716487

Research Project:

THE STUDY OF IRRADIATION EFFECTS ON THE HUMAN TESTIS: INCLUDING HISTOLOGIC, CHROMOSOMAL AND HORMONAL ASPECTS

Request for Renewal

of

AEC Contract #AT(45-1)-1781

1968-69

Submitted By

C. Alvin Paulsen, M.D.
Associate Professor of Medicine
University of Washington School of Medicine
Seattle, Washington

Program Director

Authorized Signature
University of Washington

3003085

I. TITLE OF PROJECT

Effect of Irradiation on Human Testis: Changes in Spermatogenesis, Chromosomal Morphology, Leydig Cell Function and Pituitary-Gonadal Interrelationships as a Function of Radiation Dose.

II. INSTITUTION SPONSORING INVESTIGATION

University of Washington School of Medicine, Department of Medicine

III. SCIENTIFIC SCOPE OF PROPOSED RESEARCH

A. Principal Aims: 1) To relate radiation dosage to changes in gonadal function, 2) to utilize the radiation gonadal changes as the means for studying anterior pituitary interrelationships, 3) to explore therapeutic and medical protective measures with respect to gonadal irradiation, 4) to explore our current concepts concerning radiation dosage expressed in physical terms and their relation to biologic effects.

B. Method of Procedure:

1. Research Subjects: Our initial proposal was reviewed by the Clinical Investigation Committee of the University of Washington. As mentioned previously, our proposal was considered to be appropriate with respect to the rights of our research subjects and to our procedural details. Before proceeding with the neutron aspect of our project, we resubmitted our proposal for review. This phase of our work was passed on favorably but contingent upon approval by the University's Isotope Safety Committee. Subsequently we appeared before this committee and received approval contingent upon our dosimetry data. These data were completed by the Radiation Physics department of Battelle-Northwest Laboratories under the supervision of Dr. W. Wilson. We submitted these data (see Progress Report) to the Isotope Safety Committee for evaluation. At the present time the Isotope Safety Committee is re-evaluating the entire scope of our project. They have reconsidered the hazards vs. the benefits of our project in light of present day concern over human experimentation. Although their deliberations are not final, we have received word that we will be able to proceed with additional modifying recommendations. These recommendations should not restrict our ability to determine the RBE for human spermatogenesis. Indeed, since we are now concentrating our efforts on the lower portion of the dose response curve, we will reduce the theoretical hazards of our study to an acceptable level.

All neutron exposures will be carried out on subjects who have not been previously biopsied. Adequate seminal fluid studies will be conducted during the control period as well as urinary FSH excretion assays and plasma testosterone determinations.

2. X-Ray Dosage: At the present time we have dose-related seminal fluid data on 20 men. The other 28 men who have been irradiated were used for testicular biopsy studies or chromosomal investigation. We consider it important to extend our sperm count study at the following dose levels in order to construct an appropriate dose-response curve: 50r, 15r and 7.5r. It may be necessary to make additional observations at the 30r level (see Progress Report for up-to-date results).

3. Neutron Dosage: We plan to utilize 2.5 and 14.5 MEV energy levels. Dose levels will include 0.5, 1.0 and 2.0 rads for the lower energy levels, and 2.5, 5.0, 10 and possible 20 rads for the higher energy levels.

4. Histologic "Scoring:" Correlation of specific germ cell counts with specific urinary FSH titers demonstrates that there is no direct relationship. For example, if Ad and Ap spermatogonia scores are related to FSH titers, no definite pattern exists as to predicting the presence of elevated FSH levels when the Ad and Ap spermatogonia are significantly reduced in numbers. This holds true for RLZ spermatocytes and Pachytene spermatocytes as well. These data suggest that the control of FSH secretion is not related to the numbers of any given germ cell type. (See Progress Report for further details.)

5. Hormonal Assays: The establishment of a radioimmunoassay for serum luteinizing hormone levels has enabled us to extend our observations regarding the possible effect of irradiation on Leydig cell function. Presently we have data before and after irradiation in six men. No change in serum HLH levels has been noted. These data support the observations on plasma testosterone titers which we previously have accumulated. Thus acute x-ray exposure up to doses of 100r does not significantly alter Leydig cell function.

6. Sperm Motility, Viability and Morphology: Extensive serial observations of fresh seminal fluid specimens have failed to demonstrate any significant departure from the correlation of sperm motility and viability to sperm concentration. Changes in sperm morphology, particularly with respect to amorphous forms, are at variance with sperm concentration but for practical purposes do not afford one a more sensitive parameter in evaluating the effect of irradiation on spermatogenesis.

7. Electron Microscopy: This year we conducted preliminary studies as to ultrastructure changes following x-ray irradiation. Two subjects were irradiated and then biopsied within 45 minutes. One received 100r and the other 400r. No changes were observed in the subject receiving 100r. On the other hand, definite ultrastructure changes were encountered in the patient who was exposed to 400r. These were primarily confined to alterations in the cytoplasmic cellular membranes of the Sertoli cell and type A spermatogonia. In view of these findings, it will be important to extend our observations to additional patients. If further studies confirm our preliminary findings, it would suggest that cytoplasmic alterations precede nuclear changes following irradiation.

IV. SCIENTIFIC PERSONNEL

C. Alvin Paulsen, M.D.
Walt Wilson, Ph.D.
Kenneth Swinth, M.S.
Les Braby, M.S.
Duane Espeland, M.D.
Richard Sherins, M.D.
John Leonard, M.D.

Curriculum vitae for Dr. Richard Sherins and Dr. John Leonard are enclosed. Dr. Sherins has been working with us for the past year (since July 1, 1967). Dr. Leonard will join us this July. We indicated previously that Dr. Werrbach would join our group this past year. His plans were changed and he is with another division of endocrinology at the University.

V. OTHER PERSONNEL

Donald J. Moore, B.A., and Mrs. Marian Ursic continue to work on this project as before. Mrs. Hueckel, who has devoted her attention to the chromosomal studies, will continue her work but this aspect will receive support from our NIH grants.

VI. RELATED FINANCIAL ASSISTANCE

The project director has the following financial support from NIH for various aspects of related studies.

AM 05436-08: Pituitary-Gonadal Interrelationship, $39,806, 9/1/68 to 8/31/69
T1 AM 5161-10: Training Grant in Endocrinology, $32,082, 7/1/68 to 6/30/69

VII. MATERIALS, EQUIPMENT AND FACILITIES

A. All materials, equipment and facilities are the same as listed in the 1967 project renewal request except for the equipment acquired during this year. The new equipment is listed in the progress report.

B. Justification of equipment to be procured:

1. Replacement parts for neutron generator and maintenance: To insure proper operation of the neutron generator we have requested funds for replacement targets and overhauling of the ion pump as well as for necessary replacement of miscellaneous parts as the need arises.

2. Rental of G. E. Maximar x-ray apparatus: This item will continue to be leased for this next year.

VIII. TRAVEL AND OTHER ITEMS

The amount requested for travel represents our requirements based on the experience of previous years.

To facilitate the documentation of our data for publication and the processing of our photomicrography film, funds are requested to cover the estimated cost of photomicrographs, charts, and illustrations.

Salary increases as listed are the result of a University-wide salary scale increase. Vasectomy costs will increase as more volunteers complete participation in the program.

Because of the need for insuring proper operation of the Coulter counter and for having available substitute equipment during breakdown or maintenance periods, a service contract was obtained through Coulter Electronics during the current year. Renewal of this contract is planned.

Since Dr. Vilar has all the major equipment for performing the electron microscopy studies, the amount requested represents a minimal expenditure for the amount of data that will be derived.

PRIVACY ACT MATERIAL REMOVED

ESTIMATED EXPENDITURES

June 1, 1967 - July 31, 1968

Salaries

Salary costs

Consumable supplies

Equipment
- Vacuum gate valve for neutron generator
- Vacuum oven and two hi-vacuum evaporators
- Monroe laboratory computer
- Miscellaneous equipment, under $100
- Pro-File cabinet for laboratory data

Travel

Volunteer stipends and contract physician

Miscellaneous expense
- Maximar rental
- Communications
- Coulter maintenance contract
- Specimen shipping costs
- Photographic and artist expense
- Repair of laboratory equipment

Indirect costs, at 21.5% of salaries and wages

TOTAL CONTRACT COSTS • 94,825

3003089

PRIVACY ACT MATERIAL REMOVED

Contract # AT(45-1)-1781

Proposed Budget
Contract Year 1968-69

SALARIES

a) Professional -- C. Alvin Paulsen, Program Director (25%) U of W *
Research Assistant Professor, Kathleen O'Keefe, 50% time

b) Non-professional
Technician III, Donald Moore, full-time
Technician II, Constance Lowe, full-time
Technician II, Shirley Jokisch, 30% time
Technician II, Florida Flor, 25% time
Technician I, Margaret Couture, full-time 3 mos.
Lab Helper I, Annie Washington, 60% time
Secretary III, 25% time
Statistical Assistant, Marian Ursic, 85% time
Heilund $250/month

SALARY COSTS: State retirement (or TIAA premiums), FICA, Medical Aid and Life/Health Insurance premiums

SUPPLIES

a) Laboratory
Glassware
Reagents
Supplies for radioimmunoassay, including I^{131}, I^{125}
Assay rats: 1800 immature female rats @1.10
Supplies for Coulter counter (saponin, replacement tubes, saline, etc.)
Supplies for Dr. Gandy
Acetic H_3 anhydride, 1200 mc
20 β-hydroxy steroid dehydrogenase, 50 mg
Supplies for Dr. Vilar
Photographic supplies
Grids, etc., for electron microscope
Solvents, plastic, osmium tetroxide

b) Office

EQUIPMENT

a) Replacement items and maintenance of neutron generator
Targets
Deuterium gas
Miscellaneous parts and tools
Ion pump, refurbishing

TRAVEL

a) Two people, 2 times monthly to Walla Walla
b) Four members of research project to scientific meetings

VOLUNTEER STIPENDS

a) 100 inmate volunteers @10.00/month
b) 80 biopsies/year @15.00
c) 20 vasectomies @100.00/inmate and 60.00 contract physician

MISCELLANEOUS

a) Shipping specimen containers to and from Walla Walla
b) Photomicrographs, charts, illustrations
c) Rental, G.E. Maximar
d) Service contract for Coulter Counter
e) Communications costs
f) Vivarium costs

INDIRECT COSTS: 21.5% of salaries and wages

* See following page

TOTAL 90,000

PRIVACY ACT MATERIAL REMOVED

CONTRACT NUMBER AT(45-1)-1781
Contract Year 1968-69

University Contributed Effort

C. Alvin Paulsen
Program Director

25% Time, 12 mos.

Employee Benefits

Indirect Costs @ 21.5% Salaries

University of Washington Contribution

It is not intended that this University of Washington Contribution be included in the proration of costs.

3003091

CURRICULUM VITAE

Name: Richard Joseph Sherins

Born: 1937, Brooklyn, New York

Education and Training:
University of California at Los Angeles, A.B., 1959
University of California Medical School, San Francisco, M.D., 1963
V. A. Hospital, Los Angeles, Internship in Medicine, 1963-64
UCLA Medical Center, Los Angeles, Residency in Medicine, 1964-66, Chief Resident, 1966-67
USPHS Hospital, Seattle, Fellow in Endocrinology, 1967-
University of Washington School of Medicine, Seattle, Senior Fellow in Medicine, 1967-

Name: John Michael Leonard

Born: 1939, Belview, Minnesota

Education and Training:
St. John's University, Collegeville, Minn., B.S., [illegible]
University of Minnesota, Minneapolis, M.D., 1964
Rotating Internship, Harbor General Hospital, Torrance, Calif., 1964-65
Residency in Medicine, Harbor General Hospital, Torrance, Calif., 1965-68
University of Washington School of Medicine, Seattle, Senior Fellow in Medicine, 1968-

3003092

REPOSITORY: DOE-RICHLAND
COLLECTION: GSS HUMAN TEST SUBJECTS STUDIES
PRISONER STUDY

BOX: 046264

FOLDER: 1780 - HELLER PACIFIC NW RES. FOUNDA.

ASSIGNED NUMBER: RLHTS 94-0059

3003092-A