716479

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

1969-1970

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

Submitted by

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

3003056

Program Director

Authorized Signature
University of Washington

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.

B. Method of Procedure:

1) Neutron Exposure: Although the University of Washington Radiation Safety Committee approved our proposal to expose 20 men to neutron irradiation (limit of 15 rads), three committees that pass on human experimentation at the University of Washington (University Hospital Clinical Investigation Committee, Biomedical Sciences Review Committee, and the Human Subjects Policy Board) judged that the hazards of the experiment were greater than the possible benefits to society. As a result, the human neutron studies will not be carried out in the foreseeable future.

We therefore propose to move our neutron generator from the Washington State Penitentiary to Hanford for the purpose of determining the effects of neutron and X-ray irradiation on spermatogenesis in a suitable animal such as the goat. The experimental design and background material for these studies will be detailed in a supplementary proposal. That is after consultation with Drs. Clarke and Alpen, and other interested parties at Hanford.

2) X-ray Exposure:

a. Introduction: We are prepared to initiate the last phase of our X-ray studies. As mentioned in our Comprehensive Progress

Report (April 1969), Dr. Todd Thorslund has developed a satisfactory model for analyzing our sperm count data. With respect to the first part, or regression (damage) portion of the curve, we have observations on 28 men who did not have a post-irradiation testicular biopsy within a period of 180 days following exposure to X-ray doses ranging from 7.5 to 400 rads. At 210 days post-irradiation, we have seminal fluid observations on 21 men (see Page 11, Progress Report 1969). By means of a computer program, we have estimated the ED_{50} and its 95% confidence limits for that dose which results in sperm counts of less than 5 million per cc, as well as for that dose which results in azoospermia (see Page 13, 1969 Progress Report).

These estimates can be considerably improved by obtaining observations on only 12 additional men. Thirty (30) rads would be used as the X-ray dose for these additional men. Dr. Thorslund has calculated that by providing these additional data, the 95% confidence limits will be narrowed to $\pm$ 6 r for the endpoint of "less than 5 million per cc", and $\pm$ 18 r for the endpoint of "azoospermia." Information of this precision with respect to the dose-related irradiation effects in human beings, does not exist.

Furthermore, our proposed studies will increase the power of the statistical test for evaluating the applicability of the postulated "one-hit curve theory." This hypothesis has been suggested as a possible mechanism for decreased spermatogenesis following exposure to ionizing irradiation (see Pages 7 and 8 of 1969 Progress Report).

Simultaneous with the exposure of 12 additional men to 30 rads, we propose to evaluate the ability of testosterone administration to alter the radiation damage pattern manifest by the testis. Since testosterone administration in suitable doses (e.g., 200 mg testosterone enanthate/wk) suppresses spermatogenesis by inhibiting pituitary gonadotrophin secretion, mitotic and meiotic activity in the germ cells practically ceases. If the administration of testosterone is carried out for circa 16 weeks or longer, the germ cell population within the seminiferous tubules decreases markedly, leaving only a few spermatogonia and an occasional more advanced germ cell. Therefore from a theoretical point of view, testosterone administration prior to irradiation and for 3 to 4 weeks following irradiation, should afford protection to the stem-cells. This should enable the testis to recover much more rapidly and <u>in fact</u> recover at that rate it would if only testosterone had been administered.

b. <u>Scientific Background</u>: With respect to the beneficial effects of testosterone administration, Joël in 1942 published the results of his studies in rats, in "Zur Wirkung des Testosteronpropionats auf die Regeneration des rontgengeschadigten Hodens" (<u>Endocrinologie</u>,

Bd. 24 Heft, May 6, 1942). He exposed albino rats (160-180 gm) to either 360 r or 450 r of 180 Kv X-ray. Some of the rats received, in addition, testosterone in total dose of 30 mg over the next 3 or 4 weeks, while others received only the X-ray. Histologic observations were made at 25 and 50 days post-irradiation. Of extreme interest was the observation that the testosterone-treated X-ray-exposed rats had virtually recovered by 50 days, while the X-ray control rats remained depopulated insofar as the germinal epithelium was concerned. To our knowledge, Joël's studies have never been tested in the human being.

c. Experimental Design: The primary purpose of the design is to increase the amount of "information" available about the damage phase of the dose-response curve for sperm production. The term, "information", is used in its technical sense which is defined as "minus the expected value of the second derivative of the maximum liklihood equation." In our case, this may be written:

$$-E\left\{\frac{d^2L}{d^2\beta}\right\} = I(\beta) = \sum_{i=1}^{k} \frac{n_i d_i^2}{(e^{\beta d_i} - 1)}$$

where d_i is the ith dose, k is the number of dose levels, n_i is the number of subjects exposed to the ith dose, and β is the defining parameter (sensitive volume) of the dose response curve.

It can be shown that the maximum amount of information about the parameter β, and thus the ED_{50}, is obtained by exposing all subjects to the dose level $d_i = 1.594/\beta$.

Using our preliminary estimates of β, this would mean that for the endpoint ≤ 5 million per cc, the optimal dose to use would be approximately 30 rads. If twelve (12) more subjects are exposed to 30 rads, then the amount of information generated would be about equal to that we previously obtained for the endpoint ≤ 5 million per cc, and about 2/3 as much as we previously obtained for the endpoint azoospermia.

Furthermore, this new material can be used as a radiation control for the proposed testosterone protection mechanism experiment. Additional hormonal, chromosomal, and histologic measurements would be obtained to take maximum advantage of the unique "before" and "after" radiation experience.

With this in mind, an experimental design is proposed in TABLE 1, where the experiment is divided into three complete identical sections, carried out two (2) weeks apart. This is done to insure a high degree of quality control in the measurements obtained.

TABLE 1

Dose	Week #1 Group A		Week #3 Group B		Week #5 Group C		Total subjects
	Biopsy group**	Non-biopsy group	Biopsy group**	Non-biopsy group	Biopsy group**	Non-biopsy group	
30 r	2	2	2	2	2	2	12
30 r + T*	2	2	2	2	2	2	12
Sham X-ray + T*	2	2	2	2	2	2	12
TOTAL	6	6	6	6	6	6	36

*T = Testosterone enanthate 200 mg/wk IM X 16 weeks, prior to X-ray and for 4 weeks post-irradiation.

** = Control biopsy plus biopsy 250 days following irradiation.

3) Histologic Scoring: In order to strengthen our histologic data (see 1969 Progress Report), we will obtain control biopsy specimens as outlined in TABLE 1 of this report. Thereafter, during the post-irradiation period, we shall schedule repeat testicular biopsies after 210 days. Since no new regression changes in seminal fluid sperm concentration occur later than 210 days, a testicular biopsy performed at 250 days will not interfere with our analyses.

Furthermore, we are studying our present data with the point of view of developing a more realistic mathematical model.

4) Hormonal Assays:

a. Serum FSH: Now that we have established a sensitive, accurate radioimmunoassay method for determining serum FSH levels, we can definitely establish the inter-relationship between anterior pituitary function and sperm production. Our data with respect to

the relationship between urinary FSH excretion titers and sperm production, suggest that the two parameters are not directly interrelated. This raises the question of an "independent station" for the control of FSH secretion. By using the radioimmunoassay with its more precise measurements (e.g., coefficient of variation of 10% or less) and the ability to make more frequent measurements, we can correlate the FSH levels with histologic scoring of the germinal epithelium and sperm counts. We plan to obtain three control serum FSH levels, then obtain serum FSH levels at weekly intervals, following irradiation. This will coincide with the day on which each subject submits his seminal fluid specimen. Thus the temporal relationship between the rise in serum FSH and the decline in sperm counts can be intercorrelated in a meaningful fashion.

b. Serum HLH: Prior to our measuring serum HLH levels by radioimmunoassay, we measured LH "secretion" by performing bioassays for urinary LH excretion titers. This led us to the probably erroneous conclusion that LH secretion was not altered following X-ray irradiation. This, of course, was related to the fact that plasma testosterone levels remained unchanged.

However, our preliminary data, with respect to post-irradiation serum HLH levels, suggest that there is an increase. Unfortunately, we had very little data which were directed towards following serum HLH levels in the same patient at frequent intervals. Our data dealt primarily with comparisons between a control population and populations of subjects who had received varying doses of irradiation (see Page 83, 1969 Progress Report). Nonetheless, the preliminary results indicate that there is an increase in serum HLH levels, which if confirmed would suggest that Leydig-cell function may be altered following irradiation requiring higher levels of pituitary LH to maintain normal Leydig-cell testosterone production. This set of circumstances has been noted by our laboratory in patients with Klinefelter's Syndrome and in otherwise normal but aged men. We propose to determine HLH levels, along with plasma testosterone titers, at the same intervals as we have mentioned for serum FSH -- namely, three (3) control determinations and weekly specimens following irradiation.

c. Plasma Testosterone: These determinations will be carried out as before, in conjunction with Dr. Hortense Gandy at Cornell University. She uses the double-isotope derivative method, which has proven accuracy. It may be possible to use a newer and a more economical method which has been developed in our laboratory and represents a modification of Nugent's method. This technique is based on the displacement of labelled testosterone from its binding protein by the addition of "cold" testosterone contained in the patient's serum. It is too early to tell whether or not this newer technique will be feasible, but parallel determinations by both techniques are planned for further evaluation.

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5) Chromosomal Studies: As mentioned in our 1969 Progress Report (see Pages 38 and 39), our chromosomal studies have been hampered by a lack of time-related observations in the same individual and a good mathematical model for analysis. With the experimental design outlined in TABLE 1 of this report and the mathematical model detailed in our 1969 Progress Report, both problems can be overcome. Samples of testicular tissue will be obtained prior to irradiation and at 250 days post-irradiation for mitotic chromosomal analysis.

Meiotic chromosomal studies will be carried out on control testicular tissue and on testicular tissue obtained after full recovery of spermatogenesis. These data will enable us to detect chronic chromosomal aberrations as a consequence of irradiation. Moreover, these data will be essential in evaluating the possible beneficial effects of testosterone administration.

6) Immunologic Studies: (See Pages 84-88, 1969 Prog. Rep.) Using the experimental design for exposure to 30 rads (Table 1, this report) and the time interval for obtaining serum FSH and HLH levels, it will be very easy to obtain the serum for immunologic studies at these weekly intervals. Seminal fluid for sperm, both from the individual and control subjects, will be readily available. Thus we shall be able to extend our preliminary work. As before, this study will be performed in conjunction with Dr. William Clarke's group at Hanford.

IV. SCIENTIFIC PERSONNEL

C. Alvin Paulsen, M.D.
Duane Espeland, M.D.
John Leonard, M.D.
David de Kretser, M.D.
Richard Santen, M.D.
Nancy Purcell, M.D.
Todd Thorslund, Sc.D.

Curricula vitae for Drs. de Kretser, Santen and Purcell are enclosed (Appendix A). Data on all other personnel have been previously submitted in our other reports.

V. OTHER PERSONNEL

Since it may seem at first glance that the number of our technical staff is out of proportion to this project, the following documents the area for which each of the personnel is responsible.

Donald Moore, head technician, supervises the entire technical staff and in addition, performs the FSH radioimmunoassay.

Constance Lowe - examines all seminal fluid specimens for sperm concentration and morphologic characteristics.

Shirley Jokisch - performs the serum testosterone determinations in our laboratory.

Florida Flor - previously performed all bioassays for urinary gonadotrophin titers - will switch to the LH radioimmunoassay procedure.

Margaret Couture - prepares the testicular biopsy specimens for histologic examination. Also performs the histologic scoring of all the testicular biopsy specimens.

Annie Washington - assists in preparing reagents, washing glassware, etc, for the assay and/or examination of gonadotrophins, testosterone and seminal fluid.

Marian Ursic - maintains all research records, collates material in proper fashion for Dr. Thorslund's statistical analyses - liaison for transmittal of information between our laboratory, Hanford, and the Washington State Penitentiary.

Geneva Green, secretary, handles all correspondence, manuscripts, reports and travel arrangements for this project.

In addition to these personnel who are supported by this contract, we have four other technical personnel who perform the chromosomal studies and assist in the radioimmunoassay procedures, but who are supported by other funds.

VI. RELATED FINANCIAL ASSISTANCE

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

R01 AM 05436-09: $32,525 (direct costs)
T01 AM 5161-11: $42,923 (direct costs)

VII. MATERIALS, EQUIPMENT AND FACILITIES

A. All materials, equipment and facilities are the same as listed in the 1968 project renewal request, except for the acquisition of the Chicago Nuclear Gamma Counter.

B. 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 minimal requirements, based on our past experience. To facilitate the documentation of our data for reports and publication, and the processing of our photo-micrography films, 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. We have had to increase the research subjects' stipends due to the proposed frequent blood sampling.

Because of the need for insuring proper operation of the Coulter Counter and for having available substitute equipment during possible breakdown periods, and for maintenance, we have an ongoing service contract from Coulter Electronics.

We have deleted from the proposed budget those items which were related to the neutron work and the electron microscopy.

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SELECTED REFERENCES

1. JOËL, C. A.: Zur Wirkung des Testosteronpropionats auf die Regeneration des röntgengeschädigten Hodens. Endocrinologie, Bd. 24 Heft, May 6, 1942.

2. PAULSEN, C. A.: Disorders of spermatogenesis in man. Clinical Endocrinology, Vol. II. Grune & Stratton, Inc., 1968.

3. PAULSEN, C. A., GORDON, D. L., CARPENTER, R. W., GANDY, H. M., and DRUCKER, W. D.: Klinefelter's Syndrome and its variants. A Hormonal and chromosomal study. Recent Prog. Hormone Research, 24:321, 1968.

4. PAULSEN, C. A.: The Testis. Chapter in William's Textbook of Endocrinology. W. B. Sanders & Co., 1968.

5. ODELL, W. D., ROSS, G. T., and RAYFORD, P. L.: Radioimmunoassay for luteinizing hormone in human plasma or serum: Physiologic studies. J. Clin. Invest., 46:248, 1967.

6. OAKBERG, E. F. and CLARK, E.: Species comparison of radiation response of the gonads. Proc. of the Int. Symp. on Effects of Ionizing Radiation in the Reproductive System. Oxford, Pergamon Press, 1963. pp. 11-24.

7. PAULSEN, C. A.: The study of irradiation effects on the human testis: including histologic, chromosomal and hormonal aspects. Nuclear Science Abstracts, Vol. 21: Abst. 408, 1967.

8. MACLEOD, J., HOTCHKISS, R. S., and SITTERSON, B. W.: Recovery of male infertility after sterilization by nuclear radiation. JAMA, 187:637, 1964.

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PRIVACY ACT MATERIAL REMOVED

Contract #AT(45-1)-1781
Proposed 12-month Budget
Contract Year 1970-1971

	AEC	U of W
SALARIES		
a) Professional		
C. Alvin Paulsen, M.D., Associate Professor, 25% time		
Todd Thorslund, Sc.D., Biostatistician, 25% time		
b) Non-professional		
Research Technologist II, Donald Moore, full-time		
Research Technologist I, Constance Lowe, full-time		
Research Technologist I, Shirley Jokisch, 30% time		
Research Technologist I, Florida Flor, 25% time		
Laboratory Technician, Margaret Couture, 50% time		
Laboratory Helper I, Annie Washington, 60% time		
Secretary, Geneva Green, 50% time		
Statistical Assistant, Marian Ursic, 85% time		
Total salaries		
SALARY COSTS: State retirement, TIAA premiums, FICA, Medical Aid and Life/Health Insurance premiums		
SUPPLIES		
a) Laboratory		
Glassware		
Reagents		
Supplies for radioimmunoassay, including I^{131}, I^{125}		
Supplies for Coulter counter (saponin, replacement tubes, saline, etc.)		
Supplies for Dr. Gandy		
Acetic H_3 anhydride, 1200 mCi		
20β-hydroxy steroid dehydrogenase, 50 mg		
Miscellaneous laboratory supplies		
Surgical supplies		
b) Office		
Total supplies		
TRAVEL		
a) Two people, two times monthly to Walla Walla		
b) Four members of research project to scientific meetings		
Total travel		
VOLUNTEER STIPENDS		
a) 64 inmate volunteers @$15/month		
b) 36 biopsies/year @$15		
c) 8 vasectomies @$100/inmate and $60/contract physician		
Total stipends		
MISCELLANEOUS SERVICES		
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		
g) Computer costs		
Total miscellaneous		
INDIRECT COSTS: 27% of salaries and wages		
TOTAL BUDGET	88,685	9,018

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PRIVACY ACT MATERIAL REMOVED

Contract #AT(45-1)-1781
Proposed 6-Month Budget
Contract Year 1970

	AEC	U of W
SALARIES		
a) Professional		
C. Alvin Paulsen, M.D., Associate Professor, 25% time		
Todd Thorslund, Sc.D., Biostatistician, 25% time		
b) Non-professional		
Research Technologist II, Donald Moore, full-time		
Research Technologist I, Constance Lowe, full-time		
Research Technologist I, Shirley Jokisch, 30% time		
Research Technologist I, Florida Flor, 25% time		
Laboratory Technician, Margaret Couture, 50% time		
Laboratory Helper I, Annie Washington, 60% time		
Secretary, Geneva Green, 50% time		
Statistical Assistant, Marian Ursic, 85% time		
Total salaries		
SALARY COSTS: State retirement, TIAA premiums, FICA, Medical Aid and Life/Health Insurance premiums		
SUPPLIES		
a) Laboratory		
Glassware		
Reagents		
Supplies for radioimmunoassay, including I^{131}, I^{125}		
Supplies for Coulter counter (saponin, replacement tubes, saline, etc.)		
Supplies for Dr. Gandy		
Acetic H_3 anhydride, 600 mCi		
20β-hydroxy steroid dehydrogenase, 25 mg		
Miscellaneous laboratory supplies		
Surgical supplies		
b) Office		
Total supplies		
TRAVEL		
a) Two people, two times monthly to Walla Walla		
b) Two members of research project to scientific meetings		
Total travel		
VOLUNTEER STIPENDS		
a) 64 inmate volunteers @$15/month		
b) 18 biopsies @$15		
c) 4 vasectomies @$100/inmate and $60 contract physician		
Total stipends		
MISCELLANEOUS SERVICES		
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		
g) Computer costs		
Total miscellaneous		
INDIRECT COSTS: 27% of salaries and wages		
TOTAL BUDGET		

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PRIVACY ACT MATERIAL REMOVED

CURRICULUM VITAE

Name:	Nancy Lee Purcell* (Medlock)
Born:	1941
Education:	Northwestern University, Evanston, Illinois B.A., 1963
Medical Education:	University of Missouri Medical School, Columbia, Missouri; M.D., 1967 Internship, Baptist Hospital, Memphis, Tenn., 1967-68 Asst. Residency, Baptist Hospital, Memphis, Tenn., 1968-69
Current Appointment: (as of 9/12/69)	USPHS Hospital, Seattle, Fellow in Endocrinology, 1969 University of Washington School of Medicine, Seattle, Senior Fellow in Medicine, 1969

*Purcell is maiden name, used for professional purposes.

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PRIVACY ACT MATERIAL REMOVED

CURRICULUM VITAE

Name:	Richard Joseph Santen
Born:	, 1939
Education:	Holy Cross College, Worcester, Massachusetts A.B., 1961
Medical Education:	University of Michigan, Ann Arbor, Michigan M.D., 1965 Internship, New York Hospital, 1965-66 Asst. Residency, New York Hospital, 1966-67 Residency, University of Michigan Hospital, 1967-69
Current Appointment: (as of 9/12/69)	USPHS Hospital, Seattle, Fellow in Endocrinology, 1969 University of Washington School of Medicine, Seattle, Senior Fellow in Medicine, 1969

Publications:

1. SANTEN, R. J. and AGRANOFF, B. W.: Studies on the Estimation of Deoxyribonucleic Acid and Ribonucleic Acid in Rat Brain. Biochim. Biophys. Acta, 72:251-262, 1963.

2. DAVIS, G. A., SANTEN, R. J., and AGRANOFF, B. W.: The Production of a Linear Density Gradient by Means of a Proportioning Pump. Anal. Biochem., 11:153-154, 1965.

3. SANTEN, R. J.: Automated Estimation of Diploid and Tetraploid Nuclei with an Electronic Particle Counter. Exp. Cell Res., 40:413-420, 1965.

4. SANTEN, R. J. and WRIGHT, I. S.: Systemic Lupus Erythematosus with Pulmonary Nocardiosis. Arch. Int. Med., 119:202, 1967.

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PRIVACY ACT MATERIAL REMOVED

CURRICULUM VITAE:

NAME: DR. David Morritz de Kretser.

DEPARTMENTAL ADDRESS:

Department of Anatomy,
Monash University,
Clayton, Victoria 3168
Australia.

PRIVATE ADDRESS:

DATE OF BIRTH: 1939 at Colombo, Ceylon.

NATIONALITY: Australian.

MARITAL STATUS: Married. 2 children aged 5 years, 2 years.

ACADEMIC RECORD:

A. MEDICAL COURSE UNIVERSITY OF MELBOURNE (1957-1962)

Honours during course:

1st. class in Physics and Chemistry (1st year)
2nd. class in Biochemistry & Physiology (2nd.yr)
1st. class in Biochemistry (3rd. year)
2nd. class in Physiology including Exhibition in Physiology (3rd. year).
2nd. class in Pathology, 3rd. class in Microbiology (4th. year).

Final Examination:

1st. class in Surgery, including Exhibition.
3rd. class in both Medicine, Obstetrics and Gynaecology.

Position in class of 180 at Final Examination: 2nd.

GRADUATED: Bachelor of Medicine, Bachelor of Surgery (M.B., B.S.) 1962.

B. POSITIONS SINCE GRADUATION:

1963: Junior Resident Medical Officer, Prince Henry's Hospital, Melbourne, with terms in Medicine, Surgery, Casuality and Anaesthetics.

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1964: Senior Resident Medical Officer, Prince Henry's Hospital with terms as Hospital Admitting Officer, Orthopaedic Surgery, Gynaecology and Ear, Nose and Throat Diseases.

1965: Demonstrator Department of Anatomy, Monash University.

1966-1968: Lecturer, Department of Anatomy, Monash University.

Clinical Assistant, Endocrine Clinic, Royal Women's Hospital, Melbourne.

1968: Senior Lecturer, Department of Anatomy, Monash University.

C. ACADEMIC RECORD SINCE GRADUATION:

1966: Passed Primary Examination for Royal Australasian College of Surgeons.

1967: Holder of National Health and Medical Research Council Grant for investigation into the Structure and function of the human testes and its response to gonadotrophic treatment.

1968: Thesis for Doctor of Medicine ready for submission.

1968: Recipient of grant from Rural Credits Fund of Australia.

D. PUBLICATIONS:

1. The fine structure of the testicular interstitial cells in men of normal androgenic status. Z. Zellforsch., 80: 594, 1967.

2. Endocrine and histological studies during human pituitary and chorionic gonadotrophin treatment of oligospermia. With H.P. Taft. Med. J. Aust., Vol. II for 1967, p. 513. Proc. Aust. Endocrine Society, 1967.

3. Changes in the fine structure of the interstitial cells of the human testis after treatment with human pituitary and chorionic gonadotrophin. Z. Zellforsch., 83, 344, 1967.

4. Endocrine and histological studies on oligospermic men treated with human pituitary and chorionic gonadotrophin. With H.P. Taft, J.B. Brown, J.H. Evans, and B. Hudson. J. Endocr.: 40; 107, 1968.

5. The fine structure of the human testis in hypogonadotrophic hypogonadism. Proc. Aust. Conf. on Electron Microscopy, p. 53, 1968.

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6. Ultrastructural studies on the human Sertoli cell. J. Anat. (Lond.), 103: (In Press), 1968. Proc. Anatomical Society of Aust. and New Zealand. 1967.

7. Ultrastructural features of human testicular interstitial cells. J. Anat. (Lond.), 103: (In Press), 1968. Proc. Anatomical Society of Aust and New Zealand. 1967.

8. Crystals of Reinke in the nuclei of human testicular interstitial cells. Experientia 24: 587, 1968.

9. The clinical uses of human gonadotrophins. With H.P. Taft, F.D. Adey, J.B. Brown, J.H. Evans, and B. Hudson. Aust. Ann. Med. (In Press), 1968.

10. The fine structure of the immature human testis in hypogonadotrophic hypogonadism. Virchow's Archives (In Press), 1968.

11. Studies on the autoradiographic localisation of I^{125} labelled luteinizing and growth hormone in the immature rat. With H.G. Burger, K.J. Catt, and G.C. Smith. J. Anat. (In Press), Proc. Anatomical Society of Australia and New Zealand (1968).

12. The human testicular interstitial cell. Demonstration at 2nd. Conf. of New Zealand Society for Electron Microscopy, Dunedin, 1967.

13. Autoradiographic Studies on the localisation of I^{125} labelled human luteinizing and human growth hormone in immature male rats. With K.J. Catt, H.G. Burger, and G.C. Smith. Submitted to J. Endocrinol.

14. The conversion of cholesterol to Androgens by Rat Testes; Comparison of interstitial cells and seminiferous tubules. With D. Irby and P.F. Hall. Submitted to Endocrinology.

15. Histochemical demonstration of Δ^5 3β Hydroxy-steroid dehydrogenase activity in the developing rat testis, with D.W. Lording. Proc. of Australian Endocrine Society in Med. J. Australia, In Press.

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16. On the presence of immunoreactive growth hormone in a bronchogenic carcinoma. With D.P. Cameron, H.G. Burger, K. J. Catt and J.B. Best. Aust. Ann. Med. (In Press).
17. Ultrastructural features of human spermiogenesis. Z. Zellforsch. (In Press).
18. Ultrastructural features of human spermiogenesis. Proc. of Anatomical Society of Aust. and New Zealand. J. Anat. (Lond.) Abst. (In Press).
19. Interstitial cells in the developing rat testis. With D.W. Lording. Proc. of Anatomical Society of Aust. and New Zealand. J. Anat. (Lond.) Abst. (In Press).
20. Thesis: "Studies on the structure and function of the human testis". Submitted for Doctorate in Medicine at Monash University, Clayton, Victoria, Australia.

CURRENT APPOINTMENT: Senior Fellow in Medicine, University of Washington School of Medicine, effective 9/18/69. (NIH International Postdoctoral Fellowship awardee.)

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