis of significant radiation injury was necessary. Use of this medication would prevent individual capability degradation and would consequently diminish the overall casualty rate by allowing tactical mission completion. Unfortunately, eliminating these symptoms rules out the medical officer's ability to clinically estimate radiation exposure without research-level diagnostic modalities.

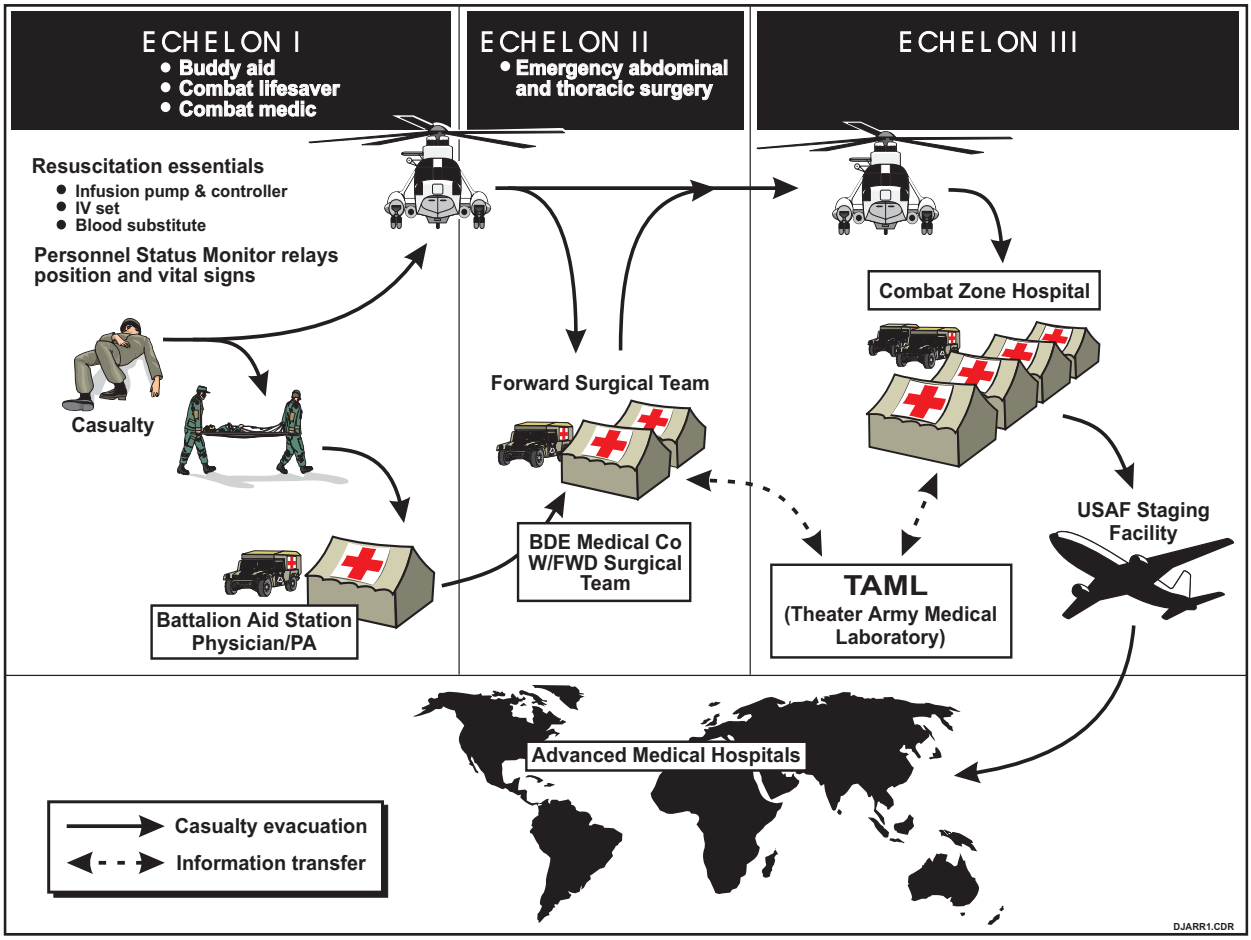

Fig. 1. Routes of medical evacuation from the far-forward field.

Status and Limitations of Physical Dosimetry in the Field Environment

Peacetime occupational radiation exposures are monitored using thermoluminescent dosimeter (TLD) systems accredited by the National Voluntary Laboratory Accreditation Program (NVLAP). These systems are designed for centrally located and controlled programs and are not suitable for field operations. War-time dosimetry is based and controlled at the unit level. The primary individual dosimeter system currently fielded is the high-range photoluminescent AN/PDR-75. This system consists of the ruggedized DT-236 wristband dosimeter that is capable of measuring cumulative neutron and gamma-ray doses in the range of 0–999 cGy and the CP-696 nondestructive dosimeter reader. The CP-696 is issued to company-sized units, and results are recorded at company level. The system is not considered a medical-issue item, and dosimeters are not routinely distributed to deploying soldiers. Future dosimetry systems include the platoon-based AN/UDR-13, a direct-reading dose-rate meter and a total gamma-plus-neutron dosimeter. Next-generation systems should include the capability of teledosimetry that allows remote monitoring of individual dose-rate exposure.

Current NATO Policy and Guidance on Antiemetic Usage

The North Atlantic Treaty Organization (NATO) project group (PG-29) has recommended granisetron as the deployable radiation emesis prevention drug of choice. NATO members will develop individual operational plans for implementation under the draft Standardization Agreement (STANAG 4510). Under draft STANAG 4511, multiple prophylactic antiemetic medications and regimens were evaluated prior to adoption of granisetron.

Two drugs exceeded the criteria (shown below), granisetron and ondansetron. The former was adopted due to a better technical profile and the operational advantage of once daily oral administration.

Review of Potential Biomarkers of Radiation Exposure

The human body is the ultimate dosimeter, and measurable changes in tissues and biosamples are the most important indicators of whole-body dose. Two types of biodosimeters are possible: biophysical indicators that are direct measures of absorbed

Summarized NATO criteria for an acceptable antiemetic

Approval by individual national pharmaceutical regulatory authorities.

Effective antiemetic for radiation doses up to 10 Gy.

Rapidly effective after a single self-administered oral or auto-injectable dose.

Compatible with other normal prophylactic and emergency therapeutic measures.

No militarily significant side effects, and no potential for abuse.

Effective in extremes of climate without compromising individual environmental conditioning.

Packaged for 1-week dosages utilizable by individuals in protective equipment.

Minimum of 36-month shelf life stability between 0 and 50 degrees Celsius.

dose and are not influenced by repair mechanisms, and biological indicators that record absorbed dose by a biological manifestation of radiation exposure. A biophysical indicator, such as electron spin resonance (ESR), is instrument-based and is usually more amenable to automation. It is analogous to a physical personal dosimeter. A biological dosimeter can include physiological, hematological, biochemical, immunological, and cytological assays. Consequently, it measures the biologically relevant effects of radiation to estimate the effective dose received. Testing usually requires experienced technicians to minimize method variability and subjectivity for reliable dose estimation. Relevant portions of this talk are summarized in subsequent sessions.

Summary of Session II

Estimation of Exposure Using Blood Markers and Clinical Indicators

Thomas M. Seed, Ph.D.
Chairman

CDR Michael E. Dobson, LTC Daniel C. Garner,
LT Tracy B. Kneisler, and Dr. Mark H. Whitnall
Session Panelists

Armed Forces Radiobiology Research Institute, Bethesda, MD

- Alterations of Hematological Parameters by Radiation
  Niel Wald, M.D.
  Department of Environmental and Occupational Health, Graduate School of Public Health
  University of Pittsburgh, Pittsburgh, PA

- Prediction of Clinical Course Through Serial Determinations
  Hauke Kindler, D. Densow, T. M. Fliedner
  Institute of Occupational and Social Medicine, University of Ulm, Ulm, Germany

- Dose Estimation Using Lymphocyte Depletion Kinetics
  Ronald E. Goans, Elizabeth C. Holloway, Mary Ellen Berger, Robert C. Ricks
  Radiation Emergency Assistance Center/Training Center (REAC/TS)
  Oak Ridge Institute for Science and Education
  Oak Ridge, TN

- Fatigability and Weakness as Clinical Indicators of Exposure
  George H. Anno
  Pacific-Sierra Research Corporation
  Santa Monica, CA

Overview

This session's goal was to examine the usefulness and practicality of attempting to assess—for the purpose of triage—early clinical and blood-cell responses that would occur in irradiated military personnel operating within radiation contaminated far-forward battlefields.[1]

The operational necessity to rapidly and accurately assess the physiological responses induced by radiation exposure and the possible concomitant negative impact on troop performance (and to a lesser extent, long-term medical complications and subsequent treatment protocols), provided the orientation for this session's presentations and topics.

The session featured four presentations by invited experts who spoke on various aspects of radiation-induced blood alterations, the clinical responses, and their applicability as clinical indicators for medical triage of irradiated military personnel in the far-forward field.[2] Two presentations (by Drs. Niel Wald, University of Pittsburgh, and Hauke Kindler, University of Ulm) provided overviews of the temporal and exposure-dependent hematological response patterns of acutely irradiated individuals. An additional presentation (by Dr. Ron Goans, REACT/S, Oak Ridge) focused on the biodosimetric potential of assessing lymphocyte depletion kinetics. The fourth presentation (by George Anno, Pacific-Sierra Research Corp.) discussed the possibility of using the clinical responses of fatigability and weakness as early indicators of the extent of radiation exposure.

An open discussion followed the presentations in which presenters and audience alike examined and provided comment, not only on the accuracy, sensitivity, and reliability of these measured, well-documented clinical and hematological endpoints, but also on the practicality of such assessments given the constraints of a narrow time window (24-hr postexposure), the possibility that antiemetics were given, and the far-forward medical echelon I and II settings.

The general consensus was that under such constraints (time, technology, and echelon setting) these blood and clinical indicators are not adequate for initial triage in the far-forward field. First-line triage would be better served by the application of physical dosimetry, rather than by blood/clinical indicator-based biodosimetric procedures.[3] *The latter procedures would serve a more useful function in secondary triage processes during which clinical management/treatment decisions can be made.*

Presentation Details and Comments

Comparisons of attributes of the three blood marker-based assays, along with a single clinical-indicator assay, are presented in Table 1.

Blood Markers in Estimating Exposure

A single parameter assessment strategy, offered by Dr. Ron Goans (ORISE, Oak Ridge, TN), is based on monitoring the rate of lymphocyte depletion during the initial 24-hr postexposure period. This biodosimetric tool seems to provide a moderately

[1]Triage processes discussed relate solely to military operations under battlefield conditions, and not to possible early processing of civilian casualties by civilian medical doctors following a nuclear accident.

[2]An additional presentation relevant to this topic of early hematopoietic response indicators was made by Dr. L.G. Filion (University of Ottawa, Canada) during Session IV. For details of this presentation, the reader should refer to Appendix D, which contains the appended text of this work.

[3]Proposed use of physical dosimetry in forward fields of operation is not intended to supplant the need for medical evaluation by either the medic in the field or by the physician in a higher echelon care facility, but only as a means to more effectively sort minimally exposed "duty-ready" troops from those troops deemed "suspect" and perhaps "duty unfit" due to moderate-to-heavy exposures and associated performance and health status degradations.

reliable and consistent but fairly crude assessment of acutely delivered whole-body exposures.[4] It has the strongest biodosimetric potential in the far-forward field of operation of various assays described during this session. The technique, however, is limited in terms of threshold doses to approximately 1 Gy and to approximately 2–3 Gy in terms of resolving distinct exposure levels within the range of detection, i.e., ~1–10^{+} Gy. The relatively short time (6–8 hrs) for assay development is a major advantage; whereas the requirement for multiple sampling and the uncertainty of confounding factors (biological warfare (BW)/chemical warfare (CW) agent exposures, combined wound/burn injuries, physiological stress, etc.) represent major disadvantages.

This assay technique should be considered only in terms of its dosimetric attributes, and not as a diagnostic tool upon which treatment decisions are based.

Two **multiparameter strategies** for the hematologic assessment of the "acute radiation syndrome (ARS)" were presented—one by Dr. Niel Wald of the University of Pittsburgh, and another by Dr. Hauke Kindler of the University of Ulm (Ulm, Germany). Both strategies were designed to segregate radiation-exposed individuals into distinct severity levels (five levels) of radiation injury (ranging from minimal, nonlethal, to severe, definitively lethal), thus, providing the clinical rationale for subsequent treatment options.

Dosimetric assessment was not the primary objective of these assessments per se; although crude estimates of exposure levels can indeed be determined based on characteristic blood response profiles.[5]

The approach outlined by Wald involves ranked analyses of the degree of exposure-dependent

Table 1. Comparison of attributes of hematological/clinical indicator-based assays.

Attributes	Assay types			
	Hematologic-based			Clinical-based
No. endpoints	1-parameter	3-parameter	9-parameter	F/W
No. samples required	≥3	≥6	≥6?	>1?
Predictor function	weak	strong	strong	very weak
Biodosimeter function	moderate	weak	weak	negligible
Threshold dose	~1Gy	~1Gy	~1Gy	~<1Gy
Resolution	~2Gy	~2–3Gy	~2–3Gy	~2–3Gy?
Range of detection	~1–10+Gy	~1–10+Gy	~1–10+Gy	~1–10+Gy?
Validation of test	yes	yes	yes	?
Development time	≤24hrs	1–5d	4–7d	≤24hrs
Confounders	yes	yes	yes	yes
influence	+	-	-	+
-stress	+	±	±	±
-combined injury	+	±	±	+
-BW/CW				
Meets far forward-field use requirements	no	no	no	no

[4]The utility of such "lymphocyte" depletion-type assays to accurately and reliably estimate radiation exposure levels has been actively debated and questioned, especially within the community of physicians and researchers specializing in radiation hematology.

[5]Clinical assessments based on blood-cell counts should be used first and foremost to estimate both the extent of hematopoietic injury, as well as the capacity for injury repair, and should provide the basis for rational, medically-based, treatment decisions. Extracting prognostically useful information from simple blood-cell responses is quite possible but is clearly and absolutely time dependent.

hematologic abnormality. The assay is based on the serial assessment and abnormality scoring of nine individual blood parameters (hemoglobin levels, erythrocyte counts, hematocrit values, erythrocyte sedimentation rates, reticulocyte counts, total leukocyte counts, absolute neutrophil levels, lymphocyte counts, and platelet levels) and, in turn, the folding of the individual abnormality scores into a single score of hematopoietic injury.

The major advantage of this approach is its strong predicator function of clinical outcome; whereas its major disadvantages are the relatively long development times (~1–5 days) and low resolution of the dose-dependent clinical responses.

The ARS assessment approach presented by Kindler is similar to Wald's approach, in terms of its multiparameter nature, but employs fewer parameters which are analyzed individually and not in aggregate at distinct times over the course of the initial week following exposure. This assessment process has been labeled the "sequential diagnosis" technique.

Response profiles for given parameters were based on a detailed, retrospective study of 543 ARS patient records from the International Computer Database for Radiation Exposure Case Histories (ICDREC). These profiles were used in determining patient management/treatment decisions. It should be noted that the majority of cases (390/543 or 71%) exhibited minimal injury profiles and required no specific treatment for radiation injury. The next largest group (101/543 or 18%) had substantial levels of injury but were clearly treatable with standard clinical support and cytokine therapy. Only a minor group (52/543 or 9%) exhibited radiation injuries so severe as to require intense, technologically complex levels of support (e.g., marrow transplantation).

Based on data presented by Kindler, reliable assessments of injury severity can be made within a 4- to 7-day window if blood granulocyte, lymphocyte, and platelet levels are sequentially monitored (at 6-hr intervals during the initial 36-hr postexposure period). However, accurate dose-dependent injury assessment within the targeted 24-hr postexposure period is not possible using this assay procedure.

The multiparameter assessment (sequential diagnosis) procedure developed by the Ulm group (led by Professor T.M. Fliedner) has strong prognostic capabilities and can provide a solid basis for subsequent medical management and treatment decisions. When compared to Wald's "folded multiparameter" scoring assay, this procedure enjoys roughly the same sensitivity (~1 Gy), resolution (~2–3 Gy), as well as the overall range of detection (~1–10+ Gy). The major weaknesses (in terms of its biodosimetric potential) are again the long development times (~4 to 7 days) and the requirement for multiple sampling.

Clinical Indicators in Estimating Exposure

A physiological-based model using empirical observations of the well recognized radiation associated clinical syndrome of fatigability and weakness (F/W) were presented by Mr. George Anno of Pacific-Sierra Research Corporation. This syndrome was discussed, not only in terms of eliciting radiological and temporal parameters, but also as a very early (<24 hrs) indicator of the magnitude and occurrence of radiation exposure.

This discussion was driven by underlying questions as to whether F/W can serve as a reliable, meaningful indicator of radiation exposure if the prominent clinical indicators of nausea and vomiting are stripped away by the application of antiemetics. The consensus answer to this question was clearly and simply—no.

The F/W model, founded on a lymphocyte-depletion kinetics construct, seems to provide reasonably consistent exposure-dependent response profiles (comparing "observed" to "expected" response profiles). This consistency along with early assessment times of 24 hrs or less and the prospect of indirectly quantifying the highly subjective F/W parameter through a simple lymphocyte count are all attractive attributes. Nevertheless, near-term application of the F/W modeled parameter to triage in the forward field is extremely doubtful, due not only to the uncertainty of individual response variations (lack of confidence intervals) but also to the uncertainty of the basic mechanism(s) governing the F/W response.

Discussion and Conclusions

This session, with its focus on "blood markers and clinical indicators," primarily addressed the third issue raised in Chapter 4 of the *Army Field Manual 8-10-7: Methods for Estimating Exposure in Personnel Who Have Received Antiemetics Before or Shortly After Exposure.*

In principle, both the single- and multiparameter-hematologic methods described during this session can be used to provide estimates of exposure within irradiated personnel regardless of whether antiemetics have been given.

The sensitivity, resolution, and range of detection displayed by these assays are reasonable and probably would be effective as supplemental procedures for triage under select conditions. For example, the rapid one-parameter/lymphocyte-depletion kinetics assay might be suitable to provide rough estimates of radiation casualty numbers needed for medical logistics; whereas the slower, more prognostic multiparameter assays (3- and 9-parameter assays) might be effectively applied for determining the extent of injury and subsequent treatment options. However, the utility of these procedures for triage in a forward-field operation is questionable. This concern was raised principally by Dr. Robert H. Mosebar, a recently retired chief medical operations planner (U.S. Army Medical Department Center, Fort Sam Houston, Texas) and by others in the audience as well. The constraints of time, medical resources, and the operation itself seem to preclude use of these assays. The status of existing blood-analysis technology restricts these assays to a minimum echelon II facility—a facility designed for high throughput of short-term emergencies, and not for the prolonged sequential monitoring required by these hematologic assays, especially the multiparameter-based assays.[6]

Nevertheless, the multiparameter hematologic assays and their strong prognostic attributes are absolutely essential, perhaps not in the very early phases of triage but a little downstream in the process. These assays are essential in determining the severity of radiation-induced injuries and the probability of organ-system repair and recovery. Such determinations provide the basis for subsequent treatment decisions.

In contrast to the hematologic assays, it is extremely doubtful that the clinical F/W response assay, as it currently stands, can provide a useful vehicle for estimating exposure levels, regardless of whether antiemetics are administered. The highly subjective nature of the F/W clinical response and the lack of quantitative methods for determining its measurement, effectively rules out the use of this endpoint as a biodosimeter.

The aforementioned operational problems of using the F/W bioassay in the initial triage of radiation-injured personnel in far-forward combat environments led to considering physical dosimetry as a possible interim solution to the rapid (<24 hrs) throughput requirements for the initial phase of the triage process.[7] Dosimetry could be rapidly read, exposure levels estimated, and casualty probabilities determined—all in an echelon II facility. With these dose estimates, troops with registered doses (free-in-air) of 1.5 Gy or greater, would be medically evacuated to an echelon III facility for clinical and hematologic evaluations on which subsequent treatment decisions would be based. Troops with estimated exposures of less than 1.5 Gy (as assessed by initial physical dosimetry) or lacking subsequent

[6]The suggestion was offered that with the advent of new technology (in the form of hand-held blood cell analysis units) the above mentioned shortcomings of the hematologic assays in far-forward fields of operation might be largely overcome. With such hand-held units, medics should be able to perform these hematologic assays on putatively injured troops directly in the field (or in an echelon I facility) with high efficiency and accuracy. However, it needs to be noted that the utility of applying such advanced monitoring devices in far-forward fields of operation has been seriously questioned by several radiation hematologists.

[7]The suggested use of physical dosimetry in the initial phases of the triage process is intended to supplement, not to minimize, nor eliminate the need for full symptomatologic assessment by the field medic or physician in a forward-field care facility. Physical dosimetry is suggested as a possible solution to the substantial problem imposed by the constraints of time, resources, and casualty-care logistics under battlefield conditions. See footnotes 1, 3, and 5 for additional comments.

clinical/hematologic indicators of radiation injury (assessed in the echelon III facility) would be sent back to duty.

The remaining two issues addressed by the workshop, namely, (1) operational effectiveness of irradiated personnel, and (2) operational effectiveness of previously exposed personnel, were only briefly considered, specifically in terms of the expected performance decrement following onset of selected clinical syndromes (upper/lower gastrointestinal and hematologic syndromes). Changes in operational performance caused by radiation exposure need to be considered within a temporal framework of both "early effects" (less than 24 hrs) and "late effects" (>24 hrs, days to weeks). In terms of the latter, the consensus was clear: The prognostically useful hematologic assays relate to long-term performance and not to short-term capacity, due to the delayed onset (days to weeks) of the potential, performance-degrading hemopathologic responses (granulocytopenia and thrombocytopenia, with increased susceptibility to infection and uncontrolled bleeding).

The dose-dependency of decreased performance under acute radiation exposure scenarios has been extensively studied and modeled (as indicated in the Session III presentation by Dr. Gene McClellan of Pacific-Sierra Research Corp.). However, the appropriateness of these models, either in terms of their basic biology or to the triage process itself, was not fully addressed.

Early changes in operational performance can be elicited by induction of the F/W syndrome. Even at fairly moderate radiation doses, where long-term survival would be expected, there is rapid onset (<~3 hrs) of a moderately intense F/W response with the potential to degrade short-term performance (<24 hrs). In this regard, there was general agreement among workshop participants that (1) the F/W syndrome is a very real and important component of performance and (2) its induction and expression is governed by a standard set of radiological parameters. However, there was also agreement that the F/W response is highly subjective and resists quantitation. This restricts the assignment of confidence intervals to F/W response components (threshold, magnitude, intensity) and, in turn, limits its power and utility as a "folded parameter" in the model of radiation-associated performance degradation.

Recommendations

1. Physical dosimetry should be the principal tool in the initial assessment of radiation exposure levels received by military personnel operating within far-forward fields of operation.[7]

   1.1. Exposure estimates would be carried out in an echelon II facility and would be used solely for logistical purposes and not for treatment decisions.

   1.2. Personnel with estimated exposures of 1.5 cGy or greater (free-in-air doses) would be medically evacuated to an echelon III facility for confirmation of performance/health degrading radiation exposure. Personnel with estimated exposures of less than 1.5 cGy would be deemed fit and would be returned to duty.

2. Application of the slower developing, highly prognostic, multiparameter hematologic assays should be restricted to echelon III facilities. These assays would be applied to (a) confirm initial exposure assessments made by physical dosimetry in far-forward fields of operation, (b) assess the extent of radiation injury to the vital lymphohematopoietic system and, (c) provide the basis for subsequent treatment decisions.

3. The possibility of far-forward fielding the single parameter lymphocyte-depletion assay for biodosimetry needs to be reconsidered and delayed until (a) its efficacy is more thoroughly evaluated, (b) confounding factors affecting assay performance are more fully determined, and (c) hardened, hand-held electronic blood cell counting devices become available.

3.1. Comprehensive testing of the assay and the instrument will be required prior to any consideration of fielding.

4. F/W syndrome should not be considered as an adequate substitute for the more demonstrative clinical indicators (nausea and vomiting) of radiation exposure, regardless of whether anti- emetics are involved.

4.1. Improved methods to better quantitate F/W are needed to support radiation-associated performance decrement evaluation models.

Summary of Session III

Predicting the Effects of Multiple Radiation Exposures

Gregory L. King, Ph.D.
Chairman

André Dubois, M.D., Ph.D., LTJG Matthew Hamilton, MSC, USN,
Michael R. Landauer, Ph.D., and G. David Ledney, Ph.D.
Session Panelists

Armed Forces Radiobiology Research Institute, Bethesda, MD

- Large Animal Radiation Experiments
  E. John Ainsworth, Ph.D.
  Armed Forces Radiobiology Research Institute
  Bethesda, MD

- Estimating Lethality Risks for Complex Exposure Patterns
  Bobby R. Scott, Ph.D.
  Lovelace Research Foundation
  Albuquerque, NM

- An Integrated, Physiologically-Based Model of Human Response to Multiple Exposures
  Gene McClellan, Ph.D.
  Pacific-Sierra Research Corporation
  Arlington, VA

- Operational Performance Decrement After Radiation Exposure
  George H. Anno
  Pacific-Sierra Research Corporation
  Santa Monica, CA

Overview

This session's goal was to describe the impact on the operational effectiveness of military personnel who have received multiple radiation exposures within a relatively short time frame and who have not been medicated. Participants were asked to estimate the effects of two low-dose radiation exposures—without medication—on the human response by either mathematical models or extrapolation from published human and animal data. While the mathematical models provided useful general predictions, most of the workshop participants agreed that further validation of these models was necessary. The panelists and participants also agreed that no animal model completely predicts the effects of acute, protracted, or multiple radiation exposures in man; and that fatigability and weakness would worsen with multiple radiation exposures regardless of the fractionation interval between exposures. An effort was made to incorporate the data and models that were presented into a table for use in the *U.S. Army Field Manual 8-10-7, Health Service Support in a Nuclear, Biological, and Chemical Environment*.

Introduction

The goal of this session was to describe the injuries of military personnel who have been exposed to multiple radiations within a relatively short time frame and who do not receive medication, as well as to describe the impact of these radiation injuries on operational effectiveness. Due to the paucity of human data that directly bear on this issue, the session focused on assessing the accuracy, reliability, and validity of both animal and human data that have been used to predict outcomes from such scenarios. Because of the infinite possibilities of scenarios for multiple-radiation exposures, the participants were requested to limit their presentations and analyses to two specific time-related scenarios that had varied radiation doses. Both scenarios were for two radiation exposures separated by 7 days. The first exposure was a midline-total dose (MTD) of 0.7 Gy, given promptly (Scenario 1) versus a protracted dose over the course of 7 days (Scenario 2). The second exposure for both scenarios was a variable prompt dose: 0.5, 1.5, or 3.0 Gy. In general, military personnel exposed to a dose of 1.5 Gy or greater will not be allowed exposure to a second radiation incident. Thus, the lower 0.7-Gy radiation dose was chosen for the first exposure.

Large Animal Radiation Experiments

This presentation summarized numerous fractionated-radiation experiments that were performed prior to 1975 on sheep, swine, goats, and dogs at the U.S. Naval Shipyard in San Francisco, California, and on non-human primates at the School of Aviation Medicine in San Antonio, Texas. All of the experiments used two radiation exposures of varying doses and were designed to determine animal recovery or "residual injury" from the first radiation dose. The endpoints in most experiments were $LD_{50/30}$ or $LD_{50/60}$ survival data; and the early indicators for radiation exposure had to be inferred from the LD_{50} data, personal experience, and from examining the differences among species. In general, the first radiation dose was two-thirds of the $LD_{50/30}$ or $LD_{50/60}$ value for a given animal species and was delivered at different dose rates for many of the experiments. The second and different radiation dose was delivered at varying intervals. This general experimental design did not allow for extrapolation to the lower, more survivable doses suggested for the scenarios described for this workshop. The overall conclusions were that various species show quite varied $LD_{50/30}$ values in response to an acute dose of ionizing radiation. Furthermore, the recovery of each species from the first radiation dose, as measured by survival to a second radiation dose, also varies across species. It was emphasized that the residual injury observed in some species in response to the second radiation dose could not be predicted from hematological measures. The discussion centered on the issue of which radiation response in a particular animal species might best correlate with the human response. The general consensus was that no single species is an ideal correlate.

Estimating Lethality Risks for Complex Exposure Patterns

This presentation described a mathematical model that could predict the hematopoietic lethality for humans exposed to complex dose-rate patterns of

gamma rays. An analysis of the model, background, and definitions were also presented. The model is dose-rate dependent and was developed from data accrued from both laboratory animals and humans. In the context of this workshop, the major limitation of the model is that it can estimate lethality only if there is either no recovery or full recovery from the initial irradiation. Thus, predictions for survival cannot be accurately made if partial recovery or residual injury to the first radiation exposure exists. Again, since lethality is an endpoint of this model, the early indicators of radiation injury in humans had to be inferred. The probability of lethality is the indicator of performance decrement. Despite this limitation, the model can provide useful predictions for estimating the upper and lower limits of radiation exposure under the multiple radiation scenarios described in the workshop.

With the limitations of either no or full recovery, the results calculated for the two scenarios showed that there should be no risk of hematopoietic deaths in either scenario, provided the second radiation dose did not exceed 0.5 Gy. If the second radiation dose exceeded 0.5 Gy, the risk for hematopoietic death increased; but importantly, the lethality risk was exclusively due to the *second radiation dose*. In a brief comparison across species, the model showed that the ordinal value estimated for the radiosensitivity of humans to a prompt radiation dose falls between that of mice and dogs—which in turn are similar to goats and swine. The model also showed that the value estimated for the relative recovery capacity in humans falls near those values for sheep and goats. As emphasized in the previous presentation, data showing the necessary survivable endpoints are unavailable for the non-human primate. To its credit, the model does allow for the inclusion of protection and susceptibility factors such as wounds, burns, and medical support.

An Integrated Physiologically Based Model of Human Response to Multiple Exposures

This presentation provided an overview of the Radiation-Induced Performance Decrement (RIPD) software program that describes certain radiation effects in humans—thus calculating the severity of illness and the residual performance capability for numerous radiation scenarios. This mathematical and computer model uses several differential equations to describe and predict radiation effects under various conditions. Each sign and symptom of the model is based on changes in biological endpoints that occur in response to radiation, such as the clearing of humoral toxins, the cellular kinetics of the intestinal mucosa, and the kinetics of lymphocytes, cytokines, and bone-marrow cells. One limitation of the model appears to be that three of the symptom categories (nausea and vomiting, diarrhea, and fatigability and weakness) and the mortality incidence are based on independent kinetic models, while the other symptom categories (fluid loss, infection and bleeding, and hypotension) are slaved to these other kinetic models. Time restrictions prevented further explanation of the biological validity of this interdependence among the symptom categories. Although some of the kinetic models were derived from animal studies, and others from human data, the output from the animal data in the RIPD model were adjusted to match the human response. Another limitation of the RIPD model is that its dose-rate dependence under some conditions appears to be an extrapolation of the acute response to a prompt irradiation that is then protracted over time. Time did not allow for presentation of specific examples of these conditions. Without further clarification, it was thus unclear which specific endpoints measured in the RIPD model reflected results from specific radiation dose-rate studies, and which endpoints were extrapolated from the results seen after a prompt radiation dose. It was noted that some data for the prodromal aspects of the model were obtained from expert opinion and from questionnaires given to military personnel. The questionnaires were designed to establish correlations between symptoms (including their severities) and task performance, not between radiation dose and performance. While such input may be important to developing and establishing the model, this approach adds a degree of subjectivity to the model. To the credit of the RIPD model, some aspects of these prodromal responses have been validated in human studies on sea-sickness.

Two other important points were made during the general discussion of this model. First, the RIPD

model cannot provide an accurate estimate of the threshold radiation dose for some of the early signs/symptoms of radiation exposure. Second, it was noted that under fractionated radiation conditions, fatigability and weakness did not show a sparing effect to that fractionation. One attendee remarked and cited some older clinical literature describing results from fractionated radiation exposures that might provide useful data to incorporate into the model. While well received, the overall impression by the attendees was that this model requires further validation with other animal models, especially for multiple-dose scenarios.

Operational Performance Decrement After Radiation Exposure

This presentation described in detail the "operational performance" defined for the RIPD model in a military setting and further described how the severities of the various manifestations of radiation sickness alter performance. Numerous illustrations showed how performance levels with 95% confidence limits for specific tasks (e.g., for a member of a tank gun crew vs. a tank commander) varied with dose and time after exposure. Due to time constraints, this presentation did not provide details on the multiple-radiation scenarios that were suggested in advance. However, and of perhaps greater importance, operational effectiveness was evaluated in response to the presence or absence of an antiemetic. Since the human response to antiemetics varies considerably, and a complete set of human data under such conditions is unavailable, the speaker was asked to assume 100% efficacy of the antiemetic drugs to give the best-case scenario. The data showed, depending on the task, that nausea and vomiting were the primary causes of performance degradation; and that operational effectiveness could be improved by an antiemetic. However, the previous presentation showed that fatigability and weakness did not show a sparing effect to multiple radiation doses. Thus, some clarification is necessary to determine the degree to which fatigability and weakness vs. nausea and vomiting contribute to performance degradation after multiple exposures to radiation.

Discussion

The discussion centered on issues involved in the construction of Table 2, *Effects of a Second Radiation Dose on Combat Effectiveness of Military Personnel*, that could hypothetically be used in the Army field manual. As seen in the table, the first radiation doses in a multiple radiation scenario are placed in two bands (1–70 cGy and 71–140 cGy) and are identical to those radiation dose bands currently described in *Army Field Manuel 8-10-7*. By consensus, it was agreed that if this first dose was $\leq$ 70 cGy (either prompt or protracted), military personnel would remain combat effective as long as the sum of it and the second dose did not exceed 150 cGy. This should be true for short intervals of up to 14 days. Beyond 14 days, the panelists and audience could not determine whether personnel could be exposed to a greater second dose. That is, even at low radiation doses, it is unclear whether the biological repair mechanisms would render a human the same as if he or she had never been irradiated. Regardless, lymphocyte counts should be followed in such individuals. Again by consensus, the participants agreed that if the first dose were protracted and > 70cGy, any prompt second dose at any time interval after the first dose would likely evoke partial to full performance decrement in military personnel. This reflects one of the major points gained from this portion of the workshop: the symptoms of fatigability and weakness do not show a sparing effect after fractionated radiation. The workshop participants agreed that the authors of the Army field manual should provide, if possible, military medical personnel with a definition, operational or otherwise, of radiation-induced fatigability and weakness so that medics can distinguish this symptom from battle fatigue. From the aforementioned table, it also can be discerned that there are not enough data to estimate what level-III clinical remarks might be most salient for such irradiated personnel. However, under such multiple-dose scenarios; it is possible that some of the serial measures of biological dosimetry explored in other portions of the workshop could provide invaluable assistance to the field medic.

It became readily apparent from the presentations in this session that no single animal species is the best

model for the radiation response in humans. Moreover, very little data exist that describe the survival of the non-human primate after irradiation, especially in response to multiple exposures to radiation. Since the non-human primate may be the best animal model to substitute for humans, there should be further studies with them using fractionated radiation scenarios.

As a side point, it was suggested that the Armed Forces Radiobiology Research Institute should become a central repository for older government data that deal with radiation studies and should also include newer collections of human radiotherapy data. This would provide a central database that could be accessed by future generations of radiation biologists.

The mathematical models presented were sophisticated and summarized most of the existing information on human radiation effects. They are useful as working hypotheses for future testing. Unfortunately, much of the human data used to derive the models are from events in which uncertainty exists concerning radiation dose, dose distribution, and even the clinical parameters. The panelists and other participants did not have adequate time to evaluate their validity for the overall human response to radiation. The chairman and panelists of this session believe that scientific peer reviews of the models would benefit the authors and developers of these models. These models need further work before conclusions can be derived for establishing military standards for triage. Such work should focus on validating the models across several species, with special emphasis on validating the effects of multiple radiation exposures.

Recommendations and Research Directions

The panelists and participants in this session recommended that (1) Table 2, *Effects of a Second Radiation Dose on Combat Effectiveness of Military Personnel*, should assume that no confounding variables exist (e.g., combined injury, infection, exposure to a threat agent); (2) physical dosimeters should be issued to personnel at risk of a second exposure; (3) field commanders should be made aware that the fatigability and weakness response does not show recovery; (4) multiple-radiation exposure studies should focus on end points other than lethality; (5) radiation studies should address the effects of other combined injuries, such as physical trauma or infection; and (6) an attempt should be made to quantitate fatigability and weakness in either humans or in an animal model to approximate the human response.

Table 2. Effects of a second radiation dose on combat effectiveness of military personnel.

1st dose		Prompt 2nd dose			
Prompt or protracted[1]	Time interval between doses	Maximum 2nd dose allowed[2]	Expected performance capability of unit	Field symptoms	Level III clinical remarks
1–70 cGy	1–14 days >14 days	149–80 cGy ?	Combat effective	Mild nausea and vomiting	Mildly decreased lymphocytes, platelets, and granulocytes—monitor lymphocyte count
Protracted[1, 3]					
71–140 cGy	1–7 days >7 days	79–10 cGy ?	Partial/full decrement	Fatigability and weakness, greater nausea and vomiting	?

[1]All individuals are considered combat effective after the 1st dose, from Table 4-1, FM 8-10-7.
[2]Maximum total dose received should not exceed 1.5 Gy.
[3]This group should receive no further radiation exposure after 1st dose.

Summary of Session IV

Forward-Field Bioindicators for Dose Assessment: Possible Alternatives

William F. Blakely, Ph.D., and Thomas M. Seed, Ph.D.
Chairmen

Pataje G.S. Prasanna, Alasdair J. Carmichael, Narayani Ramakrishnan,
David A. Schauer[1], and Clive L. Greenstock[2]
Session Panelists

Armed Forces Radiobiology Research Institute, Bethesda, MD,
[1]Naval Dosimetry Center, Navy Environmental Health Center Detachment, Bethesda, MD,
and [2]Atomic Energy of Canada Limited (AECL), Chalk River, Ontario, Canada

- NATO Perspectives on Biological Indicators of Radiation Exposure
  Dr. Govert P. van der Schans
  TNO Prins Maurits Laboratory, Rijswijk, Netherlands

- Radiation-Induced Apoptosis in Human Lymphocytes
  Dr. Douglas R. Boreham
  AECL, Chalk River, Ontario, Canada

- Halo-Comet Assay
  Dr. Juong Gile Rhee, Jie Liu, Mohan Suntharalingam
  University of Maryland Medical School, Baltimore, MD

- Radiation Damage in the Hematopoietic System
  Dr. Lionel G. Filion
  University of Ottawa, Ottawa, Canada

- Automated Cytogenetic Assays in a Field Environment: Consideration of the Halo-Comet Assay
  Mr. Harry L. Loats
  Loats Associates, Westminster, MD

- Potential Use of *In Vivo* Electron Paramagnetic Resonance, Electron Spin Resonance (EPR, ESR) for *In Vivo* Dosimetry Under Field Conditions
  Dr. Harold M. Swartz
  Dartmouth Medical School, Hanover, NH

- EPR-Based Dosimetry and Its Present Suitability for Field Usage
  Dr. Arthur H. Heiss
  Bruker Instruments, Inc., Billerica, MA

Overview

The goals of Session IV were to evaluate the status of several alternatives to peripheral blood counts and prodromal symptoms for forward field radiation-dose assessment. The suitability of selected biochemical-based (DNA single strand breaks), cytogenetic-based (apoptosis, halo-comet), and biophysical-based (free radicals in solid matrix materials) bioindicators of radiation exposure was evaluated. The current status of fielding systems to automate the measurements was also evaluated. The session consensus was that no one assay is presently suitable for military use. It was also recommended that a research program be implemented to evaluate the development of a multiassay strategy characterized by *in vivo* evaluation studies, acute versus protracted radiation exposures, and critical comparisons between techniques with the greatest potential for both robust dosimetric capability and automation. Table 3 shows the classes of bioindicators, the type of assays, and the presenters.

Introduction

Suitable forward-field bioindicators should exhibit the following characteristics: (1) negligible post-sampling incubation, (2) rapid processing suitable for a high degree of automation and high throughput, (3) low-threshold, broad dose-rate, and variable radiation quality capability, (4) relatively noninvasive sample collection, and (5) equipment hardware for which components are or soon will be available.

Dr. Clive L. Greenstock's (AECL, Chalk River, Ontario, Canada) review of potential biomarkers of radiation exposure (presented in session I) provided excellent background. In addition, Dr. Govert P. van der Schans, chairman of the Bioindicator subgroup of NATO Research Study Group No. 23/Panel VIII (Assessment, Prophylaxis, and Treatment of Ionizing Radiation Injury in Nuclear Environments), provided a brief summary of related research efforts. He noted the limitations inherent to dose assessment methods involving lymphocyte counts and chromosome aberrations. Dr. van der Schans said the NATO group is studying the use of dextran sulfate to stimulate resting immune cells in peripheral blood as well as their dose-dependent cytogenetic-based response and the micronucleus assay. Further progress with cytological dosimetry is possible using premature chromosome condensation (PCC), chromosome painting using hybridization probes, and automated data collection and analysis using a metaphase finder. However, these techniques are inherently time consuming, subjective, and labor intensive. In addition, the analysis of more than five samples per day is problematical unless the assay is automated.

Presenters for Session IV were selected to permit an inspection and review of potential bioindicators from a broad spectrum or class of candidates (Table 4). All presenters were asked to address the status and practicality of fielding an automated dose-measurement system. The seven presentations in Session IV were each limited to 20 minutes and reflected an intent to bridge the gap between science and industry. Representatives from two science-application companies, Mr. Harry L. Loats (Loats Associates, Westminster, MD) and Dr. Authur H. Heiss (Bruker Instruments, Inc., Billerica, MA), gave presentations on automated cytogenetic assays and EPR-based dosimetry, respectively.

An open discussion evaluating and comparing the various biomarkers for radiation exposure followed the presentations.

Table 3. Class of bioindicator, type of assay, and presenter.

Class	Assays	Presenter(s)
Biochemical	DNA single-strand breaks	van der Schans
Cytogenetic	Apoptosis	Boreham; Filion
	Halo-comet	Rhee; Loats
Biophysical	Free radicals in solid matrix (EPR)	Swartz; Heiss

Possible Alternative Bioindicators for Dose Assessment

Biochemical

The use of an immunochemical-based method to detect radiation damage to DNA appears to offer the possibility of providing the necessary requirements of a fast, simple, direct biological indicator using a blood sample. The assay involves using specific monoclonal antibodies against DNA single-strand breaks attached to the surface of multiwell plates. Small volume blood samples (3µl) are diluted in alkali to unwind the DNA at single-strand breakage sites. The blood samples are neutralized and sonicated to release single-strand fragments. The fragments as antigens are allowed to form complexes with the coated monoclonal antibodies; and the complexes are conjugated with alkaline phosphatase and incubated with an FITC-labeled substrate—the fluorescent intensity of which is directly proportional to the amount of single-strand fragments which in turn is proportional to the radiation exposure. The assay requires only small samples, takes 1–2 hours, does not require cell culture, and has a lower limit of detection of ~0.2 Gy.

Because of rapid DNA repair, *in vivo* samples must be collected immediately after exposure (<1 hour) or a much lower sensitivity is achieved—since DNA strand-break damage is rapidly repaired. In a practical situation (the far-forward field), the reliable lower limit of detection is probably 1–2 Gy—taking into account the wide variation in individual radiosensitivities and the controls' baseline level DNA breaks. More *in vivo* tests are required to validate this promising potential biodosimeter and to compare acute versus chronic or protracted exposures as well as the varying effects that result from differences in radiation quality.

Cytogenetic

Apoptosis Assay. Dr. D. R. Boreham addressed the possibility of using apoptotic death in human peripheral-blood lymphocytes as a biological dosimeter and reviewed the steps involved in human lymphocyte apoptosis—a rapid, sensitive, reproducible biological response to low-dose radiation exposure. Although most research involves assays requiring cell culture, the kinetic changes involved in the process of apoptosis offer the possibility of using apoptosis as a potential biological dosimeter, provided that a blood sample is obtained within hours of human exposure. The characteristic DNA fragmentation is detected using either the comet technique, by *in situ* terminal deoxynucleotidyl transferase (TdT) assay, or the fluorescence analysis of DNA unwinding (FADU) assay. For *in vitro* exposures the induction of apoptosis is proportional to dose; the lower limit of detection is ~ 0.05 Gy. Overall radiation-induced DNA damage is repairable with a half-life of ~1 hour. After about 4 hours postexposure, the ordered DNA fragmentation

Table 4. Selected list of alternative bioindicators.

Clinical chemistry kits for low molecular weight products in body fluids	• Electrolytes, creatine, taurine
	• Prostaglandins, enzymes, metabolites, nucleotides
	• Molecular/chemical biosensors
	• Immunochemicals, antibody tests
Immunochemical tests	• Cytokines, lymphocytes, hormones
	• Membrane markers
	• Cyclins, integrins, etc.
Genetic engineering	• Differential display (multiple gene expression)
	• DNA probes (FISH, PCR, RFLP, mutation spectral analysis)

characteristic of active apoptosis becomes apparent and increases over 24 to 48 hours.

In-vivo exposures require the removal of lymphocytes from the body as soon after exposure as possible (within hours), otherwise apoptotic cells will disappear as a result of phagocytosis. One technique that can potentially measure apoptosis is flow cytometric-based analysis of lymphocyte plasma membrane changes—the early and critical events in apoptosis. Dr. Lionel G. Filion emphasized (see session II manuscript) the potential benefits from the use of flow cytometry-based methodology. Clearly the use of multiple parametric endpoints derived from several distinct cell populations should provide a significant improvement in clinical dose assessment.

Because individual radiation-induced apoptotic responses vary greatly, this assay measures biological radiosensitivity rather than physical absorbed dose. Apoptosis has considerable potential as a future biodosimeter and is amenable to the development of a fast, automated, clinical kit to test for radiation exposure using a small (0.1 ml) blood sample; however, *in vivo* (animal or radiotherapy patient) testing is urgently required.

Halo-Comet Assay. Dr. J. G. Rhee presented results from a modified version of the "halo assay," designated the halo-comet assay. The halo-comet assay appears to quantify alterations of an individual cell's DNA organization. Dr. Rhee used two *in vitro* cultured mammalian cell lines for these studies. Agarose gels containing single cells, which had been exposed to different doses of x-rays and various repair intervals, were prepared on glass slides. Following electrophoresis (pH-7 conditions), the cell preparations were stained with propidium iodide. The dye was excited, and image data acquisition detected with fluorescent light (excitation: 545 nm, emission at 580 nm). Data were analyzed by image analysis. A linear increase of up to 6 Gy in the "amount of DNA pulled from the nucleoids" was suggested by the results. Significant differences between 0 and 0.5 Gy induced damage, with no repair, suggests that this assay is sensitive enough for triage purposes. The analysis of residual damage after 30 min of repair following exposure to 2 and 4 Gy of x-rays indicated a significant difference between irradiated and control samples. This was evident even after 1 or 6 days of repair, indicating that some damage could still be measured after a time lapse. Dose-dependent alterations following fractionated doses (2 Gy x 3 days) were also observed after 5 days of repair following the last fraction. These results should also be confirmed by *in vivo* studies.

The assay is rapid and can be automated by image analysis, which was the subject of Harry L. Loats' presentation. Loats presented a system based on the halo-comet assay designed to automate cytogenetic assays in a field environment. The system components are based on the existing automated systems produced by Loats Associates, Inc., for clinical and research laboratory applications. To accommodate the throughput requirements inherent in the military-field scenario, a parallel processor and multichannel design was presented with characteristics including (1) robotic slide selection and delivery system, (2) automated cell finder using nonfluorescent lighting, (3) a new technique for image-based low-light level range extension to provide dynamic range extension for capturing the head and tail of the halo comet in the same image, and (4) a digital method to produce composite images from a series of closely spaced images neighboring the plane of best focus.

The system uses off-the-shelf and proven hardware and software, can be operated by non-specialist personnel, and would be applicable to both forward-field and rear-support echelon facilities.

The detection system for dose assessment using the halo-comet assay has distinct possibilities. It likely will exhibit a broad dose range and can potentially be performed with blood, making the sample collection relatively noninvasive. A halo-comet assay system has the potential to handle a large number of samples using automated image analysis; its relatively short assay time is a major benefit over alternative biomarkers. The possible applicability of this assay for use in human dose-assessment applications needs to be explored with animal models and radiotherapy patients. However, studies addressing the effect of individual variations in radiosensitivity

and effects from confounding factors (e.g., prior exposure to genotoxins, dose protractions, and different exposure scenarios) need to be performed.

Biophysical

Free Radicals in Solid Matrix Material. Free radicals in solid matrix can be measured by electron paramagnetic resonance (EPR) spectroscopy, a well established and accepted technique for determining absorbed radiation in cases of accidental radiation exposure. Dr. Harold M. Swartz and Dr. Arthur H. Heiss presented aspects of this subject. Dr. Swartz provided results from EPR spectroscopy using tooth enamel and bone dosimetry, although several alternatives (clothing buttons, nail clippings) are presented in his manuscript. Swartz also emphasized the need to investigate other biological sample systems for EPR dosimetry measurements. The workings of the EMS 104 portable EPR analyzer, designed specifically for dosimetry purposes and now in use in many clinical settings, was presented by Dr. Heiss. In addition to using it for alanine dosimetry, Heiss presented additional potential uses for this EPR instrument, including the red blood cell receptor assay being developed at AFRRI by Dr. Alasdair Carmichael using spin-labeled insulin. Application of the Bruker EMS 104 for use in military forward-field applications was also discussed.

While EPR-based dosimetry has several desirable features, there are also significant limitations. The requirement to either assess in advance each individual's radiosensitivity in relation to their solid matrix material (teeth enamel, bone, etc.), or to establish a dose response calibration curve from a test sample, restricts practical use of this approach for military applications. This second approach requires a radiation source in the far-forward field laboratory; however, use of an isotope-based gamma-ray source for this purpose is not advisable in battlefield applications.

Other Bioindicators to Consider

Several other potential bioindicators were identified that may have merit as alternative biomarkers for military forward-fielding as dose assessment assays (Table 4). Unfortunately due to time constraints, discussion of these assays was limited.

Discussion

Accomplishments

Advances in biotechnology, digital imaging, and data handling and analysis can effectively eliminate manual analysis procedures for biological dose assessment—which are subjective, time-consuming, and labor-intensive. Parallel development of equipment with improved fieldability characteristics (compact, rugged, portable multiplexing technology to dramatically increase throughput with fewer moving parts) coupled with these radiation bioindicator assays is feasible. For example, the automation of cytogenetic assays (metaphase finder, image processing, chromosome aberration/micronucleus/fluorescence *in situ* hybridization (FISH)/premature chromosome condensation (PCC scoring)) were demonstrated. There is a need to develop alternative *persistent* damage endpoints (halo-comet, membrane markers, *in vivo* ESR biological dosimetry) that do not require cell culturing. These assays require tests of individual radiosensitivity with appropriate *in vivo* validation.

Remaining Research Questions

These findings, along with contributions from workshop participants, permitted a delineation of relevant remaining research questions. Several significant questions that were identified include the need to (1) improve existing assays or develop new assays to make the process faster, simpler, more direct, and definitive, (2) look for mechanisms underlying intraindividual and interindividual variability, (3) search for a radiation-specific response or signature, (4) carry out interlaboratory comparison, standardization, and validation, (5) overcome the problem of needing prior knowledge of an individual's radiation history (dose-rate, LET, etc.) and baseline responses, and (6) establish necessary criteria (and weigh the advantages and disadvantages) of a biological *dose* indicator versus a biological *effect* indicator.

Recommendations

The consensus of the session was that none of the dose assessment biomarkers has all of the features representing the "ideal" assay; alternatively, a multi-assay approach represents the best design to meet mission requirements. To accomplish the goal of fielding a practical dose-assessment assay, a research program should (1) concentrate future experiments on *in vivo* testing (animals or radiotherapy patients), (2) compare results from acute *versus* protracted exposures, (3) move toward standardized protocols using the same *in vitro* cell lines (preferably human), (4) carry out critical comparisons between the techniques with the greatest potential, and (5) develop combinations of assays performed sequentially or in parallel (preferable).

Operational Effectiveness of Exposed Personnel

The consensus was that personnel receiving radiation of 1.50 Gy or more should be evacuated to the rear, while most personnel can be returned to duty even after exposure to a "significant" amount of radiation, up to 1.50 Gy (free-in-air). All irradiated individuals will be at increased levels of susceptibility to morbidity and mortality from other illness and injury (e.g., communicable and infectious disease, mechanical and/or thermal trauma, etc.). Up to 30% of personnel receiving exposures approaching 1.50 Gy will be too clinically ill to return to duty, and will require evacuation to an echelon III or higher-level facility. After recovery from the acute effects, many will experience fatigue and weakness of varying degrees for up to several weeks, although they otherwise will be able to continue their duties. The decision of whether to leave in place either individuals or units that have been exposed to radiation is ultimately an operational—not a medical—decision. (But see below, final paragraph of this section.)

An important point: The general consensus was that clinical symptoms and hematological indicators are inadequate for initial triage in a forward-field setting, given the rapid time constraints, limited personnel and equipment, and potential use of prophylactic emetics in this situation. First-line triage and dose assessment would be better served by the application of physical dosimetry. Clinical, serial hematological, and other biological parameters will be more useful in secondary triage processes and in rearward medical facilities.

During the discussion Dr. Vic Bond, who was one of the physicians involved in caring for the Marshallese Islanders exposed to fallout in 1954, made an important point regarding medical evaluation of radiation-injured patients. The clinical presentation and course, *not* the physical dosimeter's reading or other laboratory parameters, will determine the priority and nature of treatment.

In interpreting Dr. Bond's comments and his single view graph (Fig. 2), the problem of placing reliance on physical dosimetry for medical assessment purposes stems from inherent differences in slopes of the dose-response functions for the primary biological endpoints of interest, namely fatality and injury severity (i.e., injury to organ systems, tissues, and selected target cells). Physical dosimetry best serves the narrow, steeply-sloped "probability of fatality" dose function (Fig. 2.a), while serving poorly the broader, initially shallow-sloped "severity of injury" function (Fig. 2.b.) The integration of the two functions (fatality vs. injury severity) tends to an extremely narrow window of expression of fatal-type responses, relative to the overall extent of injury severity (Fig. 2.c).

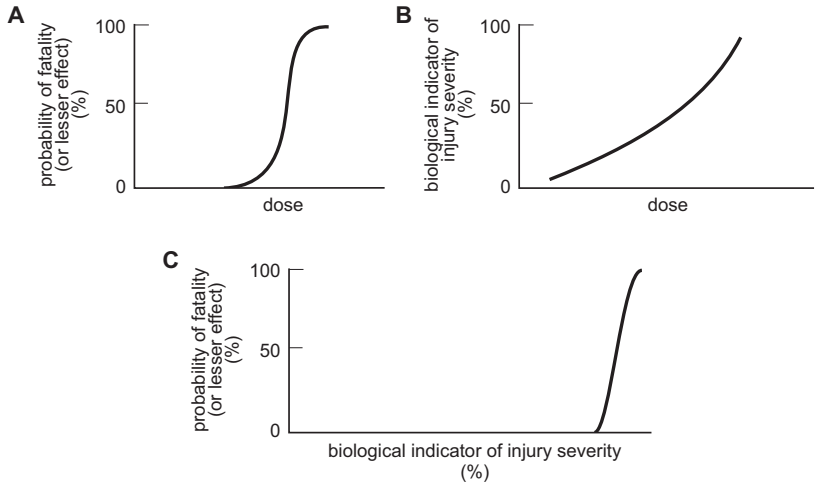

Fig. 2. Differences in slopes of the dose-response functions for the primary biological endpoints of interest.

As a result, the major fraction (and degree) of the injury-severity response appears to be poorly represented at the sublethal response levels. Accordingly, the use of physical dosimetry for medical triage would be based on a fatality probability function, rather than on an injury severity function, and thus would tend to ineffectively represent the degree of treatable injury, measured more appropriately by biomedical methods.

To summarize: physical dosimetry is required in triage at forward medical facilities, given the rapid (24 hr.) time constraints and personnel and resource limitations, to determine if exposure was high enough (1.5 Gy or more) to require evacuation, and to determine the probability of lethality. Biomedical response indicators become necessary, primarily at rearward facilities, to determine the severity of (survivable) injury and the optimal clinical management of the patient.

Operational Effectiveness of Personnel with Multiple Exposures

There were three major consensus conclusions regarding this topic: (1) No animal model completely predicts the effects of either acute, protracted, or multiple radiation exposures in humans; (2) fatigue and weakness are cumulative; and (3) physical dosimetry is required for personnel at risk of a second exposure.

The models used to address this question need further experimental validation in terms of dose-rate and fractionation intervals. Large animal data have been used to develop human LD_{50} models, but the correlation of survival curves between species let alone between large animals and man, is not always constant. Marrow kinetics are certainly related to mortality, and the pathologic sequelae that contribute to a fatal response; though there are probably other factors besides marrow damage, even at this dose range, that influence lethality.

Fatigue and weakness start at only 1 Gy, and there is no apparent repair coefficient or fractionation effect; i.e., the effects from multiple doses are cumulative. This also appears to be independent of dose-rate effect, as well as for the interval between discrete prompt doses. Emesis, however, is affected by factors of dose rate and fractionation. In terms of marrow kinetics, repair does take place; the degree to which it occurs is dependent on radiation dose, dose rate, radiation quality, the volume of marrow irradiated, and the species being irradiated.

Estimating Exposure in Personnel Who Received Antiemetics Before or Shortly After Exposure

The three symptoms currently used to clinically assess the degree of radiation exposure are nausea, vomiting, and diarrhea. Use of antiemetics before or shortly after known exposure clearly masks the response of the exposed person to radiation and could actually improve operational effectiveness. Even so, there is individual variability in the effectiveness of antiemetics. Although multiparameter hematological indices are probably not affected by the use of antiemetics, there is no reliable clinical or laboratory bioassay at echelon I and II facilities capable of exploiting this fact. Fatigue and weakness, even if unaffected by antiemetics, are too highly subjective to provide a reliable, reproducible, quantifiable, and accurate measurement of exposure. As mentioned earlier, physical dosimetry remains at present the only reliable tool for exposure estimates, regardless of whether personnel have received antiemetics. Accordingly we recommend the following procedures:

1. Obtain a base level complete blood count and differential if exposure is anticipated.

2. Provide physical dosimetry, readable at this level, and make available for 100% of the troops.

3. Perform serial blood counts as soon as possible postexposure.

4. Consider the above procedures carefully before ordering administration of prophylactic antiemetics. The decision to administer these drugs must be made by the commander;

drugs should not be issued until exposure is likely and should not be taken until directed.

There are three areas of development for biological dose indicators that may become available at echelon I and II facilities in the near future: (1) develop a hand-held, durable electronic blood-cell counting device capable of performing either single or multiple blood cell (lymphocyte) depletion assays; (2) find, if possible, more reliable, precise, and quantifiable means of defining fatigability and weakness (which would also serve to better support radiation associated performance decrement evaluation models); or (3) use hardened, automated, and sophisticated cytogenetic (or other) assays (see final paragraph).

The application of multiparameter hematologic assays as well as other assays in echelon III facilities and beyond is critically important. Assays at this level serve to confirm initial exposure estimates made by physical dosimetry, assess the extent of injury to the lymphohematopoietic system, and provide the basis for therapeutic management.

One encouraging note is that there are near-term technologies that will provide additional bioassays (besides serial lymphocyte and multiparameter blood counts) at echelon III facilities. These include biochemical assays (radiation-induced single strand DNA breaks), biophysical assays (electron paramagnetic resonance (EPR) analysis of free radicals in solid matrix materials), and cytogenetic assays (apoptosis, halo-comet assays.) At present, the chief drawbacks for most of these techniques are the high level of skill required to run these generally time-consuming and labor-intensive procedures (with resultant low throughput) and their current unsuitability for field conditions (harsh environment, mobility, ruggedness). Also, further research into individual radiosensititivity, *in vivo* validation, results of acute vs. protracted exposures, etc., is required. With the near-term development of automation and field hardening, some of these procedures may become useful options—and perhaps can be used as far forward as echelon II facilities.

Appendices

Appendix A. Session I

Appendix B. Session II

Appendix C. Session III

Appendix D. Session IV

Appendix E. List of Attendees

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13. ABSTRACT *(Maximum 200 words)*

AFRRI was tasked by the Army Office of the Surgeon General to answer operational questions concerning three issues related to the triage of irradiated personnel deployed forward. These issues, and the workshop participants' consensus responses, are:

1) **Effects of radiation injuries on exposed personnel, assuming Level I and Level II medical care and facilities.** Individuals receiving over 1.5 Gy should be evacuated; those receiving less than this amount may return to duty. Even at this level, 30% of exposed personnel may be too ill to return to duty. Those who recover will experience varying degrees of persistent fatigue and weakness. Dose assessment at this level is best served by physical dosimetry.

2) **Describe these effects in previously exposed personnel.** Physical dosimetry is required for personnel who are at risk of a second exposure; no animal model completely predicts the effects of either protracted or multiple radiation exposure in humans. Fatigue and weakness in multiply exposed personnel will be cumulative.

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