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EFFECTS OF IONIZING RADIATION ON THE TESTICULAR FUNCTION OF MAN

AT (45-1) 1780

PROGRESS REPORT: 8/1/70 - 7/31/71

Division of Reproductive Physiology
Pacific Northwest Research Foundation
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PROGRESS REPORT 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

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

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

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I. OBJECTIVES

The objectives stated in this proposal will not be changed from those stated in the current year's research objectives. These are: 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 times; 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.

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).

II. CHARTS

(See following seven pages)

A. BIOPSY TIMES FOLLOWING IRRADIATION (A1-A5)
B. PARAMETERS MEASURED AND RESPONSE RECORDED DURING RECOVERY
C. PARAMETERS MEASURED AND RESPONSE RECORDED DURING DEPLETION

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5wk	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					
	29wk												

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A. 1

-2-

DOSE	SUBJECT	1 day	1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
8r		PRIVACY ACT MATERIAL REMOVED									
8r											
8r											17wk
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											
20r				11d		26d					

h hour
d day
wk week

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A. 2

-3-

PRIVACY ACT MATERIAL REMOVED

DOSE	SUBJECT	1day	1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
25r		6h				24d	40d				
25r		24h			15d		29d		64d		18wk
50r		4½*/ 7*h				24d	40d				
50r											
50r											
50r											20wk
55r											17wk
78r											
78r											
78r			3d		17d	24d					
78r											
100r		24h		2wk		25d		7wk			16wk
100r		16h*					32½d*	46½d*	62d*		

h hour (N.C.) No control biopsy
d day * Cannot be quantitated
wk week Second irradiation

3001079+

25wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk
	29wk			60wk									
	27wk				69wk	84wk							
								121wk					
						85wk	109wk						
21wk													
25wk													
		37wk											
	30wk			51wk		113wk	118wk						
		36wk			70wk								

3001080

PRIVACY ACT MATERIAL REMOVED

DOSE	SUBJECT	1day	1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
100r	)	4*/ 6½*h					31d*				
100r										15wk	
100r										11wk	
100r										11wk	
100r		24h			15d		29d		64d		17wk
100r											
100r		24h		2wk			35d				17wk
200r		13h*			14½d*			46½d*			
200r		22½h			14½d		29d			13wk	
200r											
200r											
200r											19wk
200r				11d		26d					

h hour
d day
wk week

(N.C.) No control biopsy
* Cannot be quantitated
+ Second irradiation

25wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk
						87wk	104wk	125wk	153wk		183wk		232wk
	28wk					81/ 99wk	109wk	129wk					
		37wk			61wk			125/ 135wk					
			45wk										
		31wk											
		35wk											
23wk			43wk	55wk		82wk							
		31wk	47wk										
								139wk				203wk	
	27wk			54wk	67wk	81wk	102/ 119wk	136wk		165wk			
21wk													

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[redacted]

PRIVACY ACT MATERIAL REMOVED

DOSE	SUBJECT		1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
200r				11d				8wk			
200r				11d		26d					
200r					17d	24d					
200r											
200r											
300r		15h					33/ 40½d	62½d			
300r							40d				
400r		4½/ 6h				24d	40d				
400r										72d	
600r		4h				26d		44d		13wk	
600r		22½h			14½d		29d			12wk	
600r											20wk
600r											

h hour (N.C.) No control biopsy
d day + Second irradiation
wk week

25wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk
	29wk												
22wk	30wk												
			44wk	53wk	70wk	89wk	111wk						
					71wk	90wk		123wk					
24wk		35wk	41wk		70wk			121wk		169wk		209wk	
21wk	27wk												
			42wk	55wk	69/ 77wk	87wk	104/ 119wk						
		33wk	42wk						148/ 160wk	179wk		209/ 219wk	246wk
23wk		36wk	46wk		63wk	81wk							
	29wk												
22wk		31wk											

260wk	280wk	
260wk	272wk	

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PRIVACY ACT MATERIAL REMOVED

DOSE	SUBJECT	1day	1wk	2wk	3wk	4wk	6wk	8wk	10wk	15wk	20wk
600r											
600r		18min				24d		8wk			
600r		16min				24d			9wk		
600r			1wk					46d		13wk	
600r			1wk				6wk			13/ 15wk	
600r							5wk			15wk	
600r							5wk			15wk	
600r			3d		17d						
600r			3d		17d	24d					
600r											

h hour
d day
wk week

\+ Second irradiation
++ Third irradiation

5wk	30wk	40wk	50wk	60wk	80wk	100wk	120wk	140wk	160wk	180wk	200wk	220wk	240wk
						99wk			154wk				
2wk		37wk*	45wk	58wk			101/ 119wk						
2wk		37wk*	45wk	57wk	67wk	89wk	106wk	125wk					
	26wk			51/ 57wk	67wk	89wk	106wk						
			45wk										
		33wk	47wk										
21wk													

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	Dose (r)	Number of subjects	B. PARAMETERS MEASURED AND RESPONSE RECORDI				
			C Y T O I				
			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 Seminal Fluid
Current status of all samples collected to date	10-25r	12	Incom-plete	Complete	Incom-plete	Incom-plete	Complete
Number of subjects to be irradiated to complete adequate analysis of each parameter	20r	3	3	3	3	3	3
Current status of all samples collected to date	50-100r	21	Incom-plete	Complete	Incom-plete	Incom-plete	Complete
Number of subjects to be irradiated to complete adequate analysis of each parameter	75r	2	2	2	2	2	2
Current status of all samples collected to date	200-300r	15	Incom-plete	Complete	Incom-plete	Incom-plete	Complete
Number of subjects to be irradiated to complete adequate analysis of each parameter	200r	2	2	2	2	2	2
Current status of all samples collected to date	400-600r	17	Incom-plete	Complete	Incom-plete	Incom-plete	Incom-plete
Number of subjects to be irradiated to complete adequate analysis of each parameter	600r	0	0	0	0	0	0

DURING DEPLETION

LOGICAL		HORMONAL						
		URINARY				PLASMA		
Leydig Cells	Sertoli Cells	ICSH	FSH	Estrogen	Testosterone & Epitestosterone	ICSH	FSH	Testosterone
Incomplete 3	Incomplete 3	Complete 0	Complete 0	Complete 0	Complete 0	Complete 3	Complete 3	Incomplete 3
Incomplete 2	Incomplete 2	Complete 0	Complete 0	Complete 0	Complete 0	Complete 2	Complete 2	Incomplete 2
Incomplete 2	Incomplete 2	Complete 0	Complete 0	Complete 0	Complete 0	Complete 2	Complete 2	Incomplete 2
Incomplete 0	Incomplete 0	Complete 0	Complete 0	Complete 0	Complete 0	Complete 0	Complete 0	Incomplete 0

	Dose	Number of subjects	C. PARAMETERS MEASURED AND RESPONSE RECORDED				
							C Y T
			GERMINAL CELL QUANTITATION				
			Sperma-togonia	Sperma-tocytes	Sperma-tids	Germinal Cell Ultra-structure	Sperm Concen-tration i Seminal Fluid
urrent status of all samples collected to date	10-25r	12	Complete	Complete	Complete	Incomplete	Complete
umber of subjects to be irradiated to complete adequate analysis of each parameter	20r	3	3	3	3	3	3
urrent status of all samples collected to date	50-100r	21	Complete	Complete	Complete	Incomplete	Complete
umber of subjects to be irradiated to complete adequate analysis of each parameter	75r	2	2	2	2	2	0
urrent status of all samples collected to date	200-300r	15	Complete	Complete	Complete	Incomplete	Complete
umber of subjects to be irradiated to complete adequate analysis of each parameter	200r	2	0	0	0	2	0
urrent status of all samples collected to date	400-600r	17	Complete	Complete	Complete	Incomplete	Complete
umber of subjects to be irradiated to complete adequate analysis of each parameter	600r	0	0	0	0	0	0

)URING RECOVERY

I C A L		H O R M O N A L						
		URINARY				PLASMA		
ydig ells	Sertoli Cells	ICSH	FSH	Estrogen	Testos-terone & Epi-testos-terone	ICSH	FSH	Testos-terone
ncomplete 3	Incomplete 3	Complete 0	Complete 0	Complete 0	Complete 0	Complete 3	Complete 3	Incomplete 3
ncomplete 2	Incomplete 2	Complete 0	Complete 0	Complete 0	Complete 0	Complete 2	Complete 2	Incomplete 2
ncomplete 2	Incomplete 2	Incomplete 0	Incomplete 0	Complete 0	Complete 0	Complete 2	Complete 2	Incomplete 2
ncomplete 0	Incomplete 0	Incomplete 0	Incomplete 0	Complete 0	Complete 0	Complete 0	Complete 0	Incomplete 0

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III. IRRADIATION SCHEDULE

The irradiation schedule that we have been following is as follows:

600r	6 subjects	November 1969
200r	6 subjects	May 1970
75r	4 subjects	November 1970
20r	4 subjects	May 1971

As of this date (April, 1971) we have the following yet uncompleted:

600r	0 subjects
200r	2 subjects
75r	2 subjects
20r	3 subjects

The men are presently being prepared for irradiation and should all be irradiated by the time this report is read. The reason the doses were not given exactly in the order originally shown was because we wanted to be sure that we chose the correct volunteers for each dose (i.e., the ones with the longest sentence received 600r; the ones with the shortest sentence received 20r). This insures that we will be able to follow them through to recovery.

IV. RESULTS

A. HISTOLOGICAL

As reported previously we have observed an increase in the number of Leydig cells following irradiation with 600r using the Leydig cell/Sertoli cell ratio method (Heller, Lalli, Pearson and

Leach, 1971). Although the results are preliminary, the data suggest this rise begins approximately 90-95 days post-irradiation. Thus far, four subjects show an increase in Leydig cell numbers and one subject shows a slight decrease; however, his later biopsies must still be quantitated.

Although a total of 14 subjects have received 600r of irradiation only 11 have sufficient biopsies taken after 90 days to ascertain if an increase has taken place. Of these there is only one subject that has been followed for a long enough time to begin to show a recovery in Leydig cell numbers - this being roughly 1,900 days. His Leydig cell/ Sertoli cell ratios are shown in the following:

Subject #199
LC/SC Ratios

	Right Testis	Left Testis
Control	.45	.47
26 days	.44	-
92 days	.53	-
232 days	-	.52
295 days	.63	-
1022 days	.55	-
1120 days	-	.75
1253 days	.49	-
1722 days	-	.88
1904 days	-	.61

The number of men that will be available after this amount of time has elapsed can only be postulated. At this time eight subjects

who have received 600r are actively participating in the irradiation program and three have biopsies after 700 days post-irradiation.

We shall continue to follow these subjects for as long as possible after irradiation. Hopefully, until they again reach control levels.

If indeed, we do find that there is a significant rise in Leydig cells in the population of subjects who have received 600r, we shall then begin quantitation of biopsies from subjects who have received lower doses of irradiation. Should increases in Leydig cells be found at these doses then we shall determine if these increases correspond with those at 600r. Questions we shall be answering are: 1) are the increases at these lower doses, if they do occur, as statistically significant as those at 600r, i.e., are the increases as great, 2) are the intervals of time to notice an increase and to notice recovery the same, 3) is there possibly a dose-response relationship involved?

Quantitation of the germinal epithelium has proceeded by accumulating more data for adequate statistical analysis. No "new" findings can be reported although initial findings are being further substantiated. Examples of results at different dose levels by tubule counts (Rowley and Heller, 1971) are as follows:

	Ad	Ap	B	R	L	Z	P	Sa	Sb	Sc	Sd
	Spermatogonia			Spermatocytes				Spermatids			
Control	0.93	0.80	0.49	0.42	0.76	0.11	2.56	1.56	3.09	2 67	2.45
25r											
6hrs	0.68	0.63	0.25	0.09	0.45	0.01	2.87	1.78	2.62	1.13	1.54
24days	0.74	0.64	0.29	0.05	0.14	0.02	2.85	2.65	2.00	0.27	0.35
40days	0.28	0.23	0.03	0.02	0.04	0	0.20	0.30		1.16	
201days	0.36	0.28	0.07	0.03	0.04	0	0.31	0.21		0.41	
420days	0.96	0.88	0.30	0.45	0.25	0.25	3.31	0.99	2.45	3.49	
Control	0.71	0.53	0.28	0.24	0.43	0.06	1.99	1.43	1.29	1.29	1.00
100r											
24hrs	0.62	0.44	0.14	0.14	0.33	0.02	1.32	0.72	0.79	0.71	0.74
14days	0.59	0.06	0.003	0	0.009	0	1.05	0.55	0.59	0.73	0.49
25days	0.20	0.08	0.04	0.02	0	0	0.27	0.81	1.06	0.75	0.73
49days	0.27	0.12	0.02	0.03	0.04	0	0.20	0.17		0.32	
112days	0.06	0.02	0	0	0	0	0.03	0.02		0.06	
210days	0.06	0.06	0.005	0	0	0	0.06	0.03		0.02	
Control	0.56	0.44	0.29	0.33	0.61	0.01	2.60	1.58	2.20	1.83	1.60
600r											
22hrs	0.47	0.24	0.07	0.07	0.74	0.04	2.90	1.88	2.24	2.22	1.68
14days	0.28	0.23	0.004	0	0.01	0	1.39	0.44	0.99	0.71	0.72
29days	0.21	0.14	0.01	0	0	0	0.01	1.34		2.37	
84days	0.01	0.002	0	0	0	0	0	0	0	0	0
151days	0.002	0	0	0	0	0	0	0	0	0	0
252days	0.006	0	0	0	0	0	0	0	0	0	0
322days	0.003	0.01	0.02	0.005	0	0	0.05	0.04		0.01	
477days	0.001	0	0	0.006	0	0	0.01	0	0	0	0

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Ultrastructural examination indicates Leydig cells are affected by irradiation within two days. With the aid of the electron microscope we shall continue to study the morphological changes of the Leydig cells which cannot be seen with the light microscope following irradiation. Again we are attempting to answer questions concerning dose-response relationships of the morphological effects of X-ray irradiation on the Leydig cell. See photo section for one example of a possible change due to x-ray.

Ultrastructural examination of the germinal epithelium has revealed many morphological changes, some of which we have not seen in either normal or otherwise altered testis. For example, at 24 days after irradiation at 600r, we have found macrophages traveling through the basal lamina into the tubules. We believe they pick up damaged cellular material and then move into the lumen. The Sertoli cells, however, also act as disposals for damaged tissue releasing acid phosphatase into the cell to break it up and then acting as a transporting medium for the broken-up cells to pass through into the lumen (see photo section).

Although much progress has been made we have really only scratched the surface. Because of the number of biopsies taken and the wealth of information available in each biopsy, much of the material has not yet been examined.

B. HORMONAL

Plasma testosterone is being measured by the method of Murphy (1970). This method consists of extraction of steroids from

plasma with diethyl ether, isolation of testosterone with the use of a column of Sephadex LH-20, and quantitation by competitive protein binding using L.P.P. and charcoal uptake.

Although there are many methods currently available in the literature, the above method seems most suitable due to its relative speed and simplicity. The other methods are characterized by extensive solvent preparation and multi-stage isolation steps (often both thin-layer and paper chromatography). The normal male control value obtained in this laboratory is 212 ± 62 (S.D.) ng/100ml with a 65% recovery.

The methods that we use for the radioimmunoassay of plasma FSH and ICSH are modifications of methods by Odell et al (1967), and Midgley (1966). We use the NIH standard LER 907. The method involves iodinating 2 μg of highly purified HLH (or 1 μg of FSH with 2 mc of I^{131} by the modified method of Greenwood, Hunter and Glover (1963). The iodinated hormone is separated from the inorganic I^{131} by passing the sample through a G-75 Sephadex column. The trailing edge of the earliest peak is used in the assay. The specific activity ranges from 200 to 600 μc per μg.

The buffer system and assay procedure differ from that of Odell in incubation and concentration of rabbit serum. After adding the buffer, EDTA, plasma and antibody, we incubate for 1 day, add iodinated hormone and further incubate for 4 days. We prefer this because the sensitivity of the assay is increased by the creation of a non-equilibrating system. The plasma ICSH control value (50 men) is 4.34 ± 1.27 (S.D.) (mIU/ml LER 907, RIA) with a range of 2.28 to 7.33 mIU/ml.

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The plasma FSH control value (34 normal adult males) is 6.85 $\pm$ 1.71 (S.D.) (mIU/ml LER 907, RIA) with a range of 4.40 to 9.08 mIU/ml. One man has had all of the collected samples completed (other samples are run randomly to insure our double blind system). His values are shown as an example of the data being collected.

PLASMA ICSH AND FSH DETERMINED BY RADIOIMMUNOASSAY. SPERM COUNTS ARE GIVEN FOR APPROXIMATE PLASMA COLLECTION DATES FOR REFERENCE.

Collection Date	ICSH (mIU/ml)	FSH (mIU/ml)	Collection Date	S.F. Count M/cc
1-20-68	5.50	4.73	1-16-68	157
2-3-68	3.35	6.23	1-30-68	126
2-17-68	3.38	6.75	2-13-68	258
5-5-68	4.58	5.00	4-23-68	213
5-12-68	4.20	6.65	5-14-68	160
10-8-68	4.30	6.45	10-7-68	236
11-14-68	4.35	6.05	11-4-68	125
11-14-68	600r			
11-28-68	4.90	9.15	11-25-68	87
12-20-68	8.92	19.00	12-16-68	94
1-8-69	10.42	20.25	1-10-69	27
1-10-69	9.00	22.45	1-24-69	10
1-22-69	7.83	16.25	1-31-69	1.5
2-18-69	7.84	21.25	2-7-69	0.3
4-25-69	5.50	17.25	2-28-69	0
5-12-69	4.75	18.25	5-16-69	0
5-29-69	8.13	17.40	5-23-69	0
6-30-69	6.23	18.50	6-20-69	0
8-5-69	7.07	16.00	7-24-69	0
8-22-69	4.65	15.38	8-21-69	0
9-29-69	10.38	22.00	9-18-69	0
10-28-69	6.95	23.00	10-9-69	0
11-29-69	8.65	15.05	11-26-69	0
12-29-69	5.08	15.88	12-29-69	0
1-30-70	9.80	21.25	1-19-70	0

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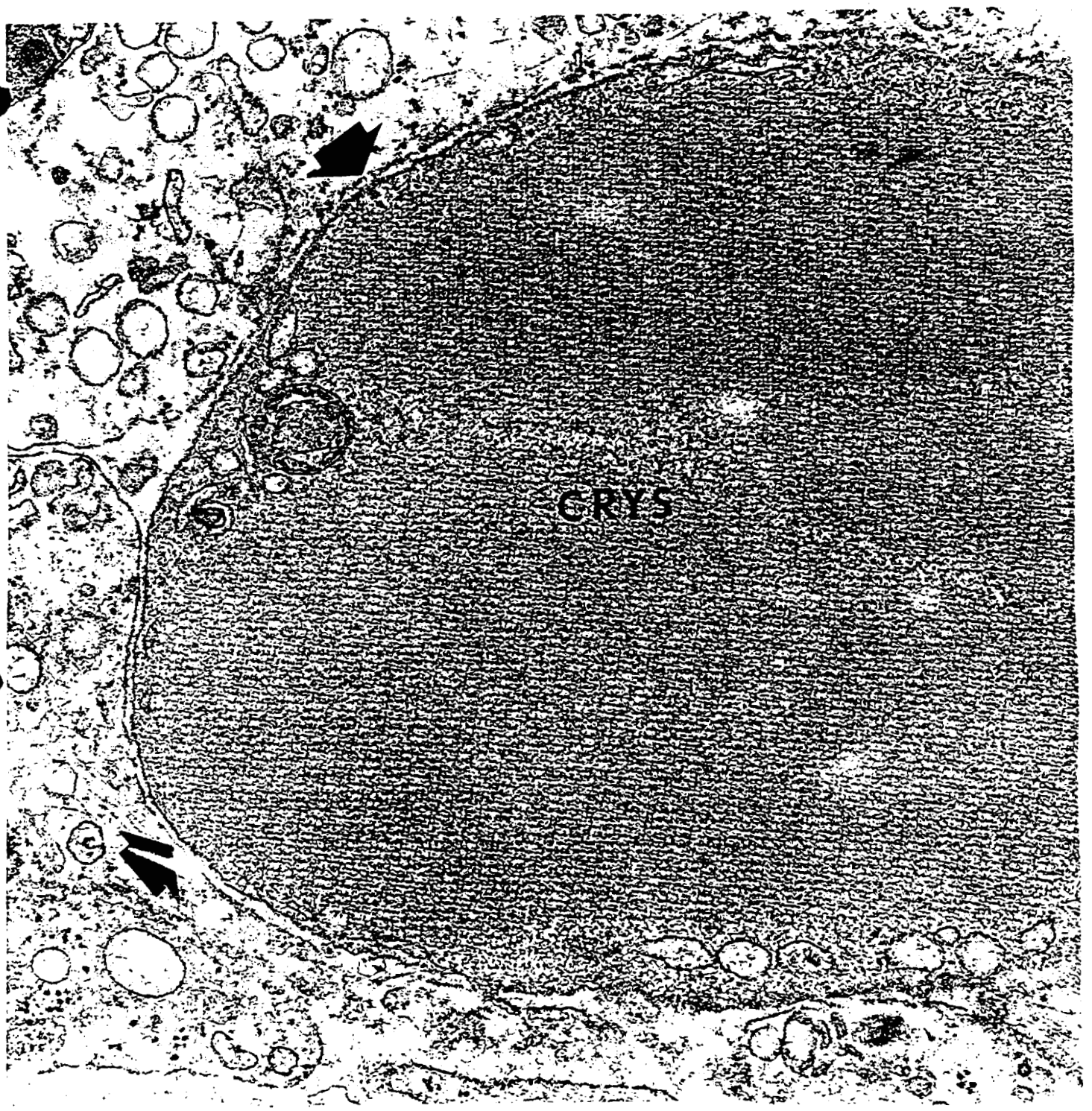
6-30-70	5.65	15.50	--	--
7-20-70	10.25	17.50	7-10-70	0
10-20-70	10.18	17.00	10-26-70	0.1
11-20-70	8.25	16.40	11-20-70	0.2
1-21-71	6.50	15.50	2-5-71	4
2-19-71	7.35	14.00	3-29-71	6
3-20-71			4-5-71	0.3

Concerning urinary hormones (FSH, ICSH) we are now in the process of re-analyzing the vast amount of data we have accumulated. Each assay is being carefully evaluated both personally and with the aid of a computer. This analysis will continue for some time because of the time involved in evaluating each response that has been obtained in all subjects who have received irradiation. After this careful analysis has been completed it will be inspected further and the same questions applied as before - is there a dose response, etc.

C. SEMINAL FLUID

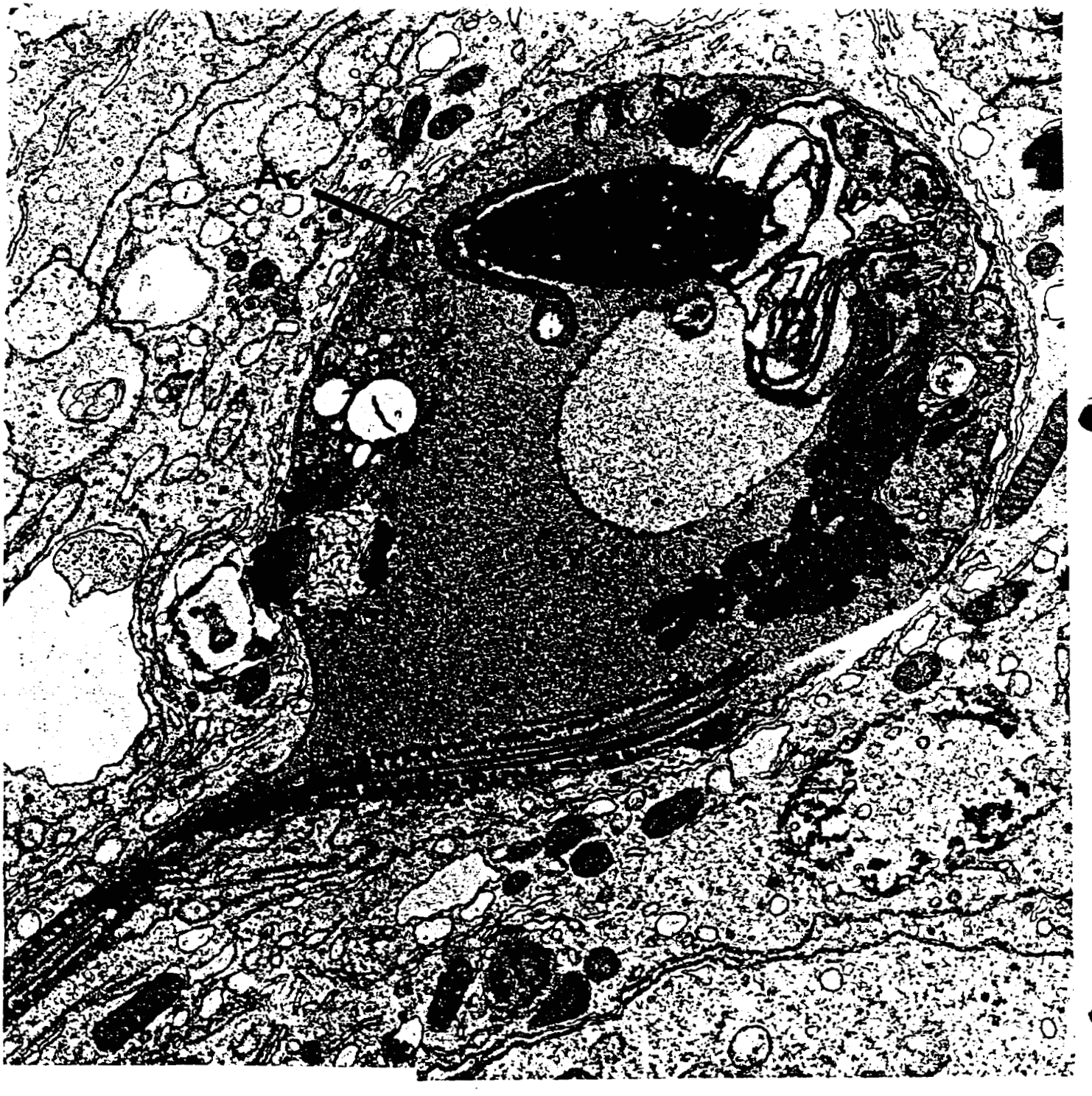
Sperm counts and sperm morphological examination will continue to be done on a weekly basis. Analysis of sperm count will be done on a dose irradiated basis to determine a possible dose response effect and length and degree of effect for each dose.



Crystal of Reinke in Leydig cell 22 hours after 600r. Surrounding membrane is pointed out by arrows. Membranes around crystals of Reinke have not been seen except after x-ray irradiation.

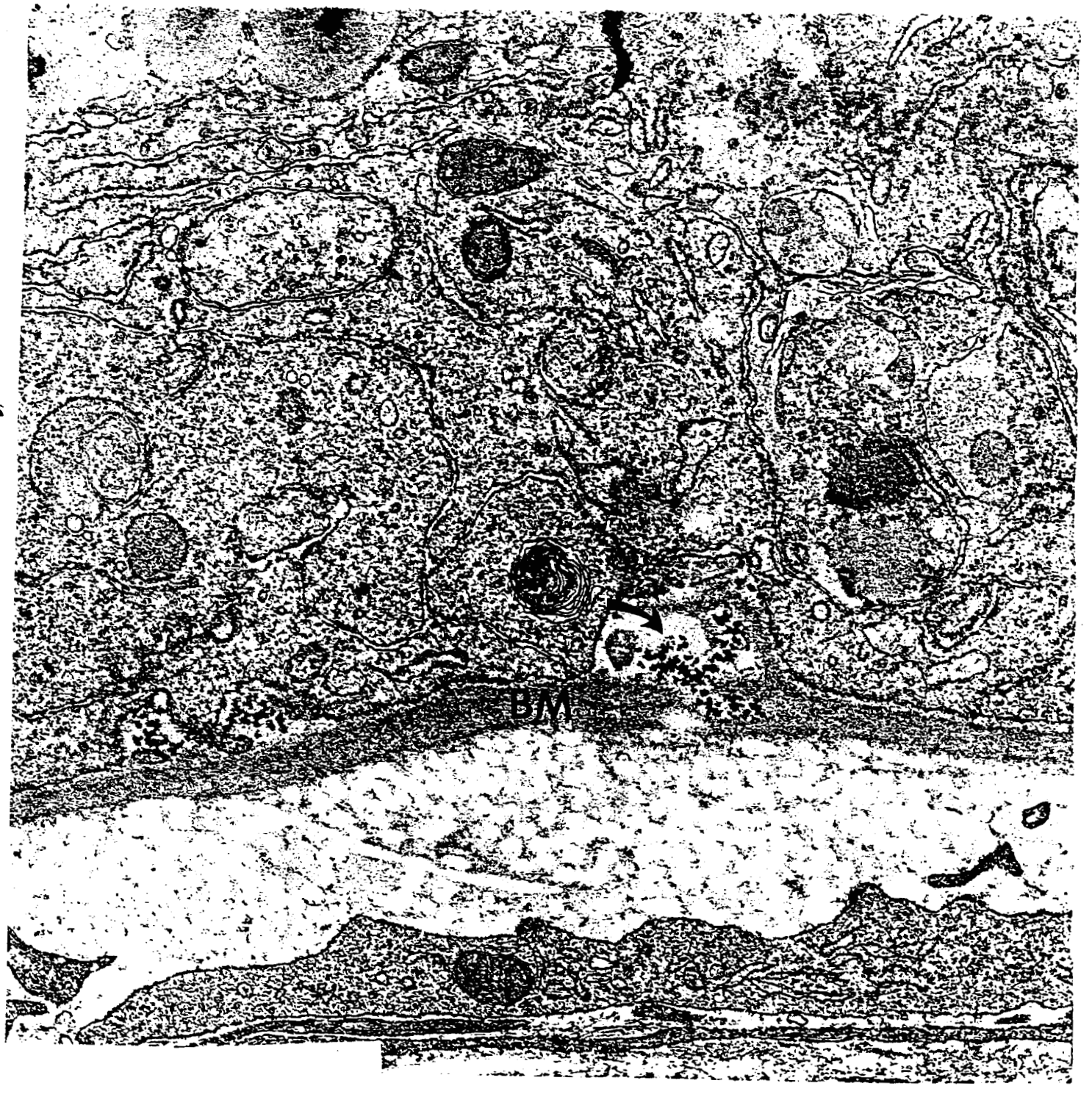
3001102

Abnormal spermatid 22 hours after 600r. The acrosome (Ac) is peeling off of sperm head instead of covering it. The head of sperm appears trapped within cytoplasmic droplet (Cy) instead of pushing itself out.

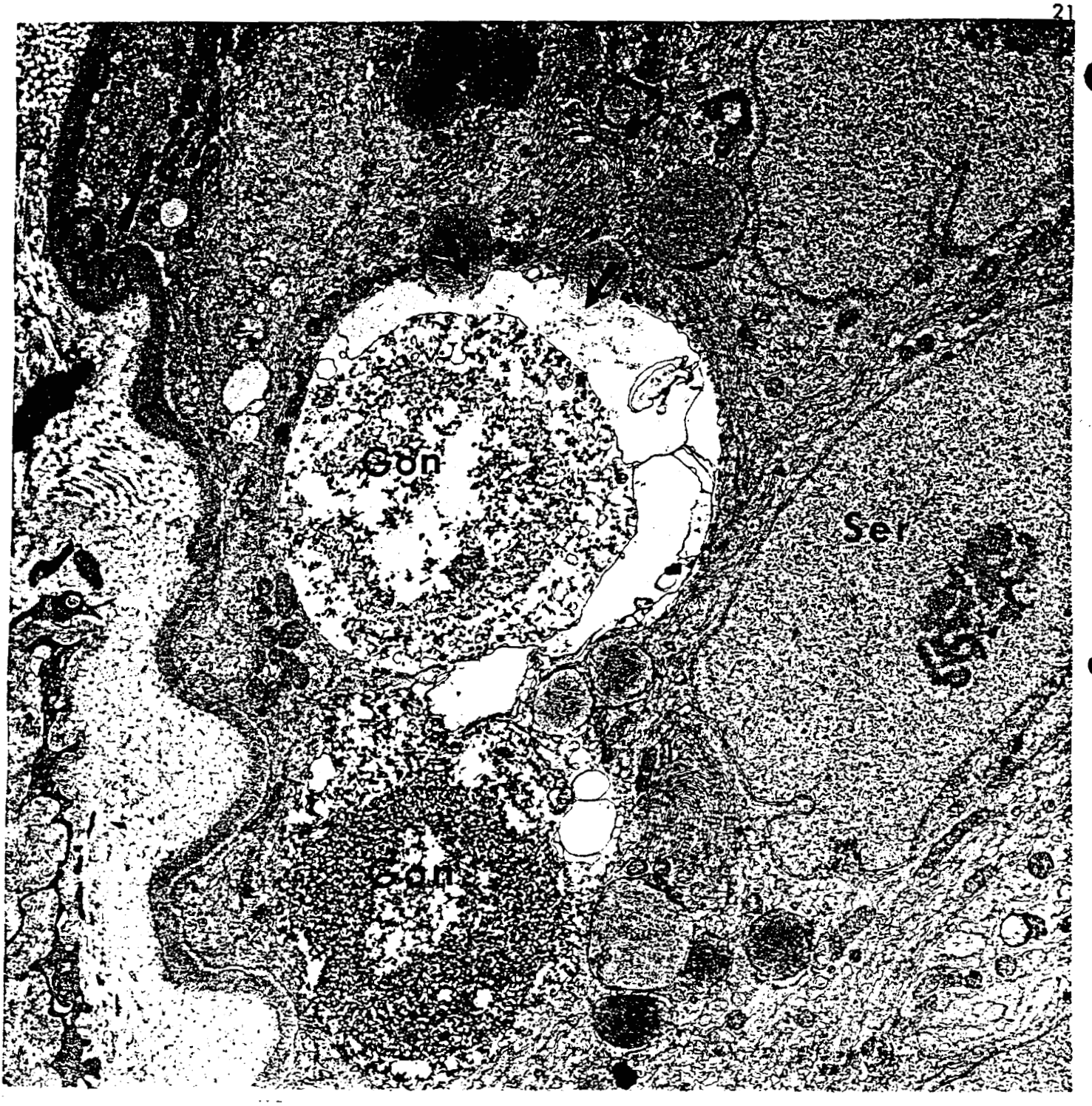


3001103

Particulate material (arrow) between basement membrane (BM) and seminiferous tubule cells 22 hours after 600r. This is not found in normal testicular material.



3001104



Disintegrating spermatogonia (Gon) 22hrs after 600r. Note release of acid phosphatase material (arrows) into gonia from Sertoli cell.Ser indicates Sertoli cell nucleus and BM indicates basement membrane.

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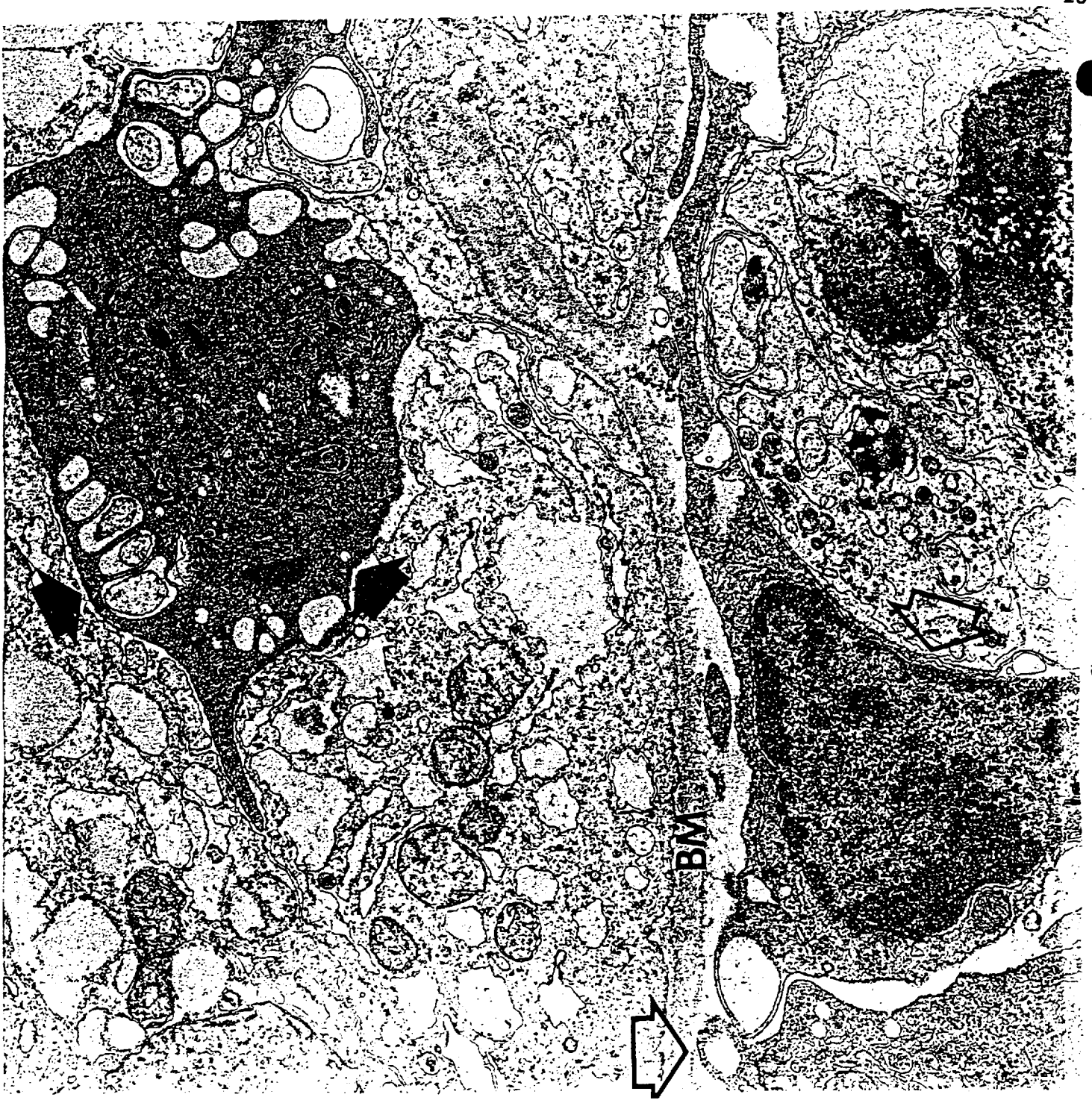
Macrophage entering the seminiferous tubule 24 days after 600r. Macrophage material within the tubule is indicated by black large arrows, material outside tubule is indicated by open arrows. Small black arrow indicates intracellular pathway used by macrophage when entering tubule. BM indicates basement membrane.



Macrophages inside the seminiferous tubules have been found only at 600r after 24 days so dar. Macrophage within tubule (black arrow) and outside of tubule (open arrows) are definitely separated by the basement membrane (BM).

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Seminiferous tubule 24 days after 600r. Cells marked M indicate macrophages which have entered the tubule through the basement membrane (BM) area. Macrophages outside of tubule are indicated by arrows. One cell, possibly a spermatogonium (Gon) is degenerating.

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V. QUALIFICATIONS OF SCIENTIFIC PERSONNEL

PRIVACY ACT MATERIAL REMOVED

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

Born:

Nationality:

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.

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.

Personal Publications:

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Rowley, M. J. and Heller, C. G.: Embryology, anatomy and histology of the male sexual organs, in Fertility Disturbances in Men and Women, pp. 48-64, Karger/Basel, 1971.

Rowley, M. J., Berlin, J. D. and Heller, C. G.: The ultrastructure of four types of human spermatogonia, Zeitschrfit fur Zellforschung, 112:139-157, 1971.

Heller, C. G. and Leach, D. R.: Quantification of Leydig cells and measurement of Leydig-cell size following administration of human chorionic gonadotrophin to normal men, Journal of Reproduction and Fertility, 25:_____, 1971 (in press)

Heller, C. G., Lalli, M. F., Pearson, J. E. and Leach, D. R.: A method for the quantification of Leydig cells in man, Journal of Reproduction and Fertility, 25:_____, 1971 (in press)

Rowley, M. J. and Heller, C. G.: Quantitation of the cells of the seminiferous epithelium of the human testis employing the Sertoli cell as a constant, Zeitschrift fur Zellforschung, 115:461-472, 1971.

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PRIVACY ACT MATERIAL REMOVED

Mavis J. Rowley

Born:

Nationality:

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.

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.

Rowley, M. J. and Heller, C. G.: An analysis of the effect of one or more testicular biopsies upon sperm count. Proc. Northwest Soc. Clin. Med., 1965 (abstract).

Heller, C. G., Wootton, P., Rowley, M. J., Lalli, M. D. and Brusca, D.R.: Action of radiation upon human spermatogenesis. Proc. VI Congreso Panamericano de Endocrinologia, Excerpta Medica International Congress Series, No. 112, pp. 408-410, 1966.

Rowley, M. J. and Heller, C. G.: The duration of each cell association (stages) of the human testis, Fed. Proc., 25:313, 1966 (abstract).

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Rowley, M. J. and Heller, C. G.: The depletion of the human germinal epithelium by x-irradiation: a study of the timing of spermatogenesis, Clin. Res., 15:127, 1967 (abstract).

Heller, C. G., Lalli, M. F. and Rowley, M. J.: Factors affecting testicular function in man. II. International Pharmacological Congress, Pharmacology of Reproduction, Vol. 2, pp. 61-73, Pergamon Press, E. Diczfalusy (ed.), 1968.

Rowley, M. J., Teshima, F. and Heller, C. G.: Duration of transport of spermatozoa through the ductular system, Clin. Res., 16:150, 1968 (abstract).

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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.

Rowley, M. J. and Heller, C. G.: The use of the "rebound phenomenon" in the treatment of the infertile male, Clin. Res., 17:109, 1969. (abstract).

Heller, C. G., Rowley, M. J. and Heller, G. V.: Clomiphene citrate: a correlation of its effect on sperm concentration and morphology, Total gonadotropins, ICSH, estrogen and testosterone excretion, and testicular cytology in normal men, J. Clin. Endo. & Metab., 29:638, 1969.

Heller, C. G., Heller, G. V. and Rowley, M. J.: Human spermatogenesis: an estimate of the duration of each cell association and of each cell type, III International Congress of Endocrinology, Excerpta Medica Foundation, International Congress Series, Progress in Endocrinology, pp. 1012, 1969.

Heller, C. G., Teshima, F. and Rowley, M. J.: Duration of transport of spermatozoa through the ductular system, Advances in the Biosciences 4, Schering Symposium on Mechanisms Involved in Conception, Berlin, 1969, Pergamon Press, pp. 121-131.

Heller, G. V. and Rowley, M. J.: The effect of clomiphene citrate on spermatogenesis in normal men, Soc. Study of Reproduction, 2nd Annual Meeting, University of California, Davis, California, September 8-10, 1969 (abstract).

Rowley, M. J., Berlin, J.D. and Heller, C. G.: The fine structure of human spermatogonia, Soc. Study of Reproduction, 2nd Annual Meeting, University of California, Davis, California, September 8-10, 1969 (abstract).

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, in Advances in Experimental Medicine & Biology, Vol. 10. "The Human Testis", Eugenia Rosemberg and C. A. Paulsen (eds.), Plenum Publishing Corporation, New York, 1970, pp. 249-259.

Rowley, M. J., Teshima, F. and Heller, C. G.: Duration of transit of spermatozoa through the human male ductular system, Fertil. & Steril., 21:390-396, 1970.

IBID: Urology Digest, 9:62, 1970 (abstract).

Heller, C. G., Morse, H. C. and Rowley, M. J.: The effect of testosterone on the normal testis, Proceedings of the 52nd Annual Meeting of The Endocrine Society, St. Louis, Missouri, June 10-12, 1970, pp. 50 (abstract).

Rowley, M. J. and Heller, C. G.: Embryology, anatomy and histology of the male sexual organs, in Fertility Disturbances in Men and Women, pp. 48-64, Karger/Basel, 1971.

Rowley, M. J., Berlin, J. D. and Heller, C. G.: The ultrastructure of four types of human spermatogonia, Zeitschrfit fur Zellforschung, 112:139-157, 1971.

Rowley, M. J. and Heller, C. G.: Quantitation of the cells of the seminiferous epithelium of the human testis employing the Sertoli cell as a constant, Zeitschrfit fur Zellforschung, 115:461-472, 1971.

PRIVACY ACT MATERIAL REMOVED

Howard C. Morse, Ph.D.

Born:

Nationality:

Education:

1961	B.S. - Biology, George Fox College, Newberg, Oregon
1963	M.S. - Zoology-cytology, Oregon State University, Corvallis, Oregon
1967	Ph.D.- Cytology-biochemistry, Oregon State University, Corvallis, Oregon

Honors:

National Science Foundation Graduate Fellow, 1964-66

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	Sr. Investigator, 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.

Morse, H. C., Harris, P. and Dornfeld, E.: Pacifastacus Leniusculus: fine structure of arthrobranch with reference to active ion uptake, Trans. Amer. Microsc. Soc., 89:12, 1970.

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, in Advances in Experimental Medicine & Biology, Vol. 10, "The Human Testis", Eugenia Rosemberg and C. Alvin Paulsen (eds.), (Proceedings of the Workshop Conference on the Human Testis, Positano, Italy, April 23-25, 1970), Plenum Publishing Corp., New York, New York, pp. 249-259, 1970.

Heller, C. G., Morse, H. C. and Rowley, M. J.: The effect of testosterone on the normal testis. Presented to the 52nd Meeeting of The Endocrine Society, St. Louis, Missouri, June 10-12, 1970. Proceedings of The Endocrine Society, p. 50 (abstract).

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PRIVACY ACT MATERIAL REMOVED

George A. Langford, Ph.D.

Born:

Nationality:

Education:

1964	B.Sc. - Zoology and Biochemistry, University of British Columbia, Vancouver, B.C.
1965-67	M.Sc. - Zoology/cell biology, University of British Columbia, Vancouver, B.C.
1968-71	Ph.D. - Pharmacology, Loyola University, Chicago, Illinois

Honors:

Queen's Commission in the Royal Naval Reserve, 1964

Experience:

1965-67	Laboratory Teaching Assistantship in Cytology, Embryology and Histology, Department of Zoology, University of British Columbia, Vancouver, B.C.
1967-70	Laboratory Teaching Assistantship in the Department of Pharmacology and Therapeutics, Loyola University Stritch School of Medicine, Chicago, Illinois
1969	Graduate Student Lecturer in general sophomore Medical Pharmacology
1971--	Sr. Investigator, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington

Personal Publications:

Langford, G. A.: Degeneration of the germinal epithelium in the mouse and rat testis with respect to the seminiferous cycle following ligation of the vasa efferentia, M.Sc. Thesis, University of British Columbia, Vancouver, B.C. (1967).

Langford, G. A., Hollinger, M. A. and Davis, J. R.: Effect of nitrofurazone on the metabolism of D-glucose-U-^{14}C in slices of rat testes, Fed. Proc., 27:568, 1968.

Kirby, P. J., Langford, G. A. and Davis, J. R.: Effect of chlorpromazine on the incorporation of L-lysine-U-^{14}C into protein of rat testis slices, Fed. Proc., 28:774, 1969.

Davis, J. R. and Langford, G. A.: Response of the testicular capsule to acetylcholine and norepinephrine, Nature, 222:386-387, 1969.

Davis, J. R. and Langford, G. A.: The testicular capsule: a new isolated tissue preparation, The Pharmacologist, 11:276, 1969.

Davis, J. R. and Langford, G. A.: Response of the testicular capsule of the rat to autonomic drugs, J. Reprod. Fertil., 19:595-598, 1969.

Davis, J. R. and Langford, G. A.: Isolated testicular capsule: response to autonomic drugs in the rat. Second Annual Meeting of the Society for the Study of Reproduction, abstr. pp. 28, (Davis, California, 1969).

Davis, J. R., Langford, G. A. and Kirby, P. J.: The Testicular Capsule, In: "The Testis" (A. D. Johnson, W. R. Gomes and N. L. Vandemark, eds.), Vol. I, 281-337, Academic Press, New York, New York, 1970.

Davis, J. R. and Langford, G. A.: Testicular proteins, In: "The Testis" (A. D. Johnson, W. R. Gomes and N. L. Vandemark, eds.), Vol. II, 259-306, Academic Press, New York, New York, 1970.

Langford, G. A. and Davis, J. R.: Spontaneous and drug-induced contractions of the isolated testicular capsule and parenchyma, Fed. Proc., 29:248, 1970.

Davis, J. R., Langford, G. A. and Eggers, R. J.: Spontaneous contractions of the intact rabbit testis in vivo. Third Annual Meeting of the Society for the Study of Reproduction, abstr. pp. 22. (Columbus, Ohio, 1970).

Davis, J. R. and Langford, G. A.: Pharmacological studies on the testicular capsule in relation to sperm transport. In: "The Human Testis" (E. Rosemberg and C. A. Paulsen, eds.), pp. 495-514, Plenum Press, New York, 1970.

Langford, G. A.: Pharmacological and anatomical studies on the testicular capsule. Dissertation Abstr. 1971 (in press).

Davis, J. R. and Langford, G. A.: Comparative responses of the isolated testicular capsule and parenchyma to autonomic drugs, J. Reprod. Fertil., 1971 (in press).

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PRIVACY ACT MATERIAL REMOVED

Neil Horike

Born:

Nationality:

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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PRIVACY ACT MATERIAL REMOVED

David R. Leach

Born:

Nationality:

Education:

1967 B.A. - Biology, University of Texas, Austin, Texas

Experience:

1967-present Research Associate, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington

Personal Publications:

Leach, D. R. and Heller, C. G.: A method for the quantitation of Leydig cells in man, Clin. Res., 17:106, 1969 (abstract).

Heller, C. G., Lalli, M. F., Pearson, J. E. and Leach, D. R.: A method for the quantification of Leydig cells in man, J. Reprod. & Fert., 25: ___ ___, 1971 (in press)

Heller, C. G. and Leach, D. R.: Quantification of Leydig cells and measurement of Leydig-cell size following administration of human chorionic gonadotrophin to normal men, J. Reprod. & Fert., 25: ___ ___, 1971 (in press).

Leach, D. R. and Heller, C. G.: Effect of cyproterone acetate on testicular histology, sperm count, and levels of urinary and plasma gonadotropins and testosterone in the normal human male, Presented to the 53rd Annual Meeting of The Endocrine Society, San Francisco, California, June 24-26, 1971, Proceedings of The Endocrine Society.

PRIVACY ACT MATERIAL REMOVED

Michael H. H. Su

Born:

Nationality:

Education:

1958-62	B.A. National Taiwan University, Teipei, Taiwan
1963-65	B.S. Chemistry, University of South Carolina, Columbia, South Carolina
1965-67	M.S. University of Washington, Seattle, Washington

Experience:

1965 (summer)	Research Assistant, Department of Chemistry, University of South Carolina, Columbia, South Caroline (NIH Grant)
1965-66	Teaching Assistant, Department of Chemistry, University of Washington, Seattle, Washington
1966-67	Research Assistant, Department of Chemistry, University of Washington, Seattle, Washington (NIH Grant)
1967-68	Research Technologist, University of Washington Medical Center, Seattle, Washington
1968-present	Research Associate, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington

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, in Advances in Experimental Medicine & Biology, Vol. 10, "The Human Testis", Eugenia Rosemberg and C. A. Paulsen (eds.), Plenum Publishing Corporation, New York, 1970, pp. 249-259.

PRIVACY ACT MATERIAL REMOVED

Florence Teshima

Born:

Nationality:

Education:

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

1951-62 Technician for Department of Anatomy, University of Oregon Medical School, Portland, Oregon.

1964-present Research Assistant, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington.

Personal Publications:

Rowley, M. J., Teshima, F. and Heller, C. G.: Duration of transport of spermatozoa through the ductular system, Clin. Res., 16:150, 1968 (abstract).

Heller, C. G., Teshima, F. and Rowley, M. J.: Duration of transport of spermatozoa through the ductular system, Advances in the Biosciences 4, Schering Symposium on Mechanisms Involved in Conception, Berlin, 1969, Pergamon Press, pp. 121-131.

Rowley, M. J., Teshima, F. and Heller, C. G.: Duration of transit of spermatozoa through the human male ductular system, Fertil. & Steril., 21:309-396, 1970.

Rowley, M. J., Teshima, F. and Heller, C. G.: Duration of transit of spermatozoa through the human male ductular system, Urology Digest, 9:62, 1970 (abstract).

PRIVACY ACT MATERIAL REMOVED

Glenn A. Warner, M.D.

Born:

Nationality:

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).

PRIVACY ACT MATERIAL REMOVED

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.
1946-68	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, Medical Service, Oregon State Penitentiary, Salem, Oregon.
1956-66	Division Surgeon, Oregon National Guard.

Yoshiko Osborne

Born:

Nationality:

Education:

High School - Hiranuma School, Yokohama, Japan
Graduated, 1949.

Experience:

1965-67	Photographic Assistant, Pacific Northwest Research Foundation, Seattle, Washington.
1967-present	Photographic Assistant and Histology Technician, Division of Reproductive Physiology, Pacific Northwest Research Foundation, Seattle, Washington.

VI. FINANCIAL INTERACTIONS

A. OTHER RESEARCH SUPPORT

The Ford Foundation: "Hormonal and chemical agents as contraceptives im men - An investigation of their effectiveness and mechanism of action".

Grant period: August 1, 1968 through July 31, 1971

Grant award: $357,370.00

As of July 31, 1971, this grant period will be concluded.

B. TRAVEL

It has been our pattern for Dr. Heller to go to the Oregon State Penitentiary at least twice a month, usually spending two working days each time. Transportation to Salem may be by own car (12¢/mile) or more usually by airplane, renting a car in Portland or Salem. If plane transportation is used, the cost per trip is more expensive.

We are requesting travel funds for two meetings: The Laurentian Hormone Conference in Mt. Tremblant, to which Dr. Heller has been invited, and the 1972 Endocrine Society meeting to be held in Washington, D.C. (together with the IV International Congress of Endocrinology). We consider these to be the most important annual meetings in our field occurring during this grant year.

C. STIPENDS FOR INMATE VOLUNTEERS AT THE OREGON STATE PENITENTIARY

We are requesting $270 per individual subject to pay for exposure to radiation, submission to several subsequent testicular biopsies, the collection of urine for hormone studies, the collection of weekly

samples of seminal fluid and for vasectomies. The volunteers are paid $10.00 per month while on the program. This includes, at times, many months of control studies. They receive $10.00 for each testicular biopsy (including control), and $150.00 bonus for satisfactory completion of the program. At Christmas and on other occasions the subjects who are cooperating well are advanced money against their anticipated bonus. Occasionally additional "bonus" payments are made. Incidental costs at the Penitentiary laboratory are also taken from this fund.

D. INDIRECT COST ALLOCATION RATE

We propose that the 20% indirect cost rate be continued. Based on figures verified by Benson & McLaughlin, Auditors for the Pacific Northwest Research Foundation, the indirect cost rate for the fiscal year ending June 30, 1970 is 23.6% of total direct costs. Substantiating data can be furnished if required. Therefore the 20% rate has again been used in this budget.

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 - 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 function 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 teaching, 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 a Corning pH meter; Kahn-type automatic shaker, Burrell wrist-action automatic shaker, Beckman Model B spectrophotometer, Labine incubator, Rotovapor, water baths, hot plates; drying 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 also have 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 revised policy of the Pacific Northwest Research Foundation with regard to research involving human subjects was accepted by the Department of Health, Education, and Welfare, National Institutes of Health, in June of 1970. Copies of the letter of acceptance from the Institutional Relations Section, Division of Research Grants and our current Policy and Procedures of the Pacific Northwest Research Foundation with regard to investigations involving human subjects, are attached.

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.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

June 23, 1970

William B. Hutchinson, M.D.
President and Director
Pacific Northwest Research Foundation
1102 Columbia Street
Seattle, Washington 98104

Dear Dr. Hutchinson:

The revised assurance dated May 28, 1970 submitted by the Pacific Northwest Research Foundation for protection of the individual as a research subject is hereby accepted.

We appreciate your cooperation and trust you will continue to keep us informed of any changes in policies, procedures, or committee composition as they occur.

Sincerely yours,

R. C. Backus

R. C. Backus
Institutional Relations Section
Division of Research Grants

3001140

May 27, 1970

Owen W. Scott
Institutional Relations Section
Division of Research Grants
Department of Health, Education,
and Welfare
National Institutes of Health
Bethesda, Maryland 20014

Dear Mr. Scott:

Enclosed is the revised Policy and Procedures of the Pacific Northwest Research Foundation with regard to Investigations Involving Human Subjects. We have changed the membership of our Review Committee to include an attorney, a nurse and a local businessman. (See Attachment B). We feel that our reviews will benefit greatly from the participation of individuals not directly involved with the practice of medicine.

Our institution has had considerable experience with this problem over the last eleven years. To date our experiences have been happy, from every standpoint, and we are hoping to continue in this climate.

I hope that our revisions meet all the necessary requirements as outlined inyour letter of December 10, 1969. However, if any additional clarification is needed, please let me know.

Sincerely yours,

William B. Hutchinson, M.D.
President and Director

WBH/cmm
Encl.

3001141

POLICY AND PROCEDURES OF THE PACIFIC NORTHWEST RESEARCH FOUNDATION WITH REGARD TO INVESTIGATIONS INVOLVING HUMAN SUBJECTS

I. Ethical Policy. Since 1958 the investigators of this Foundation have conducted all research under the ethical provisions of the Nuremburg Code, modified to permit consent by parents or legal guardians.

II. Administrative Review. All applications for funds must be reviewed by the Director; this review is chiefly concerned with completeness, budget accuracy and conformance with granting agency policy. The Director is also required to ascertain that projects involving human subjects have been referred to the proper committees for scientific and ethical review.

All proposals are initially submitted to the Medical Research Board for review of their scientific merit. All applications for support of research training or general research support projects, including those of fellows and trainees, which involve the use of human subjects must be approved by the Medical Research Board and the Review Committee for Research Involving Human Subjects before approval by the Director and submission to the granting agency. Specially selected consultants are called upon to comment on any scientific or ethical questions for the information of the Medical Research Board and the Review Committee for Research Involving Human Subjects.

See also Attachment A - "Institutional Assurance on Research Involving Human Subjects".

III. Membership of Review Committee for Research Involving Human Subjects. This Review Committee bears the primary responsibility for review and approval of methods used to deal with the use of human subjects at the Pacific Northwest Research Foundation. It is made up of mature, competent individuals in the fields of surgery, internal medicine, ophthalmology and microbiology, the Director of The Swedish Hospital Medical Centerm the Head of the Department of Pathology of The Swedish Hospital Medical Center, the Director of the Tumor Institute of The Swedish Hospital Medical Center, the Chaplain of The Swedish Hospital Medical Center, an attorney, a nationally respected business man, a Registered Nurse and the President of the Board of Trustees of the Pacific Northwest Research Foundation.

See Attachment B - Membership of the Review Committee for Investigations Involving Human Subjects of the Pacific Northwest Research Foundation

IV. Initial Review by Committee. All applications are considered by the Medical Research Board in the exact form to be used in submission to the granting agency. Subsequently, all proposals involving human subjects are submitted to the Review Committee for Research Involving Human Subjects and the investigators must discuss and be prepared to defend in person the following points:

1. A detailed discussion of the possible risks to the rights and welfare of human subjects, including the right of privacy and freedom from undue harrassment, and a description of the provisions made to minimize these risks.

2. Methods used to acquire informed consent, with special emphasis on their appropriateness to the individual study situation.

3. The relative risks involved as compared to the probable benefits to the subject and to society,

Members of the Committee who are in any way directly involved in the work covered by any project being considered will be excused during pertinent discussion.

For each application, the Committee will either certify that these points have been properly dealt with and declare that the project may be submitted to the agency, or recommend to the Director that submission be delayed until specific deficiencies (spelled out in writing) are adequately dealt with. The Committee's findings will be transmitted in writing to the Director and the investigator.

V. Continuing Review by Committee. The Review Committee meets quarterly. The Committee, the membership of which is available at all times, will be convened by the Director for emergent problems. Investigators in charge of projects involving human subjects are required to submit status reports to the Committee, at appropriate intervals. Any unusual circumstances or procedural changes will be reported immediately to the Committee Chairman. The Chairman will maintain a project log summarizing all Committee actions, including discussions on these reports. If a report is delinquent, the Chairman will contact the investigator to ascertain the status of the study protocol. If at any time the Committee is dissatisfied with the conduct of the project or with the cooperation of the investigator, they shall recommend that financial support of the project be withheld immediately until the deficiencies are corrected.

If any investigator plans a change in study protocol, he will submit the proposed changes to the Committee for their approval, before putting them into practice.

VI. Provisions to protect the health and safety of human subjects. Any research conducted involving possible risk to human subjects will be done at The Swedish Hospital Medical Center where complete patient care is available in a 500-bed facility. The Pacific Northwest Research Foundation is situated on the campus of The Swedish Hospital Medical Center.

VII. Applicability of this assurance. This assurance applies to the Pacific Northwest Research Foundation.

ATTACHMENT A

INSTITUTIONAL ASSURANCE ON RESEARCH INVOLVING HUMAN SUBJECTS

The Pacific Northwest Research Foundation will comply with the principles of the Public Health Service policy with regard to research involving human subjects which requires a review independent of the investigator or director to safeguard the rights and welfare of those subjects. It assures the Public Health Service that it will establish and maintain advisory groups competent to review research plans involving human subjects, prior to the initiation of this research, in order to insure adequate safeguards. Group reviews and decisions will be carried out in reference to (1) the rights and welfare of the individuals involved, (2) the appropriateness of the methods used to obtain informed consent, and (3) the risks and potential benefits of the proposed research.

The Pacific Northwest Research Foundation agrees to a continuing exchange of information and advice between the review group and the investigator or director, particularly to deal with proposed changes in research design, and with emergent problems which may alter the investigational situation with regard to the criteria cited above. The Pacific Northwest Research Foundation will assure itself that its policies and the advice of its review groups are followed. It will also provide whatever professional attention or facilities are required to safeguard the rights and welfare of human subjects involved in research. Records of group review and decision on the use of human subjects and of informed consent will be developed and kept by this institution.

William B. Hutchinson

William B. Hutchinson, M.D.
President and Director
Pacific Northwest Research
Foundation

Date: May 25, 1970

ATTACHMENT B

LIST OF MEMBERS OF THE REVIEW COMMITTEE FOR INVESTIGATIONS INVOLVING HUMAN SUBJECTS OF THE PACIFIC NORTHWEST RESEARCH FOUNDATION

Mr. C. Spencer Clark
Chairman of the Board
Cascade Natural Gas Company, Seattle, Washington

William B. Hamlin, M.D.
Certified by the American Board of Anatomical and Clinical Pathology
Head of the Department of Pathology
The Swedish Hospital Medical Center, Seattle, Washington

Carl G. Heller, M.D.,Ph.D.
Head of the Division of Reproductive Physiology
Pacific Northwest Research Foundation, Seattle, Washington

William B. Hutchinson, M.D., F.A.C.S.
Certified by the American Board of Surgery
President and Director
Pacific Northwest Research Foundation, Seattle, Washington

Miss Olive Ihmels, R.N.
Head Nurse
The Swedish Hospital Medical Center, Seattle, Washington

Carl D. F. Jensen, M.D.
Certified by the American Board of Ophthalmology
Chairman, Medical Research Board
Pacific Northwest Research Foundation, Seattle, Washington

Reverend Richard E. Johnson, B.D.
Professional Hospital Chaplain
The Swedish Hospital Medical Center, Seattle, Washington

Allan W. Lobb, M.D., F.A.C.S.
Certified by the American Board of Surgery
Medical Director
The Swedish Hospital Medical Center, Seattle, Washington

Mr. David C. Lycette, L.L.D.
Attorney at Law
Seattle, Washington

ATTACHMENT B (Continued)

Vernon T. Riley, D.Sc.
Chairman, Department of Microbiology
Pacific Northwest Research Foundation, Seattle, Washington

Orliss Wildermuth, M.D., A.B.R.(T)
Certified American Board of Radiology
Director, The Tumor Institute of The Swedish Hospital Medical Center, Seattle, Washington

This list may be subject to change periodically

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

BOX: 046264

FOLDER: 1780 - HELLER PACIFIC NW RES. FOUNDA.

ASSIGNED NUMBER: RLHTS 94-0024

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