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EFFECTS OF IONIZING RADIATION
ON THE TESTICULAR FUNCTION OF MAN
AEC Contract No. AT(45-1)1780
PROGRESS REPORT
May 1970

Carl G. Heller, M.D.,Ph.D.
Pacific Northwest Research Foundation

3000872

PACIFIC NORTHWEST RESEARCH FOUNDATION
Division of Reproductive Physiology
1102 Columbia Street
Seattle, Washington 98104

RENEWAL PROPOSAL FOR AT (45-1) 1780

Division of Biology and Medicine
U.S. Atomic Energy Commission
Washington, D.C. 20025

TITLE

EFFECTS OF IONIZING RADIATION ON THE TESTICULAR FUNCTION OF MAN

Principal Investigator: Carl G. Heller, M.D.,Ph.D.

Support Period: August 1, 1970 - July 31, 1971

Amount:	First year	$ 99,631
	Second year	87,000 + 8,113 modification
	Third year	94,023
	Fourth year	96,000
	Fifth year	100,000 + 22,000 modification
	Sixth year:	
	6-1-68/7-31-68	20,000
	8-1-68/7-31-69	120,000
	Seventh year	120,000
	Succeeding years	To be arranged

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I. OBJECTIVES

In the progress report and proposal for the current year's research (1969-70) we stated that our objectives were 1) to determine the exact nature of the cytological defect produced in the development of the germinal epithelium and to relate the extent of the defect to dosage and time; 2) to find the minimal dosage that will affect the germinal epithelium; 3) to determine the time of recovery from any given dosage; 4) to determine the minimal dosage that leads to permanent damage of spermatogenic cells; 5) to determine the simultaneous effects of any dosage upon Leydig cell cytology; 6) to determine the influence of any given radiation-produced testicular alteration upon other parameters such as the excretion of total gonadotropic hormones, follicle-stimulating hormone (FSH), interstitial cell-stimulating hormone (ICSH), estrogens and androgenic hormones; and 7) to determine the influence of any given radiation-produced testicular alteration upon plasma FSH, ICSH and testosterone. Our final objective is a complete statistical examination of all parameters and their interactions.

These objectives will not change for the coming year. We have been working and accumulating data to help fulfill these parameters during this current year although only the determinations involving urinary estrogens, total gonadotropins and pregnanediol and pregnanetriol have been completed.

The following charts, similar to those submitted last year, will demonstrate data collected during the current year (Charts A, B, & C), and data to be collected during the coming year (Charts B & C).

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II. CHARTS

A. BIOPSY TIMES FOLLOWING IRRADIATION

1. - 5.

B. PARAMETERS MEASURED AND RESPONSE RECORDED DURING RECOVERY

C. PARAMETERS MEASURED AND RESPONSE RECORDED DURING DEPLETION

A 1.

DOSE	SUBJECT	1 day	1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
8r											
8r											
8r											17wk
8r	+										
10r											
10r		24h		2wk							
10r		24h		2wk		25d		7wk			16wk
15r											
20r		4h				26d		44d			17wk
20r		24h			15d		29d		64d		17wk
20r											
20r											
20r											

+ second irradiation
* cannot be quantitated
N.C. no control biopsy

h hour
d day
wk week

PRIVACY ACT MATERIAL REMOVED

3000616

25wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk
		31wk											
		32wk											
		39wk			70wk								
	30wk			51wk	79wk								
					76wk								
	27wk	35wk			61wk	84wk		121wk					
		39wk			77wk								
									151wk				
								123wk					

3000811

A 2.

DOSE	SUBJECT	1 day		1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
25r		6h					24d	40d				
25r	+		24h			15d		29d		64d		18wk
50r	(N.C.)	4½*/ 7*h					24d	40d				
50r												
50r												
50r	+											20wk
55r												17wk
78r												
78r												
78r												
78r												
100r												
100r			24h		2wk		25d		7wk			16wk

+ second irradiation
* cannot be quantitated
N.C. no control biopsy

h hour
d day
wk week

PRIVACY ACT MATERIAL REMOVED

3000818

25wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk
	29wk			60wk									
	27wk				70wk	84wk							
								121wk					
						85wk	109wk						
21wk													
		37wk											
	30wk			51wk		113wk	118wk						

A 3.

DOSE	SUBJECT	1 day		1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
100r	(N.C.)		16h*					33d*	46½d*	62½d*		
100r	(N.C.)	4*/ 6½*h						31d*				
100r											15wk	
100r											11wk	
100r											11wk	
100r	+		24h			15d		29/ 37d			14wk	
100r												
100r			24h		2wk			35d				17wk
200r	(N.C.)		13h*		14½d*				46½d			
200r			22½h		14½d			29d			12wk	
200r												
200r												
200r												19wk

+ second irradiation
* cannot be quantitated
N.C. no control biopsy

h hour
d day
wk

PRIVACY ACT MATERIAL REMOVED

3000880

25wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk
	29wk	36wk			70wk								
						87wk	105wk	125wk	153wk		183wk		232wk
	28wk					81/89/ 99wk	109wk	129wk					
		37wk			61wk			125/ 135wk					
			45wk										
		31wk											
		35wk											
21wk		33wk	43wk	57wk		81wk							
22wk		37wk											
								139wk				203wk	
	30wk			53wk	66/ 80wk		101/ 119wk	136wk		165wk			

3000801

A 4.

DOSE	SUBJECT	1day		1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
200r												
200r												
235r												
300r	(N.C.)		15h*					33/ 40½d	62½d			
300r								40½d				
400r		6/ 4½h					24d	40d				
400r											72d	
600r		4h					26d		44d		13wk	
600r			22½h		14½d			29d			12wk	
600r												20wk
600r												
600r												

+	second irradiation	h	hour
*	cannot be quantitated	d	day
N.C.	no control biopsy	wk	week

PRIVACY ACT MATERIAL REMOVED

3000882

25wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk	260wk	280wk
			43wk	53wk	70wk	89wk	111wk								
					71wk	90wk		122wk							
24wk		35wk	41wk		70/ 73wk			121wk		169wk		209wk			
21wk	27wk														
			42wk	55wk	69/ 77wk	87wk	104/ 119wk								
		33wk	42wk						146/ 160wk	179wk		209/ 219wk	246wk	260wk	270wk
23wk		36wk	46wk		63wk	81wk									
	29wk														
22wk		31wk													
						99wk			154wk						

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A 5.

DOSE	SUBJECT	1 day		1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
600r		18min					24d		8wk			
600r		16min					24d		8wk			
600r				1wk					46d		13wk	
600r	++			1wk				6wk			13wk/ 15wk	
600r								5wk				
600r								5wk				

++ third irradiation
* cannot be quantitated
N.C. no control biopsy

h hour
d day
wk week

PRIVACY ACT MATERIAL REMOVED

3000884

25wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk
22wk		37wk	45wk	58wk									
22wk		37wk	45wk	57wk	67wk								
	26wk		51wk	58wk	66wk								

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	Dose (r)	Number of subjects	B. PARAMETERS MEASURED AND RESPONSE RECORDED				
			CYTOLOGY				
			GERMINAL CELL RECOVERY				
			Start of Histo-logical Recovery	First Sperm OR First Increase of Sperm in Seminal Fluid	Complete Recovery	Germinal Cell Ultra-structure	Sperm Concen-tration in Seminal Fluid
urrent status of all samples collected to date	10-25	11	Complete	Complete	In-complete	In-complete	Complete
umber of subjects to be irradiated to complete adequate analysis of each parameter	20	4	4	4	4	4	4
urrent status of all samples collected to date	50-100	19	Complete	Complete	In-complete	In-complete	Complete
umber of subjects to be irradiated to complete adequate analysis of each parameter	75	4	4	4	4	4	4
urrent status of all samples collected to date	200-300	11	Complete	Complete	In-complete	In-complete	Complete
umber of subjects to be irradiated to complete adequate analysis of each parameter	200	6	6	6	6	6	6
urrent status of all samples collected to date	400-600	13	Complete	Complete	In-complete	In-complete	In-complete
umber of subjects to be irradiated to complete adequate analysis of each parameter	600	4	4	4	4	4	4

DURING RECOVERY

I C A L		H O R M O N A L							
		URINARY				PLASMA			
Leydig Cells	Sertoli Cells	ICSH	FSH	Estrogen	Testosterone & Epitestosterone	ICSH	FSH	Testosterone	
Incomplete 4	Incomplete 4	Complete 0	Complete 0	Complete 0	Complete 0	Complete 4	Incomplete 4	Incomplete 4	
Incomplete 4	Incomplete 4	Complete 0	Complete 0	Complete 0	Complete 0	Complete 4	Incomplete 4	Incomplete 4	
Incomplete 6	Incomplete 6	Incomplete 3	Incomplete 3	Complete 3	Incomplete 3	Complete 6	Incomplete 6	Incomplete 6	
Incomplete 4	Incomplete 4	Incomplete 1	Incomplete 1	Complete 1	Incomplete 1	Complete 4	Incomplete 4	Incomplete 4	

	Dose (r)	Number of subjects	C. PARAMETERS MEASURED AND RESPONSE RECORDED				
						C Y T O L O G I	
			GERMINAL CELL QUANTITATION				
			Sperma-togonia	Sperma-tocytes	Sperma-tids	Germinal Cell Ultra-structure	Sperm Concen-tration Seminal Fluid
Current status of all samples collected to date	10-25	11	Complete	Complete	Complete	Incomplete	Complete
Number of subjects to be irradiated to complete adequate analysis of each parameter	20	4	4	4	4	4	4
Current status of all samples collected to date	50-100	19	Complete	Complete	Complete	Incomplete	Complete
Number of subjects to be irradiated to complete adequate analysis of each parameter	75	4	4	4	4	4	0
Current status of all samples collected to date	200-300	11	Complete	Complete	Complete	Incomplete	Complete
Number of subjects to be irradiated to complete adequate analysis of each parameter	200	6	0	0	0	6	0
Current status of all samples collected to date	400-600	13	Complete	Complete	Complete	Incomplete	Complete
Number of subjects to be irradiated to complete adequate analysis of each parameter	600	4	0	0	0	4	0

DURING DEPLETION

C A L		H O R M O N A L							
		URINARY				PLASMA			
Leydig Cells	Sertoli Cells	ICSH	FSH	Estrogen	Testos-terone & Epi-testos-terone	ICSH	FSH	Testos-terone	
Incomplete 4	Incomplete 4	Complete 0	Complete 0	Complete 0	Complete 0	Complete 4	Incomplete 4	Incomplete 4	
Incomplete 4	Incomplete 4	Complete 0	Complete 0	Complete 0	Complete 0	Complete 4	Incomplete 4	Incomplete 4	
Incomplete 6	Incomplete 6	Complete 0	Complete 0	Complete 0	Complete 0	Complete 6	Incomplete 6	Incomplete 6	
Incomplete 4	Incomplete 4	Complete 0	Complete 0	Complete 0	Complete 0	Complete 4	Incomplete 4	Incomplete 4	

III. IRRADIATION SCHEDULE

The irradiation schedule approved by the committee last year is as follows:

600r - 6 subjects - November 1969

200r - 6 subjects - May 1970

75r - 4 subjects - November 1970

20r - 4 subjects - May 1971

This schedule has fallen slightly behind for three reasons:

1. We were asked not to irradiate until the Research Committee had made their recommendations. Since these were not received until the middle of November, 1969, it was already too late to complete the first section during that month.

2. When we did prepare to irradiate the six at 600r, we found that the x-ray machine was out of order. The repair took two months and several trips to Salem to discover just where the problem was.

3. After the riot at the penitentiary new programs of work release and parole were instituted. This resulted in unexpected release of some of our subjects who were previously in for long terms. New control data had to be accumulated on new subjects to be irradiated

It would indeed be easier to be back on schedule, as far as numbers of subjects irradiated, if we irradiated at either of the lower doses first (20r or 75r) - recovery on these lower doses occurring reasonably rapidly (1 - 2 years) versus 3 to 6 years for the higher doses. The reason is that we want to be very careful to use only men with long sentences for the high doses in order to follow them through

to recovery, and it is important to do the high doses first because of the time necessary for recovery.

Recently the volunteers have tended to be youthful (early 20's). We do not, for ethical reasons, want to irradiate anyone who might regret in later years that he had been vasectomized. Therefore, we are selecting only men who will obviously be apart from society most of their lives or those in their 30's and 40's who make their desicions based on more experience. As a result we have refused irradiation and vasectomy to many who have requested access to this program.

Even despite these drawbacks, we expect to be back on schedule by September 1970 and to have all of the irradiations at 600r and 200r completed by that time.

IV. RESULTS

A. HISTOLOGICAL

Results have shown that the secretory activity of Leydig cells is apparently depressed by irradiation since the urinary testosterone levels decrease in most irradiated men. Preliminary results following 600r show a definite increase in Leydig cell number in one subject, a slight increase in another and a possible, but slight, decrease in two subjects. Quantitation of biopsies from two recent subjects who received 600r are underway along with those of two other subjects who have had a series of post-irradiation biopsies. Data from these eight

subjects should give us statistically conclusive results as to whether an increase or decrease is occurring. If these data show a definite rise or a definite fall we will quantitate biopsy specimens from subjects to whom lower doses of irradiation were administered. If there is a threshold dose for effects of irradiation on Leydig cell numbers, this should be revealed by quantitating the biopsies and analyzing the data.

Quantitation of the germinal epithelium has proceeded by accumulating more data for adequate statistical analysis. No "new" findings can be reported although preliminary results previously reported are being further substantiated.

Ultrastructural examination of testicular cells indicate that major ultrastructural damage is visible within 16 minutes following irradiation of the germinal cells. (This time is the most rapid that a subject can be moved and prepared for biopsy surgery.) Sertoli cell nuclei become swollen and disintegrating cells (mainly spermatogonia) are engulfed by Sertoli cell cytoplasm. The Sertoli cell nucleus always appears to position itself directly above (toward the lumen) the disintegrating cell and the deep infolding commonly seen in the normal Sertoli cell nucleus becomes much shallower. Other ultrastructural changes also occur many of which involve smaller organelles. The significance of these changes has yet to be determined.

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B. HORMONAL

Radioimmunoassay of ICSH has proceeded very well. Although complete statistical analysis will not be done until more samples have been completed at each dose level, preliminary results indicate that plasma ICSH levels rise at all irradiation doses checked except 8r. This is a direct contrast to urinary ICSH levels which did not change following irradiation at any dose level.

The technique for the radioimmunoassay of FSH has been established and is currently being applied routinely. To date only samples taken before and after doses of 600r have been assayed. Preliminary results indicate that plasma FSH levels rise greatly following irradiation and follow the same rate pattern as denuding of the germinal epithelium. The early plasma FSH results appear to confirm the urinary FSH results.

The method of protein-binding in the determination of testosterone has been described by several investigators (1 - 9). It is reasonable to expect an accuracy of approximately 10% in the assay; however, this laboratory is experiencing problems with a nonreproducible blank. This problem is shared by other laboratories (10, 11) and seems to be independent of particular extraction or chromatography procedure. We are planning to consult with a laboratory which is not having the problem during May or June of 1970. Hopefully this will alleviate our difficulties and allow full exploitation of the collected plasma currently in storage.

Pertinent References

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3. Heyns, W., Verhoeven, G., Van Baelen, H. and DeMoore, P.: Measurement of testosterone in plasma by competitive protein binding, Ann. d'Endocr., 30:1(bis), 153, 1969.

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10. Sherins, R. (Personal communication)

11. Thorneycroft, I. (Personal communication)

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Further details of our results may be found in our SIX YEAR SUMMARY REPORT (1963-69) which was submitted in May of 1969.

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V. CURRICULUM VITAE

Carl G. Heller, M.D.,Ph.D.

Born: 1913 - Syracuse, New York

Nationality: U.S. Citizen

Education:

1936	Ph.B. - Zoology, University of Wisconsin, Madison, Wisconsin
1940	M.D., University of Wisconsin, Madison, Wisconsin
1940	Ph.D. - Physiology, University of Wisconsin, Madison, Wisconsin

Honors:

1947, Travel Award to Oxford for the International Physiological Congress
1948, Ciba Award in Endocrinology
1962, Squibb Award of the Pacific Coast Fertility Society
1965- Consultant to Space Radiation Panel, NAS-NRC
1962- Member, Medical Committee, Oral Advisory Group of the Evaluation Subcommittee, International Planned Parenthood Federation
1966, Elected to membership of Royal College of Medicine
1967-68, President, Pacific Coast Fertility Society
1968, Winner Wyeth Exchange Lectureship, Canadian Fertility Society, June 1969, Toronto, Canada

Guest Lectureships:

1965, 9th Oliver Bird Trust Lecturer at the Royal College of Physicians, London, England.
1966, Guest Lecturer, University of Buenos Aires, Human Spermatogenesis and Gonadotropins.
1966, Guest Lecturer, Third International Pharmacological Congress, Sao Paulo, Brazil, Factors Affecting Testicular Function in Man.
1966, Guest Lecturer, Council for the Advancement of Science Writing, Gatlinburg, Tennessee, Factors Depressing Sperm Production in Men.
1967, Guest Lecturer, Gordon Research Conference on Medicinal Chemistry, Crystal Mountain, Washington, Approaches to the Control of Male Fertility.
1968, Guest discussant, Sixth Annual Meeting of the American Association of Planned Parenthood Physicians, San Antonio, Texas, Human Male Fertility/The Inhibition of Human Spermatogenesis.
1968, Guest Lecturer, III International Congress on Endocrinology, Mexico City, June 30-July 5, Mammalian Spermatogenesis:Human Spermatogenesis.
1969, Guest Lecturer, III Schering Symposium on Mechanisms Involved in Conception, Berlin, Germany, March 12-15.

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1970, Guest Lecturer, Workshop Conference on the Human Testis, Positano, Italy, April 23-25, The Role of FSH, ICSH, and Endogenous Testosterone During Testicular Suppression by Exogenous Testosterone in Normal Men.

1970, Guest participant, Conference on the Regulation of Mammalian Reproduction, The Center for Population Research and the Fogarty International Center, DHEW, NIH, Bethesda, Maryland, June 21-25.

Experience:

1940-41	Internship, Wisconsin General Hospital.
1941-44	Residency Training, City of Detroit Receiving Hospital, Internal Medicine.
1941-42	Fellowship, Wayne State Hospital.
1942-43	American College of Physicians Fellowship.
1942-44	Instructor, Wayne State University, Internal Medicine.
1944-45	Assistant Professor, Wayne State University, Physiology.
1945-48	Associate Professor, University of Oregon Medical School, Physiology and Internal Medicine.
1948-57	Head, Division of Endocrinology and Associate Professor of Medicine, University of Oregon Medical School.
1958-present	Head, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington.

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Personal Publications:

Lauson, H., Heller, C. G. and Sevringhaus, E. L.: The effect of graded doses of estrin upon the pituitary, adrenal and thymus weights of mature ovariectomized rats, Endocrinology, 21:735, November, 1937.

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Heller, C. G., Lauson, H. D., Golden, J. B. and Sevringhaus, E. L.: The immature rat uterus in the assay of estrogenic substances, and a comparison of estradiol, estrone and estriol, Endocrinology, 24:34, January, 1939.

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Heller, E. J., Heller, C. G. and Sevringhaus, E. L.: Gonadotropic hormone: Assay of human male urine, Endocrinology, 29:1, July, 1941.

Heller, C. G.: Gonadotropin excretion in women, J. Clin. Endocrinol., October, 1941.

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Heller, C. G., Farney, J. P., Morgan, D. N. and Myers, G. B.: Relation of gonadotropin hormone to oophorectomy, climacteric symptoms and diethylstilbestrol therapy in women, Endocrinology, 30:S1031, 1942 (abstract).

Heller, C. G. and Chandler, R. E.: Gonadotropin hormone:Modification of the alcohol-precipitation assay method, J. Clin. Endocrinol., 2:252, April, 1942.

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Heller, C. G., Segaloff, A. and Nelson, W. O.: Effect of testosterone propionate on the pituitary gonadotropic potency of the castrated male rat, Endocrinology, 33:186, September, 1943.

Heller, C. G. and Heller, E. J.: Metabolism of estrogens: Effect of pregnancy upon metabolism in vitro of estrone, estradiol and estriol, Endocrinology, 32:64, January, 1943.

Heller, C. G., Nelson, W. O. and Roth, A. A.: Functional prepuberal castration in males, J. Clin. Endocrinol., 3:573, November, 1943.

Heller, C. G., Chandler, R. E. and Myers, G. B.: Effect of small and large doses of diethylstilbestrol upon menopausal symptoms, vaginal smear and urinary gonadotrophins in 23 oophorectomized women, J. Clin. Endocrinol., 4:109, March, 1944.

Heller, C. G., Farney, J. P., Morgan, D. N. and Myers, G. B.: A correlation of the ovarian and endometrial histology, vaginal epithelium, gonadotrophic hormonal excretion and the day of the menstrual cycle in 28 women, J. Clin. Endocrinol., 4:95, March, 1944.

Heller, C. G., Farney, J. P. and Myers, G. B.: Development and correlation of menopausal symptoms, vaginal smear and urinary gonadotrophin changes following castration in 27 women, Clin. Endocrinol., 4:101, March, 1944.

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Nelson, W. O. and Heller, C. G.: Hyalinization of the seminiferous tubules associated with normal or failing Leydig cell function; microscopic picture of the testis and associated changes in the breast, J. Clin. Endocrinol., 5:13, 1945.

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Maddock, W. O. and Heller, C. G.: Gonadotrophic hormone: Protection against inactivation, Endocrinology, 41:177, August, 1947.

Heller, C. G. and Maddock, W. O.: The clinical uses of testosterone in the male, Vitamine & Hormones, 5:393, 1947.

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3000907

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Born: 1939 - Porterville, California

Nationality: U.S. Citizen

Education:

1961 B.S. - Biology-chemistry, Pacific Lutheran University, Parkland, Washington
1962 ASCP - Histology-cytology, The Swedish Hospital Medical Center, Seattle, Washington
1963-66 Postgraduate courses, The University of Washington, Seattle, Washington

Honors:

Carl Raymond Gray Scholarship
Union Pacific Railroad Scholarship
Captain Carl Beard Trophy and Scholarship
National Honor Society Scholarship
Women of the Moose Science Scholarship
Invitational speaker, Postgraduate Seminar of the American Fertility Society, San Francisco, California - March 27-30, 1968.
Winner. Wyeth Exchange Lectureship, Canadian Fertility Society, June 1969, Toronto, Canada

Experience:

1960-61 Clinical Histology, The Swedish Hospital Medical Center, Seattle, Washington
1961-62 Electron microscopy, The Swedish Hospital Medical Center, Seattle, Washington
1963- Senior Investigator, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington.

Personal Publications:

Heller, C. G., Roscoe, R. T. and Rowley, M. J.: Hormonal alterations in normal men and women receiving Delalutin: their correlation with spermatogenesis and Leydig cell morphology or menstruation. Squibb Symposium on Delalutin in Advanced Endometrial Cancer in Women, 1964.

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1961 B.S. - Biology, George Fox College, Newberg, Oregon
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Honors:

National Science Foundation Graduate Fellow, 1964-1966

Experience:

1963-64 Research Associate, Department of Biochemistry, Oregon State University
1964-66 Graduate Student, Oregon State University
1966-69 Professor of Biology, Northwest Nazarene College, Nampa, Idaho
1969-present Research Associate, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington

Personal Publications:

Coffey, R. G., Morse, H. and Newburgh, R. W.: The synthesis of nucleic acid constituents in the early chick embryo, Biochim. et Biophys. Acta, 114:547, 1966.

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Experience:

1946-48	Research Assistant, Statistical Laboratory, University of California, Berkeley, California
1949-50	Research Assistant, Department of Labor Economics, University of Washington, Seattle, Washington
1950-52	Research Assistant, Department of Poultry Husbandry, University of California, Berkeley, California
1952-54	Research Assistant, Statistical Laboratory, University of California, Berkeley, California
1953-57	College Teaching, Mathematics and Statistics, College of the Holy Names, Oakland, California
1957-59	College Teaching, Mathematics and Statistics, Hunter College, New York
1959-67	Assistant Professor of Mathematics, University of Washington, Seattle, Washington
1967-	Bio-statistician, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington

Selected Personal Publications:

O'Keefe, K. B.: A property of the differential ideal (y^P), Trans. Amer. Math. Soc., 94:483, 1960.

O'Keefe, K. B.: A symmetry theorem for the differential ideal (uv). Proc. Amer. Math. Soc., 12:654, 1961.

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Rowley, M. J., O'Keefe, K. B. and Heller, C. G.: Decreases in sperm concentration due to testicular biopsy procedure in man. J. Urol., 101:347, 1969.

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1943-45 William Smith College, Geneva, New York, Major in Biology and Minor in Chemistry

Experience:

1946-48 – Physicians Medical Laboratory, Technician, Portland, Oregon

1948-51 Technician to Archie R. Tunturi, Ph.D., University of Oregon Medical School; Portland, Oregon

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Personal Publications:

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Heller, C. G., Teshima, F. and Rowley, M. J.: Duration of transport of spermatozoa through the ductular system, Advances in the Biosciences, Schering Symposium on Mechanisms Involved in Conception, Berlin, 1969, Pergamon Press, pp. 121-131, 1969.

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1967-68 Research Technologist, University of Washington Medical Center, Seattle, Washington
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Personal Publications:

Heller, C. G., Morse, H. C., Su, M. and Rowley, M. J.: The role of FSH, ICSH and endogenous testosterone during testicular suppression by exogenous testosterone in normal men, Proceedings of the Workshop Conference on the Human Testis, Positano, Italy, April 23-25, 1970, Eugenia Rosemberg and C. Alvin Paulsen (eds.), Plenum Publishing Corporation, New York, New York.

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Personal Publications:

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Education:

1965	B.S. - Chemistry, University of Washington, Seattle, Washington
1965-67	Graduate Study, Brown University, Providence, Rhode Island

Honors:

National Merit Commendation

Experience:

1964-June-August	Undergraduate Research Participant (National Science Foundation), Oregon State University, Corvallis, Oregon
1964-65	Undergraduate Research Assistant, Department of Chemistry, University of Washington, Seattle, Washington
1968-present	Research Associate, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington

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Glenn A. Warner, M.D. Radiological Consultant

Born: 1919, Orting, Washington

Nationality: U.S. Citizen

Education:

1948	M.D. - George Washington University, Washington, D.C.

Experience:

1949	Internship, Southern Pacific Hospital, San Francisco, California
1950	Residency, County Hospital, San Mateo, California
1951-53	General Practice, Othello, Washington
1953-56	Residency-Surgery, Westside Veterans Administration Hospital, Chicago, Illinois
1956-59	Surgical Practice, Yakima, Washington
1959-60	Residency, Tumor Pathology, The Swedish Hospital Medical Center, Seattle, Washington
1960-63	Fellowship, Radiation Therapy, Tumor Institute of The Swedish Hospital Medical Center, Seattle, Washington
1963-65	Fellow, National Cancer Institute, Project: Chemotherapy of Malignant Disease
1966-present	Staff, Tumor Institute of The Swedish Hospital Medical Center, Seattle, Washington
1966	Diplomat, American Board of Radiology

Personal Publications:

Heller, C. G., Heller, G. V., Warner, G. A. and Rowley, M. J.: Effects of graded doses of ionizing radiation on testicular cytology and sperm count in man, Rad. Res., 35:493, 1968 (abstract).

Daniel E. DiIaconi, M.D. Surgical Consultant

Education:

1942	M.D. - Marquette University Medical School, Milwaukee, Wisconsin

Experience:

1942-43	Rotating Internship, St. Francis Hospital, Pittsburgh, Pennsylvania
1943-46	U.S. Army Medical Corps - European Theater, Captain M.C.
1946-48	General Surgery Residency, Mt. Carmel Mercy Hospital, Detroit, Michigan
1948-53	Surgeon, Veterans Administration Hospital, Vancouver, Washington
1953	Fellow American College of Surgeons
1953-56	Private Practice, General Surgery, Salem Memorial Hospital Staff and Salem General Hospital Staff
1966	Secretary-Treasurer, Staff Salem Memorial Hospital, Salem, Oregon
1958-59	Secretary-Treasurer, Salem Surgical Society
1959-66	Director of Medical Services, Oregon State Penitentiary, Salem, Oregon
1956-66	Division Surgeon, Oregon National Guard

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VII. FACILITIES AVAILABLE

A. The Oregon State Penitentiary at Salem, Oregon, is our most unique and prized facility, for only here can we find normal subjects who are willing to have repeated observations made on samples of seminal fluid, urine and testicular tissue, who are willing to take experimental drugs and who, of course, are available for such observations over a period of years. Since 1957 excellent rapport has been established between our group and the administrative officers, the medical staff and the hospital staff. Salem, though 221 miles distant from Seattle, is readily reached by plane, train or automobile, so that the investigators can and do conduct the experiments personally, spending 6 to 8 days per month at the prison.

Also at the Oregon State Penitentiary hospital we have available a completely equipped modern operating room, the hospital beds we need (biopsy patients are all hospitalized for 24 hours or more) and a complete staff of inmate nurses, orderlies, surgical assistants, etc. In addition, a well-equipped routine laboratory is available for performing routine urinalyses and hematological studies and liver functions tests, such as cephalin flocculation, B.S.P., thymol turbidity, transaminase, blood sugar, urinary PABA, etc. These tests are used to protect the subjects from any untoward or unanticipated toxic reaction from any of the medications administered.

B. Facilities available at the Pacific Northwest Research Foundation in Seattle: The Reproductive Physiology Division has laboratories in a former nurses' dormitory comprising a total of 3,294 square feet. These include: (a) a completely equipped histological laboratory; (b) a light microscopy room; (c) an electron microscope room with adjoining dark room for developing photomicrographs and radioautography; (d) small animal room; (e) hydrolysis and extraction room for steroids; (f) steroid analysis laboratory; (g) larger general laboratory used for gonadotropin analysis, rat autopsy and general chemical analysis; (h) small office; (i) cytochemical laboratory for frozen sectioning and enzyme localization; (j) a completely equipped photographic dark room containing, in part, a 45H Bessler Manual Model enlarger, Schneider Componon lenses, 1620 A loadmaster print washer; A-25 Arkay electric print dryer; and a macro photography unit that can be attached to the Bessler Enlarger. All these are for our exclusive use and do not include joint facilities of the Foundation.

C. Major permanent equipment available includes the following: Two Zeiss Model W1 binocular research microscopes; two Zeiss Photomicroscopes equipped to allow us to use phase contrast, darkfield, brightfield, and polarized illumination. A Zeiss Model GL microscope with accessories and a Wild M-5 stereomicroscope Model 1250 are also available. We also have a Norelco Closed Circuit Television Camera and Receiver for use with one of our microscopes. This instrument facilitates teching, and also speeds scanning of tissue sections.

Other equipment includes a complete micro-technique set-up including an A.O. Model 820 microtome, paraffin embedding oven, etc.; a Voland analytic balance, Harvard trip double-beam balance, triple-beam balances, and a Roller-Smith Torsion balance for bioassay purposes; Spinco Duostat and Durrum electrophoretic cell; Spincraft automatic speed filter; International centrifuge and Beckman Zeromatic pH meter for gonadotropin processing; Kahn-type automatic shaker, Burrell wrist-action automatic shaker, Beckman Model B spectrophotometer, Labine incubator, Rotovapor, water baths, hot plates, crying oven, Gilson volumetric fractionator, Brinkmann equipment for thin-layer chromatography, automatic pipette washer and continuous flow extraction apparatus for steroid determinations; refrigeration facilities for storing urine and seminal fluid specimens; biopsy racks and an autoclave for their sterilization; two Monroe calculators, a typewriter and miscellaneous other small equipment.

We have recently added an R.C.A. electron microscope EMU 3B, improved, and an Automatic Reichert Ultramicrotome OMU 2. A Packard Instrument Company Model 7201 Radiochromatogram Scanning System complete with automatic localization of radioactivity on paper strip chromatograms or thin layer plates is also available.

D. The Foundation provides for our joint use with other investigators a Barnstead still and a Beckman Model L-2 Ultracentrifuge, a Vir-Tis tissue homogenizer and additional paper chromatography apparatus, a Blackstone Ultrasonic cleaner, an International Equipment Company Cryostat and a Packard Tri-Carb Liquid Scintillation Spectrometer.

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IX. MISCELLANEOUS

A. REGULATIONS GOVERNING RESEARCH INVOLVING HUMAN SUBJECTS

The policy of the Pacific Northwest Research Foundation with regard to research involving human subjects is currently being revised. Our Review Committee is being expanded to include paramedical and lay individuals and the policy itself is being outlined in much greater detail than in the past. This new policy will be finalized as of June 1st, 1970 and a copy will be forwarded to you at that time.

Also attached is a copy of the minutes of the Meeting of the Review Committee for Human Experimentation of the Pacific Northwest Research Foundation, September 16, 1969, at which our project was evaluated in detail and approved.

B. We agree to the general provisions as provided: "Equal Employment Opportunity" clause (HEW-386) - Revised December 1968, Clause 6. "Patent Rights" (July 1967) Clause 20.

MINUTES OF THE MEETING OF THE REVIEW COMMITTEE FOR HUMAN EXPERIMENTATION OF THE PACIFIC NORTHWEST RESEARCH FOUNDATION

September 16, 1969

The regular meeting of the Review Committee for Human Experimentation of the Pacific Northwest Research Foundation, was held at 4:00 p.m., Tuesday, September 16, 1969 in Room 105, Eklind Hall.

Members present:

John L. Bakke, M.D., F.A.C.P., Principal Investigator, Endocrinology, Pacific Northwest Research Foundation
Carl G. Heller, M.D., Ph.D., Principal Investigator, Reproductive Physiology, Pacific Northwest Research Foundation
Carteret Lawrence, M.D., Principal Investigator, Ophthalmology, Pacific Northwest Research Foundation
Vernon T. Riley, D.Sc., Principal Investigator, Microbiology, Pacific Northwest Research Foundation
Sherman W. Day, M.D., F.A.C.S., Co-Principal Investigator, Surgery, Pacific Northwest Research Foundation
Orliss Wildermuth, M.D., Radiotherapist, Diplomat of the American Board of Radiology, Director of the Tumor Institute of The Swedish Hospital Medical Center
William B. Hamlin, M.D., Pathologist, Diplomat of the American Board of Pathology, Director of the Department of Pathology of The Swedish Hospital Medical Center
Carl D. F. Jensen, M.D., Ophthalmologist, Diplomat of the American Board of Ophthalmology, Chairman of the Medical Research Board of the Pacific Northwest Research Foundation
William B. Hutchinson, M.D., F.A.C.S., Surgeon, Diplomat of the American Board of Surgery, President of the Board of Trustees of the Pacific Northwest Research Foundation
Reverend Richard Johnson, Chaplain, The Swedish Hospital Medical Center

Member absent:

Allan W. Lobb, M.D., F.A.C.S., Surgeon, Diplomat of the American Board of Surgery, Medical Director, The Swedish Hospital Medical Center

Included during the meeting was a review of an Atomic Energy Commission Contract application submitted by Dr. Carl G. Heller, with regard to research involving human subjects. Dr. Heller outlined the methods used to obtain volunteers for the experiments, the tests and interviews involved in screening the volunteers, possible effects of the experiments proposed, and results obtained during clinical and experimental observation.

A lengthy discussion followed in which details of the research, methods, patient health and risks were enlarged upon. Particular emphasis was placed in two areas, i.e.:

1. Informed consent and volunteer motivation for being on an experimental program.
2. Dosage of radiation to be used during the coming year (6 men at 600r, 10 men at 200r and perhaps others at lower doses.) and experimental procedures (collection of samples, etc.).

The Review Committee was particularly impressed with the thoroughness shown in these two areas and voted unanimous approval of all aspects of the application.

The meeting adjourned at 5:00 p.m.

Respectfully submitted,

Grace E. Plummer

(Mrs.) Grace E. Plummer
Secretary

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

BOX: 046264

FOLDER: 1780 - HELLER PACIFIC NW RES. FOUNDA.

ASSIGNED NUMBER: RLHTS 94-0021

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