MEMO ROUTE SLIP

Form AEC-93 (Rev. May 14, 1957)

☐ See me about this. ☐ Note and return. ☐ For c[illegible]rence. ☐ For signature. ☐ For action. ☐ For information.

TO (Name and unit)	INITIALS / DATE	REMARKS
Division of Technical Information Extension Box 62 Oak Ridge, Tennessee		
TO (Name and unit)	INITIALS / DATE	REMARKS
TO (Name and unit)	INITIALS / DATE	REMARKS

FROM (Name and unit)	REMARKS
Nell W. Fraser Radiation Sciences Br. Research and Development Division RLOO	Attached is one copy each of First and Second yearly Progress Report under Contract AT(45-1)-1780, Pacific Northwest Research Foundation. This material is assigned RLO 1780-7 and RLO 1780-8 respectively under the numbering system for research reports attached.
PHONE NO. / DATE: 5/4/66	

Form AEC-427

USE OTHER SIDE FOR ADDITIONAL REMARKS

U. S. GOVERNMENT PRINTING OFFICE : 1957 -O-422007

BEST COPY AVAILABLE

727341

RLHTS94-0072

1190268

REPOSITORY DOE-Richland
GSSC Human Test Subject Studies
COLLECTION Prisoner Study
BOX No. 027253
FOLDER N/A

MEMO ROUTE SLIP

Form AEC-93 (Rev. May 14, 1947)

☐ See me about this. ☐ Note and return. ☐ For c[illegible]ence. ☐ For signature. ☐ For action. ☐ For information.

TO (Name and unit)	INITIALS / DATE	REMARKS
Div. of Technical Information Extension Oak Ridge Operations Office		
TO (Name and unit)	INITIALS / DATE	REMARKS
TO (Name and unit)	INITIALS / DATE	REMARKS

FROM (Name and unit)	REMARKS
N.W.Fraser, Radiation Sciences Branch Research & Development Division RLOO	Attached are completed forms AEC-427 which are applicable to various abstracts and material submitted by Pacific Northwest Research Foundation. This material was transmitted to you on January 26, 1966.
PHONE NO. / DATE 3-22-66	

USE OTHER SIDE FOR ADDITIONAL REMARKS

U. S. GOVERNMENT PRINTING OFFICE : 1957—O-422007

1190269

RLHTS94-0073

KLO-1780-5

THE ENDOCRINE SOCIETY

Palmer House
Chicago, Illinois
June 20 - 22, 1966

URINARY TESTOSTERONE EXCRETION AS AN INDEX OF TESTICULAR SECRETION. Donald R. Brusca, Ph.D. (by invitation), Janice M. Kastella, B.A. (by invitation), and Carl G. Heller, M.D.,Ph.D., Pacific Northwest Research Foundation, Seattle, Wash.

Urinary testosterone (both epimers) has been quantitated by a gas-chromatographic method to determine if excretion of testosterone in the urine truly reflects testicular secretion of this hormone. The mean total testosterone excretion for thirty normal males was 96μg/day (range 49-158); for three normal females was 6μg/day (3-8); and for a castrate subject was less than 17μg/day. Testicular Leydig-cell stimulation was induced with human chorionic gonadotrophin or Clomiphene citrate. Administration of HCG to four subjects increased urinary testosterone from 85μg/day to 252μg/day. Clomiphene citrate administration increased testosterone excretion from 72μg/day to 230μg/day. Identical treatment of the castrate subject with HCG and Clomiphene citrate produced no increase in urinary testosterone excretion. A biphasic urinary testosterone reaction resulted from a 600r X-ray dose to the testes. Testosterone excretion increased from 102μg/day to 170μg/day one week after irradiation and then decreased to 50μg/day for twelve weeks. These studies suggest that the excretion of testosterone in the urine is a good index of testicular production of this hormone.

1190270

MEMO ROUTE SLIP
Form AEC-93 (Rev. May 14, ...)

See me about this.	For co... ...rence.	For action.
Note and return.	For sig... ...ure.	For information.

TO (Name and unit)	INITIALS / DATE	REMARKS
Division of Technical Information Extension Box 62 Oak Ridge, Tennessee		
TO (Name and unit)	INITIALS / DATE	REMARKS
TO (Name and unit)	INITIALS / DATE	REMARKS

FROM (Name and unit)	REMARKS
Nell W. Fraser Radiation Sciences Br. Research and Development Division RLOO	Attached is one copy of Abstract of Paper under Contract AT(45-1)-1780, Pacific Northwest Research Foundation. Form AEC-427 attached
PHONE NO. / DATE 6/1/66	

USE OTHER SIDE FOR ADDITIONAL REMARKS

U. S. GOVERNMENT PRINTING OFFICE : 1957—O-422007

1190271

RLHTS94-0074

MEMO ROUTE SLIP

Form AEC-93 (Rev. May 14, 1947)

See me about this. | For c rence. | For action.
Note and return. | For signature. | For information.

TO (Name and unit)	INITIALS / DATE	REMARKS
Paul S. Henshaw Division of Biology and Medicine Headquarters		
TO (Name and unit)	INITIALS / DATE	REMARKS
TO (Name and unit)	INITIALS / DATE	REMARKS

FROM (Name and unit)	REMARKS
Nell W. Fraser Radiation Sciences Br. Research and Development Division RLOO	Attached are 4 copies of Abstract of Paper under Contract AT(45-1)1780, Pacific Northwest Research Foundation. One copy has been forwarded to DTIE, Oak Ridge
PHONE NO. / DATE 6/1/66	

USE OTHER SIDE FOR ADDITIONAL REMARKS

U. S. GOVERNMENT PRINTING OFFICE : 1957—O-422007

1190272

P-LO-1780-6

D

III INTERNATIONAL PHARMACOLOGIC

SÃO PAULO, 24-30 July, 1966

ABSTRACT OF PAPER

Maximum: 300 words

TITLE. Author/s (Laboratory, City and Country).

CLASSIFY YOUR PAPER IN ONE OF THE SUBJECTS MENTIONED: N.° 11

TITLE OF PAPER Factors Affecting Testicular Function in Man

NAME(s) OF AUTHOR(s) Carl G. Heller, M.D., Ph.D.

FULL MAILING ADDRESS Pacific Northwest Research Foundation
1102 Columbia Street, Seattle, Washington 98104 U.S.A.

☐ Short Communication

☐ Lecture

☒ Contribution to Symposium or Round Table Discussions

31 May 1966 (Date)

Carl G. Heller (Signature)

PLEASE TYPE AND RETURN NOT LATER THAN FEBRUARY 15.

1190273

FACTORS AFFECTING TESTICULAR FUNCTION IN MAN

Drugs that increase testicular function in man:

1. Human chorionic gonadotropin (HCG) 4000 IU injected thrice weekly increases Leydig-cell function in hypogonadotropic eunuchoids, delayed adolescence and normal men. This is manifest clinically by maturation, increased urinary testosterone, estrogen and 17-ketosteroid output. At the same time spermatogenesis falls to zero in normal men.

2. Clomiphene 50 to 100 mgm daily orally, increases pituitary interstitial-cell-stimulating hormone (ICSH), urinary testosterone, estrogens, 17-ketosteroids and spermatogenesis. At 400 mgm daily spermatogenesis is depressed.

3. Testosterone rebound. Most forms of testosterone and norethandrolone, given in doses that will suppress spermatogenesis to azoospermia in 6 - 10 weeks, will result in increases in sperm output circa 6 - 12 months after discontinuing. This applies to normal as well as infertile men.

Drugs that decrease testicular function in man:

1. Testosterones.

2. Estrogens.

3. Progestins (including norethynodrel, norethindrone, norethandrolone, progesterone, 17α-hydroxyprogesterone caproate).

Each of the above reduces spermatogenesis, for the most part, to azoospermic levels. At the same time Leydig-cell function is depressed. For each, reduction in urinary gonadotropins, ICSH, testosterone and 17-ketosteroids is found. Libido and potentia are reduced by each (except testosterone).

1190274

4. Bis(dichloroacetyl) diamines. These compounds reduce spermatogenesis to zero without affecting Leydig-cell function. They maintain azoospermia as long as administered. An undesirable side-effect is an antabuse-like reaction to imbibing alcohol.

5. X-radiation. Administering 15 to 600 r to the human testes causes a marked reduction in spermatogenesis while affecting Leydig-cell function slightly. Azoospermia endures for months to years at 100 to 600 r.

B

III INTERNATIONAL PHARMACOLOGICAL CONGRESS

SÃO PAULO, 24 - 30 July, 1966

SUBMISSION OF PAPERS

NAME(s) OF AUTHOR(s) Carl G. Heller MD, Ph.D.

MAILING ADDRESS (of presenting Author) Pacific Northwest Research Fndn.
1102 Columbia Street
Seattle, Washington 98104 U.S.A.

☐ Short Communication ☐ Lecture (by invitation) ☒ Symposium or Round Table Discussion (by inviation)

Title of paper Factors Affecting Testicular Function in Man

Please classify your paper in one of the subjects mentioned on pg. 11 of the Booklet N.° 11

Slide projector needed 3¼" x 4" ☐ 2"x2" (5x5cm) ☐ 8x8cm ☐

Epidiascope needed yes ☐ no ☐

Film projector needed 8mm ☐ 16mm ☐

Duration of film .....min.

I want to make a demonstration, for which I will need the following material: .....

☐ permanent ☐ at time of presentation Duration.....min.

I will give the demonstration..... times

The authors are requested to express measures and weights in the metric system and abbreviations in the style of Pharmacological Reviews.

To be completed by the Congress office:

☐ The above paper will be read at Lecture Room.....

on .....July, 1966, at.....

☐ As the completed abstract has not been received until February 15, it can not be published in the Proceedings.

PLEASE TYPE AND RETURN BEFORE JANUARY 31.

1190276

MEMO ROUTE SLIP
Form AEC-93 (Rev. May 14, 194[illegible])

See m[illegible]ut this.	For cor[illegible]ence.	For action.
Note and return.	For sig[illegible]re.	For information.

TO (Name and unit)	INITIALS / DATE	REMARKS
Paul S. Henshaw Division of Biology and Medicine Headquarters		
TO (Name and unit)	INITIALS / DATE	REMARKS
TO (Name and unit)	INITIALS / DATE	REMARKS
FROM (Name and unit)		REMARKS
Nell W. Fraser Radiation Sciences Br. Research and Development Division RLOO		ea. ~~Attached are 4 copies/of abstract under Contract AT(45-1)-~~ 1780, Pacific Northwest Research Foundation. One copy of each ~~forwarded to UTIE, Oak Ridge.~~
PHONE NO.	DATE 5/9/66	

USE OTHER SIDE FOR ADDITIONAL REMARKS

U. S. GOVERNMENT PRINTING OFFICE : 1957—O-422007

RLHTS94-0075

1190277

MEMO ROUTE SLIP
Form AEC-93 (Rev. May 14, 1947)

See m[illegible]ut this.	For co[illegible]ence.	For action.
Note and return.	For signature.	For information.

TO (Name and unit)	INITIALS / DATE	REMARKS
Division of Technical Information Extension Box 62 Oak Ridge, Tennessee		
TO (Name and unit)	INITIALS / DATE	REMARKS
TO (Name and unit)	INITIALS / DATE	REMARKS

FROM (Name and unit)	REMARKS
Nell W. Fraser Radiation Sciences Br. Research and Development Division RLO	Attached is one copy each of abstract under Contract AT(45-1)-1780, Pacific Northwest Research Foundation This material assigned Number RLO 1780-9 and RLO 1780-10 under the numbering system for research reports. Form AEC-427 attached.
PHONE NO. / DATE 5/9/66	

USE OTHER SIDE FOR ADDITIONAL REMARKS

U. S. GOVERNMENT PRINTING OFFICE : 1957—O-422007

1190278

RL01780-9

May 2, 1966

TIMING OF HUMAN SPERMATOGENESIS BY RADIATION DEPLETION**

M. J. Rowley, B.S.* and C. G. Heller, M.D., Ph.D.
Pacific Northwest Research Foundation
1102 Columbia Street
Seattle, Washington 98104

The testes of normal male volunteers were exposed to single doses of ionizing radiation from 100r to 300r. This dosage range was sufficient to cause degeneration of spermatogonia present at the time of radiation. At this dosage spermatocytes and spermatids do not undergo degeneration and thus are permitted to proceed with maturation; reduction division, and sperm formation in a normal manner. These biopsies were compared directly with the H^3-Thymidine biopsies of Heller and Clermont (1964). In the thymidine experiment the most advanced labeled cell was followed. In the radiation experiment the least advanced remaining cell was followed. The least advanced cell to complete the process of spermatogenesis by forming spermatozoa was the pre-leptotene spermatocyte following radiation. The most advanced labeled cell following injection of thymidine was also the pre-leptotene spermatocyte. In each instance the time required for a pre-leptotene spermatocyte to become a mature spermatozoa was determined to be 46 days. These data reveal that after exposure to radiation the germinal epithelium denudes at the same rate as the normal germinal cells mature.

* Applying for membership to PCFS.

** This investigation was supported by Public Health Service Research Grant number HD-00804 from the National Institute of Child Health and Human Development and by Atomic Energy Commission Grant number AT(45-3)-1780 from the Division of Biology and Medicine.

1190279

CO 1780-10

URINARY TESTOSTERONE EXCRETION AS AN INDEX OF TESTICULAR SECRETION*

Donald R. Brusca, Ph.D., Janice M. Kastella, B.A., and Carl G. Heller, M.D.,Ph.D.
Pacific Northwest Research Foundation, 1102 Columbia Street, Seattle, Wash. 98104

Urinary testosterone has been quantitated by a gas-chromatographic method to determine if excretion of testosterone in the urine reflects testicular secretion of this hormone. The mean urinary testosterone excretion for 47 normal adult males (ages 24-56) was 89 μg/24 hrs. (range 30-176); for three normal females was 6 μg/24 hrs. (3-8); and, for a castrate male was less than 17 μg/24 hrs. Testicular Leydig-cell stimulation was induced with human chorionic gonadotropin and clomiphene citrate. Administration of HCG to five normal males increased the mean urinary testosterone from 82 μg/24 hrs. to 247 μg/24 hrs. Clomiphene citrate administration increased the mean testosterone excretion from 67 μg/24 hrs. to 194 μg/24 hrs in three normal males. Identical treatment of the castrate subject with HCG and Clomiphene citrate produced no increase in urinary testosterone excretion. Mean urinary testosterone levels were depressed from 98 μg/24 hrs. to 35 μg/24 hrs. by administration of a progestational agent (SC-9022) to two male subjects. These results suggest that the excretion of testosterone in the urine may be used as a convenient and reliable index of testicular production of this hormone.

*This investigation was supported by Public Health Service Research Grant number HD-00804 from the National Institute of Child Health and Human Development and by Atomic Energy Commission Grant number AT(45-3)-1780 from the Division of Biology and Medicine.

May 2, 1966

1190280

MEMO ROUTE SLIP

Form AEC-93 (Rev. May 14, 1947)

See me about this.	For concurrence.
Note and return.	For signature.
	For action.
	For information.

TO (Name and unit)	INITIALS / DATE	REMARKS
Paul Henshaw Division of Biology and Medicine Headquarters		
TO (Name and unit)	INITIALS / DATE	REMARKS
TO (Name and unit)	INITIALS / DATE	REMARKS

FROM (Name and unit)	PHONE NO.	DATE	REMARKS
Nell W. Fraser Radiation Sciences Br. Research and Development Division, RLCO		9/19/66	Attached is ~~one copy~~ four copies each of three documents under contract AT(45-1)-1780, Pacific Northwest Research Foundation.

USE OTHER SIDE FOR ADDITIONAL REMARKS

U. S. GOVERNMENT PRINTING OFFICE : 1957 : O-422007

RLHTS94-0076

1190281

MEMO ROUTE SLIP
Form AEC-93 (Rev. May 14, 1947)

See me about	For concurrence.	For action.
Note and return.	For signature.	For information.

TO (Name and unit)	INITIALS / DATE	REMARKS
Division of Technical Information Extension Oakk Ridge, Tennessee		
TO (Name and unit)	INITIALS / DATE	REMARKS
TO (Name and unit)	INITIALS / DATE	REMARKS

FROM (Name and unit)	REMARKS
Nell W. Fraser Radiation Sciences Br. Research and Development Division, RLOO	Attached is one copy each of three documents under Contract AT(45-1)-1790, Pacific Northwest Research Foundation. Also enclosed are Form-427 for each.
PHONE NO. / DATE 9/19/66	

USE OTHER SIDE FOR ADDITIONAL REMARKS

U. S. GOVERNMENT PRINTING OFFICE : 1957 - O-422007

1190282

KLO-1780-12

Timing of Human Germinal Cell Depletion Following X-Radiation*

Mavis J. Rowley, B.S. and Carl G. Heller, M.D., Ph.D.
Pacific Northwest Research Foundation
1102 Columbia Street
Seattle, Washington 98104

We exposed the testes of normal male volunteers to single doses of ionizing radiation. 100r to 300r was sufficient radiation to cause degeneration of spermatogonia without causing damage of spermatocytes and spermatids. Thus spermatocytes and spermatids are permitted to proceed with maturation, reduction division and sperm formation in a normal fashion. Biopsies were taken at intervals during cell depletion and compared with the H^3-thymidine biopsies of Heller and Clermont (1964). In the thymidine experiment the most advanced remaining cell was followed. After radiation the least advanced remaining cell to complete maturation to spermatozoa was the pre-leptotene spermatocyte. Following thymidine injection, the most advanced labeled cell was also the pre-leptotene spermatocyte. Maturation from a pre-leptotene spermatocyte to spermatozoa required 46 days in each instance. Thus we find from these data that following radiation the germinal epithelium denudes at the same rate as the normal germinal epithelium matures.

*This investigation was supported by Public Health Service Research Grant number HD-00804 from the National Institute of Child Health and Human Development and by Atomic Energy Commission Grant number AT(45-3)-1780 from the Division of Biology and Medicine.

1190283

RLO-1780-13

The Effect of Human Chorionic Gonadotropin on Leydig-Cell Number and Size*

Joyce E. Pearson, M.S., Michael F. Lalli, M.A., and
Carl G. Heller, M.D., Ph.D.
Pacific Northwest Research Foundation
1102 Columbia Street
Seattle, Washington 98104

Four normal men were given 4000 I.U. injections of human chorionic gonadotropin (HCG) three times a week for six weeks. Biopsies obtained after one and/or six weeks of treatment were compared with control biopsies using a new method for quantitating Leydig-cells. The number of Leydig-cells counted in a given area was compared to the number of Sertoli-cells in the same area, results being expressed as a ratio (Leydig-cell/Sertoli-cell). The cytoplasm, nucleus, and nucleolus were measured with a Filar ocular micrometer at 1000X. There was no statistical increase in the size of the cells after treatment. The number of Leydig-cells present during the control period is generally reflected by the control urinary testosterone values. Maddock and Nelson in 1952 (Journal of Clinical Endocrinology and Metabolism 12: 985-1011) reported an increase in Leydig-cell numbers after chorionic gonadotropin stimulation. However, in this study the Leydig-cells did not increase in number after stimulation with HCG even though urinary testosterone levels increased threefold.

*This investigation was supported by Public Health Service Research Grant number HD-00804 from the National Institute of Child Health and Human Development and by Atomic Energy Commission Grant number AT(45-3)-1780 from the Division of Biology and Medicine.

1190284

KLO-1780-14

Urinary Testosterone: Index of Leydig-Cell Function*

Janice M. Kastella, B.A., Donald R. Brusca, Ph.D.,
and Carl G. Heller, M.D., Ph.D.
Pacific Northwest Research Foundation
1102 Columbia Street
Seattle, Washington 98104

Combined urinary epitestosterone and testosterone have been quantitated using a gas-chromatographic method to establish an index of testicular Leydig-cell function. Data from 47 normal male subjects showed a mean daily output of 89μg (range 30 to 176); from 4 normal females 7μg/day (range 3 to 10); and from one orchiectomized subject 17μg/day. Stimulation of testicular steroid production with human chorionic gonadotropin (HCG) caused increases in urinary testosterone from 80μg/day to 247μg/day and with clomiphene citrate the increase is from 60μg to 176μg/day. Similar treatment of the castrate male produced no rise in testosterone excretion. Administration of a progestational agent (SC-9022) to two male subjects caused depression of testosterone levels from 98μg/day to 35μg/day. These data indicate that urinary testosterone values are a valid and useful index of testicular production of this hormone.

*This investigation was supported by Public Health Service Research Grant number HD-00804 from the National Institute of Child Health and Human Development and by Atomic Energy Commission Grant number AT(45-3)-1780 from the Division of Biology and Medicine.

1190285