THE STUDY OF THERAPY OF RADIATION INJURY
IN THE SOLDIER

Final Report

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SUMMARY

This final report reviews the discussions and recommendations presented in the three comprehensive reports previously published in this study. It concludes with consolidated recommendations for future research on the diagnosis and treatment of ionizing radiation injury in the soldier. Specifically identified are mechanisms of recovery and repair after radiation injury; supportive measures for transplantation of bone marrow; the use of immunosuppressive agents; control of bacterial infections, septic shock, and radiation-induced emesis; biotransformation of drugs and essential nutrients; the need for more data on hematologic changes in man after radiation; and the use of new measures to estimate stem cell reserves and granulocyte kinetics. An attempt was made to select most promising topics that are germane to requirements of the Army nuclear medicine program.
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1. INTRODUCTION

The diagnosis and treatment of ionizing radiation injury (radiation injury) in the soldier is the obligation of the United States Army Medical Department. To meet this requirement Army medical officers receive training in the biomedical aspects of radiation injury and therapy. In addition, the Office of The Surgeon General, Department of the Army, through its Medical Research and Development Command, conducts a research program in military nuclear medicine.

In recent years, there has been a decreased interest on the part of the scientific community in the biological effects of radiation. In the immediate postwar period of 1945 to 1950, a ferment was evident that stimulated a great volume of excellent scientific work on the nature of the changes in living tissues induced by radiation. At that time, the subject of radiation biology represented a new frontier of knowledge. Subsequently, a large body of literature has accumulated. However, the decreasing interest among biologists reflects an assumption in the nation as a whole that it is not possible to provide successful therapy to victims of a nuclear disaster.

Unfortunately, the nuclear threat has not disappeared but still demands serious consideration and future research planning. This study was conducted to assemble existing knowledge on diagnosis and therapy of radiation injury as applicable to man, collate this information in comprehensive reports, and relate it to the specific needs of the Army. Planning of these reviews emphasized the importance of excluding from consideration the logistical aspects of medical care of a large number of radiation casualties. In addition, the three reports do not discuss the potential use of chemical protective agents against radiation hazards, shielding, and related physical protective measures.

The reviews and reports provide information that will facilitate the evolution of future research and development programs on the management of radiation injury and in the general area of military nuclear medicine. The studies have been predicated on the value of a reassessment of the state of the art as a necessary step to uncover leads for exploitation. The reports of
these studies serve to encourage and assist military and academic scientists working in nuclear medicine research. It is recognized that sound diagnosis and adequate therapy of radiation injury under military conditions can only evolve from a successful and long-term research program that profits from basic scientific discoveries.
II. SYNOPSIS OF THE REPORTS

A. A STUDY OF THE IMMUNOLOGIC ASPECTS OF THERAPY OF RADIATION INJURY IN THE SOLDIER

This report (1) is based on a study that was conducted to explore new approaches to an understanding of the nature of the reactions of cells and body tissues to ionizing radiation, and to exploit this knowledge in developing better methods to manage radiation injury in the soldier. The constraints imposed by the military requirements include unique features of radiation exposure, protection, and recovery that are related to the special demands of the Army. Therefore, the evaluation of diagnosis and therapy of radiation injury under combat conditions includes aspects of the subject that are different from peacetime radiation accidents or the concerns of civilian defense.

In reviewing methods for the treatment of radiation injury in the soldier, the immunologic aspects of bone marrow allografts were selected as most timely. A review of this subject revealed not only a number of potential difficulties but also many opportunities for profitable study that are directly related to military needs. The scope of the study included the nature of the hematopoietic injury and recovery, immunologic changes that influence both bone marrow transplants and decreased resistance to infection, animal models used to study allograft responses, use of antilymphocyte sera and antilymphocyte globulin as immunosuppressive substances, and the phenomena of host-versus-graft and graft-versus-host reactions. One of the major problems of tissue transplantation is the difficulty of proper donor selection. The evidence for the reported success with leukocyte typing for donor selection was reviewed as this technique may be applied to bone marrow transplantation.

Fundamental problems in bone marrow transplant immunology were reviewed and the opportunities for future research were identified. Emphasis was on the use of tissue replacement for the treatment of radiation injury. The ultimate success of this therapeutic measure will depend on understanding and controlling the
immune reactions that pose such formidable problems at the present time. The potential military exposures that are most amenable to therapy involve lower dose levels and reversible hematologic changes are known to follow exposure to these radiation doses.

Basic studies in immunochemistry have introduced new understanding of the physical nature of some protein antigens. The opportunity exists to use newly developed methods to study these substances and explore the relationships between molecular geometry and immunologic properties. This is a primary step in explaining the complex nature of the antigen-antibody reaction. It is possible that new forms of therapy may be evolved from the knowledge of the phenomena of immunological tolerance in terms of protein structure. Physical chemical techniques are now available to make precise measurements of the geometry of certain protein molecules. This information should be useful in developing new insights into the immune response and perhaps the delicate physical changes in cellular protein structure induced by radiation.

Histocompatibility matching may be made more readily for bone marrow transplants than for whole organ transplants. This is but one encouraging aspect of recent developments in this field. The influences of radiation on metabolic transformations and modification of the normal biochemistry and physiology of the body's absorption, distribution, and excretion mechanisms require additional study. The fate of essential nutrients, water, and drugs may be determined by changes in the gastrointestinal tract induced by radiation exposure. The solution of these fundamental problems may be achieved by further study of the biological changes induced by irradiation.

Suggested areas for future research emphasis are identified in the report and are summarized in Section VII, p 16 (1). An annotated, evaluative bibliographic review was prepared as an integral part of the study and is included as an appendix to this report.
B. A STUDY OF EARLY RADIATION-INDUCED BIOLOGICAL CHANGES AS INDICATORS OF RADIATION INJURY

This report (2) is concerned with the early biological changes that reliably indicate the degree of radiation injury a soldier has received. Determination of the degree of radiation injury would simplify the triage and treatment of casualties. Prompt diagnosis of the radiation-induced injury the individual has experienced and a precise estimate of his prognosis are important. In military operations it is not only necessary to save lives, but also it is desirable to preserve and use available manpower. Early radiation-induced biological indicators of the degree of injury would be extremely useful in meeting such manpower demands. In addition, dependable indices would have potential use in the assessment of the severity and extent of radiation injury in civilian populations.

The following criteria were selected as pertinent to suitable biological indices that would be appropriate to the military requirements: men receiving radiation doses below 1,000 rads were considered most amenable to management; biological indicators of radiation-induced injury should provide results within one to two days after exposure; techniques of measurement should not require exotic equipment; radiation-induced biological changes should have a high probability of occurring only after radiation exposure; and biological samples should be easily obtainable and available for sequential studies.

The scope of the study included: the use of physical dosimetry; characterization of radiation-induced emesis; radiation-induced cytological changes in the testes; urinary constituents as predictors of radiation injury; hematologic changes; serum iron levels as indicators of hematopoietic dysfunction or injury; use of etiocholanolone in estimating bone marrow granulocyte reserves; total protein-bound neutral hexoses in the plasma as related to radiation sensitivity; effects of radiation on detoxification enzymes, drug metabolism, and biochemical changes; and chromosome aberrations as indices of radiation injury.

The developments in the field of thermoluminescence may have applications in the personal dosimetry of the soldier. Post-
irradiation emesis is a reliable clinical sign indicative of radiation exposure; there is need to understand the mechanisms involved in radiation-induced emesis to enhance early diagnosis and treatment measures of casualties. Cytological changes in certain cells of the testes are a critical measure of radiation exposure. However, the feasibility of using testicular biopsies in the field as a measure of radiation-induced injury has been questioned. Excretion of certain urinary constituents has been shown to be increased following radiation exposure of animals but the value of these changes has not been proved in man. The hematologic changes that follow a single exposure to radiation have been documented and provide a basis for the current understanding and prediction of the degree of radiation injury. There is a pressing need for more information on all types of hematologic alterations that will be produced by the anticipated multiple radiation exposures to gamma and neutron radiations in nuclear combat.

Additional research is necessary to explore the potential usefulness of the dynamics of monocyte changes as predictors of radiation injury, and to evaluate the capacity of the bone marrow of radiation casualties to recover. Radiation exposure as reflected in decreased bone marrow erythropoiesis is usually mirrored by a subsequent increased serum iron level. It may be possible to utilize this serum iron change as a prognostic measure of the degree of radiation injury. Administration of the steroid metabolite, etiocholanolone, has proved a useful tool in assessing the bone marrow granulocyte reserves in radiation therapy of cancer. Additional research emphasis on granulocyte kinetics with exogenous etiocholanolone may be rewarding in developing a test to measure granulocyte reserves as a means to determine the effects of multiple radiation exposure damage in the soldier. Total protein-bound neutral hexoses in the plasma have been found to be modified after radiation exposure of animals. These preliminary observations should be extended to man using the newer physicochemical analytical methods. In a similar manner, radiation-induced alterations in the metabolism of drugs or chemical test substances may provide a measure of some aspects of radiation injury. Preliminary evidence of biological changes of this character is sufficiently encouraging to warrant research emphasis on this aspect of the subject. The scoring of radiation-induced leukocyte chromosome aberrations is a useful and reliable technique to determine the approximate degree of radiation injury. Unfortunately, the test requires a number of days to conduct and in its present state the
method is not suitable for military field use. Development of computer technology would augment the requirements of rapid scoring in the field situation.

Suggested areas for future research emphasis are summarized in Section VII, p 61 (2). A critical review entitled Clinical and Laboratory Observations Useful in Estimating Degree of Radiation Injury and an annotated evaluative bibliography constitute Part II of the report.
A STUDY OF THE METABOLIC ASPECTS OF THERAPY OF RADIATION INJURY IN THE SOLDIER

Early signs and symptoms produced by whole-body radiation exposure are generally related to the abnormal physiology and cellular lesions of the gastrointestinal tract. These signs and symptoms have diagnostic value but, at present, the pathologic changes are not fully amenable to medical treatment. This report (3) reviews recent research on the effects of radiation on the gastrointestinal tract of man and experimental animals including: gastrointestinal symptomatology; immediate post-irradiation cellular events; morphologic responses; gastrointestinal and hematopoietic correlations; intestinal motility and malabsorption; intestinal flora changes; antibiotics in radiation therapy; radiation-induced emesis; transport of fluid, electrolytes, nutrients, and other essential elements; and alterations in drug metabolism. In reviewing these aspects of the radiation-induced "gastrointestinal syndrome", potential therapeutic opportunities were identified.

Suggested areas for future research emphasis are summarized in Section VII, p 53 of the report (3). A critical literature review entitled The Gastrointestinal Syndrome in Acute Radiation Injury and an annotated evaluative bibliography constitute Part II of the report.
III. CONCLUSIONS OF THE STUDY

A selected group of scientists met with representatives of the military nuclear medicine program, U.S. Army Medical Research and Development Command, Office of The Surgeon General, Department of the Army, and the staff of the Life Sciences Research Office, Federation of American Societies for Experimental Biology, to review the recommendations of the three reports (1, 2, 3). An attempt was made to select most promising topics that have not received sufficient emphasis and research support to date, as well as those areas most germane to military requirements. Topics not identified in this final report should not be considered any less deserving of emphasis and support within the ultimate goals of nuclear medicine. Rather, these conclusions suggest the most pertinent opportunities for future research within the context of the Army nuclear medicine program.

Recovery and Repair Mechanisms

It is clear from these reviews that emphasis for future research should be based upon the concept that radiation-sensitive tissues of the body have a remarkable capacity for recovery. This concept is of great significance and not generally recognized by the biomedical community. There is abundant evidence that if the patient can be kept alive for a critical period of time, recovery from radiation injury is possible.

Recent studies have shown that the capacity for repair is measurable and repair mechanisms operate in favor of recovery. The existence of repair mechanisms that can be manipulated underscores the importance of research on enhancement and stimulation of these mechanisms. Management of radiation injury in the sense of repair may be considered not only at the molecular level of cell constituents but also at levels of tissue and organ repair. The success that has been attained with supportive measures for bone marrow transplantation in terms of histocompatibility matching, and the use of immunosuppressive agents are outlined in the reports. The supportive techniques that allow repair and recovery to take place suggest that successful management of radiation injury is
highly probable (see Ref. 1, Section B, p 5; and Ref. 3, Sections A, p 23 and I, p 50).

Infection in Radiation Injury

Microbial proliferation, infection, and subsequent endotoxin or "septic" shock may occur as complications of radiation injury. Morbidity and sudden mortality are very often associated with uncontrolled infection and septic shock following radiation injury of the gastrointestinal tract. The control of septic shock would be a significant step in enhancing repair mechanisms and recovery following radiation exposure. The advances in hemorrhagic shock studies, microbiology, and immunology suggest that tolerance to endotoxin shock might be augmented by development of prophylactic measures that prevent this sequel to radiation injury. Techniques of this kind may have considerable military significance in management of radiation injuries (see Ref. 1, Section D, p 12; and Ref. 3, Sections F, p 43 and G, p 45).

Radiation-Induced Emesis

Radiation-induced emesis is of diagnostic significance. Any investigation that improves the control of emesis would be useful in radiation therapy and in preventing incapacitation of the man as a result of radiation. Understanding the mechanisms involved in radiation emesis would enhance our knowledge of radiation injury as well as contribute to an understanding of the fundamental aspects of emesis per se (see Ref. 2, Section B, p 22; and Ref. 3, Section H, p 47).

Biotransformation Following Radiation

Radiation-induced changes in transformation of nutrients, essential elements, and drugs within the body constitute factors of diagnostic significance that may enhance the therapy of radiation injury. Intestinal motility and malabsorption, alterations in therapeutic drug metabolism, changes in urinary constituents, blood biochemical changes such as protein-bound neutral hexoses, and enzyme-substrate interactions are involved in these biotransfor-
mation effects (see Ref. 2, Sections D, p 25; F, p 34; H, p 42; and I, p 47; and Ref. 3, Sections E, p 40; I, p 50; and J, p 55).

**Radiation-Induced Hematologic Changes**

Measurement of radiation-induced hematologic changes is universally recognized as the best method currently available for assessment of the degree of injury of the individual. This is the most active field of study and likely the most significant at the present time. More data on human exposure to radiation in terms of the hematologic changes are required for the future successful control of the radiation injured patient (see Ref. 1, Section A, p 4; Ref. 2, Section E, p 28; and Ref. 3, Section D, p 37).

**Utilization of Stem Cell Reserves**

Human bone marrow specimens measured in vitro in colony units provide an indicator of stem cell reserves of the individual and a clue to prognosis and eventual recovery. Further knowledge of the mechanism of stem cell recovery will permit significant augmentation of the repair process, but it is essential to know when and where the augmentation should be applied. The use of etiocholanolone as an assay mechanism to measure granulocyte kinetics is useful in elucidating the dynamics of the myelopoietic system in man. Potentially, this agent may be used both in the unexposed or radiation-injured man (see Ref. 1, Sections B, p 5; E, p 13; and Ref. 3, Sections D, p 37).

**Chromosome Aberrations**

The use of leukocyte chromosome aberrations to detect and predict the extent and severity of radiation-induced injury of the individual warrants additional study. Although intensively studied, at the present time, the method is not sufficiently reliable and practical for military use (see Ref. 2, Section J, p 49).
IV. REFERENCES CITED

1. Staff Report, Life Sciences Research Office
   A Study of the Immunologic Aspects of Therapy of Radiation Injury in the Soldier.
   Federation of American Societies for Experimental Biology, Bethesda, Maryland, 119 p (1968), AD 674262.

2. Staff Report, Life Sciences Research Office
   A Study of Early Radiation-Induced Biological Changes as Indicators of Radiation Injury.
   Federation of American Societies for Experimental Biology, Bethesda, Maryland, 214 p (1969), AD 685840.

3. Staff Report, Life Sciences Research Office
   A Study of the Metabolic Aspects of Therapy of Radiation Injury in the Soldier.
   Federation of American Societies for Experimental Biology, Bethesda, Maryland, 180 p (1969), AD ____.
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Staff Report, Life Sciences Research Office

October, 1969

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None


This is the final report on this contract. The research recommendations of the three technical reports, entitled A Study of the Immunologic Aspects of Therapy of Radiation Injury in the Soldier, AD 674262, A Study of Early Radiation-Induced Biological Changes as Indicators of Radiation Injury, AD 685840, and A Study of the Metabolic Aspects of Therapy of Radiation Injury in the Soldier, AD ____, are reviewed and specific suggestions are made because of their relevance to military requirements. Specifically identified are: mechanisms of recovery and repair after radiation injury; supportive measures for transplantation of bone marrow; the use of immunosuppressive agents; control of bacterial infections, septic shock, and radiation-induced emesis; biotransformation of drugs and essential nutrients; the need for more data on hematologic changes in man after radiation; and the use of new measures to estimate stem cell reserves and granulocyte kinetics.
Biological Effects of Radiation

Gastrointestinal Effects
Hematopoietic Changes
Immunologic Changes
Metabolic Aspects

Radiation Injury

Treatment of Radiation Injury