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MAILING ADDRESS
RADIOISOTOPE LABORATORY
CINCINNATI GENERAL HOSPITAL
CINCINNATI 29, OHIO

May 8, 1961

Project No. GB-0

RESEARCH PROPOSAL FOR SUB-TASK IN
NUCLEAR WEAPONS EFFECTS RESEARCH

- Item 1. Weapons Effects Board Number and Title. WEB No. 03.009 *Whole Body R*
- Item 2. DASA CMAS Code. A 3c *Biochemical - Medical Aspects of Dosing R*
Effects of Total - or Partial Body Irradiation
- Item 3. Directing Agency. Defense Atomic Support Agency
- Item 4. Contractor. Department of Radiology, University of Cincinnati College of Medicine
- Item 5. Contract Number. DA-49-146-XZ-029
- Item 6. Estimated Funding (Thousands \$)

FY 62	35
FY 63	40
FY 64	45
FY 65	45
FY 66	50
- Item 7. Estimated Completion Date. 1967

AFR1.940913.003

Item 8. Justification. In handling individuals or large groups of people exposed to nuclear radiations in high doses, it is necessary to know much more concerning their metabolic changes. At present the chance of survival at dose level above 600 rad appears to be minimal. By means of detailed studies of change at levels of 50 - 200r it may be possible to find metabolic changes which will help to prolong survival at higher dose ranges. The biochemical and immunological changes within the human during the first several weeks post exposure have received little attention. The only estimates of dose of radiation received are at present provided by personnel dosimeters, film badges and serial blood counts. The dosimeters may not be available or of the correct range. The film badges require special and difficult laboratory processing. Blood counts are sometimes difficult to do especially for masses of people. Little is known of nutritional requirements of exposed individuals.

The studies being carried out seek to find new biochemical and immunological tests to evaluate damage. The detailed clinical studies will provide new data useful in the prognosis and therapy of such individuals.

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Project No. GB-029

Item 9. Brief Proposal and Objective.

A. Brief:

The problem is that of obtaining detailed data of the clinical and laboratory findings in humans who have received total body radiation therapy in order to obtain new diagnostic tests and to obtain information to aid in their management.

B. Approach:

These studies are designed to obtain new information about the metabolic effects of total body and partial body irradiation so as to have a better understanding of the acute and subacute effects of irradiation in the human.

The initial studies are pointed toward the elucidation of biological indicators of radiation effects in humans. The major parameters being investigated at present are urinary aminoaciduria and alterations in immunological patterns. Certain other parameters such as creatine and creatinine excretion and hematological effects are also being followed.

The long term program envisions carrying out the various observations at dose levels of 100 rad and gradually increasing the dose to 150, 200, 250 and 300 rad. Eventually doses up to 600 rad are anticipated. Also comparison of effects of radiomimetic drugs with total body radiation will be studied. Comparison of effects of total vs. partial body radiation will be studied.

Selection of Patients.

Patients must be in relatively good nutritional status, i.e., able to maintain their body weight. Women with an active menstrual cycle are usually not utilized because of variations in aminoaciduria with menstruation. The patients usually have normal hematological values.

During the first year only patients with metastatic malignancy were selected. It now appears feasible to include cancer patients who do not necessarily have distant metastases.

Technique of Study.

For an individual entering the study, his program is divided into two phases: A pre-irradiation (control) period of about 2 weeks and a post irradiation period of 4 - 5 weeks.

The pre-irradiation period allows for the most part at least six determinations of each test to be done. These observations are listed in Table I.

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Item 9. Approach (Technique of study-- continued)

Table I

PRE AND POST IRRADIATION OBSERVATIONS

1. Complete history and physical examination
2. Temperature, pulse, respiration
3. Body weight
4. Urine
 - a) Volume
 - b) Routine urinalysis
 - c) Creatine and creatinine
 - d) Chromatography for aminoacids
5. Hematology - Hg; RBC; WBC; Differential; Hematocrit; Platelets; Reticulocytes; Erythrocyte sedimentation rate
6. Fluid intake
7. Medications - Fluids, Antibiotics; Steroids; Narcotics
8. Blood electrophoresis; immunoelectrophoresis; complement fixation tests
9. Blood total proteins; urea nitrogen; sodium potassium; chlorides; CO₂ ; creatinine

All data is reviewed by the medical group prior to irradiation to be certain that the values are within normal limits and that there are no glaring technical errors. Several sham irradiations are given to permit accurate dosimetry. The patient is told that he is to receive treatment to help his sickness. There is no discussion of subjective reactions resulting from the treatment. Other physicians, nurses and ward personnel are instructed not to discuss these aspects with the patient.

The patient is then given total body irradiation. All of the tests are then performed on the following days after exposure: 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36.

It would be desirable to have each patient on a metabolic ward but at present this facility is only in the planning phase. When it becomes operative, one bed will be allotted for this program. Meanwhile through the cooperation of the Department of Psychiatry a bed has been made available on the Psychosomatic Ward of the hospital. In addition to the studies described above, the patient is given a careful psychiatric evaluation and more individual attention than is possible on the Tumor Ward. The environment is far more attractive and there are no other patients receiving radiation therapy with whom the patient can exchange experiences. Thus the emotional and psychometric response of the patient can be better evaluated in this milieu.

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Item 9. B. Approach (continued)

Analysis of Data

The design of the study at present is such that the patient serves as his own control. Since the radiosensitivity of the underlying neoplasm is either known or determinable, it will also be possible to make comparison of patients with radioresistant vs. radiosensitive tumors.

The collection of data follows with some modifications the plan described by Thoma and Wald (J. Occup. Med. 1:420-447, 1959) and described in Tables VI and VII of Saenger's paper (Am. J. Roentgenol, Rad. Therapy and Nuc. Med. 84:715-728, 1960).

All data are recorded on score sheets (5 at present) for transfer to IBM cards in the usual way. It thus will be possible to perform any type of analysis either in our laboratory or elsewhere. These sheets can be readily adapted to other similar studies to facilitate comparison of raw data between institutions.

The major difficulties to be overcome are as follows:

The appropriate immunological techniques are not well understood. At present we utilize the standard paper electrophoresis of blood proteins which is insensitive. Initial studies with immunoelectrophoresis using polyvalent anti-human sera from the goat and horse provided patterns whose interpretation was too complex to be useful. This aspect of the work is being reoriented toward the use of univalent sera.

Techniques for identification of breakdown products of DNA by paper chromatography are just being developed and will be improved over the next several years.

C. Related Sub-Tasks.

The projects of Drs. James Nickson at Memorial Hospital, New York; Dr. Vincent Collins at Baylor University, Houston, Texas; and of the group at the Naval Medical Center, Bethesda, Maryland, are investigating other aspects from somewhat similar view points.

There is close cooperation between our laboratory and that of Dr. A. Luzzi at the Army Medical Research Laboratory, Ft. Knox, Ky. Dr. Luzzio is working on the development of complement fixation tests as an immunological technique utilizing in part blood from patients irradiated by us.

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Item 9. D. Other Information.

The project is supported by a team composed of qualified investigators from several departments of the University of Cincinnati College of Medicine. The project director is E. L. Saenger, M.D., Associate Clinical Professor of Radiology and Director of the Radioisotope Laboratory.

All physical aspects of the study such as dosimetry and supervision of certain laboratory studies is under the direction of J.G. Kereiakes, Ph.D., Assistant Professor of Radiology and Director of Physics, Department of Radiology. Total body therapy and the partial body irradiation is directed by H. Perry, M.D., Assistant Professor of Radiology assisted by H. Horwitz, M.D., Assistant Professor of Radiology. Drs. Perry and Horwitz are also concerned with clinical care of the patient.

The selection of patients, their workup, clinical care and supervision of many of the laboratory studies is under the direction of B.I. Friedman, M.D., Assistant Clinical Professor of Medicine and T. Wright, M.D. Instructor in Medicine.

Aminoaciduria and some preliminary studies of purine and pyrimidine metabolism are carried out by H. Berry, M.S., Research Associate in Pediatrics and G. Guest, M.D., Research Professor of Pediatrics.

The design of the study and analysis of data is directed by T. Sterling, Ph.D., Assistant Professor of Preventive Medicine.

Certain aspects of patient care and preliminary studies of some psychometric tests administered before and after irradiation are directed by D. Ross, M.D., Associate Professor of Psychiatry and S. Kaplan, M.D., Assistant Professor of Psychiatry.

This study is therefore a cooperative one of the Departments of Radiology, Internal Medicine, Pediatrics, Psychiatry and Preventive Medicine.

A new metabolic ward will be built within the next several years. At that time these study patients will be assigned to that ward.

E. Background History and Progress.

(1) The background of this project is presented as follows: Several reports have described changes in nitrogen metabolism following irradiation. All have shown increase in nitrogen excretion following total body irradiation to various laboratory animals. Mefford and Martens have studied aminoaciduria by paper chromatography in rats. Katz and Hasterlik, and Hempelmann, Lisco and Hoffman have studied aminoaciduria following radiation in humans by means of paper chromatography. Hempelmann, et al, found aminoaciduria in 3 of their 9 cases.

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Item 9. E. Background History and Progress. (1 continued)

Katz and Hasterlik reported increases of as high as ten times normal values of total daily aminoacid excretion in 4 patients. Quantities of individual aminoacids excreted varied from 2 - 20 times normal values. Abnormal values were found as early as 12 hours following exposure, and increased levels persisted for as long as 5 months. No direct quantitative relation to radiation dose could be established.

These findings suggest that aminoaciduria may serve as an indicator of the biological response of humans to irradiation. The reports of aminoaciduria in humans have described the findings in individuals exposed in reactor accidents and no control measurements were possible. Studies of 5 patients exposed at the Y-12 accident at Oak Ridge in June 1958 showed elevated excretion of beta aminoisobutyric acid with levels related to the total dose received by the individual.

(2) The project was initiated as of February 1, 1960 and only the first year of work has been completed. In that time six patients have been studied thoroughly and the annual report is being compiled at present. It is too early to define progress in terms of the final goals of the proposal but the investigative program for each patient is functioning quite smoothly and results of the first year will be submitted in approximately two months.

F. Future Plans.

During the next two years patients will be studied as outlined above. As the various tests are evaluated, certain non contributory ones will be dropped.

Over a five year period plans include the development of the following aspects:

1. Studies of nucleic acid metabolism before and after irradiation utilizing appropriately tagged intermediate metabolites (using C-14 or H-3).
2. Intensification of newer immunological techniques.
3. Chromosome studies of white blood cells.
4. Newer tests of clotting mechanisms.

The entire program will be accelerated by the rebuilding of the General Hospital for which \$17.5 million have been voted. Our laboratory facilities and capabilities will be greatly expanded.

G. References.

Additional information may be obtained from Dr. Eugene L. Saenger, Radioisotope Laboratory, Cincinnati General Hospital, Cincinnati 29, Ohio