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UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-5611

Interagency Agreement
Contract No. AT-(40-1)-3884
Contract No. V5234P-448
January 27, 1971

Veterans' Administration
Little Rock, Arkansas 72207

Attention: K. J. O'Brien
Hospital Director

A RADIOBIOLOGIC EVALUATION OF AN IN VITRO MAMMALIAN CELL
RENEWAL SYSTEM (deleted version)

Gentlemen:

Reference is made to your letter of November 23, 1970, requesting
the subject contract be extended for an additional year.

It is proposed that the portion of the said Appendix "A" which
reads "For the Contract Period January 1, 1970 through December 31,
1971." be revised to read "For the Contract Period July 1, 1970
through June 30, 1972."

If this proposal is satisfactory to the Veterans' Administration,
please have the proper official indicate acceptance thereof in the
appropriate space below and return one copy to this office.

Sincerely,

UNITED STATES ATOMIC ENERGY COMMISSION

BY: /s/ Herman M. Roth

Herman M. Roth

TITLE: Director

Laboratory and University Division

MC:JJM

ACCEPTED:

VETERANS' ADMINISTRATION

BY: /s/ W. U. Gibson

W. U. GIBSON

TITLE: Contracting Officer

DATE: February 2, 1971

CONTRACTS-3884 Veterans

W. U. Gibson

REPOSITORY *Oak Ridge Operations*
COLLECTION *Records & Admin Area*
BOX NO. *A-78-3 Bldg. 2714-H*
FOLDER *Contract 3884 Veterans*
Admin 9100P. - Dr. Glenn
Palmyra

1138181



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8811

Interagency Agreement
Contract No. AT-(40-1)-3884
Contract No. V5234P-448
June 26, 1970

Veterans' Administration
Little Rock, Arkansas 72207

Attention: K. J. O'Brien
Hospital Director

A RADIOBIOLOGIC EVALUATION OF AN IN VITRO MAMMALIAN CELL
RENEWAL SYSTEM

Gentlemen:

Reference is made to your proposal to extend the subject contract until June 30, 1971, in view of the six months' delay in the commencement of the work as described in the Appendix "A" to the Commission's letter, dated April 29, 1970, addressed to and accepted by the Veterans' Administration.

It is proposed that the portion of the said Appendix "A" which reads "For the Contract Period January 1, 1970 through December 31, 1970." be revised to read "For the Contract Period July 1, 1970 through June 30, 1971."

If this proposal is satisfactory to the Veterans' Administration, please have the proper official indicate acceptance thereof in the appropriate space below and return one copy to this office.

Sincerely,

UNITED STATES ATOMIC ENERGY COMMISSION

BY: /s/ Herman M. Roth
Herman M. Roth
Director
TITLE: Laboratory and University Division

MC:JJM

ACCEPTED:

VETERANS' ADMINISTRATION

BY: /s/ E. W. Fisher
E. W. FISHER
Contracting Officer
TITLE: _____

DATE: July 1, 1970

CONTRACTS - 388 - Veterans

CERTIFIED A TRUE COPY
BY Gilce Brown

1138182



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

Interagency Agreement
Contract No. AT-(40-1)-3884
Contract No. V5234P-448
April 29, 1970

Veterans' Administration
Little Rock, Arkansas 72207

Attention: K. J. O'Brien
Hospital Director

A RADIOBIOLOGIC EVALUATION OF AN IN VITRO MAMMALIAN CELL
RENEWAL SYSTEM

Gentlemen:

Reference is made to your proposal, as amended, for the renewal of the subject contract for the period from January 1, 1970, through December 31, 1970.

Attached hereto as Appendix "A" is a proposed summary description of the work and outline of the estimated costs for the renewal period. For the performance of this work for such period, the Commission will reimburse the Veterans' Administration forty-nine percent (49%) of the project cost estimated as \$31,238.00; provided, however, the Commission's monetary liability hereunder shall not exceed \$15,000.00. We understand the remainder of the funds required are available from your appropriation or other sources.

CONTRACTS-3884 (Veterans)

CERTIFIED A TRUE COPY

BY

Glice Brown

1138183

If this proposal is satisfactory to the Veterans' Administration, please have the proper official indicate acceptance thereof in the appropriate space below and return one copy to this office.

Sincerely,

UNITED STATES ATOMIC ENERGY COMMISSION

BY: /s/ Herman M. Roth
Herman M. Roth, Director
TITLE: Laboratory and University Division

MC:JJM

Enclosure:
Appendix "A"

ACCEPTED:

VETERANS' ADMINISTRATION

BY: /s/ H. W. Fisher
H. W. FISHER

TITLE: Contracting Officer

DATE: May 4, 1970

APPENDIX "A"

For the Contract Period January 1, 1970 through December 31, 1970.

A-I RESEARCH TO BE PERFORMED BY AGENCY

The Agency will continue studies and evaluation of the effects of fast neutrons on repair of radiation injury by cultured mammalian cells to include measurements of the rejoining of DNA breaks by L cells and Chinese Hamster cells, using both the polynucleotide kinase method and with alkaline sucrose gradients after the neutron irradiation. Results will be compared to parallel experiments in which cells are exposed to X-rays. Measurement of DNA rejoining will be compared with single cell survival studies. RBE estimates for a specific biochemical process involved in the rejoining will be developed.

The Principal Investigator expects to devote approximately 25% of his time or effort to the project.

A-II WAYS AND MEANS OF PERFORMANCE(a) Items Included in Total Estimated Cost:

| | |
|---|-------------|
| (1) <u>Salaries and Wages:</u> | \$22,396.00 |
| Dr. G. V. Dalrymple, Principal Investigator (25% of time) - \$8,000.00* | |
| Research Associate (50% of time) - \$7,215.00* | |
| Research Technician (8% of time) - \$ 826.00* | |
| Research Technician (100% of time) - \$6,355.00 | |
| (2) <u>Supplies and Materials:</u> | 6,560.00 |
| Culture Medium, Biochemicals and Radiosotopes, CO ₂ Air Mixture, Glassware, etc. | |
| (3) <u>Travel:</u> | 300.00 |
| (4) <u>Communications:</u> | 200.00 |
| (5) <u>Publications:</u> | 400.00 |
| (6) <u>Indirect Cost</u> (10% of Direct Cost exclusive of amount marked * (\$16,041.00), which are being contributed by the Agency.) | 1,382.00 |

(b) Items Significant to the Performance of This Agreement,
But Excluded From Computation of Total Cost and From
Consideration in Proportioning Costs:

None

A-III The total estimated cost of A-II (a) above for the period stated above is \$31,238.00.



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 485-4411

MC:JJM/HL

January 15, 1969

Interagency Agreement
Contract No. AT-(40-1)-3884

Veterans' Administration Hospital
Little Rock, Arkansas 72207

Attention: K. J. O'Brien
Hospital Director

Subject: A RADIOBIOLOGIC EVALUATION OF AN IN VITRO MAMMALIAN
CELL RENEWAL SYSTEM

Gentlemen:

Reference is made to a proposal, subject as above, submitted with the approval of Mr. O'Brien to the Atomic Energy Commission for its partial support. This letter and its attachments are intended as the statement of agreement between our agencies for the accomplishment of the project generally as proposed. For convenience, a summary description and outline of estimated costs is attached as Appendix "A".

Some more general provisions which we propose for inclusion are attached as Appendix "B".

For the performance of this work, the Commission will reimburse the Veterans' Administration fifty-seven percent (57%) of the project cost estimated as \$30,865.00; provided, however, that the Commission's monetary liability hereunder shall not exceed \$17,490.00. We understand that the remainder of the funds are available from your appropriation or other sources.

If this proposal is satisfactory to the Veterans' Administration, please have the proper official indicate acceptance thereof in

CONTRACTS-3884 (VET.
rdn)

CERTIFIED A TRUE COPY

BY W. J. Brown

1138187

Veterans' Administration
Hospital

- 2 -

the appropriate space below and return one copy of the agreement
to this office.

Very truly yours,

UNITED STATES ATOMIC ENERGY
COMMISSION

BY: /s/ Herman M. Roth
Herman M. Roth, Director
TITLE: Laboratory and University Division

ACCEPTED:

VETERANS' ADMINISTRATION

BY: /s/ E. W. Fisher

TITLE: Contracting Officer

DATE: January 16, 1969

CONTRACT NUMBER V5234P-448

1138188

APPENDIX "A"

For the period January 1, 1969, through December 31, 1969.

A-I RESEARCH TO BE PERFORMED BY AGENCY

The Agency will study a steady state population of cultured mammalian cells in the plateau phase by using a combination of cell survival, autoradiographic and biochemical techniques to verify the cell renewal system. These experiments will be followed by studies designed to measure the distribution of the cells within the various compartments of the intermitotic interval, as the cells move from log growth into plateau. Experiments of a converse nature will be carried out to characterize the behavior of plateau phase cells as they move into log growth. The radiobiological properties of plateau phase cells which survive an initial dose of irradiation will be measured and compared with other non-irradiated cells. The response of plateau phase cells to metabolic inhibitors of DNA, RNA, and protein synthesis will be studied.

The two Co-Principal Investigators expect to devote approximately 25% and 50%, respectively, of their time or effort to the work.

A-II WAYS AND MEANS OF PERFORMANCE(a) Items Included in Total Estimated Cost:

(1) Salaries and Wages: \$25,375.00

Dr. G. V. Dalrymple, Co-Principal Investigator
(25% of time) - \$6,000.00*
Dr. J. L. Sanders, Co-Principal Investigator
(50% of time) - \$5,875.00*
Research Associate
(100% of time)
Research Technician
(100% of time)
Research Technician
(20% of time) - \$1,500.00*

- | | |
|---|------------|
| (2) <u>Supplies and Materials:</u> | \$3,500.00 |
| Culture Medium, Biochemicals and Radioisotopes, Co ₂ Air Mixture, Glassware, etc. | |
| (3) <u>Travel:</u> | 300.00 |
| (4) <u>Publications:</u> | 100.00 |
| (5) <u>Indirect Costs</u> (10% of direct costs exclusive of amounts marked* (\$13,375.00), which are being contributed by the Veterans' Administration Hospital) | 1,590.00 |
- (b) Items Significant to the Performance of This Agree-
ment, But Excluded From Computation of Total Cost
and From Consideration in Proportioning Costs:

None

A-III The total estimated project cost of A-II (a) above for the period
stated above is \$30,865.00.

1138190

APPENDIX "B"

A. Definitions

For purposes of this agreement, "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, and "Agency" means the Veterans' Administration or any duly authorized representative thereof.

B. Costs Chargeable to Commission Funds

Subject to limitations and conditions specified in the letter agreement incorporating this Appendix, the Agency may charge the Commission, except as otherwise provided in Articles H and I hereof, the actually incurred costs necessary or incident to the performance of the work, except that no charge shall be made for general administrative or central agency overhead except to the extent otherwise provided in the letter agreement.

C. Financing

Reimbursement Agreement

Upon presentation by the Agency of proper vouchers, the Commission will reimburse the Agency for costs actually incurred on Commission work subject to any limitations on costs otherwise provided in this agreement. Requests for reimbursement shall show separately the amounts to be reimbursed for (a) operating costs, (b) capital equipment (as defined in H below), and (c) acquisition or condemnation of any real property or any facility or for plant or facility acquisition, construction or expansion.

D. Notice of Costs Approaching Total Estimated Costs

Whenever the Agency has reason to believe that the total cost of the work under this agreement will be substantially greater or less than the presently estimated cost of the work, the Agency shall promptly notify the Commission in writing. The Agency shall also notify the Commission, in writing, when the aggregate of costs incurred and outstanding commitments allowable under this agreement is equal to ninety percent (90%) (or such other percentage as the Commission may from time to time establish by notice to the Agency) of the presently estimated total costs under this agreement. When the costs incurred and outstanding commitments equal one hundred percent (100%) of such estimated total costs, the Agency shall make no further

commitments or expenditures (except to meet existing commitments) and shall be excused from further performance of the work unless and until the Commission shall increase the total estimated costs to be incurred with respect to this agreement.

E. Financial Reports

The Agency shall furnish the Commission, not later than 15 days after the close of each reporting period, monthly or other periodic cost or financial reports in such form and detail as may be required by the Commission. Any costs incurred for capital equipment or other assets shall be supported by a list showing the description, make, any serial number, and the cost of each item acquired.

F. Accounting Records

The Agency shall accumulate and account for obligations and costs incurred in connection with the work being performed under this agreement in such form and detail as may be required by the Commission.

G. Termination

The Commission may terminate this agreement upon 30 days' written notice of such termination addressed to the Agency. In the event of such termination the Agency shall be reimbursed, to the extent permitted, for obligations actually incurred to the effective date of termination, and for commitments extending beyond the effective date of termination to a date not later than the date upon which the agreement would have expired if not terminated under this paragraph, which the Agency, in the exercise of due diligence, is unable to cancel. Payments under this agreement, including payments under this article, shall not exceed the ceiling amount elsewhere specified in this agreement.

H. Capital Equipment

- (a) "Capital Equipment" means each item of equipment which is expected to have an extended period of service, generally a year or more, and has sufficient monetary value, generally of \$100 or more, to justify continuing accounting records for the item.

- (b) Unless expressly authorized by the contracting officer in advance, the Agency shall not be reimbursed or use funds made available under this agreement for the procurement or fabrication of capital equipment.
- (c) If capital equipment is purchased or otherwise acquired pursuant to an authorization under paragraph (b) above, except as may be otherwise agreed by the Commission and the Agency,
 - (1) the title thereto shall vest in the Commission;
 - (2) the Agency shall be responsible for the maintenance and safeguarding thereof; and
 - (3) the Agency shall maintain a record in such a manner as to insure adequate control and accounting satisfactory to the Commission, of capital equipment procured or fabricated.

I. Real Property and Facilities

- (a) Unless expressly authorized by the Contracting Officer in advance, the Agency shall not be reimbursed or use funds made available under this agreement for the acquisition or condemnation of any real property or any facility or for plant or facility acquisition, construction or expansion.
- (b) If the Agency acquires or condemns any real property or any facility or acquires, constructs, or expands any plant or facility pursuant to an authorization under (a) above, except as may be otherwise agreed by the Commission and the Agency,
 - (1) the title thereto shall vest in the Commission;
 - (2) the Agency shall be responsible for the maintenance and safeguarding thereof; and
 - (3) the Agency shall maintain a record thereof in such a manner as to insure adequate control and accounting satisfactory to the Commission.

J. Patents

- (a) Whenever any invention or discovery is made or conceived by an employee, a consultant, or a contractor of the Agency in the course of or under the terms of this agreement, the Agency shall furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not, and where a patent application shall be filed, and to determine the disposition of the title to and the rights under any application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Agency, for itself and for its employees, consultants, or contractors shall agree that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission, including aiding the Commission (at Government expense by proper arrangements) in the prosecution of applications for the patents and in the defense of the Government's rights in any country.
- (b) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Acts of 1946 and 1954 shall be asserted by the Agency, its employees, consultants or contractors with respect to any invention or discovery made or conceived in the course of, or under the terms of this agreement.
- (c) Except as otherwise authorized in writing by the Commission, the Agency will obtain patent agreements to effectuate the purposes of paragraphs (a) and (b) of this Article from all persons (except such clerical and manual labor personnel as will not have access to technical data) who perform any part of the work under this agreement and any other contracts entered into for performance of work called for under this agreement.
- (d) It is recognized that during the course of the work under this agreement, the Agency or its employees, consultants or contractors may from time to time desire to publish, within the limits of security requirements information regarding scientific or technical developments made or conceived in the course of or under this interagency agreement. In order that public disclosure of such information will not adversely affect the patent interests of the Commission or Agency, patent approval for release and publication shall be secured from the Commission prior to any such release or publication.

(e) In order that the regulations of the Agency may be made applicable to inventions, discoveries, or improvements, in which the Commission determines that it does not desire to file or retain all rights, the Commission agrees, if requested by the Agency, to inform it as to all such inventions, discoveries and improvements reported to the Commission hereunder which do not involve classified information or Restricted Data, and the regulations of the Agency shall be applicable thereto.

K. Security

It is not expected that work under this agreement will involve Restricted Data or other classified matter. In the event Restricted Data or classified matter do become involved, the Agency shall so advise the Commission and subject such data to safeguards specified by the Commission. As used in this section, "Restricted Data" means all data concerning (1) design, manufacture, or utilization of atomic weapons; (2) the production of special nuclear material; or (3) the use of special nuclear material in production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to Section 142 of the Atomic Energy Act of 1954.

L. Technical Progress Reports; Publication

The Agency will make such reports to the Commission on the progress of the work under this agreement as may be mutually agreed upon.

November 13, 1972

Dr. Glenn V. Dalrymple
Acting Chief, Nuclear Medicine Service
Veterans Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

CONTRACT NO. AT-(40-1)-3884

Dear Dr. Dalrymple:

The final report submitted by you covering work performed under Contract No. AT-(40-1)-3884 is satisfactory and concludes the obligations of the Veterans Administration under the contract.

The Statements of Costs submitted by the V. A. indicates that all of the contract funds were expended. Therefore, since full payment has been made to the V. A., we are proceeding to close out the contract.

Sincerely,

ORIGINAL SIGNED BY
— Lamar Medley

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

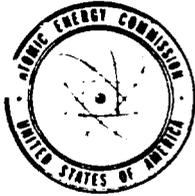
ACR:LM

CONTRACTS - 3884 (Veterans Adm. keep)

(2946

| | | | | | | |
|-----------|-----------------------------------|--|--|--|--|--|
| OFFICE ▶ | RCP&R Br. | | | | | |
| SURNAME ▶ | <i>L. Medley</i> L. Medley: cm | | | | | |
| DATE ▶ | 11-13-72 | | | | | |

1138196



UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

November 7, 1972

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division, Oak Ridge Operations Office

FINAL REPORT

Reference is made to your memorandum dated October 27, 1972.
Please be advised that the final report submitted by Glenn
Dalrymple covering work performed under Contract No. AT(04-1)3884
at Veterans Administration Hospital is satisfactory and this con-
tract may now be closed out.

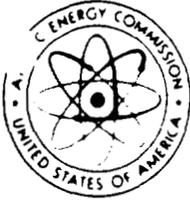
George E. Stapleton

George E. Stapleton
Radiation Biologist, Biology Branch
Division of Biomedical and
Environmental Research

(2896

CONTRACTS - 2894 - Veterans Admin
NOV 10 1972
(keep)

1138197



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 484-4411

October 27, 1972

J. R. Totter, Director, Division of
Biomedical and Environmental Research, AEC HQ

FINAL REPORT UNDER CONTRACT NO. AT-(40-1)-3884 - VETERANS ADMINISTRATION
HOSPITAL

We are enclosing two copies of the final report submitted under
Contract No. AT-(40-1)-3884.

We shall appreciate your reviewing the report and advising us whether it
is acceptable as the complete scientific report as required in Article "I"
of Appendix "B" of the contract. The concluding payment, if any, will be
made upon acceptance of the report and a Certified Expenditure Statement
covering the current period under the contract. Appropriate distribution
of the report will be made at that time.

ORIGINAL SIGNED BY

Lamar Medley

for A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR:LM

Enclosure:
Final Report (2)

RCP&R Br:

Medley
LMedley:cm

10-27-72

(2675

CONTRACTS - 3884 (2 of 4)

1138198

November 13, 1972

W. H. Henderson, Director, Finance Division, ORO

CONTRACT NO. AT-(40-1)-3884 WITH VETERANS ADMINISTRATION HOSPITAL

The work under Contract No. AT-(40-1)-3884 with the Veterans Administration Hospital has been completed and a final report has been received and accepted as satisfactory. Therefore, the obligations of the V. A. are concluded and the contract should be closed out.

Attached are one copy each of two Statements of Costs submitted by the V. A. which indicates that all of the contract funds were expended. Full payment of the Commission's monetary liability under the contract has been made to the V. A.

ORIGINAL SIGNED BY
Lamar Medley

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR:LM

Enclosures: ²
2 Statements of Costs

cc: D. E. Zachry, Patent

(2947

2947

CONTRACTS - 3884 (Veterans Admin. Hosp)

| | | | | | | |
|-----------|-----------|--|--|--|--|--|
| OFFICE ▶ | RCP&R Br. | | | | | |
| SURNAME ▶ | Medley:cm | | | | | |
| DATE ▶ | 11-13-72 | | | | | |

1138199

October 17, 1972

FINANCIAL STATEMENT 1/1/70 through 6/30/72

AEC Contract No. AT-(40-1)-3884

| | <u>Vet. Adm.</u> | <u>AEC</u> | <u>Total</u> |
|---------------------------------------|------------------|------------|-----------------|
| INCOME | \$23,728 | \$15,000 | <u>\$38,728</u> |
| EXPENSES: | | | |
| Salaries: | | | |
| Princ. Invest. (G.V. Dalrymple, M.D.) | 12,923 | | 12,923 |
| Res. Assoc. (J. L. Sanders, M. D.) | 5,737 | | 5,737 |
| Res. Tech. (S. Robinette) | | 8,371 | 8,371 |
| Res. Tech. (K. Wilkinson) | 2,911 | | 2,911 |
| Total Salaries | 21,571 | 8,371 | 29,942 |
| Materials and Supplies | -0- | 5,265 | 5,265 |
| Indirect Costs | 2,157 | 1,364 | 3,521 |
| TOTAL EXPENSES | 23,728 | 15,000 | <u>38,728</u> |

OCT 26 1972
CONTRACTS - 3884
2650

1138200

October 17, 1972

FINANCIAL STATEMENT 1/1/69 - 12/31/69

AEC Contract No. AT-(40-1)-3884

| | <u>Vet. Adm.</u> | <u>AEC</u> | <u>Total</u> |
|---------------------------------------|------------------|------------|-----------------|
| INCOME | \$19,636 | \$17,490 | <u>\$37,126</u> |
| EXPENSES: | | | |
| Salaries: | | | |
| Princ. Invest. (G.V. Dalrymple, M.D.) | \$ 6,750 | \$ -0- | \$ 6,750 |
| Res. Assoc. (J.L. Sanders, M. D.) | 8,013 | -0- | 8,013 |
| Res. Tech. (S. Robinette) | -0- | 7,387 | 7,387 |
| Res. Tech. (R. Milliken) | -0- | 5,490 | 5,490 |
| Res. Tech. (K. Wilkinson) | <u>1,500</u> | <u>-0-</u> | <u>1,500</u> |
| Total Salaries | \$16,263 | \$12,877 | \$29,140 |
| Materials and Supplies: | \$ 1,836 | \$ 3,023 | \$ 4,859 |
| Indirect Costs | \$ 1,810 | \$ 1,590 | \$ 3,400 |
| TOTAL EXPENSES | \$19,909 | \$17,490 | <u>\$37,399</u> |

OCT 26 1972

(2650

1138201

Type B-L

Contract No.

Institution

Project Leader

AT-(40-1)-3884

Veterans Administration Hospital

J. L. Sanders
G. V. Dalrymple

Purpose

"A Radiobiologic Evaluation of an In Vitro
Mammalian Cell Renewal System"

Contracting Officer

C. S. Shoup, Chief

Contract Period

1-1-69 - 12-31-69
1-1-70 - 12-31-70
1-1-70 - 6-30-72

Amount of Funds

\$17,490.00
15,000.00
No Additional Funds.

Vouchers Paid

| Amount | Disposition | Date | Amount | Disposition | Date |
|-----------------|-------------|--------------------|---------|-------------|----------|
| 1153.31 | rent pay | 2-14-69 | 2299.20 | rent pay | 10-28-70 |
| 1555.16 | " | 3-13-69 | 394.63 | " | 11-16-70 |
| 1862.48 | " | 4-15-69 | 710.60 | " | 12-16-70 |
| 1876.12 | " | 5-14-69 | 410.93 | " | 1-22-71 |
| 1272.11 | " | 6-13-69 | 388.51 | " | 2-25-71 |
| 1530.93 | " | 7-7-69 | 397.98 | " | 3-24-71 |
| 1715.64 | " | 8-29-69 | 1069.88 | " | 4-22-71 |
| 1378.35 | " | 9-20-69 | 1568.99 | " | 5-17-71 |
| 1936.77 | " | 10-27-69 | 595.01 | " | 6-16-71 |
| 1325.08 | " | 11-12-69 | 481.61 | " | 7-15-71 |
| 1287.12 | " | 12-15-69 | 458.46 | " | 8-16-71 |
| 1669 | " | 1-11-70 | 468.90 | " | 9-21-71 |
| 479.65 | " | 1-11-70 | 865.83 | " | 10-28-71 |
| 510.20 | " | 9-15-70 | 444.65 | " | 11-23-71 |
| 1254.64 | " | 9-24-70 | 667.54 | " | 1-4-72 |
| | | | 463.57 | " | 2-15-72 |
| | | | 469.41 | " | 3-8-72 |
| | | | 785.04 | " | 4-20-72 |

1138202



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 484-4411

November 13, 1972

R. A. Anderson, Assistant General Counsel for Patents, HO
R. L. Shannon, Manager, TIC, with Form AEC-427

FINAL REPORT - CONTRACT NO. AT-(40-1)-~~388~~ - **VETERANS ADMINISTRATION HOSPITAL**

In accordance with the distribution established by AEC Procurement Regulation 9-4.51, we are enclosing the final report of the work performed under Contract No. AT-(40-1)-~~388~~. This report has received patent clearance. **The report has been reviewed and accepted by the Division of Biomedical and Environmental Research, AEC HQ, as the final report required under the contract.**

A. H. Frost, Jr. Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR:LM

Enclosure:
Final Report

CC: D. S. Zachry

RCP&R Br.

LMedley:cm

11-13-72

2915

CONTRACTS - 3884 (Veterans Admin. Hosp)

1138203

October 30, 1972

Dr. Glenn V. Dalrymple
Acting Chief, Nuclear Medicine Service
Veterans Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

CONTRACT NO. AT-(40-1)-3884

Dear Dr. Dalrymple:

Enclosed, in triplicate, is a Certificate as to Reports, Notebooks and Inventions for the above contract.

If you believe that you have made any inventions under your contract with the A.E.C., please indicate to this office briefly the nature of such inventions and we will furnish you the necessary forms for reporting the invention in more detail. Our records indicate that no inventions have been reported thus far.

We find that the reports and papers listed on the Certificate have been received by the A.E.C. Please list on the Certificate any other papers presented or reports prepared in addition to those which we have listed.

Please execute the Certificates before a witness or a Notary Public and return two signed copies in the enclosed postage-free envelope. The third copy may be retained for your files.

Sincerely,

D. S. Zachry, Chief
Oak Ridge Patent Group

MCP:DSZ:dys

Enclosures:

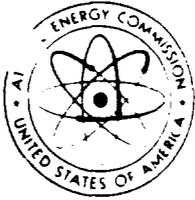
1. Certificate (in trip.)
2. Envelope

CC: A. H. Frost, Jr. ✓

(2705

CONTRACTS - 3884 (with 1000)

1138204



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-9611

October 27, 1972

D. S. Zachry, Jr., Chief, Patent Group

PATENT REVIEW OF UNCLASSIFIED DOCUMENTS - CONTRACT NO.
AT-(40-1)-3884 - **VETERANS ADMINISTRATION HOSPITAL**

In compliance with a memorandum dated August 19, 1957, symbol MCP:DSZ, subject, "Patent Review of Documents Prior to Release," we are submitting, for your review and appropriate action, one copy of the following document prepared in connection with the work being performed under the above contract:

Final Report (ORO-3884-1)

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR:LM

Enclosure:
Document

RCP&R Br.
Fredley
LMedley:cm
10-27-72

~~(2661~~

CONTRACTS - 3884 (9/27/72...)

1138205

October 10, 1972

Dr. Glenn V. Dalrymple, Chief
Radiological Service
Veterans' Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72207

CONTRACT NO. AT-(40-1)-3884

Dear Dr. Dalrymple:

Inasmuch as Contract No. AT-(40-1)-3884 expired on June 30, 1972, we shall appreciate your advising us of the status of the final technical report as provided in Article "L" of Appendix "B" to the Contract which is implemented by item 5 (b) of AEC's letter dated January 30, 1969.

In accordance with Article "F" of Appendix "B" to the Contract, as implemented by item 3 of AEC's letter dated January 30, 1969, we shall also appreciate receiving an expenditure statement covering the actual costs for the contract periods (1) January 1, 1969 through December 31, 1969, and (2) January 1, 1970 through June 30, 1972.

If appropriate, the expenditure statement should be accompanied by a voucher for the concluding payment.

Sincerely,

ORIGINAL SIGNED BY
— Lamar Medley
A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR:LM

cc: K. J. O'Brien, Veterans' Hospital

OK
21.6

CONTRACTS

CONTRACTS - 3884 (12)

| | | | | | |
|-----------|----------------------------|--|--|--|--|
| OFFICE ▶ | RCP&R Br. | | | | |
| SURNAME ▶ | <i>Medley</i> Medley:cm | | | | |
| DATE ▶ | 10-10-72 | | | | |

1138206



VETERANS ADMINISTRATION
LITTLE ROCK HOSPITAL DIVISION
300 EAST ROOSEVELT ROAD
LITTLE ROCK, ARKANSAS 72206

VA VOLUNTARY SERVICE
1946-1971
25 Years of Service
to Veteran-Patients

June 26, 1972

IN REPLY
REFER TO: 598/134

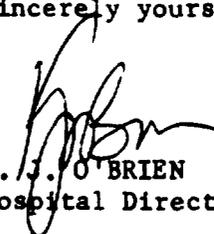
A. H. Frost, Jr., Chief
Research Contracts, Procedures and Reports Branch
Contract Division
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee 37830

Gentlemen:

This is to acknowledge receipt of letter from Mr. Ralph Elson, Director, Contract Division, notifying that Contract No. AT-(40-1)-3884 has been reassigned to you for administration, effective June 15, 1972. Appropriate administrative officials of this hospital have been notified of this reassignment.

We do not plan to request that this contract be extended beyond the expiration date of June 30, 1972.

Sincerely yours,


K. J. O'BRIEN
Hospital Director

JUN 29 1972

Show veteran's full name, VA file number, and social security number on all correspondence.

1138207



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-4444

*LND
file*

Ralph Elson, Director Contract Division

REQUEST FOR CONTRACT ACTION

It is requested that you take the necessary steps to process the following described contract action (CA):

1. Nature of Action Requested:

- Selection of New Contractor and/or Negotiation of Contract
Number:
Contractor:
- Modification of Contract
Number: AT-(40-1)-3884
Contractor: Veterans Administration Hospital

2. Nature of Services To Be Covered by Contract: Research

Title: A RADIOBIOLOGIC EVALUATION OF AN IN VITRO MAMMALIAN CELL RENEWAL SYSTEM

3. Type of Contract:

- Support Agreement
- Cost Type
- Other

4. Amount of AEC Funds To Be Obligated by this CA: None

5. AEC Percentage of Est. Total Cost To Be Shown by This CA: N/A

6. Description of Other Changes To Be Covered by This CA:

Modify the contract to extend the period from 6-30-71 - 6-30-72, without additional funds. There is no significant change in the scope of the work.

OLE

*CSShauf
1-6-71*

*OLE
Buckner
1-6-71*

7. Authority:

Form AEC-481 (Cont. Auth.) fr
J. R. Totter dated 12-29-70.

OLE: JDB

CONTRACTS -3884 (Veterans)

Herman M. Roth
Herman M. Roth, Director
Laboratory and University Division

MAR 6 1971

1138208



VETERANS ADMINISTRATION
 LITTLE ROCK HOSPITAL DIVISION
 300 EAST ROOSEVELT ROAD
 LITTLE ROCK, ARKANSAS 72206

November 23, 1970

YOUR FILE REFERENCE:

IN REPLY REFER TO:

- Mr. C. S. Shoup, Chief
 Research Contracts Branch
 Laboratory and University Division
 US Atomic Energy Commission
 P. O. Box E
 Oak Ridge, Tennessee 37830

Contract No. AT-(40-1)-3884

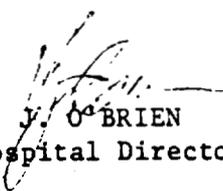
Dear Mr. Shoup:

Dr. Dalrymple, the Principal Investigator, of the project supported by the above contract, wishes to obtain an extension of this contract. Currently, the contract will terminate June 30, 1971. Because of scientific advances which have developed during the past few months, Dr. Dalrymple desires to obtain an extension--at no cost to the government--until June 30, 1972.

Dr. Dalrymple has already discussed this matter with Dr. Stapleton of the Washington office. Dr. Stapleton is agreeable to the extension--at no cost to the government.

This extension will not require any increase in government funds.

Sincerely,


 K. J. O'BRIEN
 Hospital Director

NOV 23 1970

CONTRACTS - 3884 (Veterans)

C.R.

R-10/4/6

1138211

Include Zip Code in your return address and give veteran's social security number.
 Show veteran's full name and VA file number on all correspondence. If VA number is unknown, show service number.

JAN 4 1971

Dr. E. J. O'Brien
Hospital Director
Veteran's Administration Hospital
Little Rock, Arkansas 72206

CONTRACT NO. AT-(40-1)-3884

Dear Dr. O'Brien:

In response to your letter of November 23, 1970, we have requested our Legal Office to prepare an appropriate modification to the contract to extend the period thereunder to June 30, 1972 without additional funds. The proposed modification will be forwarded to you for review and appropriate signature as soon as it is complete.

Sincerely,

ORIGINAL FILED BY
C. S. SHOUP
C. S. Shoup, Chief
Research Contracts Branch
Laboratory and University Division

OLE:JDB

CC: G. V. Dalrymple, VAH

CONTRACT - 3884 (Veteran)

1130212

| | | | | | |
|-----------|--------------|----------------|--|--|--|
| OFFICE ▶ | Adm Ser. Br. | Res. Cont. Br. | | | |
| SURNAME ▶ | BURLESON:slc | C. S. Shoup | | | |
| DATE ▶ | 1-5-71 | 1-6-71 | | | |

AUG 21 1970

Dr. K. J. O'Brien
Hospital Director
Veterans Administration
Little Rock Hospital Division
300 East Roosevelt Road
Little Rock, Arkansas 72206

CONTRACT NO. AT-(40-1)-3884

Dear Dr. O'Brien:

Thank you for your letter of August 17, 1970, requesting authorization to shift funds from one budget category to another for the current period under the above contract.

We concur in the proposed shift of funds under the contract as requested in your letter of August 17, provided no additional funds will be required from the AEC for the current period as a result of this approval.

Your letter of August 17, 1970, reflects the AEC's support to the project for the current period as \$15,197, whereas, the contract modification dated April 29, 1970, states that the AEC will reimburse the VA 49% of the project cost, provided that the AEC's monetary liability thereunder will not exceed \$15,000. You may need to change your records to reflect our support as \$15,000 rather than \$15,197.

Sincerely,

C. S. SHOUP, ACTING

C. S. Shoup, Chief
Research Contracts Branch
Laboratory and University Division

5318 OLE:JDB

~~5319~~

CONTRACTS - 3884 (Veterans)

1138213

| OFFICE | Adm. Ser. Br. | Res. Cont. Br. | | | |
|------------|-----------------|----------------|--|--|--|
| <i>Jed</i> | <i>Burleson</i> | <i>Garber</i> | | | |
| SURNAME | BURLESON:it | | | | |
| DATE | 8-20-70 | 8/21/70 | | | |



VETERANS ADMINISTRATION
LITTLE ROCK HOSPITAL DIVISION
300 EAST ROOSEVELT ROAD
LITTLE ROCK, ARKANSAS 72206
August 17, 1970

YOUR FILE REFERENCE:

IN REPLY REFER TO:

Mr. C. S. Shoup, Chief
Research Contracts Branch
Laboratory and University Division
US Atomic Energy Commission
P. O. Box E
Oak Ridge, Tennessee 37830

Contract No. AT-(40-1)-3884

Dear Mr. Shoup: ? 15,000.

Our contract funds, \$15,197.00, are divided between salaries and other categories (supplies, travel, indirect costs, etc.). In the budget revision, dated March 29, 1970, the salaries costs were to be \$6701. Since the actual salaries costs are \$4280, we request that we be allowed to transfer the remaining \$2421 into the supplies category. Also, we request that we be able to shift funds from other categories (travel, publications, etc.) into supplies, if this is needed.

This shifting of funds will not require any increase in government funds.

Sincerely,


K. J. O'BRIEN
Hospital Director

1138214

CONTRACTS - 3884-1-1
AUG 19 1970

Include Zip Code in your return address and give veteran's social security number.
Show veteran's full name and VA file number on all correspondence. If VA number is unknown, show service number.



HIGH VOLTAGE ENGINEERING CORPORATION

MIDWESTERN REGIONAL OFFICE

May 16, 1969

Dr. Dalrymple
Veterans Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

Dear Dr. Dalrymple:

Enclosed is our Proposal for moving the JN accelerator. The figure stated is slightly greater than I mentioned on the telephone, as I had forgotten to include a new target assembly, and adequate man-hours for the interconnecting wires; you will recall that all wires coming out of the accelerator base conduit have simply been cut.

We are confident that you will have excellent service from this machine in the proposed joint facility, and plan to refurbish to essentially new condition.

If you have any questions regarding the details of our Proposal, please do not hesitate to call me, Collect.

Looking forward to visiting with you again, in the future,

Sincerely,

R. J. Flimpton
Midwestern Regional Manager

RJP:lmg

Enc: HVM 76,044.

Page 2 of
Attachment 1

1138215



HIGH VOLTAGE ENGINEERING CORPORATION

BURLINGTON, MASSACHUSETTS 01803, U.S.A.

PROPOSAL NO. HVM 76,044

May 16, 1969

To: Veterans Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

Attention: Dr. Dalrymple

Fixed price proposal for transporting the Model JN Van de Graaff Accelerator, Serial No. JN-44, from the Veterans Hospital, Little Rock, to the Arkansas State Public Health Building, Little Rock, and the installation of the said unit in a designated room.

I. Equipment

The Model JN accelerator, which was previously packed by HVEC, and is in storage at the Veterans Hospital.

II. Scope of Work

a) Shipping

The pre-packed equipment will be transported by HVEC to the Arkansas State Public Health Building. All transportation expense and insurance during the moving is included in this proposal.

b) Installation

HVEC will supply necessary parts as follows:

-
1. Replace Accelerator Tube
 2. Replace Accelerator Charging Belt
 3. Replace R. F. Ion Source
 4. Replace Charging and Collecting Screens
 5. Replace Column Resistors
 6. Replace Alternator Bearings
 7. Replace Drive Motor Bearings
 8. Replace Generating Voltmeter Bearings
 9. Provide a New Beryllium Target Assembly (A-1192)
 10. Provide Interconnecting Wires to Run from Control Console to the Accelerator

It is estimated that the above components will put the accelerator in new condition. Any equipment originally supplied which is not still with the accelerator will be replaced at additional cost. Beam plumbing located outside the pressure vessel will be replaced at additional cost, if Tritium contamination is found.

HVEC will provide a Field Engineer, and the Purchaser will provide electrical power connections, and water connections, by their maintenance staff.

The Field Engineer will supervise moving, and will assemble the accelerator. The HVEC engineer will also test and demonstrate performance in accordance with the original specifications of this machine, using Hydrogen ion beam currents.

III. Training

Customer agrees to make available during the installation period a qualified technician to work under the direct supervision of the HVEC engineer. HVEC will train this personnel and any other personnel the Purchaser wishes to assign, in the proper assembly, testing and servicing procedures required for continuous top performance of the equipment. Also, the Purchaser is invited to send his personnel to our plant in Burlington for additional training.

IV. Site and Access

Purchaser will provide a room for the accelerator with necessary power, water, and drains. Wire ways or conduit between the accelerator room and the control room are the Purchaser's responsibility.

The Purchaser agrees to provide access way of sufficient size to allow the equipment to be rigged into the building.

V. Radiation Shielding

The Purchaser assumes sole responsibility for proper shielding.

VI. Schedule

The work will be scheduled in co-ordination with the Veterans Hospital. Work may start within 150 days of the date contract is signed.

VII. Drawings and Specifications

Additional copies of the original drawings will be supplied. No installation drawings for the new site will be prepared, or furnished due to the standard nature of the installation. A standard suggested installation drawing will be provided to assist the Department of Health in locating power and water terminations.

VIII. Warranty

The manufacturer warrants that the apparatus to be delivered herunder will be free from defects in materials or workmanship under recommended use and service, and no other warranty, except of title, shall be implied. The liability of the manufacturer (except as to title), arising out of the supplying of said apparatus, or its use, whether on warranty, contract or otherwise, shall not in any case exceed the manufacturer's standard replacement part price of such parts as shall, within the Warranty period, appear in the judgment of the manufacturer to have been thus defective and, upon expiration of said warranty period, all such liability shall terminate. The Warranty period commences with the date of shipment or, if the apparatus is installed or its installation supervised by the manufacturer, with the completion of installation, provided same is not unreasonably delayed by the Purchaser, and expires either one year thereafter or, in the case of particle acceleration tubes or special electronic tubes, in accordance with specifications included with the sale of said tubes.

IX. Cost

HVEC will undertake the responsibility for the aforementioned Scope of Work for a firm fixed fee of Fourteen Thousand, Seven-Hundred and Ten Dollars
 \$ 14,710.00.

X. Terms

- a) 10% down payment
- b) 40% when equipment is moved
- c) 40% upon completion of assembly at Department of Health
- d) 10% upon acceptance of performance (Voltage and Hydrogen ion beam)

PUBLICATION BY AEC AUTHORIZED

NOTICE OF RESEARCH PROJECT SCIENCE INFORMATION EXCHANGE SMITHSONIAN INSTITUTION

U.S. ATOMIC ENERGY COMMISSION

SIE NO.

AEC CONTRACT NO.

AT-40-1-2884

SUPPORTING DIV. OR OFFICE:

NAME & ADDRESS OF CONTRACTOR OR INSTITUTION: (State the division, department, or professional school, medical, graduate or other, with which this project should be identified.)

Veterans Administration Hospital, 300 E. Roosevelt Road, Little Rock, Ark. 72206 Professional Services Radiology and Radioisotope Services

TITLE OF PROJECT:

An Evaluation of the Effects of Fast Neutrons on the Repair of Radiation Injury in Cultured Mammalian Cells

NAMES, DEPARTMENT, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS AND OTHER PROFESSIONAL SCIENTIFIC PERSONNEL: (not including graduate students) engaged on the project, and fraction of man-year devoted to the project by each person.

Olson V. Dalrymple, M. D. University of Arkansas Medical Center Chief Radiologist Head, Division of Nuclear Medicine Acting Chief, Radioisotope Service Associate Professor of Radiology, Biometry, Physiology-Biophysics

3/12 year

NO. OF GRADUATE STUDENTS ON PROJECT: 1 NO. OF GRADUATE STUDENT MAN-YEARS: 3.5

SUMMARY OF PROPOSED WORK: (200-300 words, omit Confidential Data). Summaries are exchanged with government and private agencies supporting research, are supplied to investigators upon request, and may be published in AEC documents. Make summaries substantive, giving initially and for each annual revision the following: OBJECTIVE; SCIENTIFIC BACKGROUND FOR STUDY; PROPOSED PROCEDURE; TEST OBJECTS AND AGENTS.

Research during the past several years has focused upon DNA as the target primarily involved in the post-irradiation loss of proliferative capacity. Recent experiments have demonstrated that while X and gamma rays cause breaks in the DNA molecule, many of the breaks are rapidly rejoined. We have very recently shown, using the polynucleotide kinase assay system, that many post-irradiation DNA breaks are characterized by 3'OH termini. With the re-awakening of interest in neutrons for radiotherapeutic purposes, much more information is needed about the nature of radiation damage caused by neutrons. To this end we plan to measure the rejoining of DNA breaks by L cells and Chinese hamster cells (CHO) by both the polynucleotide kinase method and with alkaline sucrose gradients after neutron irradiation. These results will be compared to parallel experiments in which cells were irradiated with x-rays. The measurements of DNA rejoining will be compared with single cell survival studies. The results of the project will not only add information about the effects of neutrons on DNA rejoining, but also RBE estimates for a specific biochemical process involved in DNA rejoining will be developed. Neutron irradiations will be performed at Arkansas State Health Dept; processing of biologic samples will be performed at Little Rock Veterans Hospital. Project was started 3d Qtr, FY-1969. It is anticipated the project will be completed in FY-1972.

RESULTS TO DATE: Experiments with plateau phase Chinese hamster cells show: 1) A depression of the extrapolation number of the single cell survival curve as compared to log phase cells. 2) An increased number of endogenous single strand DNA breaks as compared to log phase cells. 3) The cells are concentrated in either the G1 or G2 phases of the inter mitotic interval. 4) Irradiated plateau phase cells show no depression of ability to repair single strand DNA breaks as compared with log phase cells.

Table with 2 columns: JUDGET (PRIMARY, SECONDARY) and PROGRAM CATEGORY NO.

Signature of Principal Investigator: Olson V. Dalrymple, MD

DATE: 16 Sep 69

INVESTIGATOR - DO NOT USE THIS SPACE

1138220

XI. Expiration Date

This Proposal is valid for thirty (30) days.

A handwritten signature in black ink that reads "R. J. Plimpton". The signature is written in a cursive style with a long horizontal line extending to the right from the end of the name.

R. J. Plimpton
Midwestern Regional Manager

RJP:lmg



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

*LUD
files*

AREA CODE 615
TELEPHONE 483-8611

JUN 11 1970

Ralph Elson, Director, Contract Division

REQUEST FOR CONTRACT ACTION

It is requested that you take the necessary steps to process the following described contract action (CA):

1. Nature of Action Requested:

Selection of New Contractor and/or Negotiation of Contract
Number:
Contractor:

Modification of Contract
Number:
Contractor: **AT-(40-1)-3884
Veteran's Administration Hospital**

2. Nature of Services To Be Covered by Contract: Research

Title: **A RADIOBIOLOGIC EVALUATION OF AN IN VITRO MAMMALIAN CELL RENEWAL**

3. Type of Contract: **SYSTEM**

Support Agreement Cost Type Other

4. Amount of AEC Funds To Be Obligated by This CA: None

5. AEC Percentage of Est. Total Cost To Be Shown by This CA: N/A

6. Description of Other Changes To Be Covered by This CA:

Please extend the period under the above contract to June 30, 1971, without additional funds. There is no significant change in the scope of the work.

*DLE
Done
6-11-70*

DLE

7. Authority:

Form AEC-481 (CA) fr
J. R. Totter dated June 5, 1970.

Herman M. Roth

Herman M. Roth, Director
Laboratory and University Division

*CS Schauf
6-11-70*

3738 JDB

AT-(40-1)-3884 (Veteran)

3738

1138222

| | | |
|---|-----------------------|------------------------------------|
| U. S. ATOMIC ENERGY COMMISSION CONTRACT AUTHORIZATION | 1. DATE JUN 5 1970 | 2. AUTHORIZATION NO. EM-70-378B |
|---|-----------------------|------------------------------------|

| | |
|---|---|
| TO S. E. Sapirie, Manager Oak Ridge Operations Office | 3.B. FROM John R. Totter, Director Division of Biology and Medicine |
|---|---|

| | |
|---|---|
| 4.A. CONTRACTOR (Name, Address, Department, etc.) VETERANS ADMINISTRATION HOSPITAL Little Rock, Arkansas 72206 Radiology Service, LR Division | 4.B. PRINCIPAL INVESTIGATOR(S) GLENN V. DALRYMPLE T. L. SANDERS |
|---|---|

| | | |
|---|--|--|
| 5. EXTENSION <input type="checkbox"/> NEW CONTRACT <input type="checkbox"/> RENEWAL <input checked="" type="checkbox"/> OTHER | 6. TERM OF CONTRACT 12-31-70 thru 6-30-71 | 7. CONTRACT NUMBER AT(40-1)3884 |
| 8. RECOMMENDED TYPE OF CONTRACT: <input type="checkbox"/> FIXED PRICE <input type="checkbox"/> OTHER <input type="checkbox"/> COST REIMBURSEMENT <input checked="" type="checkbox"/> SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA) | 9. EQUIPMENT TITLE TO VEST IN: <input type="checkbox"/> AEC <input checked="" type="checkbox"/> CONTRACTOR | 10. SECURITY CLASSIFICATION: Work to be performed is under category <u>I</u> as defined by AEC Manual Appendix 3401. |

11. PROJECT TITLE
"A Radiobiologic Evaluation of an In Vitro Mammalian Cell Renewal System"

12. HEADQUARTERS TECHNICAL CONTACT
George E. Stapleton

13. FINANCING

A. OPERATING EXPENSES

| | | |
|---|----|--------------|
| New AEC Funds | \$ | 0 |
| Estimated AEC Balance From Prior Term, if any | \$ | _____ |
| | \$ | _____ |
| Estimated Contractor Contribution, On Proportionate Sharing Basis, if any | \$ | _____ |
| Estimated Project Cost, For Pertinent Budget Period | \$ | _____ |

Budget and Reporting Classification: **06 01 01**
 Allotment Transfer: **06 01 91(24)**

B. PLANT AND CAPITAL EQUIPMENT\$
 Budget and Reporting Classification:
 Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

THIS SHALL BE THE TERMINAL YEAR FOR THIS CONTRACT.

15. SCOPE OF WORK

DNA strand-breakage and repair in logarithmic and plateau phase mammalian cells and their correlation with changes in radiosensitivity.

CONTRACT-3884 (V. A. d.)
JUN 1970



VETERANS ADMINISTRATION
LITTLE ROCK HOSPITAL DIVISION
300 EAST ROOSEVELT ROAD
LITTLE ROCK, ARKANSAS 72206

May 5, 1970

YOUR FILE REFERENCE:

IN REPLY REFER TO: 598-00

• Mr. C. S. Shoup
Chief, Research Contracts Branch
Laboratory and University Division
US Atomic Energy Commission
P. O. Box E
Oak Ridge, Tennessee 37830

Contract No. AT-(40-1)-3884

Dear Mr. Shoup:

The above contract arrived and has been processed. Under the terms of this contract, the contract period will cover January 1, 1970 - December 31, 1970. As you know, the contract did not become finalized until after May 1, 1970.

Because of the delay in funding, Dr. Dalrymple suspended work on the project. Consequently, he did not incur expenses for supplies or personnel. The project, as described, will require one year of effort to complete, however. Therefore, Dr. Dalrymple requests that the termination period be extended until June 30, 1971. This will not cause any increase in required funding because he does not plan to make expenditures against the contract until July 1, 1970.


K. J. O'BRIEN
Hospital Director

contracts
CONTRACTS - 38841-3884

MAY 8 1970

Include Zip Code in your return address and give veteran's social security number.

Show veteran's full name and VA file number on all correspondence. If VA number is unknown, show service number.

1138224

MAY 21 1970

John R. Totter, Director, Division of Biology and Medicine, HQ

CONTRACT NO. AT-(40-1)-3884 - WITH VETERANS ADMINISTRATION

Enclosed is a self-explanatory letter from the Veterans Administration dated May 5, 1970.

Please advise us whether you concur in the extension of the contract period from December 31, 1970 to June 30, 1971 without additional funds.

ORIGINAL SIGNED BY

ORIGINAL SIGNED BY
C. S. ...

JR
Herman M. Roth, Director
Laboratory and University Division
Oak Ridge Operations

OLE:JDB

Enclosure:
Ltr fr KJO dtd 5-5-70

RECEIVED
MAY 21 5 38 14 1970

MAY 21 5 38 14 1970

CONTRACTS - 3884 - Veterans

2 2812

| | | | | | | |
|-----------|---------------|-----------------|----------|--|--|--|
| OFFICE ▶ | Adm. Ser. Br. | Res. Cont. Br. | L&U Div. | | | |
| SURNAME ▶ | Burleson: lbd | <i>S. Shoup</i> | | | | |
| DATE ▶ | 5/19/70 | 5-21-70 | | | | |

1138225

JUN 11 1970

Dr. K. J. O'Brien
Hospital Director
Veterans Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

CONTRACT NO. AT-(40-1)-3884

Dear Dr. O'Brien:

Pursuant to the request made in your letter of May 5, 1970,
we have initiated action for the preparation of a modification
to Contract No. AT-(40-1)-3884 to extend the period thereunder
to June 30, 1971, without additional funds.

The contract modification will be forwarded to the Hospital
for review and appropriate signature as soon as it is complete.

Sincerely,

ORIGINAL SIGNED BY

C. S. SHOUP

C. S. Shoup, Chief

Research Contracts Branch

Laboratory and University Division

OLE:JDB *OK*

CC: G. V. Dalrymple, Vet. Adm.

6737

*ST. BIRD...
THU 11...
1970*

*-3884
(U2 team)*

| | | | | | |
|-----------|---------------------------------|--------------------|--|--|--|
| OFFICE ▶ | Adm. Ser. Br. | Res. Cont. Br. | | | |
| SURNAME ▶ | <i>Burleson</i> BURLESON:s1c | <i>C. S. Shoup</i> | | | |
| DATE ▶ | 6-11-70 | 6-11-70 | | | |

1138226



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

L of 300
[Signature]

AREA CODE 615
TELEPHONE 493-6611

MAR 30 1970

Ralph Elson, Director, Contract Division

REQUEST FOR CONTRACT ACTION

It is requested that you take the necessary steps to process the following described contract action (CA):

1. Nature of Action Requested:

Selection of New Contractor and/or Negotiation of Contract
Number:
Contractor:

Modification of Contract
Number: **AT-(40-1)-3884**
Contractor: **Veterans Administration Hospital**

2. Nature of Services To Be Covered by Contract: Research

Title: **A RADIOBIOLOGIST EVALUATION OF AN IN VITRO MAMMALIAN CELL RENEWAL SYSTEM**

3. Type of Contract:

Support Agreement Cost Type Other

4. Amount of AEC Funds To Be Obligated by This CA: **EXTENSION \$15,000.00**

5. AEC Percentage of Est. Total Cost To Be Shown by This CA: **~~100%~~ 49%**

6. Description of Other Changes To Be Covered by This CA:

Modify contract to provide for the performance of additional research to be completed during the period January 1, 1970 through December 31, 1970. The AEC' support will not exceed \$15,000.00.

OK E
Bond
3-30-70

OK
C. E. H. H.
3-30-70

7. Authority:

**Form AEC-481 (CA) fr J. R. Totter 6000.
to S. R. Sapirie dtd 2-20-70**

Herman M. Roth
Herman M. Roth, Director
Laboratory and University Division

OLE:JDB

CONTRACTS - 3884 (Veterans)

2 1970

1138227

APPENDIX "A"

For the Contract Period January 1, 1970 through December 31, 1970.

A-I RESEARCH TO BE PERFORMED BY AGENCY

The Agency will continue studies and evaluation of the effects of fast neutrons on repair of radiation injury by cultured mammalian cells to include measurements of the rejoining of DNA breaks by L cells and Chinese Hamster cells, using both the polynucleotide kinase method and with alkaline sucrose gradients after the neutron irradiation. Results will be compared to parallel experiments in which cells are exposed to X-rays. Measurement of DNA rejoining will be compared with single cell survival studies. RBE estimates for a specific biochemical process involved in the rejoining will be developed.

The Principal Investigator expects to devote approximately 25% of his time or effort to the project.

A-II WAYS AND MEANS OF PERFORMANCE(a) Items Included in Total Estimated Cost:

| | |
|---|-------------|
| (1) <u>Salaries and Wages:</u> | \$22,396.00 |
| Dr. G. V. Dalrymple, Principal Investigator (25% of time) - \$8,000.00* | |
| Research Associate (50% of time) - \$7,215.00* | |
| Research Technician (8% of time) - \$ 826.00* | |
| Research Technician (100% of time) - \$6,355.00 | |
| (2) <u>Supplies and Materials:</u> | 6,560.00 |
| Culture Medium, Biochemicals and Radiosotopes, CO ₂ Air Mixture, Glassware, etc. | |
| (3) <u>Travel:</u> | 300.00 |
| (4) <u>Communications:</u> | 200.00 |
| (5) <u>Publications:</u> | 400.00 |
| (6) <u>Indirect Cost</u> (10% of Direct Cost exclusive of amount marked * (\$16,041.00), which are being contributed by the Agency.) | 1,382.00 |

(b) Items Significant to the Performance of This Agreement,
But Excluded From Computation of Total Cost and From
Consideration in Proportioning Costs:

None

A-III The total estimated cost of A-II (a) above for the period stated above is \$31,238.00.



VETERANS ADMINISTRATION
 LITTLE ROCK HOSPITAL DIVISION
 300 EAST ROOSEVELT ROAD
 LITTLE ROCK, ARKANSAS 72206

March 29, 1970

YOUR FILE REFERENCE:

IN REPLY REFER TO:

Mr. C. S. Shoup, Chief
 Research Contracts Branch
 Laboratory and University Division
 US Atomic Energy Commission
 P. O. Box E
 Oak Ridge, Tennessee 37830

Contract No. AT-(40-1)-3884

*\$15,000
 confirmed*

Dear Mr. Shoup:

Enclosed is the revised budget for Contract No. AT-(40-1)-3884. The US AEC contribution is \$15,197 (\$13,815 plus 10% indirect). The Veterans Administration-University of Arkansas Medical Center contribution is \$16,041.

If you need more information please communicate with Dr. Dalrymple.

James C. Hickey

K. J. O'BRIEN
 Hospital Director
 Veterans Administration Hospital
 Little Rock, Arkansas

Glenn V. Dalrymple

GLENN V. DALRYMPLE, M. D.
 Head, Division of Nuclear Medicine
 Associate Professor of Radiology
 Biometry, Physiology--Biophysics
 University of Arkansas Medical Center
 Chief Radiologist
 Acting Chief, Radioisotope Service
 Veterans Administration Hospital
 Little Rock, Arkansas

Include Zip Code in your return address and give veteran's social security number.

Show veteran's full name and VA file number on all correspondence. If VA number is unknown, show service number.

1138232

BUDGET

a. Salaries †

Principal Investigator \$ 8,000

Glenn V. Dalrymple, M. D.
Head, Division of Nuclear Medicine
Associate Professor, Radiology,
Biometry, Physiology-Biophysics,
UAMC. Acting Chief, Radioisotope
Service, VAH
(3/12 time for 12 mo/year)

Research Associate 7,215 *

A. J. Moss, Jr., M. S.
(6/12 time for 12 mo/year)
FICA (371)

Research Technicians

K. P. Wilkinson, B. S., B. A. 826
(1/12 time 12 mo/year)

Rowena Millikin 6,355
(12/12 time 12 mo/year)
FICA & Uniform Allowance (346)

† All salaries include fringe
benefits. Amount of FICA
in parenthesis.

* GS-12 Salary Scale

b. Equipment

Miscellaneous Glassware \$ 500

c. Expendable Items

Tissue Culture Medium, Serum, \$ 2,000
Bacterial Culture Medium

Radioisotopes ($^{32}\text{PO}_4$), Tritiated
Compounds 1,000

Biochemicals, Small Items 1,000
Glassware

1138233

c. Expendable Items, Contd

| | |
|--|-----------|
| Plastic Flasks, Petri Dishes, Tubes, etc. | \$ 500 |
| CO ₂ --Air Mixture (\$30 per week x 52) | 1,560 |
| d. Travel | 300 |
| e. Communications | 200 |
| f. Publications (Includes page charges and reprints of publications) | 400 |
| <u>Total Project Cost</u> | \$ 29,856 |

| | |
|---|----------|
| Contribution--Veterans Administration (Dr. Dalrymple's and Mrs. Wilkinson's Salaries) | \$ 8,826 |
|---|----------|

| | |
|--|-------|
| Contribution--University of Arkansas Medical Center (Mr. Moss' Salary) | 7,215 |
|--|-------|

| | |
|----------------------------|-----------|
| <u>Total Contributions</u> | \$ 16,041 |
|----------------------------|-----------|

| | |
|--|-----------|
| Difference--Total Project Cost less Contributions | \$ 13,815 |
|--|-----------|

| | |
|------------------------------------|-------|
| Indirect Costs (10% of Difference) | 1,382 |
|------------------------------------|-------|

| | |
|-------------------------------------|-----------|
| <u>Amount requested from US AEC</u> | \$ 15,197 |
|-------------------------------------|-----------|



VETERANS ADMINISTRATION
 LITTLE ROCK HOSPITAL DIVISION
 300 EAST ROOSEVELT ROAD
 LITTLE ROCK, ARKANSAS 72206
 September 17, 1969

YOUR FILE REFERENCE:

IN REPLY REFER TO:

FINANCIAL STATEMENT 1/1/69 - 12/31/69

AEC Contract No. AT-(40-1)-3884

As of 9/17/69

| | <u>Vet. Adm.</u> | <u>AEC</u> | <u>Total</u> |
|--|--------------------|--------------------|--------------------|
| INCOME | \$19,636 | \$17,490 | <u>\$37,126</u> |
| EXPENSES: | | | |
| Salaries: | | | |
| Dr. Dalrymple (Physician) | | | |
| Actual 1/1/69-8/31/69 | \$ 4,250 | \$ -0- | \$ 4,250 |
| Est. 9/1/69-12/31/69 | 2,500 | -0- | 2,500 |
| Dr. Sanders (Physician) | | | |
| Actual 1/1/69-8/31/69 | 5,543 | -0- | 5,543 |
| Est. 9/1/69-12/31/69 | 2,470 | -0- | 2,470 |
| Robinette (Technician) | | | |
| Actual 1/1/69-8/31/69 | -0- | 4,755 | 4,755 |
| Est. 9/1/69-12/31/69 | -0- | 2,684 | 2,684 |
| Milliken (Technician) | | | |
| Actual 1/1/69-8/31/69 | -0- | 3,548 | 3,548 |
| Est. 9/1/69-12/31/69 | -0- | 1,942 | 1,942 |
| Sundry Technician Hours | | | |
| Actual 1/1/69-8/31/69 | 1,000 | | 1,000 |
| Est. 9/1/69-12/31/69 | 500 | | 500 |
| Total Salaries | <u>1/ \$16,263</u> | <u>1/ \$12,929</u> | <u>1/ \$29,192</u> |
| Materials and Supplies: | | | |
| Actual 1/1/69-8/31/69 | \$ -0- | \$ 3,039 | \$ 3,039 |
| Est. 9/1/69-12/31/69 | -0- | 1,520 | 1,520 |
| Total Materials and Supplies | \$ -0- | <u>2/ \$ 4,559</u> | \$ 4,559 |
| Indirect Costs (Includes Adm., 3/ \$ 1,626 overhead, etc., 10%) | | <u>3/ \$ 1,749</u> | <u>3/ \$ 3,375</u> |
| TOTAL EXPENSES | <u>4/ \$17,889</u> | <u>4/ \$19,237</u> | <u>4/ \$37,126</u> |

Include Zip Code in your return address and give veteran's social security number.

Show veteran's full name and VA file number on all correspondence. If VA number is unknown, show service number.

1138235

Financial Statement 1/1/69-12/31/69, Cont'd.

Footnotes:

- 1/ Salaries - This represents 25% of Dr. Dalrymple, 50% of Dr. Sanders, 100% of Kobinette and Milliken, and approximately 400 hours of various VA technicians' time or 20% of one full-time equivalent.
- 2/ Materials and Supplies - This represents actual identifiable purchase orders and documents through 8/31/69 and a prorated amount of this actual amount for the estimate through 12/31/69.
- 3/ Indirect Costs - This represents 10% of the salary and supplies paid for by AEC and the VA.
- 4/ Total Expenses - The difference between total expense and total received by AEC Grant will be absorbed by VA financing.

I certify that the above financial statement accurately reflects the status of these accounts to my best knowledge and belief.



JOHN R. PAULETTE
Chief, Fiscal Division

MAR 19 1970

Dr. Glenn V. Dalrymple
Chief, Radiology Service
Veterans Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

Dear Dr. Dalrymple:

This is to inform you that we have approved renewal of your Research Contract No. AT(40-1)3884, "A Radiobiologic Evaluation of an *in Vitro* Mammalian Cell Renewal System", for an additional year ending December 31, 1970, at a level of support considerably less than that requested. It was decided this should be the terminal year for this contract. You will be contacted by someone from the Oak Ridge Operations Office in the near future regarding negotiation of the renewal contract.

At the termination of this contract, please submit a final progress report which includes a detailed summary of your accomplishments during the period of the contract, the number of students trained, the post-doctoral fellows who have worked on the project, and the publications which have resulted from the support of your research by the Atomic Energy Commission.

Sincerely,

George E. Stapleton
Radiation Biologist, Biology Branch
Division of Biology and Medicine

cc: K. J. O'Brien
Hospital Director

EMB

STAPLETON/njb

3-17-70

1138237

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USAEC
C. S. SHOUP, CHIEF
RESEARCH CONTRACTS BRANCH
LABORATORY AND UNIVERSITY DIVISION
OAK RIDGE, TENNESSEE

RECEIVED BY
C. S. SHOUP

MAR 13 1970

GLENN V. DALRYMPLE, VETERANS ADMINISTRATION HOSPITAL, LITTLE ROCK, ARKANSAS
RADIOLOGY SERVICE, LR DIVISION

WE HAVE AUTHORIZATION TO EXTEND CONTRACT NO. AT-(40-1)-3884 TO MARCH 31, 1970,
WITH AEC FUNDS IN AMOUNT OF \$4,372. THE RENEWAL PROPOSAL IS CURRENTLY BEING
REVIEWED BY AEC HEADQUARTERS FOR FULL 12 - MONTH EXTENSION TO DECEMBER 31, 1970.
WE HAVE NOT PREPARED CONTRACT MODIFICATION FOR 3 - MONTH PERIOD SINCE WE EXPECT
ANSWER ON FULL 12 - MONTH EXTENSION SOON. 67

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|-----------|---------------|----------------|-----------|-----------------|--|--|
| OFFICE ▶ | Adm. Ser. Br. | Res. Cont. Br. | CONTRACTS | 3884 (Veterans) | | |
| SURNAME ▶ | Burleson:cte | C. S. Shoup | | | | |
| DATE ▶ | 3-13-70 | 3-13-70 | | | | |

FEB 20 1970

Dr. Glenn V. Dalrymple
Chief Radiologist
Veterans Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

Dear Dr. Dalrymple:

This is to inform you that we are extending your contract, AT(40-1)3884, 'A Radiobiologic Evaluation of an In Vitro Mammalian Cell Renewal System,' for three months beginning January 1, 1970 through March 31, 1970, at an amount pro-rated at last year's level of support.

You will be hearing from the Oak Ridge Operations Office in connection with the extension of your contract.

Sincerely,

George E. Stapleton
Radiation Biologist, Biology Branch
Division of Biology and Medicine

cc: K. J. O'Brien
Hospital Director

EMS

Stapleton:sds

2-18-70

1138239

CONTRACTS-37 (1/27)

B 1458

FEB 24 1970



VETERANS ADMINISTRATION
LITTLE ROCK HOSPITAL DIVISION
300 EAST ROOSEVELT ROAD
LITTLE ROCK, ARKANSAS 72206

September 18, 1969

YOUR FILE REFERENCE:

IN REPLY REFER TO:

- Mr. Herman M. Roth
Director
Laboratory and University Division
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee 37830

Dear Mr. Roth:

SUBJ: Renewal of Contract No. AT-(40-1)-3884

Dear Mr. Roth:

The information requested for continuation of the above contract is enclosed. You will notice that the "Progress Report" is also a portion of the renewal proposal. The copy containing the original signatures is identified.

If additional technical information is needed, please contact Dr. Dalrymple.

Sincerely,


K. J. O'BRIEN
Hospital Director

Enclosures: *4*

1. Progress Report (7)
Form AEC-427 (1)
2. Renewal Proposal (6)
3. Expenditure Statement (6)
4. Notice of Research Project (4)

cc:
US AEC, Washington, D. C.
Chief of Staff
Chief Radiologist

CONTRACTS-3357 (Veteran)

SEP 19 1969

Include Zip Code in your return address and give veteran's social security number.

Show veteran's full name and VA file number on all correspondence. If VA number is unknown, show service number.

1138240

copy



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA OFFICE #15
TELEPHONE 483-6111

September 26, 1969

John R. Totter, Director, Division of Biology & Medicine, HQ

**RENEWAL OF CONTRACT NO. AT-(40-1)- 3884 VETERANS ADMINISTRATION
HOSPITAL (Dr. K. J. O'Brien)**

**We are submitting for your review and appropriate action the
following information concerning the contract which will expire
on December 31, 1969**

- 1. Renewal Proposal (4)
- 2. Progress Report (4)
- 3. Financial Statement (4)
- 4. 200-Word Summary (3)

**We shall appreciate your advising us of your decision so that we
may proceed with the necessary contract action at the earliest
possible date.**

Herman M. Roth

Herman M. Roth, Director
Laboratory and University Division
Oak Ridge Operations

OLE:JDB

**Enclosures:
As Listed Above**

- BC: Alice Brown
- D. S. Zachry, w/cy Progress Report
- R. L. Shannon, DTIE, w/cy Progress Report & Form AEC-427
- C. S. Shoup, w/cy encls.

Burleson

Adm. Ser. Br.

Burleson:ERB

September 26, 1969

CONTRACTS-3884 (Veterans)

H. Roth

0 03/7

1138241

AN EVALUATION OF THE EFFECTS OF FAST NEUTRONS
ON THE
REPAIR OF RADIATION INJURY BY CULTURED MAMMALIAN CELLS

A Proposal for the Renewal of
Contract No. AT-(40-1)-3884
Submitted to the
United States Atomic Energy Commission

1138242

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| VI. Other Financial Assistance | 23. |
| VII. Premises, Facilities Available | 23. |
| VIII. Budget | 25. |
| IX Attachments: | |
| No. 1. HVEC Proposal | |
| No. 2. Floor Plan--Accelerator Facility | |
| No. 3. Radiation Safety Program | |
| No. 4. Progress Report | |
| No. 5. Curriculum Vitae | |
| (a) Dr. Glenn V. Dalrymple | |
| (b) Mr. A. J. Moss, Jr. | |
| (c) Mr. David Snellings, Jr. | |
| (d) Mr. James Vandergrift | |
| (e) Mrs. Sylvia Johnson | |
| (f) Mr. R. R. Beck | |
| (g) Dr. R. L. Tanner | |
| X. Authentication | |

1. Title An Evaluation of the Effects of Fast Neutrons on the Repair of Radiation Injury by Cultured Mammalian Cells
2. Institution Radioisotope Service
Veterans Administration Hospital
Little Rock, Arkansas
3. Project Abstract

Research during the past several years has focused upon DNA as the target primarily involved in the post-irradiation loss of proliferative capacity. Recent experiments have demonstrated that while X and γ rays cause breaks in the DNA molecule, many of the breaks are rapidly rejoined. We have very recently shown, using the polynucleotide kinase assay system, that many post-irradiation DNA breaks are characterized by 5' PO_4 termini. With the re-awakening of interest in neutrons for radiotherapeutic purposes, much more information is needed about the nature of radiation damage caused by neutrons. To this end we plan to measure the rejoining of DNA breaks by L cells and Chinese Hamster cells (CHO) by both the polynucleotide kinase method and with alkaline sucrose gradients after neutron irradiation. These results will be compared to parallel experiments in which cells were irradiated with x-rays. The measurements of DNA rejoining will be compared with single cell survival studies. The results of the project will not only add information about the effects of neutrons on DNA rejoining, but also RBE estimates for a specific biochemical process involved in DNA rejoining will be developed.

4. Scientific Background

As research during the past two decades has shown, DNA represents a site of considerable radiobiologic importance. According to current thought, radiation causes the cell to lose proliferative integrity via damage to DNA. To date, two basic biochemical techniques have been used to demonstrate radiation induced DNA breaks in cultured mammalian cells. The first, and older method, uses the ultracentrifuge. (1 - 7) Single stranded DNA breaks are detected by studying DNA sedimentation patterns at alkaline pH, while double stranded breaks are measured at neutral pH. Within the past few months, we have introduced another method to measure DNA breaks. (8, 9) This requires an enzyme known as polynucleotide kinase. Reprints of our papers (Biochemical and Biophysical Research Communications, Vol. 35, No. 2, 300, 1969 and Vol. 36, No. 2, 284, 1969) are attached for your reference. This method allows the detection of DNA breaks characterized by 5' PO₄ termini. The results of our experiments have suggested several interesting points:

1) The appearance and rejoining of the 5' PO₄ termini after irradiation requires energy.

2) The rate of rejoining of these termini, as measured by polynucleotide kinase, is virtually identical to results from ultracentrifuge experiments.

3) Rejoining of these 5' PO₄ termini occurs in spite of inhibition of DNA synthesis.

4) Solid tissues, such as liver and rat sarcoma,

show rejoining of the 5' PO₄ termini.

From our experience with low L. E. T. radiation (250 kVp X-rays), the development of DNA breaks requires energy (2). Treatment of L cells with dinitrophenol (which uncouples oxidative phosphorylation) before irradiation prevents the appearance of DNA breaks. Removal of the dinitrophenol after irradiation, however, allows the breaks to appear. A very important question concerns the behaviour of DNA irradiated with high L. E. T. radiations--such as neutrons. Does high L. E. T. radiation produce DNA breaks, per se, or is metabolic intervention necessary ?

High L. E. T. radiations (such as neutrons) are known to change the recovery characteristics of cultured mammalian cells. Single dose survival curves show a decreased extrapolation number (N) and a decreased D₀, as compared with low L. E. T. radiations (10, 11).

At present, to the best of our knowledge, all of the experiments concerned with rejoining of DNA breaks have been performed with low L. E. T. radiations. High L. E. T. radiations have not, as yet, been studied. Consequently, experiments concerned with the influence of high L. E. T. radiations on the processes responsible for rejoining broken DNA molecules is of considerable importance, per se. The development of RBE data for these processes also has considerable interest.

We plan to study rejoining of DNA breaks after irradiation with neutrons, as compared with x-rays. We will use both alkaline sucrose ultracentrifuge methods and the polynucleotide kinase method. Two lines of cultured cells, L cells and Chinese Hamster (CHO)

cells, will be studied. From the data, we will be able to develop RBE values for a highly specific (and we believe very important) type of radiation damage.

Some questions we plan to consider are listed (not necessarily in order of importance) below.

1. Do neutrons produce a change in 1) the rate of appearance and 2) the rate of rejoining of 5' PO₄ termini in cultured mammalian cell DNA as compared with 250 kVp x-rays ? Do neutrons produce an increased number of these termini--as compared to x-rays ?

2. Do neutrons produce an increased number of breaks characterized by 5' PO₄ termini in cultured mammalian cell DNA while the cells are under the influence of dinitrophenol ? Is energy required for the appearance of these breaks--as it seems to be in the case of x-irradiated cells ?

3. Do dose modifying agents such as cysteamine, N₂, and O₂ produce changes of the same type and magnitude as seen in survival experiments when the effects of x-rays and neutrons are compared ?

4. Is the RBE (neutrons vs x-rays) the same for the development of breaks characterized by 5' PO₄ termini as it is for single cell survival ? How is the RBE influenced by treatment with cysteamine, N₂, O₂, or pretreatment with BUdR ?

5. Does the production and rejoining of 5' PO₄ termini vary as a function of the position of the cell in the intermitotic interval after neutron irradiation ?

6. Do the results from alkaline sucrose gradients

experiments parallel the results from the polynucleotide kinase assay, after both neutrons and x-irradiation ?

7. Do plateau phase Chinese Hamster cells show changes in 1) survival characteristics and 2) rejoining of DNA breaks following neutron irradiation as compared with x-rays ? Is there a difference in response of log phase cells vs plateau phase cells following neutron irradiation ?

5. Scientific Scope

The methods which we plan to use are standard and they have been in use in our laboratory for several years. We have used cultured mammalian cells for both cell survival and biochemically based radiobiologic studies.

A. Cell Survival Techniques

The methods used in our laboratory are already in print (12-14). The cells are carried as monolayers until time for experimentation. The cells are trypsinized, diluted, plated, allowed a period of time to attach, irradiated and/or treated with other agents, and incubated for 1 - 2 weeks to allow colony growth. The cells are kept in a water jacketed incubator at 37°C in a high humidity, 95% air 5% CO₂ atmosphere.

B. Autoradiographic Methods

We use several techniques which involve either cells attached to glass slides, or to plastic petri plates. Briefly, the procedure used is as follows (this is a modification of that described by Joffes (15)). The surface containing the cells is coated with

Kodak NTB 3 emulsion, an appropriate exposure time allowed (usually 2 weeks) after which the preparations are developed, stained, and the cells counted.

C. Biochemical Methods

1. Polynucleotide kinase assay system

The method described by Richardson is used for the measurement of the 5' PO₄ termini (16). The application of this method to irradiated DNA has already been published from this laboratory (8,9). Briefly, cells are irradiated and then lysed with sodium dodecyl sulphate. Following lysis, they are treated with pronase, boiled RNase, chloroform-isoamyl alcohol, and dialysis. After dialysis, the DNA is treated with alkaline phosphatase. The 5' PO₄ termini are then identified by reaction of the DNA with AT³²P labeled in the gamma position and polynucleotide kinase. the AT³²P is prepared by the method of Glynn and Chappell (17); the polynucleotide kinase is prepared by the method described by Richardson (16). Following the reaction, the DNA (containing the 5' PO₄ termini which are now labeled with ³²PO₄) is precipitated with perchloric acid, collected on a milipore filter disc, and then counted in a liquid scintillation counter. The amount of radioactivity is proportional to the number of 5' PO₄ termini. The quantity of DNA is measured by Burton's diphenylamine method (18). The results are expressed as DNA specific activity (see references 1 and 2).

2. Alkaline Sucrose Methods

We use a modification of the method described by McGrath and Williams (4). Cells are pre-labeled with high specific

activity $^3\text{HTdR}$. Following irradiation, the cells are lysed with sodium dodecyl sulphate and then gently layered onto 5 - 20% alkaline (pH 12.8) sucrose gradients. The tubes are allowed to stand in the cold for 30 min. after which they are centrifuged at 35,000 rpm for 2 hours. Usually, five drop fractions are collected directly in liquid scintillation vials; after collection, 10 ml of toluene base counting fluid is added. For some experiments, measurement of the O. D. at 260 nm is needed. For these studies, the fractions are collected in test tubes, diluted to 0.5 ml and the O. D. measured with a spectrophotometer. A 0.3 ml portion of the diluted sample is then taken for radioisotope counting.

3. Cell Synchronization Methods

We are currently using the double thymidine block method to synchronize L cells. We use a slight modification of the method described by Drew and Commerford (19). Cells are seeded into complete Eagle's medium supplemented by 10% calf serum. At 24 hours after seeding, the medium is replaced with medium that contains 2 mM thymidine. Following a 24-hour application, the thymidine containing medium is replaced with fresh medium (which does not contain thymidine) for 24 hours. This is removed and the cells are treated for a final 24-hour period with medium containing 2 mM thymidine. At the end of this period 75 - 100% of the cells are in S phase. From autoradiographic experiments the duration of the different phases of the intermitotic interval are: M, $\frac{1}{2}$ hr; G_1 , 4-6 hrs; S, 6-8 hrs; and G_2 , 4-6 hrs.

4. Neutrons

a. Van de Graaff Accelerator (see Attachment No. 1, a proposal from High Voltage Engineering Corp. (H. V. M. 76, 044)).

The Veterans Administration Hospital, Little Rock, has, in storage, a model J. N. Van de Graaff accelerator. Two years ago this instrument was packed for storage by a representative of the High Voltage Corporation. The proposal includes the cost for renovating the accelerator and moving it from the Hospital to the Arkansas Health Department Building (5 miles away).

The Health Department has an excellent room (see Attachment No. 2) which was designed and shielded for a 14 Mev neutron generator. The Van de Graaff accelerator will be placed in this room. Adjacent space is available for the console, the multichannel analyzer, and the operator.

b. We plan to use the $\text{Be}^9(\text{dn})\text{B}^{10}$ reaction; the bombarding energy of the deuterons will be approximately 1.3 Mev. Fig. 1 shows the average neutron yield for this reaction, as a function of bombarding energy.

Fig. 2 shows the spectrum of neutrons as a function of bombarding energy. We anticipate about 1.5×10^8 neutrons/ $\mu\text{a-sec}$ from the accelerator. Assuming a beam current of 100 μa , the total neutron yield would be

$$1.5 \times 10^8 \times 100 \times 60 = 9 \times 10^{11} \text{ n/100 } \mu\text{a-min.}$$

Using the factor of 3.53×10^{-9} rads/n/cm² (the factor for 3 Mev neutrons*), and correcting 4π geometry, the output would be $\frac{9 \times 10^{11} \times 3.53 \times 10^{-9}}{4 \pi r^2} = \frac{250}{r^2}$ rads/min.

where r is the distance (in cm) from the target.

* As Fig. 2 indicates, the value of 3 Mev is, at best, a rough estimate of the average energy. It does, however, suggest the dose rate which can be anticipated from the accelerator. This estimate agrees with published dose rates for this reaction using 1.8 Mev deuteron bombardment (10, 22).

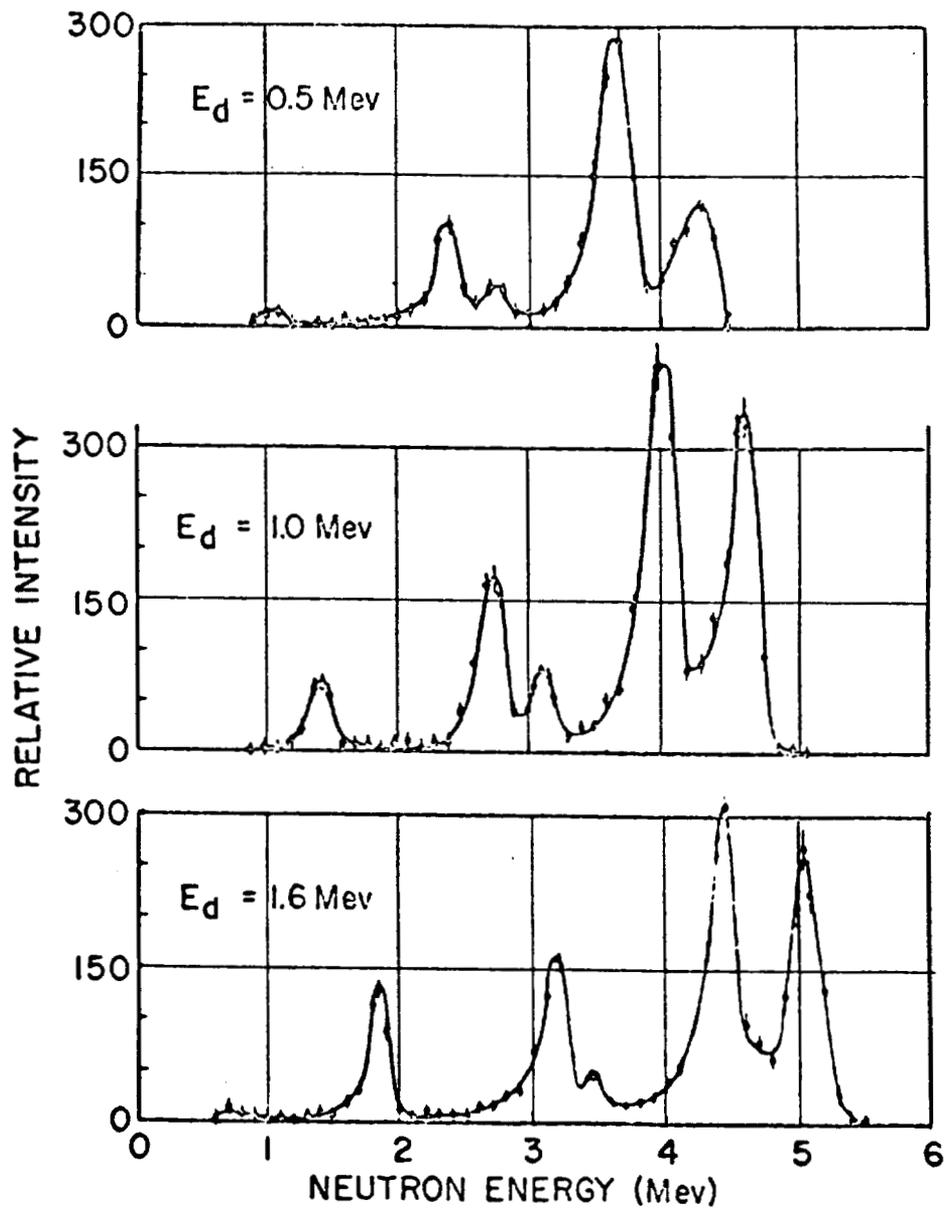


Figure 2

At 10 cm, then, we should anticipate a dose rate of approximately 2.5 rads/min. Since we plan to irradiate the cells as monolayers, in small plastic plates, or as suspension flasks, perhaps we will be able to use higher dose rates by moving the sample closer to the target. We plan to use a paraffin "cave" (such as described by Schneider and Whitmore (10)) to reduce the influence of scattered thermal neutrons.

After the accelerator is set up, we will determine the optimum conditions for irradiation--by measurement.

c. Dosimetry

The principal method planned for dose and dose distribution measurements employs the use of tissue-equivalent (22) ionization chambers.

Several physical forms of ion chambers will be needed to assess the dose as a function of sample arrangement (i. e., cells adhering to the wall of an empty culture bottle, cells in aqueous suspension in a test tube or cells on the surface of a growth medium). Spherical chambers of small dimension may be used to assess the neutron and gamma dose components as will be mentioned in the next paragraph and also for more routine measurements of dose where surface or near surface positions are not involved. These may be used as well for lateral dose distribution measurements. Using tissue equivalent extrapolation chambers constructed with a very thin (mylar) surface electrode one may, by successive additions of phantom material, evaluate the dose at any depth (including entry and exit surfaces) in a given absorber. Interpretation of the charge liberated per unit mass of gas as absorbed dose, in the cavity of such a Bragg-Gray chamber, implies a knowledge of both the

relative mass stopping power S (which is energy dependent) and of W (average energy required per ion pair produced). But, since by far the most significant energy loss mechanism of fast neutrons of $E < 10$ Mev is by elastic scattering of protons (in hydrogenous material like tissue) these values of relative stopping power and W pertain to such protons which are the true source of ionizing energy loss. For protons up to a few Mev appropriate values of S and W are available in the literature (for example, "Studies in Penetration of Charged Particles in Matter," Natl. Acad. of Sci. Natl. Research Council Publication 1133, Washington, D. C. (1964); Schaller, L., Huber, P., and Baumgartner, E., "Measurements of the work per ion pair in nitrogen for proton and helium ions in the energy region below 1 Mev," Helv. Physica Acta (Switzerland) 36, 113 (1963); Whyte, G. N., "Energy per ion pair for charged particles in gases," Rad Res, 18:265 (1963))

In these experiments, both neutrons and gamma rays will be present simultaneously, consequently the expected biological effect will depend not only upon the total dose but also on the relative contributions of each component. In order to assess accurately the relative contribution of each component both tissue equivalent and neutron "insensitive" (non hydrogenous) chambers will be employed (21). Using this procedure, the values for both the neutron dose and gamma ray dose may be estimated.

Alternate methods of neutron dosimetry which may be employed are those which utilize activation of threshold foils of various elements, which measurements lead to information about both the neutron flux above given neutron threshold energies and the energy distribution of the neutrons. To obtain both these types of information will

require use of a standard radioactive neutron source (e. g., Am-Be) with which to calibrate the foils and foil counters. This standard source will be available at the University of Tennessee Medical Center, Memphis, Tenn. In addition photographic emulsions may be used to map the lateral homogeneity of neutron dose over the area of an irradiated sample.

Routine monitoring of the neutron dose delivered during an exposure of mammalian cells will be done by monitoring the deuteron beam incident on the beryllium target. Once the stability of this beam is accomplished, the energy distribution and flux of neutrons will also remain constant such that a measurement of the charged particle flux on the target (i. e., a meter indicating beam current or total charge collected) will be directly related to the neutron dose absorbed at a particular position as determined in a prior experiment with the tissue equivalent chambers described above.

Accuracy of the radiobiological experiments is partly dependent on the accuracy of the radiation dose measurements. However, the accuracy of physical measurements such as dose are seldom the limiting factors, as is the case here where the biological errors may easily reach values of 10% or so. It is thought that errors considerably smaller than this can be attained in the measurement, by one or more of the above methods, of the neutron dose and dose distribution.

d. Radiation Safety Program

(See Attachment 3).

6. Experiments to Answer Proposed Questions

1. Do neutrons produce a change in 1) the rate of appearance and 2) the rate of rejoining of 5' PO₄ termini in cultured mammalian cell DNA as compared with 250 kVp x-rays ? Do neutrons produce an increased number of these termini--as compared to x-rays ?

We plan to follow the basic experimental design for studies which we have published (1). Namely, the cells will be brought into suspension, irradiated, and the samples processed as described. For these comparison experiments, a portion of the cell suspension will be irradiated with neutrons while the other portion will be irradiated with x-rays; sufficient samples will be collected to characterize the dose--response curve.

2. Do neutrons produce an increased number of breaks characterized by 5' PO₄ termini in cultured mammalian cell DNA while the cells are under the influence of dinitrophenol ? Is energy required for the appearance of these breaks--as it seems to be in the case of x-irradiated cells ?

Again, we plan to follow the basic experimental design for studies already in print (2). Cells will be brought into suspension--either in 10⁻⁴M DNP or in glucose free Hank's balanced salts solution (HBSS). Samples of cells in both DNP and HBSS will be irradiated with neutrons and processed as described. For comparison, other portions of cells (DNP and HBSS) will be irradiated with x-rays.

3. Do dose modifying agents such as cysteamine, N₂, and O₂ produce changes of the same type and magnitude as seen in survival experiments when the effects of x-rays and neutrons are compared ?

For these experiments, suspensions of cells will be irradiated under the following conditions: 1) in an environment equilibrated with 100% N₂, 2) in an environment equilibrated with 100% O₂, and 3) in a suspension which contains cysteamine*. We have a Yellow Springs oxygen electrode system which has been adapted for radiobiologic experiments. By charging the cell suspension with the proper gas (N₂, O₂, or air), the desired degree of oxygenation can be maintained.

Following neutron irradiation, samples will be collected and processed as described. For comparison, other samples will be collected after x-irradiation. Samples will be obtained for both survival measurements, as well as measurements of DNA rejoining.

4. Is the RBE (neutrons vs x-rays) the same for the development of breaks characterized by 5'PO₄ termini as it is for single cell survival? How is the RBE influenced by treatment with cysteamine, N₂, O₂, or pretreatment with BUdR?

Suspensions of cells will be prepared. A portion of the suspension will be used for determination of post-irradiation survival, while another portion will be used for the measurement of 5'PO₄ termini. The experimental conditions will be so set up that measurements of survival and the rejoining of 5'PO₄ termini can be made for both neutrons and x-rays from the same inoculum. Both single and split dose survival studies will be conducted. For the BUdR experiments, the cells will be grown in complete medium which contains BUdR at a concentration

* As with other chemical agents, cysteamine will be used at a concentration which produces the desired effect, but which does not reduce cell viability.

of 2×10^{-7} M.* The ability of this compound to increase radiosensitivity (as shown by cell survival studies) is well known (25). The cysteamine, N_2 , and O_2 experiments will be performed as indicated in 3 above.

5. Does the production and rejoining of 5' PO_4 termini vary as a function of the position of the cell in the intermitotic interval after neutron irradiation ?

Cells will be synchronized by the double thymidine block method, brought into suspension, irradiated with neutrons and x-rays as described before, and the rejoining of 5' PO_4 termini measured. The degree of synchrony will be monitored by autoradiography.

6. Do the results from alkaline sucrose gradients experiments parallel the results from the polynucleotide kinase assay, after both neutrons and x-irradiation ?

Cells will be pre-labeled with 3H TdR (1 μ Ci/ml) for 2 days and then brought into suspension. These cells will be irradiated (neutrons and x-rays). A portion of the cells will be applied to alkaline sucrose gradients while other portions will be analyzed by the polynucleotide kinase method.**

7. Do plateau phase Chinese Hamster cells show changes in 1) survival characteristics and 2) rejoining of DNA breaks following neutron irradiation as compared with x-rays ? Is there a difference in response of log phase cells vs plateau phase cells following neutron irradiation ?

* For both L cells and Chinese Hamster cells, this concentration of BUdR causes no loss of plating efficiency. The cells, however, show the anticipated increased radiosensitivity.

** The energy of the ^{32}P is so high in comparison with 3H that the measurements of rejoining of the 5' PO_4 termini will not be affected. We have a 3 channel liquid scintillation counter.

Cells will be allowed to come to plateau phase, suspended, and then irradiated (neutrons and x-rays). Samples will be taken for assay by the polynucleotide method; for comparison. Cells in logarithmic growth will be studied in a similar method.

7. Significance of this Research and Results Obtained by Others

To the best of our knowledge we are the first to use the polynucleotide kinase method to measure the rejoining of radiation damaged DNA. While our initial experience suggests that this method can provide much greater resolution than is possible with ultracentrifugal methods, we do not, as yet, know if the same "lesion" is measured by both techniques. This question represents the basis of Mr. Moss's Ph. D. dissertation research. He is currently comparing the response of irradiated (250 kVp x-rays) L cell DNA by both methods. The initial results suggest very strongly that, indeed, both techniques (polynucleotide kinase and alkaline sucrose gradients) measure the same type of DNA break, and that both methods reflect the same kinetics of rejoining. Because the issue has not yet been settled, we plan to perform both polynucleotide kinase and alkaline sucrose gradient measurements with both x-ray and neutron irradiated cells.

Currently, the relationship of radiation induced DNA breaks (and their rejoining) to the repair of sub-lethal radiation injury--as measured by paired dose survival experiments--is not clear. Since the half-time for rejoining of DNA breaks is of the order of minutes (as measured by both techniques described) while the paired dose "repair" half-time is of the order of 1 - 2 hours (14, 15), we are hesitant to

assume a cause-effect relationship. In this regard, we plan to parallel measurements of DNA rejoining with split dose survival studies.

We have had US AEC sponsorship of research (Contract No. AT-(40-1)-3884) for 8 months. This project concerns the response of plateau phase Chinese Hamster cells (CHO) as compared to cells in logarithmic growth. (See Attachment No. 4--a progress report of this project).

We believe that a great deal of additional information can be obtained from studies with plateau phase cells. Since they represent a cellular system with a large number of endogenous DNA breaks, the response of these cells to neutrons and x-rays would certainly be of interest, as would measurements of the response of the plateau cells to dose modifying agents. Consequently, we plan to continue experiments with plateau phase cells.

We have been synchronizing L cells by the double thymidine block method (21). Within the past year a few reports have appeared about the rejoining of DNA breaks as a function of position in the intermitotic interval. Lohman (3) (who synchronized T cells by the double thymidine block method) found cells in early S to be better able to rejoin DNA breaks (measured with alkaline sucrose gradients) as compared with cells in other periods. Humphrey, et. al., (6), however, found no difference in the ability of their Chinese Hamster cells (Don C) to rejoin DNA breaks in M, G₁, and S. The rejoining of DNA breaks during different portions of the intermitotic interval, however, has never been measured after neutron irradiation.

Experiments with neutrons and other high L. E. T.

radiation have been conducted for many years. A large number of studies with systems ranging from total body irradiation of mammals to measurements of chromosomal damage indicate that fast neutrons, generally, have an RBE greater than 2. We are aware of the extensive literature concerned with the effects of high L. E. T. radiations on many systems. To demonstrate specific points, we have selected representative publications as examples-- this in no way implies that we believe other work (not quoted) to be invalid.

The studies of Schneider and Whitmore (using cultured mammalian cells and mouse bone marrow cells) and of Hornsey and Silini (using Ehrlich ascites tumor cells) showed essentially similar findings (10,11). Both the extrapolation number and the D_0 value (the reciprocal of the slope of the log linear portion of the survival curve) were depressed for neutron irradiated cells, as compared to x-irradiated cells. Using the ratio of the D_0 's as a criterion, the RBE values were of the order of 2.1-2.5. Schneider and Whitmore irradiated H1 cells with neutrons while under nitrogen and oxygen; this provided a dose modifying factor (DMF)* of 1.3. These authors also found the DMF for x-irradiated cells to be 2.5. Consequently, the extent of alteration of radiation sensitivity (nitrogen vs oxygen) is reduced for neutrons, as compared to x-rays. Silini and Hornsey (25), and Hornsey and Silini (11) reported Oxygen Enhancement Ratios (their nomenclature) for Ehrlich ascites tumor cells of 3.1 for 200 kVp x-rays and 1.8 for neutrons (produced by the $Be^9(d,n)B^{10}$ reaction we plan to use). They reported RBE's, for neutron irradiated cells, of

* Some authors prefer the use of the term "oxygen enhancement ratio." In the context quoted, Schneider and Whitmore (10) defined the DMF as the ratio of the D_0 's, i. e., D_0 (nitrogen)/ D_0 (oxygen).

2.1 for cells under oxygen and 3.0 for cells under nitrogen.

Experiments such as these have regenerated interest among radiobiologists and radiotherapists with regard to the use of fast neutrons for the treatment of cancer. Since many tumors contain foci of hypoxic cells, these cells would have an increased radioresistance. A given dose of low L. E. T. radiation (such as x or γ rays), then, would be less effective than if the cells were at physiologic oxygen tensions. The lowered oxygen enhancement ratio for neutrons, however, would be of considerable benefit. A dose of neutrons should be able to sterilize a large proportion of hypoxic tumor cells than an equivalent dose (after correcting for RBE) of x or gamma rays. In theory, then, neutron therapy could produce better radiotherapeutic results. Although some early clinical trials were not successful (27), there has been a considerable interest in a re-evaluation of neutrons for radiotherapy (28). The fast neutrons produced by the $\text{Be}^9(\text{dn})\text{B}^{10}$ reaction have already been used by several investigators for radiobiologic studies (10, 11, 22). Consequently, these neutrons do not represent a new or "unusual" quantity. For studies with cultured cells, the range of these neutrons is sufficient to produce homogenous irradiation. Also, the amount of contamination by γ radiation is of the order of 10% (10, 22).

A final word should be added about qualifications of the staff to perform experiments with particulate radiations. While in the USAF (1963-65--see Curriculum Vitae), Dr. Dalrymple was Director of the USAF School of Aerospace Medicine's Space Radiation Section. In this capacity, he irradiated some 800 primates and more than 5000 mice

with protons ranging in energy from a few Mev to 400 Mev. Cyclotrons and a Van de Graaff accelerator were used as proton sources. The results of this work were published as a Supplement to Radiation Research (29). During this period he participated in all aspects of the dosimetry; he wrote several computer programs for dosimetric calculations. He participated in the design and check-out of the dosimetric equipment (Faraday cups, ion chambers, foil activation, etc.), in the laboratory and in the field. As the project director, he was responsible for the quality of the dosimetry. Dr. Tanner, presently at the University of Tennessee, is a Radiologic Physicist, who has had extensive experience in the areas of charged particle and neutron dosimetry. He will supervise the over-all dosimetry. He will also direct the design and construction of dosimetric equipment which is not currently available. Mr. Moss holds a Master's degree in biophysics and he is due to receive his Ph. D. in June 1970. While a Master's candidate, Mr. Moss was a frequent operator of the accelerator described in this proposal. Mr. Snellings holds a Master's degree in Radiation Sciences (Health Physics). He will be responsible for a portion of the operation and for the Health Physics aspects of the project. Mr. Vandergrift also holds a Master's degree in Radiation Science; he is the Radiation Safety Officer of the University of Arkansas Medical Center. Mrs. Johnson holds a Bachelor's degree in chemistry; she is assistant Radiation Safety Officer at the Veterans Administration Hospital, Little Rock. Mr. Beck has had many year's experience with a wide variety of electronic equipment. He has been working with Radiologic Detector devices, Radiation sources, etc., since 1950.

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8. Principal Investigator

Glenn V. Dalrymple, M. D.
(See Curriculum Vitae, No. 1 of Attachment V)

9. Other Personnel

Research Associate

A. J. Moss, Jr., M. S.
(See Curriculum Vitae, No. 2 of Attachment V)

Chairman Radiation Safety Committee
Radiation Safety Officer for Accelerator Facility
Arkansas State Health Department

D. D. Snellings, M. S.
(See Curriculum Vitae, No. 3 of Attachment V)

Member, Radiation Safety Committee
Associate Radiation Safety Officer--Accelerator Facility
University of Arkansas Medical Center Radiation Health Rept.

J. F. Vandergrift, M. S.
(See Curriculum Vitae, No. 4 of Attachment V)

Member, Radiation Safety Committee
Associate Radiation Safety Officer
Veterans Administration Radiation Health Representative

Sylvia Johnson, B. S.
(See Curriculum Vitae, No. 5 of Attachment V)

Accelerator Operator and Maintenance Technician
Arkansas State Health Department

R. R. Beck
(See Curriculum Vitae, No. 6 of Attachment V)

Research Technicians

K. P. Wilkinson, B. S., B. A.

Rowena Millikin

Susan Robinette, B. S.

10. Other Financial Assistance

The laboratory receives support from the Veterans Administration. This includes the maintenance of the area, the provision of existing equipment, and the salaries of Dr. Dalrymple, Mrs. Wilkinson, and Mrs. Johnson. The Division of Nuclear Medicine, University of Arkansas Medical Center, provides Mr. Vandergrift's salary and provides the costs for travel, communications, publications, and office expenses. The Arkansas State Health Department provides Mr. Snellings' and Mr. Beck's salaries. Also, they will cover the \$1000 cost of adapting and renovating the accelerator room to receive the Van de Graaff accelerator.

11. Premises, Facilities Available

a. Arkansas State Health Department

Attachment No. II is a floor plan of the accelerator room of the Health Department. In addition to this area, the Health Department will provide the Principal Investigator laboratory space for an incubator, and other small items of equipment necessary for collecting, freezing, and transporting samples. The Health Department has an Eberline Neutron Survey Meter which will be used in the accelerator facility.

b. Veterans Administration Hospital, Little Rock, Arkansas

The Principal Investigator's laboratory is a suite of 7 rooms (1200 sq ft) on the 10th Floor of the Veterans Administration Hospital, Little Rock. One of the rooms is a cold room, another is a sterile cell culture room.

Items of capital equipment include a 250 kVp x-ray unit, an RIDL 512 channel analyzer with crystal and well, 3 NAPCO water-jacketed

incubators, a Yellow Springs oxygen electrode system with a dual channel recorder, two Victoreen r meters, 2 Spinco preparative ultracentrifuges, a Beckman LS 200 liquid scintillation counter, a Vangard UV Analyzer, a Hitachi spectrophotometer, a high speed refrigerated centrifuge, several clinical centrifuges, a millipore filtration apparatus attached to a high vacuum pump, a Zeiss phase-contrast microscope, a Hewlett Packard programmable electronic computer, and an incubator for bacteria. A wide range of glassware and smaller items of equipment are available.

Other items of capital equipment available include a Varian EPR unit, a Cary 14 recording spectrophotometer and an Hitachi electron microscope. A CDC 3300 digital computer is available at the University of Arkansas Medical Center. A Donner analog computer is available (at no cost) at the University of Arkansas Graduate Institute of Technology.

The services of the staff of the Southern Research Support Center (located at Veterans Administration Hospital, Little Rock) are available for consultation and assistance as needed.

The Veterans Administration Hospital has a Victoreen Model 488A neutron monitor which will be used in the accelerator facility.

It is anticipated that samples will be brought from the Health Department to the laboratory in the Veterans Administration Hospital for processing. On several occasions, experiments have been performed at the University of Arkansas Medical Center (very near the Health Department), the samples frozen, and then transported to the Veterans Administration Hospital. No difficulties have been experienced; the experimental results are not altered.

12. BUDGET

| a. Salaries † | <u>1st Year</u> | <u>Estimated 2d Year</u> | <u>3d Year</u> |
|--|-----------------|------------------------------|----------------|
| <u>Principal Investigator</u> | \$ 8,000 | 8,500 | 9,000 |
| Glenn V. Dalrymple, M. D. Head, Division Nuclear Medicine Associate Professor, Radiology, Biometry, Physiology-Biophysics, UAMC. Chief Radiologist, Acting Chief, Radioisotope Service, VAH (3/12 time for 12 mo/year) | | | |
| <u>Research Associate</u> | 7,215 * | 15,873 | 17,460 |
| A. J. Moss, Jr., M. S. (12/12 time, 6 mo. 1st year, (12 mo. following years) FICA | | | |
| | (371) | (374) | (374) |
| <u>Chief, Accelerator Radiation Safety Officer</u> | 892 | 981 | 1,079 |
| D. D. Snellings, M. S. (1/12 time 12 mo/year) | | | |
| <u>Associate Radiation Safety Officer Univ. of Ark. Medical Center</u> | 1,050 | 1,125 | 1,200 |
| J. F. Vandergrift, M. S. (1/12 time 12 mo/year) | | | |
| <u>Associate Radiation Safety Officer Veterans Adm Hospital</u> | 554 | 609 | 670 |
| Sylvia Johnson, M. S. (1/24 time 12 mo/year) | | | |
| <u>Accelerator Operator and Maintenance Technician</u> | 1,560 | 1,716 | 1,888 |
| R. R. Beck (20% time 12 mo/year) | | | |
| <u>Research Technicians</u> | | | |
| K. P. Wilkinson, B. S., B. A. (1/12 time 12 mo/year) | | | |
| | 826 | 909 | 1,000 |

12. Budget, Continued

| | <u>1st Year</u> | <u>Estimated 2d Year</u> | <u>3d Year</u> |
|---|-----------------|------------------------------|----------------|
| <u>Research Technicians Contd</u> | | | |
| Rowena Millikin (12/12 time 12 mo/year) | \$ 5,777 | 6,355 | 7,991 |
| FICA & Uniform Allowance | (300) | (346) | (415) |
| Susan Robinette, B. S. (12/12 time 12 mo/year) | 7,989 | 8,788 | 9,667 |
| FICA & Uniform Allowance | (400) | (400) | (400) |
| <u>Total Salaries</u> | \$ 33,863 | 44,856 | 49,955 |

† All salaries include fringe benefits. Amount of FICA in parenthesis.

* GS-12 Salary Scale

b. Equipment

| | | | |
|--|----------|-------|-------|
| Liquid Nitrogen, Dewar Flasks (2 ea) | \$ 500 | n/a | n/a |
| Costs for Construction of Dosimetry Equipment, Irradiation Chambers, etc. | 1,500 | 500 | 500 |
| Small Items for Maintenance of Accelerator | 500 | 500 | 500 |
| Interlock System and Alarm for Accelerator Room | 1,000 | n/a | n/a |
| <u>Total Equipment</u> | \$ 3,500 | 1,000 | 1,000 |

c. Expendable Items

| | | | |
|--|----------|-------|-------|
| Tissue Culture Medium, Serum, Bacteria Culture Medium | \$ 2,000 | 2,000 | 2,000 |
| Radioisotopes ($^{32}\text{PO}_4$), Tritiated Compounds | 1,000 | 1,000 | 1,000 |
| Biochemicals, Small Items Glassware | 1,000 | 1,000 | 1,000 |
| Plastic Flasks, Petri Dishes, Tubes, etc. | 500 | 500 | 500 |

12. Budget, Continued

| | <u>1st Year</u> | <u>Estimated 2d Year</u> | <u>3d Year</u> |
|--|-----------------|------------------------------|----------------|
| <u>Expendable Items, Contd</u> | | | |
| CO ₂ --Air Mixture (\$30 per week x 52) | \$ 1,560 | 1,560 | 1,560 |
| Tissue Equivalent Gas for Ion Chamber | 200 | 200 | 200 |
| Liquid Nitrogen, Nitrogen Gas, Pump Oil, Dry Ice, etc | 1,000 | 1,000 | 1,000 |
| Computer Time (\$95 per hr for CDC 3300 time) 5 hrs. | 475 | 475 | 475 |
| <u>Total Expendable Items</u> | \$ 7,735 | 7,735 | 7,735 |
| d. Van de Graaff Accelerator Reno- vation (see attached proposal from HVEC) | \$ 15,445 ** | n/a | n/a |
| Accelerator Maintenance (based upon a recommendation from HVEC). The funds will be used for parts and labor, as needed. | 2,000 | 2,000 | 2,000 |
| Installation of water pipes, power lines, installation of interlock system, and minor renovations of accelerator room | 1,000 | n/a | n/a |
| <u>Total</u> | \$ 18,445 | n/a | n/a |
| **This price is firm through 1 Jan 70. | | | |
| e. Travel | \$ 500 | 500 | 500 |
| f. Communications | 200 | 200 | 200 |
| g. Publications (Includes page charges and reprints of publications) | 600 | 600 | 600 |
| h. Consultation | 600 | 600 | 600 |
| <u>Total Project Cost</u> | \$ 65,443 | 57,491 | 62,590 |

12. Budget, Continued

| | | <u>1st Year</u> | <u>Estimated 2d Year</u> | <u>3d Year</u> |
|---|----|-----------------|------------------------------|----------------|
| Contribution--Veterans Administration (excluding cost of multichannel analyzer and accelerator) | \$ | 9,380 | 10,018 | 10,670 |
| Contribution--Arkansas State Health Department | | 3,452 | 2,697 | 2,967 |
| Contribution--University of Arkansas Medical Center | | 2,350 | 2,425 | 2,500 |
| <u>Total Contributions</u> | \$ | 15,182 | 15,140 | 16,137 |
| Difference--Total Project Cost less Contributions) | \$ | 50,261 | 42,351 | 46,453 |
| Indirect Costs (10% of Difference) | | 5,026 | 4,235 | 4,645 |
| <u>Amount requested from US AEC</u> | \$ | 55,287 | 46,586 | 51,098 |

Justification of the Budget

Salaries

Mrs. Robinette and Mrs. Millikin are currently being paid by US AEC (Contract No. AT-(40-1)-3884). Their salaries will be continued by the funds requested. Mr. Moss is scheduled to receive his Ph. D. in June 1970. He will start working on the project at that time. Prior to that time he is paid by an NIH pre-doctoral fellowship.

Equipment

Small items of equipment for dosimetry, irradiation of cells, gassing of cells, etc, will be constructed. The costs will cover the materials needed.

Expendable Items

The items are necessary for the research. The computer time will be used for calculations necessary for the biologic experimentation, as well as dosimetry.

Van de Graaff Accelerator

As described in the HVEC proposal, the accelerator will be restored to "new" status. The HVEC recommends that we have the capability to obtain company maintenance (parts and labor). Since HVEC does not have a

local office (the nearest one is in St. Louis), costs per visit would average \$400-\$500. The figures listed represent estimates; if we experience a lower cost requirement during the first year, future (2d and 3d years) budgets will reflect this.

Travel

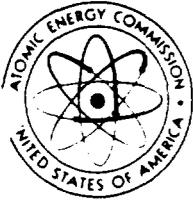
The funds will support travel by one of the Senior staff to two meetings--to present results of the research.

Consultation

The funds will be used to pay the expenses of Dr. Raymond Tanner, who will be concerned with dosimetry. He lives in Memphis, Tennessee.

Indirect Cost

The indirect cost rate is 10% of total project costs. No indirect costs are requested for funds contributed by the Veterans Administration, the University of Arkansas Medical Center, or the Arkansas State Health Department.



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

File

AREA TELETYPE
TELEPHONE 483-3611

March 30, 1970

R. L. Shannon, Extension Manager, Division of Technical Information Extension
PRINTED MATTER PREPARED UNDER CONTRACT NO. AT-(40-1)-3884 VETERANS ADMINISTRATION

In accordance with our memorandum of January 11, 1963, enclosed is a copy of the following printed matter submitted in connection with the research being performed under the subject contract:

Progress Report ORO-3884-1

The provisions of the contract do not require patent review of the above document(s).

2 200's

Alice M. Corley
Alice M. Corley, Chief
Administrative Services Branch
Laboratory and University Division

Enclosure(s):

Progress Report & Form AEC-427

Adm.

Adm. Ser. Br. Res. Cont. Br.

JDB:s1c
3-30-70

CSH
4-1-70

CONTRACTS - 3884 (Veterans)

1138275

MAR 30 1970

Dr. Glenn V. Dalrymple
Chief Radiologist
Veterans Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

CONTRACT NO. AT-(40-1)-3884

Dear Dr. Dalrymple:

Thank you for your letter of March 29, 1970, enclosing a revised budget relative to the renewal of the subject contract through December 31, 1970.

We have requested our Legal Office to prepare an appropriate modification to the contract to extend the period to December 31, 1970, with new AEC funds not to exceed \$15,000. This amount includes the \$4,372 referred to in my teletype of March 13, 1970. The modification will be forwarded to you for review and signature as soon as it is complete.

Sincerely,

ORIGINAL SIGNED BY
C. S. SHOUP

C. S. Shoup, Chief
Research Contracts Branch
Laboratory and University Division

OLE:JDB

CC: K. J. O'Brien, Vet. Adm.

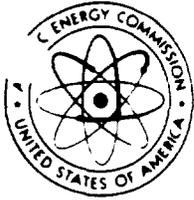
BC: J. R. Totter, HQ
w/4 cys revised budget

Z 1975

CONTRACTS-3884 (Veterans)

1138276

| | | | | | |
|-----------|---------------|----------------|--|--|--|
| OFFICE ▶ | Adm. Ser. Br. | Res. Cont. Br. | | | |
| SURNAME ▶ | JDB:slc | C. S. Shoup | | | |
| DATE ▶ | 3-27-70 | 3-30-70 | | | |



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

January 26, 1970

J. R. Tottar, Director, Division of Biology and Medicine, HQ

CONTRACT NO. AT-(40-1)- **3884 VETERANS ADMINISTRATION**

We are enclosing for your information and use copies of the following listed documents(s) submitted in connection with the research being performed under the subject contract:

- [] Monthly Status Letter
- [] Quarterly Report
- [**XX**] Annual Progress Report **ORO-3884-2 dated January 15, 1970**
- [] Reprint(s)
- [] Preprint(s)

Herman M. Roth
Herman M. Roth, Director
Laboratory and University Division
Oak Ridge Operations

OLE: **JDB**

Enclosure(s)
Progress Report (4)

BC: **R. L. Shannon, w/cy enc. & Form AEC-427**
C. S. Shoup, w/cy encl.

Burleson
Adm. Ser. Br. Res. Cont.Br.
Burleson:slc
1/26/70

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JAN 27 1970

ORO-3884

Veterans Administration



VETERANS ADMINISTRATION
LITTLE ROCK HOSPITAL DIVISION
300 EAST ROOSEVELT ROAD
LITTLE ROCK, ARKANSAS 72206

January 21, 1970

YOUR FILE REFERENCE:

IN REPLY REFER TO:

Mr. Herman M. Roth
Director
Laboratory and University Division
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee 37830

SUBJ: Annual Progress Report No. AT-(40-1)-3884

Dear Mr. Roth:

Enclosed are seven copies of the Annual Report of our contract. If you need more information, please contact me.

I would also appreciate any information that you have about the status of funding for the period starting 1 Jan 70. We have not, as yet, received any word.

Sincerely,


GLENN V. DALRYMPLE, M. D.
Chief Radiologist
Acting Chief, Radioisotope Service

Enclosures: ^{ca}

1. Form AEC 427
2. Progress Report (7)
3. Two preprints

cc:
US AEC, Washington, D. C.
Chief of Staff

B 569

AT-(40-1)-3884 (Veteran)

Show veteran's full name and VA file number on all correspondence. If VA number is unknown, show service number.

1138278



UNITED STATES
ATOMIC ENERGY COMMISSION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

September 2, 1969

Dr. K. J. O'Brien
Hospital Director
Veterans Administration Hospital
Little Rock, Arkansas 72206

RENEWAL OF CONTRACT NO. AT-(40-1)-3884

Dear Dr. O'Brien:

Your attention is invited to Article B-XXI of Appendix "B" of the contract pertaining to the submission of a renewal proposal and progress report which will be due **October 1, 1969.**

The renewal proposal and progress report may be submitted at any time after six months of performance under the current contract period. In any event, they should reach us no later than the due date. Late submission will, in all probability, result in our receipt of the decision on renewal after the current contract period has expired. Therefore, we urge you to submit any renewal proposal no later than the above date. The information to be submitted is as follows:

1. Progress Report. Include information requested in Paragraph (a) of Article B-XXI to Appendix "B". As indicated therein, the progress report should briefly describe the scope of the investigations undertaken and the significant results obtained. Technical reports and articles prepared for publication during the current period should be listed with bibliographic references. Reprints or preprints of all such material should be appended and material contained therein need not be duplicated in the reports. Progress reports, preprints, etc., should contain a report number and should be accompanied by a completed Form AEC-427 as requested in previous correspondence.
2. Renewal Proposal. Include information outlined on pages 7 through 15 of the enclosed "Guide for the Submission of Research Proposals" dated August 1967 unless the information is already contained in earlier proposals or in the accompanying progress report. Careful attention should be given to including the necessary information in the budget for the next period.

*OK
Buck
9-3-69*

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-3884(120-10)

3. Financial Statement. Include in the renewal proposal a financial statement for the present contract period. The statement should be based on the total costs of the project including support by both the institution and the AEC and should reflect (1) the total project costs for the current period to date, indicating the amount chargeable to the AEC based on the percentage set forth in Article III of the contract, (2) an estimate of the total costs to be incurred during the remainder of the current period, and (3) the difference, if any, between the estimated total cost chargeable to the AEC for the current contract period and the AEC support ceiling for this period.

The certified expenditure statement required by Article B-XXVII, following the format set forth in Appendix "C" to the contract, is to be submitted within three months after the expiration of the current contract period. Any adjustments will be taken into consideration at that time.

4. 200-Word Summary. The enclosed form "Notice of Research Project" should be completed in 200 words or less summarizing the proposed research. Four copies of the completed form should be forwarded to us together with the renewal proposal and progress report.
5. Voucher for Concluding Payment. A voucher for the concluding payment for the current period, if necessary, may be submitted with the other documents; however, we will withhold payment of the final voucher until the certified expenditure statement is submitted as contemplated in Paragraph (a) (3) of Article B-XI.

The renewal proposal and expenditure statement should be endorsed by the proper administrative officials and six copies of each, together with seven copies of the progress report and four copies of the 200-word summary, should be submitted at the same time to:

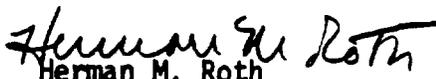
U. S. Atomic Energy Commission
Laboratory and University Division
Post Office Box E
Oak Ridge, Tennessee 37830

If you do not contemplate requesting renewal, we shall appreciate your advising us as soon as possible.

There has been a change in the AEC's policy in connection with the contractor's contribution of the time and effort by the Principal Investigator. We are enclosing an excerpt from the AEC issuance pertaining to this matter. If your organization should determine that its contribution for your time and effort be excluded from the cost sharing portion of the budget and associated maintenance of effort records, this fact should be made clear in the budget submitted for the renewal period. Even in this case, we shall need information as to the approximate percentage of time you expect to devote to the contract work and this contributed time and effort will be shown in the contract under a section excluding it from time and effort reporting.

Your cooperation and assistance in this matter are appreciated.

Very truly yours,



Herman M. Roth
Director
Laboratory and University Division

OLE:JDB

Enclosures:

1. Guide
2. Notice of Research Project Form (5)
3. Policy Statement

cc: G. V. Dalrymple, Vet. Adm. Hos.

JAN 30 1969

Dr. Glenn V. Dalrymple
Chief, Radiological Service
Veterans' Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72207

CONTRACT NO. AT-(40-1)-3884

Dear Dr. Dalrymple:

The following information is provided to you for guidance in carrying out the contract requirements:

1. The scope of the work to be performed is stated in general terms in Appendix "A" of the contract. Within this scope, the investigators have an optimum amount of latitude in their work. The evaluation of the investigators' judgment in selection of work within the scope of the contract is undertaken at the time of renewal. However, should you desire to undertake studies which would not be within the framework described in "Research to be Performed" in Appendix "A," it is expected that you would call this to our attention or directly to AEC Headquarters for program concurrence and approval. A change of this type might require a contract modification.

Also, any significant changes in the level of research effort, funding, specified results, etc., should be called to our attention. Accordingly, we would notify Headquarters.

2. Financing - Paragraph C. of Appendix "B"

Reimbursement Agreement

The Commission will reimburse the Veterans' Administration fifty-seven percent of the project cost estimated as \$30,865; provided that the Commission's monetary liability under the contract shall not exceed \$17,490.

CONTRACTS-3884 (V.A.)

JAN 30 1969

Attached is a supply of voucher forms (Standard Forms 1034 and 1034A) to be used in requesting payments, together with an instruction sheet for completing the forms. We suggest that reimbursement vouchers be forwarded to this office on a monthly basis; however, you may submit them more frequently if you desire. The vouchers should be submitted in an original (white) and two copies (yellow) to:

Laboratory and University Division
Oak Ridge Operations Office
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee 37830

3. Financial Reports - Paragraph E. of Appendix "B"

We will require the submission of an annual financial statement which will reflect the actual total project costs, including those to be contributed by the Veterans' Administration. Details concerning the submission of this statement will be forwarded to you at the time it is due. We will let you know if any other financial or specific reports are required during the course of the contract, and pertinent instructions will be forwarded to you.

4. Patents - Paragraph J.(d) of Appendix "B"

The contract provides that you have full freedom to publish the unclassified results of your work under the contract, and we urge this dissemination through customary scientific channels. However, in compliance with Subparagraph (d) of Paragraph J, it is necessary that you provide this office, for prior patent approval, a copy of any scientific or technical document generated under the contract which you plan to release to the public in any manner. We will notify you whether a delay in release of the information is necessary.

5. Technical Progress Reports; Publications - Paragraph L of Appendix "B"

We should like to receive seven copies of the following technical documents:

1138283

JAN 30 1963

- (a) An annual progress report is to be submitted three months prior to the expiration date of the contract period. This report is required only in the event you plan to request renewal of the contract. In this event, a renewal proposal should accompany the progress report.
- (b) A final scientific report is required upon the expiration of the total contract periods or termination of the contract.
- (c) A report on items of equipment purchased or fabricated with AEC funds is to be submitted to us annually following the expiration of each contract period. We will advise you of the format of this report by a separate communication just prior to the preparation of the report.

We should like to receive seven copies of the following documents, if any, as they are generated under the contract:

- (a) Reprints of Publications.
- (b) Manuscripts or preprints of articles submitted for journal publication. We will automatically review these documents from a patent standpoint as they are received.
- (c) Manuscripts of papers intended for oral presentation (when a written version exists).

To integrate data into the AEC's information dissemination channels handled by the AEC's Division of Technical Information Extension (DTIE), it will be necessary to assign special report numbers to the annual progress reports and the final technical report under the contract. To accomplish this, we request that you use a numbering system based on the format "ORO-Contract Number-Report Number." For example, your contract number is AT-(40-1)-3884. Thus, the number to be used on your first report would be ORO-3884-1, the second ORO-3884-2, and so on in consecutive order. These numbers will be used for reference purposes in Nuclear Science Abstracts, which receives world-wide distribution and will be a positive means by which the AEC and others can identify the document when making or responding to inquiries. A completed copy of Form AEC-427, "Contractor's Recommendation for Disposition of Research Document," should be submitted to us with each of the annual reports and the final technical report. A supply of this form is enclosed and additional copies should be requested from us.

1138284

Dr. Glenn V. Dalrymple

- 4 -

JAN 30 1969

6. Additional Information

Foreign travel is subject to prior approval by the Contracting Officer. This includes travel financed wholly or in part at AEC expense. If you contemplate any foreign travel, you should contact us as far in advance of the travel as possible. We will provide you with the necessary forms to be completed. The completed forms must be in our hands at least 45 days prior to the commencement of any foreign travel.

If you have any questions concerning the requirements under this contract, please let us know.

Sincerely,

ORIGINAL SIGNED BY
HERMAN M. ROTH

Herman M. Roth, Director
Laboratory and University Division
Oak Ridge Operations

NFT

Enclosures:

1. SF 1034 and 1034A
w/Instructions
2. Form AEC-427

CC: H. W. Fisher, Veterans' Administration

OC

OAK RIDGE OPERATIONS
AEC

JAN 31 2 31 PM '69

RECORDED

| | | | | | | |
|---------|---------------|------------|------------|--|--|--|
| OFFICE | Adm. Ser. Br. | Res. Cont. | L & U Div. | | | |
| SURNAME | Burleson:kb | CSShoy | Roth | | | |
| DATE | 1/29/69 | 1-29-69 | 1/30/69 | | | |

1138285



VETERANS ADMINISTRATION
LITTLE ROCK HOSPITAL DIVISION
300 EAST ROOSEVELT ROAD
LITTLE ROCK, ARKANSAS 72206

January 28, 1969

YOUR FILE REFERENCE:

IN REPLY REFER TO:

Mr. Ralph Elson, Director
Contract Division, USAEC
Oak Ridge Operations
Oak Ridge, Tennessee 37830

RE: Interagency Agreement No. AT-(40-1)-3884
(V5234P-448)

Dear Mr. Elson:

Recently we were awarded the contract indicated above. I do not know, at this time, what scientific progress reports (if any) are required. While we intend to publish the results of the research in suitable journals, does the USAEC need interim reports?

I would greatly appreciate any information that you might have concerning this matter.

Sincerely,

GLENN V. DALRYMPLE, M. D.
Chief Radiologist
Radiology Research

*Mailed Jan 30, 1969
Implementation Letter
2-3-69
JFB*

40001
A 959
FEB 3 1969

CONTRACTS - 3274 (U. S.)

Include Zip Code in your return address and give veteran's social security number.

Show veteran's full name and VA file number on all correspondence. If VA number is unknown, show service number.

1138286

AC:ARB

January 22, 1969

Veterans Administration
Little Rock Hospital Division
300 East Roosevelt Road
Little Rock, Arkansas 72206

Attention: Mr. H. W. Fisher, Contracting Officer

Subject: INTERAGENCY AGREEMENT NO. AT-(40-1)-3884 (V5234P-448)

Gentlemen:

Administration of the subject Interagency Agreement has been assigned to Dr. C. S. Shoup, Chief, Research Contracts Branch, Laboratory and University Division.

There are enclosed for your files a copy of the Statement of Authority and a copy of Assignment of Contract for Administration Form.

Very truly yours,

Original signed by
Ralph Elson

Ralph Elson, Director
Contract Division
Oak Ridge Operations

Enclosures:

1. Statement of Authority
2. Cy Form OR-169-A

cc: C. S. Shoup

CONTRACTS - 3884 (V.A.))

A 545

JAN 23 1969

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file*

UNITED STATES GOVERNMENT

Memorandum

TO : Ralph Elson, Director
Contract Division

FROM : Herman M. Roth, Director
Laboratory and University Division

SUBJECT: REQUEST FOR CONTRACT ACTION

DATE:

DEC 9 1968

OLE:JDB

It is requested that you take the necessary steps to process the following described contract action (CA):

1. Nature of Action Requested:

- Selection of New Contractor and/or Negotiation of Contract
Number: ~~AT-(40-1)-3884~~
Contractor: ~~Veterans Administration Hospital~~
- Modification ~~Left in Book; Arkansas 72206~~
Number:
Contractor:

2. Nature of Services To Be Covered by Contract: Research

Title: "A Radiobiologic Evaluation of an In Vitro Mammalian Cell Renewal System"

3. Type of Contract:

- Support Agreement
- Cost Type
- Other

4. Amount of AEC Funds To Be Obligated by This CA: \$17,490.00

5. AEC Percentage of Est. Total Cost To Be Shown by This CA: 57%

6. Description of Other Changes To Be Covered by This CA:

New contract to provide for the performance of research to be completed during the period January 1, 1969, through December 31, 1969. The AEC has approved a support ceiling of \$17,490. Title to the equipment, if any, shall vest in the contractor under authority of the Atomic Energy Act of 1954 since the contractor's contribution is expected to equal or exceed the value of the ~~submitted~~ equipment. Designate Drs. G. V. Dalrymple and J. L. Sanders as Co-Principal Investigators. The estimated ~~total cost~~ of the project is \$30,865.00.

7.

Form ABC-481 (Contract Authorization) from John R. Totter to S. R. Sepiris dated November 25, 1968.

*OLE
Booker
12-9-68*

*DLA
CSKoff
12-9-68*

R 8037

Herman M. Roth
Herman M. Roth
CONTRACTS-3884 (Veterans)
Hospital

1138288

3681

| | | | |
|---|--|---|--|
| AECPR 9 4.81 U. S. ATOMIC ENERGY COMMISSION CONTRACT AUTHORIZATION | | 1. DATE NOV 25 1968 | 2. AUTHORIZATION NO. 24-69-200 |
| TO: R. Sapirio, Manager Oak Ridge Operations Office | | 3.B. FROM John E. Tetter, Director Division of Biology and Medicine | |
| 4. CONTRACTOR (Name, Address, Department) VERDEAS ADMINISTRATION HOSPITAL Little Rock, Arkansas 72206 Radiology Service, L2 Division | | 4.B. PRINCIPAL INVESTIGATOR(S) GLENN V. BALYDYLE J. L. SAUNDERS | |
| 5. <input checked="" type="checkbox"/> NEW CONTRACT <input type="checkbox"/> RENEWAL <input type="checkbox"/> OTHER | | 6. TERM OF CONTRACT one year | 7. CONTRACT NUMBER AT-40-11-3584 |
| 8. RECOMMENDED TYPE OF CONTRACT: <input type="checkbox"/> FIXED PRICE <input type="checkbox"/> OTHER <input checked="" type="checkbox"/> COST REIMBURSEMENT <input type="checkbox"/> SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA) | | 9. PROPERTY TITLE TO VEST IN: <input checked="" type="checkbox"/> AEC <input type="checkbox"/> CONTRACTOR | 10. SECURITY CLASSIFICATION: Work to be performed is under category I as defined by AEC Manual Appendix 3401. |
| 11. PROJECT TITLE "Radiobiologic Evaluation of an In Vitro Mammalian Cell Renewal System" | | | |
| 12. HEADQUARTERS TECHNICAL CONTACT George E. Stapleton | | | |

13. FINANCING

A. OPERATING EXPENSES

| | |
|--|-----------|
| New AEC Funds (Initial AEC Support ceiling, if SRSA) | \$ 17,400 |
| Estimated AEC Balance From Prior Term, if any | \$ - |
| Total AEC Funding (If SRSA, _____% of Total Cost, up to Maximum of) | \$ 17,400 |
| Estimated Contractor Contribution, if any | \$ 13,375 |
| Total Estimated Project Cost | \$ 30,775 |

Budget and Reporting Classification: **06 01 01**
 Allotment Transfer: **06-91-91(24)**

B. PLANT AND CAPITAL EQUIPMENT \$
 Budget and Reporting Classification:
 Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

We can use Research support agreement for P. Johnston - 12-8-68
JS

18. SCOPE OF WORK
~~A kinetic study of gain or loss of radioactivity in mammalian cells and its relation to repair capability.~~

111883
 CONTRACTS-3884 (Veteran Hoop)

1138289

APPENDIX "A"

For the Contract Period January 1, 1969 through December 31, 1969.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will study a steady state population of cultured mammalian cells in the plateau phase by using a combination of cell survival, autoradiographic and biochemical techniques to verify the cell renewal system. These experiments will be followed by studies designed to measure the distribution of the cells within the various compartments of the intermitotic interval, as the cells move from log growth into plateau. Experiments of a converse nature will be carried out to characterize the behavior of plateau phase cells as they move into log growth. The radiobiological properties of plateau phase cells which survive an initial dose of irradiation will be measured and compared with other non-irradiated cells. The response of plateau phase cells to metabolic inhibitors of DNA, RNA, and protein synthesis will be studies.

The two Co-Principal Investigators expect to devote approximately 25% and 50%, respectively, of their time or effort to the work.

A-II WAYS AND MEANS OF PERFORMANCE(a) Items Included in Total Estimated Cost:

| | |
|---|-------------|
| (1) <u>Salaries and Wages:</u> | \$25,375.00 |
| Dr. G. V. Dalrymple, Co-Principal Investigator (25% of time) - \$6,000.00* | |
| Dr. J. L. Sanders, Co-Principal Investigator (50% of time) - \$5,875.00* | |
| Research Associate (100% of time) | |
| Research Technician (100% of time) | |
| Research Technician (20% of time) - \$1,500.00* | |
| (2) <u>Supplies and Materials:</u> | 3,500.00 |
| Culture Medium, Biochemicals and Radioisotopes, Co ₂ Air Mixture, Glassware, etc. | |
| (3) <u>Travel:</u> | 300.00 |
| (4) <u>Publications:</u> | 100.00 |
| (5) <u>Indirect Costs</u> (10% of direct costs exclusive of salaries paid by the Veterans Administration Hospital - \$13,375.00*) | 1,590.00 |

- (b) Items Significant to the Performance of This Contract,
But Excluded From Computation of Total Cost and From
Consideration in Proportioning Costs:

None

- (c) Time or Effort of Principal Investigator To Be Contributed
by Contractor:

None under this paragraph.

A-III The total estimated project cost of A-II (a) above for the contract period stated above is \$30,865.00.

Dr. Glenn V. Dalrymple
Chief, Radiological Service
Veterans Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

Dear Dr. Dalrymple:

I am pleased to inform you that the Research Committee has approved your research proposal entitled "A Radiobiologic Evaluation of An In Vitro Mammalian Cell Renewal System" for a period of one year at approximately the level of research support requested.

The negotiation of a contract, including financial detail is the responsibility of the Oak Ridge Operations Office and you may expect to hear from someone in that office in the near future. Responsibility for the technical aspects of the program lies with the Division of Biology and Medicine in Washington.

Sincerely,

George E. Stapleton
Radiation Biologist, Biology Branch
Division of Biology and Medicine

cc: J. L. Sanders, Instructor
in Physiology, VAH
K. J. O'Brien, Hospital
Director

EMS

Stapleton:sdv

11-22-68

1138292

A RADIOBIOLOGIC EVALUATION OF
AN IN VITRO MAMMALIAN CELL
RENEWAL SYSTEM

A Proposal Submitted to the
Division of Biology and Medicine
United States Atomic Energy Commission
Washington, D. C.

1. Title A Radiobiologic Evaluation of an in vitro Mammalian Cell Renewal System
2. Institution Radiology Service, LR Division
Veterans Administration Hospital
Little Rock, Arkansas
3. Project Abstract

Hahn has very recently described a method for producing a steady state population of cultured mammalian cells. The procedure involves allowing exponentially growing cells to form a monolayer. After 5 - 7 days, the number of cells within the monolayer become stable (plateau phase) in spite of daily medium changes. About 10% of the cells detach from the monolayers (and are replaced) per day. Hahn also found the extrapolation number of these plateau phase cells to be 1 where the extrapolation number for cells in log growth was well above 2. Paired dose experiments confirmed that plateau phase cells lose their capacity to repair sub-lethal injury.

We plan to study plateau phase cells by using a combination of cell survival, autoradiographic, and biochemical techniques. The experimentation will include studies to verify Hahn's original findings. These experiments will be followed by studies designed to measure the distribution of the cells within the various compartments of the intermitotic interval, as the cells move from log growth into plateau. Experiments of a converse nature will be carried out to characterize the behaviour of plateau phase cells as they move into log growth. The radiobiologic properties of plateau phase cells which survive an initial dose will be measured and compared to other non-irradiated cells. The response of plateau phase cells to metabolic inhibitors of DNA, RNA, and protein synthesis will be measured and correlated with the response of cells in log growth.

We believe the experiments proposed will lay the cornerstone for further more detailed investigations into the nature of the repair of radiation injury at the molecular level.

4. Scientific Background

Cell renewal systems represent the basis of life in man. A continuous process of formation and destruction of such diverse elements as blood cells, germ cells, epithelium, etc., must be balanced in order to maintain life. One of the most profound effects of ionizing radiation is to alter cell renewal systems such that the formation of new cellular elements stops while the destructive processes continue. The ultimate result is a loss (or at least a severe impairment) of the function of the tissue involved.

Two broad experimental tools have been available to those wanting to study the nature of mammalian cell renewal systems. The first is the intact animal. While valuable work certainly has been (and surely will be) done with animals, many observed effects are potentially confounded by simultaneously occurring alterations of other aspects of the animal's physiology. This is particularly true for irradiated animals. A second tool is the cultured mammalian cell. While these cells allow effects to be observed at the cellular level without the influence of uncontrolled exogenous factors, the cell population is essentially artificial. Where cell renewal systems, in vivo, are characterized by a constant number of cells, the cultured cells are usually studied while in exponential growth. The possibility of a non-proliferative compartment seems remote in exponentially growing cells.

Very recently Hahn described a means of developing a steady-state population of cultured cells which has many of the properties of a cell renewal system (1). He found that after seeding monolayer bottles, Chinese Hamster cells increased exponentially in number for some 4 - 5 days. After this, however, the number leveled off and reached a stable value. The population stayed stable even if the medium were replaced every few hours.

This seemed to exclude anoxia as an important factor. At the time of the steady state, he found about 10% of his cells to be lost from the monolayer per day. Since these lost elements were rapidly replaced by new cells, the population size stayed constant. Consequently, a cell renewal system, with a daily turnover fraction of 0.1 was produced.

Hahn performed a few pilot radiobiologic studies with this system which have considerable importance. He found the slope of the dose response curve of the steady state cells (these will be called "plateau" phase cells) to be equal to the slope of the curve for exponentially growing cells. The extrapolation number, where above 2 for exponentially growing cells, had fallen to 1 for plateau phase cells. Hahn correctly surmised the reduction in the extrapolation number to mean a decreased ability to repair sub-lethal injury, as a paired-dose experiment showed. Also, his initial experience, albeit incomplete, suggests the extrapolation number to rise when the cells began to grow exponentially again.

For several years radiobiologists have sought a method for producing cultured mammalian cells which either possess or which lack the ability to repair sub-lethal injury. Hahn's system seems, at this point, to represent a means of producing mammalian cells, in quantity, which have these characteristics.

As a consequence of the points mentioned above, we propose a series of experiments which we believe to have importance. Where either the potential of an in vitro cell renewal system, or the development of cells with a controllable capacity to repair sub-lethal injury would be of significance alone, we propose to evaluate both aspects with the Hahn system.

Some questions we plan to consider are listed (not necessarily in order of importance) below.

1. Does the lowering of the extrapolation number of the plateau phase cells occur because of collection of the cells in a particular compartment of the intermitotic interval? Do specific biochemical changes occur as compared with cells in exponential growth?
2. Does the return of the extrapolation number (and thereby the capacity to repair sub-lethal injury) once the plateau cells begin to grow exponentially occur because of a re-distribution of the cells throughout the intermitotic interval in an asynchronous manner? Are specific biochemical changes present? A corollary to 1. and 2. would be, if the plateau phase cells are collected in a specific portion of the intermitotic interval do they move as a synchronous population if they are given the opportunity for exponential growth?
3. Are the survivors of radiation injury able to "re-populate" the system? If so, do these cells pass through a stage of being able to repair sub-lethal injury to a period of losing this ability? Do the survival curve parameters, characteristic of the intermitotic period, generation, time, etc., change in the survivors? Is the amount of division delay altered as a function of plateau phase vs. exponential growth.
4. Do exponentially growing cells differ from plateau phase cells with regard to their response to agents which impair macromolecular synthesis? Do cells which would "re-populate" the system also vary in this regard?

5. Scientific Scope

The methods which we plan to use are standard and they have been in use in our laboratory for several years. We have been using cultured mammalian cells for both cell survival and biochemically based radiobiologic studies.

A. Cell Survival Techniques

The methods used in our laboratory are already in print (2). Briefly, the cells are carried as monolayers until use. For radiation experiments, the cells are trypsinized, diluted, plated, allowed a period of time to attach, irradiated and/or treated with other agents, and incubated for 1 - 2 weeks to allow colony growth. The cells are kept in a water jacketed incubator at 37°C in a high humidity, 95% air 5% CO₂ atmosphere.

B. Autoradiographic Methods

One of our technicians (Mrs. Wilkinson) is experienced (more than ten years) in autoradiography. We use several methods which involve either cells attached to glass slides or plastic petri plates, or cells which are labeled in suspension. Briefly, the procedure used is as follows (this is a modification of that described by Joffes (3). The surface containing the cells is coated with Kodak NTB 3 emulsion, an appropriate exposure time allowed (usually 2 weeks) after which the preparations are developed, stained, and the cells counted.

C. Biochemical Methods

The metabolism of DNA and RNA will be measured by two methods. The incorporation of tritiated precursors (³H TdR, ³H CdR--DNA, and ³HUR--RNA) will be measured. A ubiquitous label, ³²PO₄ will be used as an adjunct to the specific presursors (see below). The acid insoluble fraction will be resolved into the DNA and RNA components by a modified Schmidt-Thannhauser method (4). The DNA content will be measured by the diphenylamine method while the RNA content

will be measured by the orcinol method (5, 6). Radioactivity will be measured by liquid scintillation counting.

In other experiments we will assay the energy metabolic capabilities of cells. Respiration will be measured with a dual channel Model 53 Yellow Springs Oxygen electrode system (this is equipped with a dual channel strip chart recorder). The metabolism of ATP will be followed by measuring the incorporation of $^{32}\text{PO}_4$ into ATP. This technique requires the assay of the ATP content by the luciferin method (7), together with separation of the ATP from the remainder of the acid soluble fraction by Dowex-1 column chromatography (8). Since the acid insoluble fraction of these cells would already be labeled, this fraction will be separated by the Schmidt-Thannhauser method as described above.

D. Proposed Experiments

1. Initial Steps.

A. Cell Growth.

The early phases of the work are concerned with developing a source of plateau phase cells. We have already started pilot studies with milk dilution bottles for the growth of plateau phase monolayers. These bottles are seeded with a known inoculum and the medium replaced daily. Monolayers are trypsinized at daily intervals to determine 1) the kinetics of growth under these conditions and 2) the variance from bottle-to-bottle. Similar measurements will be made with cells grown on 60 mm plastic petri dishes and 90 mm glass petri plates. Our experience, at this point, indicates no basic difficulty.

B. Dose-Response Measurements

After achieving plateau phase, cells will be trypsinized, plated, allowed to attach for a brief (1-hr) period and then irradiated with

graded doses. Parallel plates with cells in exponential growth will be used. Paired dose experiments (400 rads--time--400 rads) will also be performed with with plateau and exponentially growing cells.

To this point the experimentation will serve to verify Hahn's data, in our laboratory.

2. Experiments to answer proposed questions.

A. Does the lowering of the extrapolation number of the plateau phase cells occur because of collection of cells in a particular compartment of the intermitotic interval? Do specific biochemical changes occur as compared with cells in exponential growth?

We plan to perform autoradiographic studies of cells 1) in log growth, 2) in transition between log growth and plateau, and 3) in plateau phase. Pulse labeling with ^3H TdR will be used. Cultures will be pulse labeled and samples taken at intervals to assay the kinetics of labeled cells moving through the division cycle. The autoradiographic studies of the three classes of cells will be paralleled by the measurement of respiration, ATP, DNA, and RNA metabolism.

B. Does the return of the extrapolation number (and thereby the capacity to repair sub-lethal injury) once the cells begin to grow exponentially occur because of a re-distribution of the cells throughout the intermitotic interval? If so, do the cells move as a synchronous population? Are specific biochemical changes present?

For these experiments, plateau phase cells will be handled in several ways. First, cells will be pre-labeled with ^3H TdR and allowed to come to plateau phase. They will be trypsinized, re-seeded under conditions suitable for exponential growth, fed medium without ^3H TdR and then sampled at intervals. Autoradiograms will be made to show the distribution of the cells.

Second, plateau phase cells will be trypsinized, and re-seeded under conditions suitable to support exponential growth. Samples will be pulse labeled at intervals with ^3H TdR and autoradiograms made. The autoradiographic data from both sources will be correlated.

Third, plateau phase cells will be trypsinized, re-seeded under growth conditions and samples taken at intervals for measurement of respiration, ATP, DNA, and RNA metabolism.

C. Are the survivors of radiation injury able to "re-populate" the system? If so, do these cells pass through a stage of being able to repair sub-lethal injury to a period of losing this ability? Do the survival curve parameters, the generation time, etc., change in the survivors? Is the amount of division delay altered as a function of plateau phase vs exponential growth?

For some experiments the following basic procedure will be used. A large number of monolayers of cells in plateau phase will be irradiated. The doses will be selected such that known percentages of cells will be killed. After irradiation, the medium will be replaced and the surviving cells allowed to grow. At 1-day intervals after irradiation, selected bottles of cells will be trypsinized, the cells counted, and diluted with medium and then plated. By this procedure we should gain some idea of the fraction of viable cells comprising the monolayer, as a function of time after irradiation. Certainly, experiments of this type involve considerable potential error. Consequently, the experiment will be replicated many times in order to lessen the influence of variation in plating efficiency on the data.

For other experiments monolayers of plateau cells, growing on petri dishes, will be used. At the time of irradiation, the plates will be photographed with a camera equipped Nikon Shadowgraph. The number of

cells in the dishes will be estimated from the photographs. Also, other plates will be trypsinized and the cells counted. These methods will be cross checked for the more reproducible method for estimating the total number of cells on the plate. In order to measure viable cells, the plates will be incubated (with frequent medium changes) until visible colonies grow out. Unfortunately, only a relatively low range of doses can be used because of the physical size of the colonies. Even with the aid of the Shadowgraph, colony densities larger than 20 colonies/cm² cannot be counted with accuracy.

Consequently, the results of the experiments described above will be considered together to estimate how well the plateau phase cells can re-populate. From past experience, we believe that re-population should occur.

A somewhat different approach will be necessary to categorize the characteristics of the plateau phase survivors. At intervals after irradiation (0 - 8 days), the plateau phase monolayers will be trypsinized and a wide range of dilutions used to seed plates. Some plates will not be re-irradiated. These will serve to determine how many viable cells were present (per volume) of the original inoculum. Other plates will be given graded doses for determination of the survival curve parameters. The remaining plates will be pulse labeled with ³H TdR at times corresponding to the delivery of the spaced doses. This will allow an estimate of the influence of synchrony.

For other experiments, plateau phase cells will be irradiated. The medium will be changed daily after irradiation to allow the surviving cells to form colonies. Representative colonies will be re-plated, and allowed to form monolayers. These cells will be known as "surviving" cells. The survival curve parameters will be measured for these "surviving" cells in exponential growth and in plateau phase.

Autoradiographic studies of the "surviving" cells (above) will be performed as previously described to determine if changes have occurred in parameters such as the duration of the phases of the intermitotic interval (G1, S, G2, M), and the M-M period. "Surviving" cells will be allowed to come to logarithmic growth and then given spaced doses to determine the effect of radiation on the population doubling time. Parallel autoradiographic experiments, concerned with measurement of the M-M interval will be made with "normal" and "surviving" cells.

D. Do exponentially growing cells differ from plateau phase cells with regard to their response to agents which impair macromolecular synthesis? Do cells which would re-populate the system ("surviving" cells) also vary in this regard?

While many inhibitors could be studied, we plan to use 1) 2,4-dinitrophenol (DNP), 2) actinomycin D, 3) puromycin, and 4) hydroxyurea. These agents represent inhibitors of aerobic oxidative phosphorylation, DNA, RNA, and protein synthesis. The survival curves of plateau and exponentially growing cells (both "normal" and "surviving" cells) will be measured. While not a metabolic inhibitor, the survival curves of plateau phase and exponentially growing cells pre-treated (before irradiation) with the sensitizer EudR will be determined.

E. Significance of this research and results obtained by others.

Hahn's findings are important in two broad areas. First, an in vitro mammalian cell renewal system has wide application in biology. Investigations ranging from pharmacology to cancer research, in addition to the previously described radiobiologic studies are immediately apparent. Second, Hahn's method seems to represent a method for reversably changing a mammalian

cell's ability to repair sub-lethal injury. Many individuals, both in print and in meetings, have voiced the need for a method to reduce a mammalian cell's capacity to repair sub-lethal injury without resorting to highly toxic drugs. The work of Elkind, et. al. (9), Whitmore and colleagues (10), Phillips and Tolmach (11), Dalrymple, et. al. (3), Berry (12), Bacchetti (13), and Kim, et. al. (14)--to name a few have demonstrated that only under the most adverse situations will the cultured mammalian cell lose its ability to repair sub-lethal injury. Agents ranging from hypoxia and hypothermia through a spectrum of metabolic inhibitors have been used. In spite of severe toxicity, mammalian cells, generally, retain their capacity to repair sub-lethal injury.

The excellent studies of Terasima and Tolmach (15), Sinclair and Morton (16), and Dewey and Humphrey (17) with synchronized mammalian cells suggest the presence of at least one period during the intermitotic interval where the extrapolation number falls to or near 1. Although the exact phase varied between strains of cells, the phenomenon was essentially universal.

Perhaps, then, the reason for the lack of the capacity to repair sub-lethal injury by plateau phase cells lies in the possible collection of these cells in a portion of the intermitotic interval characterized by an extrapolation number of 1. If so, we would anticipate the cells to move through the phases of the intermitotic interval in synchrony, if the cells were given the opportunity for log growth. Perhaps some biochemical variation (macro-molecular synthesis or energy metabolism) occurs. Perhaps a combination of the two factors coincide. The experiments which we plan should provide answers to these and other questions.

The studies with the "surviving" cells should allow an evaluation of the possibility that these cells are altered by the original dose. At this point we believe our results will show results similar to those described by

Elkind and Sutton in their early work (18). Namely, cells can be alternated between plateau and log growth and "surviving" cells will not have altered radiobiologic properties.* Until this is proven by experiment, however, the question is moot.

Probably the greatest significance of our proposed work lies in the laying of ground work for more basic investigations about the repair of sub-lethal injury at the molecular level. Certainly, a system where the investigator can select cells which either have or do not have the ability to repair sub-lethal injury would form the cornerstone of many investigations.

* While Elkind and Sutton were not using plateau phase cells, they did re-irradiate cells which had survived an earlier dose. They found complete repair of sub-lethal injury within a matter of hours; no alteration of the radiobiologic properties by these cells was found.

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7. Tyson, J. W., Meade, J. H., Dalrymple, G. V., and Marvin, H. N.: Investigation of Chromium 51 Metabolism in Normal Individuals, J Nuc Med, 293, 1967 (Abst.)
8. Dalrymple, G. V., Baker, M. L., and Sanders, J. L.: The Effect of CO^{60} Gamma Radiation on Respiration and Survival of L Cells, Radiat Res, Vol. 31, 1967 (Abst.)
9. Sanders, J. L., Dalrymple, G. V., Baker, M. L., and Wilkinson, K. P.: A Radiation-Induced Nucleic Acid Synthesis in L Cells Under Energy Deprivation, Radiat Res, (In press) (Abst.)

CURRICULUM VITAE

James Lynn Sanders
B. S., M. S., Ph. D.

Personal Data

Born [REDACTED] Tennessee

[REDACTED]

Education and Degrees

| | |
|------------|------------|
| [REDACTED] | [REDACTED] |

Professional

Assistant Professor of Physiology and Biophysics, University
of Arkansas Medical Center, Little Rock, Arkansas,
1968-Present

7. Other Personnel

Research Associate

R. E. Owen, B. S., M. S.

Research Technicians

K. P. Wilkinson, B. S., B. A.

Rowena Millikin

8. Other Financial Assistance

The laboratory receives support from the Veterans Administration. This includes the maintenance of the area, the purchase of the equipment, and the salaries of Dr. Sanders and Mrs. Wilkinson. Dr. Dalrymple's salary is paid indirectly by the Veterans Administration; he is on contract from the University of Arkansas Medical Center.

9. Premises, Facilities, Equipment, and Materials to be Furnished

The investigators occupy a suite of eight rooms on the 10th Floor (Research) of the Little Rock Veterans Administration Hospital. A Westinghouse 250 kVp x-ray unit is under the sole control of the investigators. Other equipment includes three double door NAPCO water jacketed incubators, a Hitachi-Perkin-Elmer Spectrophotometer, a varian E P R unit, a Vanguard U-V analyzer and fraction collector, two Yellow Springs oxygen electrode assemblies and a dual channel strip chart recorder, a Nuclear Chicago Planchet counter, a Packard Tri-Carb liquid scintillation counter, ordinary and inverted microscopes, a Nikon Shadowgraph, several metabolic shakers, a sizeable quantity of glassware for tissue culture studies, several freezers and refrigerators, and sufficient bench space to accomplish the work. A well equipped autoradiographic dark room is available at the University Medical Center, in the investigator's laboratory at that institution.

10. BUDGET

A. Salaries

Estimated First Year

Principal Investigator

Glenn V. Dalrymple, M. D.
Assistant Professor of Radiology,
Biometry, Physiology and Biophysics.
Chief, Radiology Svc, LR VAH
(1/4 time for 12 mo. each year).

\$ 6000.00

Co-Investigator

J. L. Sanders, Ph. D.
Instructor in Physiology,
Biophysicist, LR VAH
(5/10 time for 12 mo. each year).

5875.00

Estimated First Year

Research Associate

~~Research Associate~~
R. E. Owen, B. S., M. S. \$ 6000.00 7500.
(5/5 time for 12 mo. each year).

Research Technician

12% = Rowena Millikin 4500.00
(5/5 time for 12 mo. each year).

K. P. Wilkinson, B. S., B. A. 1500.00
(1/5 time for 12 mo. each year).
(All salaries include fringe benefits)

B. Supplies

Culture Medium (commercial reagents are used). ~~2000.00~~ 1500.00

Biochemicals and Radioisotopes ~~1000.00~~ 500.00

CO₂ Air Mixture (\$30.00 per week x 50 weeks) ~~1500.00~~ 1000.00

Plastic petri plates, minor items of glassware, office supplies 500.00

C. Equipment n/a

D. Travel 300.00

Attend one meeting each year to present the results of Research

E. Telephone n/a

F. Publications 100.00

Medical Illustration n/a

Reprints n/a

G. Indirect costs (based on 10% of project cost, exclusive of Salaries for Dr. Dalrymple, Dr. Sanders, and Mrs. Wilkinson). 1590.00

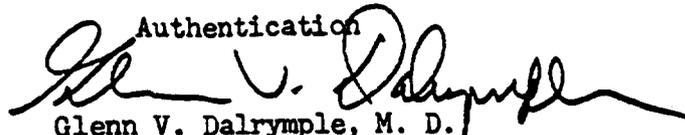
Total Cost of Project \$30,865.00

Amount contributed by LR VAH 13,375.00
(Dr. Dalrymple's, Dr. Sanders', and Mrs. Wilkinson's salaries.

Amount requested from US AEC 17,490.00

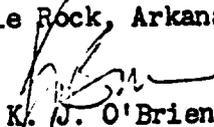
*Dr. Dalrymple
Dr. Sanders
Mrs. Wilkinson
12 3 00
9000*

Authentication



Glenn V. Dalrymple, M. D.
Assistant Professor of Radiology,
Biometry, Physiology and Biophysics
University of Arkansas
School of Medicine
Little Rock, Arkansas

Chief, Radiology Service
Veterans Administration Hospital
Little Rock, Arkansas



K. J. O'Brien
Hospital Director
Veterans Administration Hospital
Little Rock, Arkansas

OLE:JDS

DEC 9 1968

Dr Glenn V. Dalrymple
Chief, Radiological Service
Veterans Administration Hospital
300 East Roosevelt Road
Little Rock, Arkansas 72206

Subject: CONTRACT NO. AT-(40-1)-3884

Dear Dr. Dalrymple:

Reference is made to your recent telephone conversation with J. D. Barleson of this Division concerning ABC support of your project "A Radiobiologic Evaluation of an In Vitro Mammalian Cell Renewal System". As indicated by Mr. Barleson we have received authorization from ABC Headquarters to negotiate and administer an appropriate research contract with the Veterans Administration Hospital of Little Rock, Arkansas to cover the above project. Accordingly the contract will be for a period of one year commencing on January 1, 1969. The ABC's support ceiling was approved at a level of \$17,490.00 as requested in your proposal to the Commission. Dr. J. L. Sanders and you will be designated as Co-Principal Investigators of the project. The minor budget changes as requested by you will be reflected in the contract.

The contract will be forwarded to you as soon as it is complete.

Very truly yours,

ORIGINAL
OAK RIDGE
DEC 9 1968
GROUP
BY 11042

C. S. Shoup, Chief
Research Contracts Branch
Laboratory and University Division

L. Sanders, Vet. Adm. Nos.
O'Brien, Vet. Adm. Nos.

CONTRACTS-3884 (Veteran Hosp)

| | | | |
|----------------|--|--|--|
| Res. Cont. Br. | | | |
| C. S. Shoup | | | |
| 12-9-68 | | | |

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