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(NASA-CR-144439) STUDIES RELATIVE TO THE RADIOSENSITIVITY OF MAN: BASED ON RETROSPECTIVE EVALUATIONS OF THERAPEUTIC AND ACCIDENTAL TOTAL-BODY IRRADIATION Final Report (Oak Ridge Associated Universities) 93/52

N75-32733

Unclas 35077

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Study Completion Date: June 30, 1975

Report Completed: September 1, 1975

CHAPTER I

SUMMARY AND COMMENTS

This report compiles in a somewhat abbreviated fashion the bulk of the radiobiologic studies carried out with joint (AEC) ERDA and NASA support during the years 1964 to 1974 at the Medical Division of Oak Ridge Associated Universities. Their termination was directed by a decreased urgency on the part of NASA for broadly focused human radiobiologic data and on the part of ERDA for a redirection of ORAU's Medical Division efforts away from radiotherapy toward occupational medical problems that are being generated by the increasing demands for energy from non-nuclear sources.

The physiologic data generated by this study were similar in many ways to those previously observed in other medical radiobiologic experiences. They differed, however, in the methods of data acquisition and analysis. Instead of more conventional analytical methods, pulmonary impedance was recorded and quantitated as a measure of radiation-induced gastrointestinal distress and fatiguability.

While refinements in dose response related to gastrointestinal distress were accomplished we also found that through the use of Fourier analysis of pulmonary impedance waveform GI distress could easily be recognized and quantified even when the initial stages of nausea were below the subjects subjective level of recognition. Our results demonstrate that change in pulmonary impedance waveform closely parallel well-defined stages of GI distress, i.e., initial nausea, a progressive increase in nausea, and finally vomiting episodes. These stages of GI distress are

similar when induced chemically or by exposure to ionizing radiations although that induced by radiation is often sudden in onset and little nausea may proceed the actual emetic episode. Throughout the study period, pulmonary impedance waveform analysis never failed to recognize radiation-induced GI distress. Finally, these data demonstrate that real-time analysis of GI status with continuous data update can be accomplished using Fourier analysis of the pulmonary impedance waveform monitored from a remote, isolated environment.

Attempts to measure and quantify radiation-induced physical deconditioning using pulmonary impedance waveform analysis were not as clearly delineated as in the case of gastrointestinal distress. Pulmonary impedance measured before, during, and after controlled exercise stress (ergometry) correlated very well with periods of physical stress. Increased respiratory demand during submaximal exercise stress was accompanied by increased pulmonary impedance variance and within stress periods an increase or decrease in workload was accompanied by respective shifts in pulmonary impedance waveform. However, exposure to ionizing radiations resulted in amplified (increased) pulmonary impedance variance in over 80% of those humans studied although the ergometric workload remained unchanged. Thus, it would appear that exposure to radiation resulted in increased respiratory demand to perform at a constant, non-varying workload. Analysis of cardiac rate during controlled exercise stress in control volunteers and therapeutically likewise demonstrated increased response in over 70% of those patients who participated in the study. We believe that these amplified cardiac rates are indicative of diminished cardiovascular efficiency since workloads were non-varying

throughout each patient study period. Since some radiobiologists believe that venodilation and decreased venous compliance occur during early postirradiation periods (hours to several days) a pooling of blood in the venous system could account for increased cardiac rates and increased pulmonary impedance (increased mediastinal blood mass) postirradiation.

Efforts to model these data with those of other physical deconditioning experiments led to O_2 consumption measurements. Using bedrest as a typical model we found that a remarkable similarity exists between the decrement cause by 21 days of bedrest and exposure to 100 R irradiation. Unfortunately, we were able to study only one therapy patient in the time period between developing our capability for O_2 consumption measurement and the termination of the inpatient therapy program of our Division.

The important question remains unanswered as to whether or not radiation-induced physical deconditioning and that induced by bedrest (weightlessness) are additive. If they are the threshold radiation dose would be lowered as mission length was increased unless strong counter-measures were used to prevent or retard zero-G deconditioning. Another facet of this physiologic problem that remains to be considered is whether the level of physical training (vigorous in astronauts) can affect the degree of physical deconditioning. Some studies, needing to be confirmed, suggest that the well-conditioned individual may react more strongly and recover more slowly than a non-conditioned person. Our study of performance after radiation exposure using controlled exercise stress in physically trained and untrained ponies supports this suggestion in that the conditioned animals responded with a greater degree of decrement than the

unconditioned ones. The biochemical mechanisms underlying this phenomenon need to be studied without necessarily any reference to radiation exposure because of its general applicability to everyday life as well as to disease.

Our hematologic studies concerning the changing patterns of peripheral blood cell numbers after irradiation produced significant improvement in the quantitative aspects of the problem, particularly in defining the doubling times for human leukocytes in terms of repair kinetics.

The laboratory studies showed that rapid cell sizing techniques provided an additional parameter to hematologic studies that improved speed of quantitation and diagnosis. In polycythemia rubra vera, for example, changes in RBC morphology proved to be extremely useful in appraising the relative sizes of the iron and erythroblastic pools after radiation exposure. The unique observation of serum CPK rise after a large accidental radiation exposure in a man could not be confirmed in subsequent study in animals. Nevertheless, it led us to evaluate serum CPK levels before and after radiation exposure. The results of this study suggested that changes in muscle CPK as reflected in serum CPK levels may be related to fatigue and ability to perform physical work. This lead needs to be pursued further.

The simultaneous studies of human and mouse hemic responses to the same low dose rates and daily dose point up the threefold greater radiation resistance of mouse over man while suggesting what the basic lethal mechanisms may be for man under various conditions of low dose-rate irradiation as it approaches about one rad per day.

These studies are, of course, not to be considered definitive and without need for substantiation and extension. Only changing priorities places them, in our opinion, on "the back burner" for the moment.

R. C. Ricks

C. C. Luchbaugh

CHAPTER II

OBJECTIVES AND SCOPE

The objective of this study was to glean from human accidental and therapeutic irradiation case histories all pertinent radiobiologic information for reappraising and improving our knowledge of man's radiosensitivity. This study was cooperative with an ERDA supported study of total-body irradiation as a therapeutic modality for human blood dyscrasias. Where the AEC/ERDA study concerned itself with clinical aspects, this NASA study was directed toward extracting measurable information on biologic endpoints of radiation effects. Study areas that received major emphasis were: hematology, gastrointestinal side effects, dosimetry, and physiologic monitoring for performance decrement.

The need for more quantitative information on the effects of low radiation doses and low-dose-rate exposures was generated by NASA program planning that involved manned space flights. The plans for space laboratories expanded the number of persons at risk from the low doses of natural space radiation and included the possibility that an additional risk might arise from manmade radiation associated with the use of nuclear power generating systems. Our studies were intended to strengthen the confidence we presently have in our knowledge of man's ability to repair radiation damage so that ERDA, NRC, NASA, and other governmental agencies could establish nonoccupational permissible radiation exposure levels and continually review and update NASA occupational career limits for radiation exposure of astronauts as required for engineering design of advanced systems. While knowledge of the effects of larger radiation exposures at

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high and low dose rates is growing substantially, it is as yet inadequate for deriving dose/response equations that allow high-confidence predictions of the amount of acute and chronic damage that can be expected from small doses to the total body or its parts. Extrapolations that estimate effects from extremely low exposures accumulated over long periods of time on the basis of studies of high exposure sustained in short periods of time, derive all of their justification from radiobiological studies of lower mammals (chiefly mice). Some observations indicate that after a 5 to 10 rad dose, for example, the probability of a serious consequence occurring in an individual's lifetime is so low that a threshold concept is valid for practical regulatory purposes. Confidence was limited on previous conjectures concerning the levels of radiation that could cause detrimental human reactions. The inherent difficulties in evaluating voluminous clinical data containing numerous variables however have now been largely overcome. Modern research methods using computers with large memory storage capacity have enabled us to construct a human radiation injury data bank containing clinical data from more than 3000 human total body irradiation exposures in the United States. These charts have been extracted, encoded, and were analyzed by modern mathematical electronic computer methods. The Oak Ridge Associated Universities (ORAU) patient studies obtained in a radiotherapeutic program since 1957 and additional human studies (~ 3000 cases) obtained from other hospital centers with similar studies were incorporated into a study to determine dose relationships in man for anorexia, nausea, vomiting, diarrhea, fatigue, weight loss, fever, erythema, epilation, lymphopenia, granulocytopenia, anemia, thrombocytopenia, cytogenetic damage, decreased

resistance to infection, decreased antibody synthesis, increased aging, and carcinogenesis. The values were assessed for degree of clinical and mathematical confidence to permit their use in predicing man's reaction to the ambient radiations of space, and to direct further clinical exploration on the effect of ionizing radiation upon cancerous and normal processes.

Additionally, there were multiple reasons for this study overall. Therapeutic total-body irradiation is efficacious in controlling some cases of leukemia and lymphoma and ameliorating symptoms in others. The possibility that low dose rates may favor repair of normal tissue in contrast to malignant processes had not been evaluated in the present modern era of radiotherapy and radiobiology; we proposed to test this hypothesis with a radiation facility producing an isotropic flux of uniform radiation giving low rates of exposure. This irradiator was large enough for patients to live in comfortably for several weeks. Because of expanding programs in nuclear energy and space exploration, the need was more acute than ever for data derived directly by observation of man's reaction rather than assumed from animal studies. The retrospective accumulation of such data as was available showed that the old data suffered from lack of modern dosimetry, tissue depth dose knowledge, biased recording of symptomatology, and incomplete and inaccurate records. Finally, these additional unbiased clinical observations were sorely needed to defend existing environmental and occupational radiation exposure constraints from attack by well-meaning, but impractical, theorists.

CHAPTER VI

A. List of Reports and Publications Generated by Program

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CHAPTER VII

APPENDIX

A. List of Cooperating Institutions in Retrospective Studies

Hospitals Participating in Study

Albert Einstein Medical Center
Baylor University: Jefferson Davis Hospital
V.A. Hospital at Houston
Texas Medical Center
Burge Protestant Hospital
Cincinnati General Hospital
City of Hope Medical Center
Charity Hospital
Colorado General Hospital
Ellis Fischel State Cancer Center
Franklin Hospital
Jefferson Medical College
Long Beach Community Hospital
Los Alamos Hospital
Mary Imogene Bassett Hospital
Massachusetts General (McG) (LR)
M.D. Anderson Hospital
Medical College of Virginia
New York Memorial Hospital (CH) (N)
Oak Ridge Associated Universities Medical Division
Penrose Cancer Clinic
Peter Bent Brigham Hospital
Portland: Emanuel Hospital
Dr. Hyman's Clinic
Portland Medical Center
Princess Margaret Hospital
Providence Hospital
Rhode Island Accident
Spokane: Deaconess Hospital
Rockwood Clinic
Sacred Heart Hospital
Milo Harris Clinic
Swedish Hospital
Temple University
Thomas M. Fitzgerald Mercy
U.S. Naval Hospital
U. of California Medical School, S.F.
U. of Michigan
U. of Washington
V.A. Hospital at Denver
V.A. Hospital at Long Beach
V.A. Hospital at New Orleans
Vancouver: British Columbia Cancer Institute
Royal Columbian Hospital
Vancouver General Hospital
White Memorial Medical Center

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B. List of Contributing Medical Division Staff Members

Medical	Paramedical	Computer
E. G. Ammerman	E. A. Anderson	Pauletta Aaron
G. A. Andrews	Normal Asbury	Thomas Akin
Edward Bird	Mildred Bailey	Robert Beaver
F.V. Comas	Frances Banner	Linda Brown
C. L. Edwards	T. R. Barclay	Ed Frome
Dieter Emrich	W. L. Beck	Arthur Glaster
Kong-oo Goh	Per-Erik Bergner	Martha Hansard
F. A. Goswitz	Sarah Cecil	Janice Ishee
K. F. Hubner	Carol Chabot	Earl McDow
R. M. Kniseley	Kay Clayton	Daniel McFaddin
C. C. Lushbaugh	Martha Clevenger	Richard Queener
B. Nelson	R. J. Cloutier	Mona Smith
Etna Palmer	Shirley Colyer	Jimmie Sanders
Ryosaku Tanida	Lydia Corrill	
M. Van Woert	J. T. Crockett	
H. A. Vodopick	Evelyn Cunningham	
	Glenda Fritts	
	Dorothy Gaither	
Lucy Amburn	W. D. Gibbs	
Margie Bagley	J. H. Harmon	
Carol Bingham	Joyce Hewins	
Margaret Blackburn	Wanda Hodge	
Ervin Bobo	Harold Hodges	
Helen Brinker	Elizabeth Holloway	
Ruth Capshaw	Julia Hopper	
James Cozart	Mildred Hyp	
Mary Nell Craig	Gretchen Humason	
John Dean	Jane Kimbro	
Thelma Eden	Barbara LeClerc	
Eria Hartman	Kathryn Lore	
June Geldmeier	Willa Fae Loveday	
Mable Helton	Dorothy Lushbaugh	
Rita Holt	Kathryn McCulloch	
Rufus Jackson	Maryrose McGown	
Earl Jacobs	Jean McIntyre	
Sandra Landry	A. C. Morris	
Martha Laxton	Francine Pennington	
Bedford Mayott	Evalyn Repplinger	
Barbara Nance	Robert Ricks	
Benua Pack	Emily Roemer	
Garfield Porter	Elizabeth Rupp	
Naomi Presnell	Billie Ryan	
Mary Rogers	Evelyn Sipe	
Bernice Salley	Vivian Smith	
Lillie Simmons	T. R. Stokes	
Marilyn Smith	Katherine Stubbs	
Elaine Stoetzel	Mary Thomas	
Mary Sutliff	Mary Watkins	
Eugene Weaver	Allen Webb	
Martha Williams	Sondra Wilson	
Lillie Woods		