

727348

Elmer Harvey
Division of Biology and Medicine, HQ.

December 2, 1966

William M. Harris, Radiation Sciences Branch
Research and Development Division

CONTRACT AT(45-1)-1780 - PACIFIC NORTHWEST RESEARCH FOUNDATION

Enclosed are the following technical reports:

"Significance of Urinary Testosterone: Estimation of Leydig
Cell Function" *RLC-1780-18*

"The Timing of Human Spermatogenesis as Determined by
X-Irradiation Depletion" *RLC-1780-17*

"Leydig Cell size and Number: The Effect of Human Chorionic
Gonadotropin Administration in Five Normal Men" *RLC-1780-15*

These reports were submitted by Dr. Carl G. Heller, principal investigator under the subject contract. These reports have received patent clearance through the RL representative of the Chicago Patent Group.

Enclosures:
Technical Reports (4 each)

cc: DTIE, Oak Ridge w/cys.
and Forms AEC-427

BEST COPY AVAILABLE

1190312

REPOSITORY DOE-Richland
GSSE Human Test subject Studies
COLLECTION Prisoner Study

BOX No. 027253

FOLDER NIA

**REQUEST FOR PATENT CLEARANCE
FOR PUBLIC RELEASE OF UNCLASSIFIED DOCUMENT**

TO: CHIEF, CHICAGO PATENT GROUP
U. S. ATOMIC ENERGY COMMISSION
9800 S. CASS AVENUE
ARGONNE, ILLINOIS

FROM: Acting Chief, Radiation Sciences Branch, Research and Development Division
U. S. Atomic Energy Commission
P. O. Box 550
Richland, Washington 99352

1. DOCUMENT IDENTIFICATION:

Significance of Urinary Testosterone: Estimation of Leydig Cell Function
RLC-1730-13

2. RELEASE IDENTIFICATION

Document will be presented orally 1/7/67 at Northwest Society for Clinical Research



3. RETURN OF DOCUMENT IS NECESSARY



4. DOCUMENT IS SUBMITTED FOR PATENT CLEARANCE. UNLESS OTHERWISE ADVISED WITHIN THREE WEEKS OF DATE, PATENT CLEARANCE WILL BE UNDERSTOOD. IN ORDER TO MEET A PUBLICATION SCHEDULE OR SUBMISSION DEADLINE, PATENT CLEARANCE BY _____ WOULD BE DESIRABLE.



5. DOCUMENT IS SUBMITTED FOR INFORMATION ONLY, PATENT CLEARANCE BEING UNDERSTOOD BECAUSE:



**a. THE DOCUMENT WILL NOT BE PUBLISHED PRIOR TO _____
(NOT LESS THAN TWO MONTHS FROM DATE.)**



b. THE DOCUMENT CLEARLY DISCLOSES ONLY INHERENTLY UNPATENTABLE SUBJECT MATTER.



c. THE DOCUMENT CLEARLY DISCLOSES NO POSSIBLY PATENTABLE SUBJECT MATTER NOT DISCLOSED IN THE FOLLOWING PUBLISHED OR DECLASSIFIED DOCUMENTS:



d. EMERGENCY CLEARANCE HAS BEEN OBTAINED FROM THE RICHLAND REPRESENTATIVE.

6. THE SUBJECT MATTER DISCLOSED RELATES TO THE FOLLOWING INVENTION REPORTS OR AEC CASES:

7. THE SUBJECT MATTER DISCLOSED IS RELATED TO OTHER PUBLISHED OR DECLASSIFIED DOCUMENTS AS FOLLOWS:

(SIGNED) *Neil W. Fraser*

(DATE) 11/21/66

TO: INITIATOR OF REQUEST

FROM: CHIEF, CHICAGO PATENT GROUP



8. NO PATENT OBJECTION TO ABOVE-IDENTIFIED RELEASE.



9. PLEASE DEFER RELEASE UNTIL ADVISED.



a. DETERMINATION AS TO DESIRABILITY OF FOREIGN FILING MUST BE MADE PRIOR TO RELEASE.



b. FOREIGN FILING IS DESIRABLE AND A PATENT APPLICATION MUST BE FILED PRIOR TO RELEASE.



10. DOCUMENT RETURNED HERewith.

(SIGNED) *John H. ...*

(DATE) 11/30/66

SIGNIFICANCE OF URINARY TESTOSTERONE: ESTIMATION OF
LEYDIG CELL FUNCTION

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

A gas chromatographic method of quantitating the combined epimers in urinary testosterone has proved useful in establishing an index of testicular Leydig cell function. The mean daily output from 46 normal males was 89 μ g (range 40 to 176), from 4 normal females, 7 μ g (range 3 to 10), and from a single orchietomized subject, 17 μ g/day.

Stimulation of testicular steroid production with human chorionic gonadotropin (HCG) in 5 subjects for periods of 6 to 18 weeks caused increases in urinary testosterone of three- to sixfold over the control levels of each individual. Highest testosterone excretion occurred during the first 2 weeks of HCG administration and elevated excretion was not consistently maintained. Clomiphene citrate administered to 3 subjects for 6 to 12 months augmented urinary testosterone threefold but also did not maintain the increased levels. Similar treatment of the castrate male produced no rise in testosterone excretion.

Administration of a progestational agent (SC-9022) to 2 male subjects caused repression of testosterone levels from 98 μ g/day to 25 μ g/day. Testicular x-irradiation of 16 subjects with 15r to 600r generally depressed testosterone excretion from control levels.

These data indicate that urinary testosterone values are a valid and useful index of testicular production of this hormone.

**REQUEST FOR PATENT CLEARANCE
FOR PUBLIC RELEASE OF UNCLASSIFIED DOCUMENT**

TO: CHIEF, CHICAGO PATENT GROUP
U. S. ATOMIC ENERGY COMMISSION
9800 S. CASS AVENUE
ARGONNE, ILLINOIS

FROM: Acting Chief, Radiation Sciences Branch
Research and Development Division
U. S. Atomic Energy Commission
P. O. Box 550
Richland, Washington 99352

1. DOCUMENT IDENTIFICATION:
The Timing of Human Spermatogenesis as Determined by H-Irradiation Depletion
RLC-1780-19

2. RELEASE IDENTIFICATION
Document will be presented orally 1/7/67 at Northwest Society for Clinical Research

DTIC clearance required

- 3. RETURN OF DOCUMENT IS NECESSARY
- 4. DOCUMENT IS SUBMITTED FOR PATENT CLEARANCE. UNLESS OTHERWISE ADVISED WITHIN THREE WEEKS OF DATE, PATENT CLEARANCE WILL BE UNDERSTOOD. IN ORDER TO MEET A PUBLICATION SCHEDULE OR SUBMISSION DEADLINE, PATENT CLEARANCE BY _____ WOULD BE DESIRABLE.
- 5. DOCUMENT IS SUBMITTED FOR INFORMATION ONLY, PATENT CLEARANCE BEING UNDERSTOOD BECAUSE:
 - a. THE DOCUMENT WILL NOT BE PUBLISHED PRIOR TO _____ (NOT LESS THAN TWO MONTHS FROM DATE.)
 - b. THE DOCUMENT CLEARLY DISCLOSES ONLY INHERENTLY UNPATENTABLE SUBJECT MATTER.
 - c. THE DOCUMENT CLEARLY DISCLOSES NO POSSIBLY PATENTABLE SUBJECT MATTER NOT DISCLOSED IN THE FOLLOWING PUBLISHED OR DECLASSIFIED DOCUMENTS:
 - d. EMERGENCY CLEARANCE HAS BEEN OBTAINED FROM THE RICHLAND REPRESENTATIVE.
- 6. THE SUBJECT MATTER DISCLOSED RELATES TO THE FOLLOWING INVENTION REPORTS OR AEC CASES:
- 7. THE SUBJECT MATTER DISCLOSED IS RELATED TO OTHER PUBLISHED OR DECLASSIFIED DOCUMENTS AS FOLLOWS:

(SIGNED) *Neil W. Fraser*
Neil W. Fraser

(DATE) *1/21/66*

TO: INITIATOR OF REQUEST

Neil W. Fraser

FROM: CHIEF, CHICAGO PATENT GROUP

- 8. NO PATENT OBJECTION TO ABOVE-IDENTIFIED RELEASE.
- 9. PLEASE DEFER RELEASE UNTIL ADVISED.
 - a. DETERMINATION AS TO DESIRABILITY OF FOREIGN FILING MUST BE MADE PRIOR TO RELEASE.
 - b. FOREIGN FILING IS DESIRABLE AND A PATENT APPLICATION MUST BE FILED PRIOR TO RELEASE.
- 10. DOCUMENT RETURNED HEREWITH.

(SIGNED) *B. F. ...*

(DATE) *11/29/65*

THE TIMING OF HUMAN SPERMATOGENESIS AS DETERMINED
BY X-IRRADIATION DEPLETION

Mavis J. Rowley and Carl G. Heller
Pacific Northwest Research Foundation
1102 Columbia Street
Seattle, Washington 98104

The testes of normal male volunteers were exposed to single doses of ionizing radiation. 100r to 300r was sufficient radiation to cause degeneration of spermatogonia without causing damage to spermatocytes and spermatids. Thus spermatocytes and spermatids were permitted to proceed normally with maturation, reduction division and sperm formation.

Biopsies were taken at intervals during cell depletion and compared with the H^3 -thymidine labeled biopsies of Heller and Clermont (Recent Progress in Hormone Research, vol. 20, 1964). In the thymidine experiment the most advanced labeled cell, the pre-leptotene spermatocyte, was followed. After radiation the least advanced remaining cell to complete development to spermatozoa was followed to maturation. It was also a 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. These radiation depletion data confirm the timing of human spermatogenesis with tritiated thymidine.

**REQUEST FOR PATENT CLEARANCE
FOR PUBLIC RELEASE OF UNCLASSIFIED DOCUMENT**

TO: CHIEF, CHICAGO PATENT GROUP
U. S. ATOMIC ENERGY COMMISSION
9800 S. CASS AVENUE
ARGONNE, ILLINOIS

FROM: Acting Chief, Radiation Sciences Branch
Research and Development Division
U. S. Atomic Energy Commission
P. O. Box 550
Richland, Washington 99352

1. **DOCUMENT IDENTIFICATION:**
"Leydig Cell Size and Number: The Effect of Human Chorionic Gonadotropin Administration in Five Normal Men" RLO-1730-20

2. **RELEASE IDENTIFICATION**
Document will be presented orally 1/7/67 at Northwest Society for Clinical Research

3. RETURN OF DOCUMENT IS NECESSARY
4. DOCUMENT IS SUBMITTED FOR PATENT CLEARANCE. UNLESS OTHERWISE ADVISED WITHIN THREE WEEKS OF DATE, PATENT CLEARANCE WILL BE UNDERSTOOD. IN ORDER TO MEET A PUBLICATION SCHEDULE OR SUBMISSION DEADLINE, PATENT CLEARANCE BY _____ WOULD BE DESIRABLE.
5. DOCUMENT IS SUBMITTED FOR INFORMATION ONLY, PATENT CLEARANCE BEING UNDERSTOOD BECAUSE:
- a. THE DOCUMENT WILL NOT BE PUBLISHED PRIOR TO _____
(NOT LESS THAN TWO MONTHS FROM DATE.)
 - b. THE DOCUMENT CLEARLY DISCLOSES ONLY INHERENTLY UNPATENTABLE SUBJECT MATTER.
 - c. THE DOCUMENT CLEARLY DISCLOSES NO POSSIBLY PATENTABLE SUBJECT MATTER NOT DISCLOSED IN THE FOLLOWING PUBLISHED OR DECLASSIFIED DOCUMENTS:
 - d. EMERGENCY CLEARANCE HAS BEEN OBTAINED FROM THE RICHLAND REPRESENTATIVE.
6. THE SUBJECT MATTER DISCLOSED RELATES TO THE FOLLOWING INVENTION REPORTS OR AEC CASES:
7. THE SUBJECT MATTER DISCLOSED IS RELATED TO OTHER PUBLISHED OR DECLASSIFIED DOCUMENTS AS FOLLOWS:

(SIGNED)

Neil W. Fraser
Neil W. Fraser

(DATE)

11/21/66

TO: INITIATOR OF REQUEST

FROM: CHIEF, CHICAGO PATENT GROUP

8. NO PATENT OBJECTION TO ABOVE-IDENTIFIED RELEASE.
9. PLEASE DEFER RELEASE UNTIL ADVISED.
- a. DETERMINATION AS TO DESIRABILITY OF FOREIGN FILING MUST BE MADE PRIOR TO RELEASE.
 - b. FOREIGN FILING IS DESIRABLE AND A PATENT APPLICATION MUST BE FILED PRIOR TO RELEASE.
10. DOCUMENT RETURNED HEREWITH.

(SIGNED)

Richard A. Berg
Richard A. Berg

(DATE)

11/30/66

LEYDIG CELL SIZE AND NUMBER: THE EFFECT OF
HUMAN CHORIONIC GONADOTROPIN ADMINISTRATION
IN FIVE NORMAL MEN

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

Human chorionic gonadotropin (HCG) stimulates the Leydig cells of the testis to produce increased amounts of testosterone. This study was undertaken to determine if such stimulation results in an increase in the size and/or number of Leydig cells.

Five subjects received injections of HCG, 4 men for 6 weeks (4000 I.U./t.i.w.) and one man for 16 weeks (4000 I.U./q.o.d.). Biopsies taken at intervals during treatment were compared with control biopsies using a new method for quantitating Leydig cells. The number of Leydig cells counted in photographed areas was compared with the number of Sertoli cells in the same areas and results expressed as a ratio (Leydig cell/Sertoli cell). The cytoplasm, nucleus and nucleolus were measured with a Filar ocular micrometer at 1000x.

The Leydig cells did not increase in number or size even though urinary testosterone levels increased at least threefold. The Leydig cell/ Sertoli cell ratios among individuals before treatment varied widely (0.19 - 0.67). This variation is generally reflected by the control urinary testosterone values.

These data indicate that although the Leydig cells are stimulated by HCG their increased activity is not reflected by an increase in their size or number.