

August 2, 1968

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TENTATIVE AGENDA

Meeting Milton O. Lee Building

September 24-25, 1968, 9 a.m.

on

RCC1.950616.006

A STUDY OF THE METABOLIC ASPECTS OF THERAPY OF
RADIATION INJURY IN THE SOLDIER

Introductory Remarks

Gastrointestinal Symptomatology

Morphologic Response of the Gastrointestinal Tract

Alterations in the Flora of the Gastrointestinal Tract

Fluid and Electrolyte Changes in the Small Intestine

Gastrointestinal Transport of Nutrients and Other Essential Elements

Gastrointestinal and Hematopoietic Correlations

Metabolism of Drugs and Their Metabolites

Antibacterial Agents in Radiation Therapy

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File: 1303-11, Ionizing Radiation Injury, 68

A WORKING PAPER
ON
A STUDY OF THE METABOLIC ASPECTS OF THERAPY
OF RADIATION INJURY IN THE SOLDIER

This paper is neither a review nor a consensus. It is prepared as a basis for discussions to identify promising research that will improve the treatment of radiation injury. It is expected that omissions and errors in the statements will be corrected during the review of this subject to be held at the Milton O. Lee Building, Federation of American Societies for Experimental Biology, Bethesda, Maryland on September 24 and 25, 1968.

The Subject. Many of the early symptoms of the biological changes induced by radiation exposure are related to the abnormal gastrointestinal physiology and pathology. In addition, the absorption, distribution, utilization, and excretion of drugs and essential metabolites are modified. It is proposed that a study of these alterations in the body may permit better methods for treating radiation injury in the soldier.

Specific Aims. This study is being made to provide the Office of The Surgeon General of the Army with the most current information on the treatment of ionizing radiation injury in the soldier. The influence of radiation on the absorption, distribution, metabolism, and excretion of drugs, e.g. anesthetics and antibiotics, and other chemical substances, e.g. nutrients, will be considered. It would be useful to review the opportunities for research in these areas bringing together the views of knowledgeable scientists.

Application to Military Needs. Any consideration of the problems of therapy for a large number of radiation casualties imposes the determination of selection and rejection of candidates for treatment. In military situations the demands of the Army Medical Service must be based upon a realistic assessment of the degree of radiation injury of each individual. Any necessary modifications in the treatment regimen of injured irradiated soldiers is a paramount concern of the Army.

Background. The particular interest in the gastrointestinal syndrome and related metabolism stems from the recommendations stimulated during two previous study group sessions. A report entitled "A Study of the Immunologic Aspects of Therapy of Radiation Injury in the Soldier" has been completed and a second report entitled "A Study of the Early Radiation-Induced Biological Changes as Predictors of Radiation Injury in the Soldier" is in preparation.

A Study of the Metabolic Aspects of Therapy
of Radiation Injury in the Soldier

Metabolic alterations induced by radiation on the processes of absorption, distribution, and excretion of drugs and other substances is of paramount importance for gathering more information on radiation injury. There is a relative paucity of data correlating the fate of drugs with the post-irradiated state. Similarly, what alternate mechanism of action and/or routes of biotransformation occur if the irradiated individual experiences degrees of depressed liver and kidney function and other excretory and detoxifying mechanisms?

Radiation doses in excess of 2000 rads may be capable of producing the central nervous system syndrome in man and doses between 500 and 2000 rads will produce a severe gastrointestinal syndrome. Doses less than 500 rads will produce a severe hematopoietic syndrome and as the dose falls below 200 rads the gastrointestinal symptomatology will be practically absent (Cronkite, 1964).

Since there is little or no possibility of recovery from the central nervous system syndrome (>2000 rads) and doses capable of producing the severe gastrointestinal syndrome are sufficient to produce 100 percent mortality from the hematopoietic syndrome, one can predict the clinical picture in addition to mortality statistics even when there is satisfactory therapy for the severe gastrointestinal syndrome (Conrad, et. al., 1956). The whole-body irradiation dose of primary interest in the present study extends from approximately 100 to 1000 rads. In this range of radiation the "statistical individual" will have a good chance of survival. Patients exhibiting an injury syndrome equal to less than 100 rads will need minimal therapy while those exposed to 1000 rads or greater will experience the central nervous system syndrome and death. Therefore, the metabolic aspects of therapy, specifically relating to radiation exposed casualties, will be emphasized while highlighting the gastrointestinal syndrome.

The symptomatology characteristic of the gastrointestinal syndrome following lethal whole-body exposure originates in the malfunction of the intestinal mucosa and the myelocytic renewal network of the bone marrow matrix. The causation of the ensuing death cannot be assigned to either of the contributing tissue systems alone, but is the result of complex synergistic phenomena. The clinical manifestations prevalent following initiation of the gastrointestinal syndrome are anorexia, diarrhea, fever, and dehydration. Later developments include a loss of weight, probably resulting from a diminished intake of food and water, gastric retention, and impaired absorption (Bond, et. al., 1965).

Alterations in the physiology of the gastrointestinal tract after radiation exposure include impaired secretion and discontinued cell production, with symptoms of nausea and vomiting. The interval preceding

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death is characterized by uncontrollable diarrhea, protracted and continued vomiting, and exhaustion. The time span from irradiation to death is regularly 3 to 4 days. Animals irradiated in excess of a lethal whole-body dose usually die in shock due in part to fluid and electrolyte loss, infection, and nutritional impairment.

The vastness of the present problem can be more readily visualized if one focuses upon the complex physiological processes believed to be involved in the movement of a dietary constituent from the bowel lumen to the blood or lymph, as these may be inactivated or impaired by irradiation. Laster and Ingelfinger (1961) have tabulated these factors as follows:

1. Intraluminal digestion.
2. Binding of the substance to the surface of the intestinal columnar cell.
3. Transport across the luminal surface of the columnar cell membrane.
4. Intracellular metabolism and transcellular transport.
5. Release from the cell.
6. Migration across the basement membrane of the mucosal epithelium and through the lamina propria.
7. Penetration to blood or lymph capillaries.

The possibility of the soldier receiving multiple injuries in addition to radiation exposure in the event of a nuclear incident are indeed high. Therefore, the administration of various agents, for example anesthetics and antibiotics, to aid in diagnosis and treatment, may well react in an unknown manner which could be detrimental if proper doses and/or procedural changes or alterations were not implemented.

Proposed Plan of Study. The scope of the discussion will be broad. The invitees will be encouraged to actively participate in the discussions and present data or ideas originating from their own background of research and experience.

The principal concern will be to develop guidelines for future research that will be useful in advancing better techniques for treating radiation injury in the soldier.

A Study of the Metabolic Aspects of Therapy
of Radiation Injury in the Soldier

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- Conrad, R.A., E.P. Cronkite, G. Brecher, and C.P.A. Strome: Experimental Therapy of the Gastrointestinal Syndrome Produced by Lethal Doses of Ionizing Radiation. J. Appl. Physiol., 9, 227-233 (1956).
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RADIATION INJURY IN THE SOLDIER

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