

TYPED
 PREPARED
 APPROVED
 REPORT TO
 CONTRACT SECTION

Contract No. AT-(40-1)-288
 (Bowman Gray School of Medicine of
 Wake Forest College)
 Modification No. 5

BEST COPY AVAILABLE

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 16th day of June, 1954, effective as of December 31, 1953, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission"), and the BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the Government and the Contractor entered into Contract No. AT-(40-1)-288, dated June 22, 1949, for the performance by the Contractor of research projects on (1) the distribution and turnover of sodium and potassium in acute infections, (2) the formation of phospholipides in tissues, and (3) the toxicity of P³² as related to the diet and to the chemical nature of the compound; and

WHEREAS, the contract has been amended heretofore by Modifications Nos. 1 - 4; and

WHEREAS, the parties hereto desire to provide for the termination of the work under the contract, the payment of expenses in connection with showing an exhibit prepared by Dr. Harrell, the Project Leader, and the withdrawal of certain of the funds previously agreed to be furnished by the Commission; and

WHEREAS, this Supplemental Agreement is authorized by and executed under the Atomic Energy Act of 1946;

NOW, THEREFORE, the parties hereto do mutually agree that Contract No. AT-(40-1)-288 shall be deemed modified in all respects necessary to accomplish the following:

1. The fifth and final period of performance will commence on July 1, 1953 and will end on March 31, 1954.
2. Performance of the research activities outlined for the fifth period will end on December 31, 1953.
3. During the period January - March, 1954 there is included in the scope of the activities under the contract the showing of an exhibit prepared by the Project Leader.

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REPOSITORY Oak Ridge Operations
 COLLECTION Records Holding Area
Documents 1944-94
 BOX No. 2 of 2
Contracts AT-(40-1)-266-288
2714
 FOLDER Contract No. AT-(40-1)-288
Bowman Gray School of Medicine

CERTIFIED A TRUE COPY
 BY J. A. Nicholson

4. The amount of money to be paid the Contractor for the fifth period of performance (stated in Article III, subsection 1., d.) is reduced from Ten Thousand Dollars (\$10,000.00) to One Thousand Four Hundred Twenty-Three and 48/100 Dollars (\$1,423.48).

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: s/ K. Kasschau

Director, Research & Medicine Division
(Contracting Officer)

WITNESSES:

s/ Harry O. Parker - Controller
The Bowman Gray School of Medicine
Winston-Salem, North Carolina
(Address)

s/ Katherine Davis - Adm. Asst.
The Bowman Gray School of Medicine
Winston-Salem, North Carolina
(Address)

BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE
FOREST COLLEGE

BY: s/ C. C. Carpenter

TITLE: Dean

TYPED _____
PREPARED 1/2
APPROVED JJA

[Handwritten signatures and initials]
MAR 6 1953
407

Contract No. AT-(40-1)-288
(Bowman Gray School of Medicine of
Wake Forest College)
Modification No. 4

RETURN TO
CONTRACT SECTION

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 25th day of June, 1953, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission"), and the BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the Government and the Contractor entered into Contract No. AT-(40-1)-288, dated June 22, 1949, for the performance by the Contractor of research projects on (1) the distribution and turnover of sodium and potassium in acute infections, (2) the formation of phospholipides in tissues, and (3) the toxicity of P³² as related to the diet and to the chemical nature of the compound; and

WHEREAS, the contract has been amended heretofore by Modifications Nos. 1, 2 and 3; and

WHEREAS, the parties hereto desire to extend the term of the contract in order to continue and extend the research activities previously undertaken, as such extended program is described in Supplement No. 4 to Appendix "A", and to effect certain other changes hereinafter set out; and

WHEREAS, this Supplemental Agreement is authorized by and executed under the Atomic Energy Act of 1946;

NOW, THEREFORE, the parties hereto do mutually agree that Contract No. AT-(40-1)-288 is hereby modified in the following particulars, but in no others:

1. Add the following new section 4 to Article II - TERM OF CONTRACT:
"4. The fifth period of performance for the project covered by this contract will commence on July 1, 1953, and will end on June 30, 1954."

BY Alice Brown

2. Add the following new subsection d. to section 1. of Article III:

"d. In consideration of the Contractor's performance of the research activities described in Title I of Supplement No. 4 to Appendix 'A', the Government will pay to the Contractor the sum of Ten Thousand Dollars (\$10,000.00) for the fifth period of performance."

3. Add the following new section 4 to Article V - REPORTS, RECORDS, AND INSPECTION:

"4. Examination of Records

- "a. The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers and records of the Contractor involving transactions related to this contract.
- "b. The Contractor further agrees to include in all his subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract with the Government, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor involving transactions related to the subcontract. The term 'subcontract' as used herein means any purchase order or agreement to perform all or any part of the work or to make or furnish any materials required for the performance of this contract, but does not include (i) purchase orders not exceeding \$1,000, (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public, or (iii) subcontracts or purchase orders for general inventory items not specifically identifiable with the work under this contract.
- "c. Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract."

4. Add the following new Supplement No. 4 to Appendix "A":

"SUPPLEMENT NO. 4

"July 1, 1953 — June 30, 1954

"This Supplement No. 4 describes the research program and budget agreed upon between the Commission and the Contractor for the fifth period of performance.

"TITLE I

"1. PROGRAM

"a. Project Leader. The work under this TITLE I of Appendix "A" will be carried out by the Contractor under the direction of Dr. George T. Harrell as Project Leader.

"b. Scope and Plan of Approach

During this period the Contractor will continue investigations into the distribution and turnover of sodium and potassium in acute infections. Studies will be made of the alterations in edema in patients and experimental animals with relation to the electrolyte balance and exchange. Sodium and potassium space and the tissue spaces for these elements will be determined in dogs as well as in guinea pigs and rabbits, and the amount of sodium in bone will be studied with respect to its contribution to the sodium pool of the body. Intracellular and extracellular infections and their influence on the fluid changes will be determined, as will metabolic factors which are important, coupled with clinical studies on various types of diseases as they influence the fluid balance and the sodium and potassium spaces.

"2. BUDGET — Fifth Period: July 1, 1953 - June 30, 1954

"a. The Contractor will furnish as its contribution to the project:

- (1) Salaries of staff members, including the Project Leader, and other personnel engaged in the work, in excess of the Government's contribution under b. (1) below.

- (2) Use of laboratory work space; and equipment, materials and facilities needed for the project in excess of the Government's payment under b. below.
- (3) All clerical, administrative and overhead costs in excess of the Government's payment under b. below.

"b. The Government's payment as provided in section 1. d. of Article III, together with the sum of One Thousand, Two Hundred Forty-three Dollars (\$1,243.00) (which amount the parties hereby agree shall be deemed to represent the amount by which payments made by the Government for the fourth contract period exceeds total expenditures for the same period) is to cover generally the following operating estimates:

(1) Salaries and Wages

Technician	\$2,700.00
Animal Technician	2,250.00
Electronic Engineer, (part time)	<u>300.00</u>

Total Salaries and Wages **\$ 5,250.00**

(2) Equipment 502.00

(3) Isotopes 1,850.00

(4) Animals 1,800.00

(5) Supplies

Geiger-Mueller Tubes	\$ 200.00
Glassware	300.00
Chemicals	<u>300.00</u>

Total Supplies **800.00**

(6) Travel 300.00

Subtotal **\$10,502.00**

(7) Overhead 741.00

Total **\$11,243.00**

"c. Items of property procured or manufactured by the Contractor during this period, title to which will vest in the Government (See Article VI): None."

5. In Appendix "B" delete the fourth sentence of section 3. a. and substitute therefor the following:

"The Contractor agrees that it will not permit any individual to have access to restricted data until the designated investigating agency shall have made an investigation and report to the Commission on the character, associations, and loyalty of such individual and the Commission shall have determined that permitting such person to have access to restricted data will not endanger the common defense or security. As used in this paragraph the term 'designated investigating agency' means the United States Civil Service Commission or the Federal Bureau of Investigation, or both, as determined pursuant to the provisions of the Atomic Energy Act of 1946, as amended by the Act of April 5, 1952, Public Law 298, 82nd Congress, 66 Stat. 43."

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement the day and year first above written.

THE UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: /s/ K. Kasschau
Contracting Officer

WITNESSES:

/s/ Katherine Davis
Admn. Ass't. Bowman Gray School
of Medicine
Winston-Salem, N. C.

(Address)
/s/ Harry O. Parker
Controller, Bowman Gray School
of Medicine
Winston-Salem, N. C.
(Address)

BOWMAN GRAY SCHOOL OF MEDICINE OF
WAKE FOREST COLLEGE

BY: /s/ C. C. Carpenter

TITLE: Dean

ACCEPTANCE BY PROJECT LEADER

I have read the foregoing Supplemental Agreement and agree to be bound by its terms.

/s/ George T. Harrell
Project Leader

hundred eighty dollars and seventy-four cents (\$29,180.74) for the fourth period of performance. The funds to be applied to the three titles according to the budget provisions of Supplement No. 3 to Appendix 'A'."

3. Add the following new Supplement No. 3 to Appendix "A":

"SUPPLEMENT NO. 3

"July 1, 1952 - June 30, 1953

"This Supplement No. 3 describes the research projects and budgets agreed upon between the Commission and the Contractor for the fourth period of performance.

"TITLE I

"1. PROJECT

"a. Scope and Plan of Approach

During this period the Contractor will continue its investigations into the distribution and turnover of sodium and potassium in acute infections by proceeding along the following lines of endeavor:

(1) Standardization of Methods

Should it become necessary to utilize guinea pigs for the study of intracellular infections because of the difficulty of establishing a fatal or severe rickettsial infection in rats, the Contractor will design and standardize micromethods for blood volume, Na^{24} , K^{42} spaces and Na and K content of tissue in guinea pigs.

Serial determinations of the K^{42} space in normal young women will be done in order to determine the reliability and reproducibility of results. Similar serial data will be obtained in normal young men. The data obtained is expected to give information of normal physiologic variations and of the stability of the K^{42} space as a basis for interpretation of experimental data to be obtained in diseased states.

Experiments will be undertaken to determine the effect on the K^{42} space and potassium balance of bed rest alone and of starvation without immobilization on normal human beings.

Further studies on normal values in rabbits, guinea pigs and human beings for blood volume and total available protein content will be continued with serial species-specific protein fractions labeled with I^{131} .

In order to determine the effect of the normal secretion of the thyroid gland on the distribution of sodium and potassium, rabbits will be made myxedematous by the injection of I^{131} . After myxedema is established, the Na^{24} , K^{42} and I^{131} tagged protein spaces and Na^{24} , K^{42} tissue contents will be determined.

(2) Intracellular Infections

The studies on experimentally-induced Rocky Mountain spotted fever in rabbits and guinea pigs will be continued.

Further attempts will be made to increase the virulence of the rickettsias for rabbits and to induce greater physiologic changes.

Autoradiographic studies by the technique previously developed will be done on representative animals as a check on the physiologic method by an anatomic one.

(3) Extracellular Infections

The experiments previously reported on fluid changes in trichinosis, an extracellular infection, studied by non-isotopic techniques will be repeated with the application of the tracer methods previously developed.

Time permitting, further attempts will be made to standardize an extracellular interstitial infection with virulent type I pneumococci in the skin and subcutaneous tissue of rabbits.

(4) Immune Reactions Without Infection

Further attempts will be made to induce quantitatively greater physiologic changes through the sensitization of rabbits by repeated injections of a single pool of human plasma.

(5) Clinical Studies

Clinical studies will be conducted in human beings with any type of infection when at all feasible.

Between suitable cases of infection, the techniques developed and standardized will be applied to various pathologic states which are known to induce alteration.

The preliminary observations on the M^{24} space in rheumatic fever will be extended and data on K^{42} space will be obtained.

Other types of diseases which are amenable to specific therapy - such as myxedema, hyperthyroidism, diabetes, congestive heart failure, and syphilis - will be studied before and after the institution of specific therapy.

"2. BUDGET - Fourth Period: July 1, 1952 - June 30, 1953

"a. The Contractor will furnish as its contribution to the Title I project:

- (1) Salaries of staff members, including the Project Leader, and other personnel engaged in the work in excess of the Government's payment under b.(1) below.
- (2) Use of laboratory work space; and equipment, materials and facilities required for the work in excess of the Government's contribution under b. below.
- (3) Clerical, administrative and overhead costs in excess of the Government's payment under b. below.

"b. Under this Title I the Government will pay to the Contractor the sum of Sixteen Thousand Nine Hundred Eight Dollars and Twelve Cents (\$16,908.12) which, together with the sum of Eighty-Five Dollars and Sixty-Eight Cents

(\$85.68) (which amount the parties hereby agree shall be deemed to represent the amount by which the total of payments made by the Government under this Title I for the previous periods of performance exceeds total expenditures for the same periods) is to cover generally the following operating estimates:

(1) Salaries

J. K. Aikawa	\$3,000.00	
Technician (Rhoades)	2,400.00	
Technician (Brooks)	2,850.00	
House officers for clinical studies	500.00	
Electronic Engineer	<u>300.00</u>	
Total Salaries		\$ 8,450.00

(2) Permanent Equipment

Beta-gamma survey meter	275.00	
Sample storage unit	80.00	
Steel bricks	<u>200.00</u>	
Total Equipment		505.00

(3) Isotopes

Na ²⁴ and K ⁴² , handling charge and transportation	3,120.00	
Iodinated Albumin	<u>260.00</u>	
		\$,380.00

(4) Animals 1,200.00

(5) Supplies

Geiger-Mueller tubes	400.00	
Glassware	500.00	
Chemicals, etc.	<u>400.00</u>	
Total Supplies		1,300.00

(6) Travel 300.00
\$15,735.00

(7) <u>Overhead @ 8%</u>	<u>1,258.80</u>
Subtotal	\$16,993.80
Balance from previous payments	<u>85.68</u>
TOTAL	\$16,908.12

"c. Items of property procured or manufactured by the Contractor, title to which will vest in the Government (see Article VI): None.

"TITLE II

"1. PROJECT

"a. Scope and Plan of Approach

During this period the Contractor will continue and extend its studies on the formation of phospholipides in tissues, proceeding along the following lines of endeavor:

(1) Intermediate Stages in the Synthesis of the Phospholipide Molecule

The following described experiment will be undertaken, to investigate whether or not phosphorylcholine is an intermediate stage in the incorporation of choline into the phospholipides. Liver homogenates will be incubated with C¹⁴ labeled choline in the presence or in absence of non-labeled phosphorylcholine. Other experiments similar in nature will be conducted.

(2) Incorporation of Nitrogenous Constituents (Other than Choline) in the Phospholipides

The Contractor will attempt to synthesize (or obtain from other sources) a preparation of ethylanolamine labeled with C¹⁴. The incorporation of this compound into the phospholipides will be studied.

(3) Metabolic Pathways of Choline in Isolated Liver

The Contractor will attempt to improve the procedures for the separation and characterization of the probable products of choline metabolism. If this attempt is successful, the Contractor will try to

identify certain products of choline metabolism which appear to be quantitatively important.

(4) Oxidation of Fatty Acids in the Liver of Choline-Deficient Animals

The Contractor will conduct experiments testing the hypothesis that choline acts by enhancing the degradation of fatty acids in the liver itself. This will be done by studying the oxidation of isotopic fatty acids in the isolated liver from animals in choline deficiency.

(5) Other Investigations

Limitations in time and personnel permitting, the Contractor will continue certain collateral investigations, such as that on the enzymatic condensation of formaldehyde with pyruvate.

"2. BUDGET - Fourth Period: July 1, 1952 - June 30, 1953

"a. The Contractor will furnish as its contribution to the Title II project:

- (1) Salaries of staff members, including the Project Leader, and other personnel engaged in the work in excess of the Government's payment under b.(1) below.
- (2) Use of laboratory work space; and materials, equipment and facilities required for the work in excess of the Government's contribution under b. below.
- (3) Clerical, administrative and overhead costs in excess of the Government's payment under b. below.

"b. Under this Title II the Government will pay to the Contractor the sum of Seven Thousand Eight Hundred Twelve Dollars and Sixty-Seven Cents (\$7,812.67) which, together with the sum of Three Thousand Seven Hundred Ninety-Seven Dollars and Thirty-Three Cents (\$3,797.33) (which amount the parties hereby agree shall be deemed to represent the amount by which the total of payments made by the Government under this Title II for the previous periods of performance exceeds total expenditures for the same periods) is to cover generally the following operating estimates:

(1) Salaries

Research Associate	\$1,500.00	
Graduate Student (Pollard)	1,500.00	
Technician (full-time)	2,400.00	
Technician (part-time)	<u>1,200.00</u>	
Total Salaries		\$ 8,600.00

(2) Permanent Equipment

New sealing unit	800.00	
Other equipment	<u>300.00</u>	
Total Equipment		1,100.00

(3) Isotopes (C¹⁴-labeled compounds) 1,200.00

(4) Animals 200.00

(5) Supplies

Glassware	500.00	
Chemicals	<u>500.00</u>	
Total Supplies		1,000.00

(6) Travel 300.00

(7) Maintenance 350.00

\$10,750.00

(8) Overhead @ 8% 860.00

Subtotal \$11,610.00

Less Unexpended Balance 3,797.33

TOTAL \$ 7,812.67

"c. Items of property procured or manufactured by the Contractor, title to which will vest in the Government (see Article VI): None.

"TITLE III

"1. PROJECT

"a. Scope and Plan of Approach

The program under this Title III continues to be research into the toxicity of P^{32} as related to the diet and to the chemical nature of the compound. The following outline shows the general nature of the work to be performed during this period:

(1) Protective Role of Vitamins

The Contractor will extend to other factors of the B, C, and E groups its systematic study on the protective role of vitamins against P^{32} .

(2) Protective Role of Certain Hormones and Drugs

Experiments will be made with dihydrotestosterone (AT10). A study of the effects of cortical and other steroid hormones will be undertaken.

(3) Attempts to Increase the Mobilisation of P^{32} from the Bones

The Contractor will explore the effects of the introduction of inactive pyrophosphate in this field.

(4) The Effects of Repeated Exposure to Internal Radiation

Mice will be given a sublethal dose of either P^{32} or of another bone seeking radioisotope. Then, after periods varying from two to six weeks, a larger dose of P^{32} in the midlethal range will be injected. Controls run simultaneously will receive only the larger dose of P^{32} .

"2. BUDGET - Fourth Period: July 1, 1952 - June 30, 1953

"a. The Contractor will furnish as its contribution to the Title III project:

- (1) Salaries of staff members, including the Project Leader, and other personnel engaged in the work in excess of the Government's payment under b.(1) below.
- (2) Use of laboratory work space; and materials, equipment and facilities required for the work in excess of the Government's contribution under b. below.
- (3) Clerical, administrative and overhead costs in excess of the Government's payment under b. below.

"b. Under this Title III the Government will pay to the Contractor the sum of Four Thousand Four Hundred Fifty-Nine Dollars and Ninety-Five Cents (\$4,459.95) which together with the sum of One Thousand Eight Hundred Four Dollars and Five Cents (\$1,804.05) (which amount the parties hereby agree shall be deemed to represent the amount by which the total of payments made by the Government under this Title III for the previous periods of performance exceeds total expenditures for the same periods) is to cover generally the following operating estimates:

(1) Salaries

C. Downs (full-time)		
Technician	\$2,400.00	
Research Associate		
(part-time)	<u>1,600.00</u>	
Total Salaries		\$4,000.00

(2) <u>Permanent Equipment</u>		300.00
(3) <u>Isotopes</u>		600.00
(4) <u>Supplies</u>		500.00
(5) <u>Animals</u>		250.00
(6) <u>Travel</u>		250.00
		<u>\$5,800.00</u>
(7) <u>Overhead @ 8%</u>		<u>464.00</u>
	Subtotal	<u>\$6,264.00</u>
	Balance from previous period	<u>1,804.05</u>
	TOTAL	<u>\$4,459.95</u>

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"c. Items of property procured or manufactured by the Contractor during this period, title to which will vest in the Government (see Article VI): None."

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement the day and year first above written.

UNITED STATES OF AMERICA

UNITED STATES ATOMIC ENERGY COMMISSION

WITNESSES:

Katherine Davis
Winston - Salem N. C.
(Address)

BY: John R. Moore
John R. Moore
TITLE: Director, Contract Division, ORO

Jane Linbeck
Winston - Salem, N.C.
(Address)

BOWMAN GRAY SCHOOL OF MEDICINE OF
WAKE FOREST COLLEGE
BY: Harry O. Proser
TITLE: Controller

ACCEPTANCE BY PROJECT LEADERS

I have read the foregoing Supplemental Agreement and agree to be bound by its provisions to the extent that they are applicable to the project for which I am responsible.

Roy T. Howell, Jr.
Project Leader, Title I

D. Camille Arstam
Project Leader, Title II

Roy T. Howell, Jr.

D. Camille Arstam
Project Leader, Title III

TYPED _____
PREPARED *LSP*
APPROVED *JDA*
WFB
WFB

Contract No. AT-(40-1)-288
(The Bowman Gray School of Medicine
of Wake Forest College)
Modification No. 2

RETURN TO
CONTRACT SECTION *22*

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this *22nd* day of *June*, 1951, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission"), and the BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the Government and the Contractor entered into Contract No. AT-(40-1)-288, dated June 22, 1949, for the performance by the Contractor, commencing on July 1, 1949, of three separate research projects on (1) the distribution and turnover of sodium and potassium in acute infections, (2) the formation of phospholipides in tissues, and (2) the toxicity of P^{32} as related to the diet and to the chemical nature of the compound; and

WHEREAS, the contract has been amended heretofore by Modification No. 1; and

WHEREAS, the Government desires to increase its payments under the second period of performance; and

WHEREAS, the parties desire to extend the term of the contract in order to continue and expand the research activities undertaken during the initial period, as described in Supplement No. 2 to Appendix "A"; and

WHEREAS, this Supplemental Agreement is authorized by and executed under the Atomic Energy Act of 1946;

NOW, THEREFORE, the parties hereto do mutually agree that Contract No. AT-(40-1)-288 is modified in the following particulars, but in no others:

1. In order to increase by One Thousand Dollars (\$1,000.00) the Government's payment to the Contractor for work under Title I to Appendix "A" during the second period, the following changes are made effective as of April 23, 1951:

a. In ARTICLE III, Section 1, line 3, delete "Fifty-Three Thousand Seven Hundred Forty-Eight Dollars (\$53,748.00)"

and substitute therefor "fifty-Four Thousand Seven Hundred forty-eight Dollars (\$54,748.00)".

- b. In ARTICLE III, Section 2b, add the following new sentence at the end of the section:

"On or after April 23, 1951, the Government will pay to the Contractor, upon submission by the Contractor of a properly certified voucher, the sum of One Thousand Dollars (\$1,000.00)."

- c. In Supplement No. 1 to Appendix "A", Title I, Section 2B (1) delete, in line 1, "\$13,858.00" and substitute therefor "\$14,858.00"; and in Section 2B (1) c, delete, in line 5, "\$300.00" and substitute therefor "\$1,300.00", and delete, in line 8, "\$2,900.00" and substitute therefor "\$3,900.00", and delete, in line 12, "\$13,858.00" and substitute therefor "\$14,858.00".

2. Insert the section number "1." before the first word of ARTICLE II - TERM OF CONTRACT, and add the following new Section 2 to ARTICLE II:

"2. The third period of performance for the project covered by this contract will commence on July 1, 1951, and will end on June 30, 1952."

3. Insert the sub-section letter "a." between the words "Consideration." and "In" in Section 1 of ARTICLE III - PROGRAM DEVELOPMENT AND FINANCING, and add the following new sub-section b to Section 1 of ARTICLE III:

"b. In consideration of the performance of the work under the three Titles described in Supplement No. 2 to Appendix 'A', the Government will pay to the Contractor the total sum of Thirty Thousand Seven Hundred Ninety-One and 96/100 Dollars (\$30,791.96) for the third period of performance, the funds to be applied to the three Titles according to the budget provisions of Supplement No. 2 to Appendix 'A'. It is expressly agreed that the total sum of Two Thousand Five Hundred Thirty-six and 84/100 Dollars (\$2,536.84) which had been previously paid to the Contractor by the Government (this sum includes the increase effected by change number 1 of Modification No. 2) but which will remain unexpended at the end of the second

period of performance will be applied to the costs of the third period of performance according to the amount remaining to each Title.

4. Add the following new Supplement No. 2 to Appendix "A":

"SUPPLEMENT NO. 2

"TITLE I

"1. PROJECT

"During this period the Contractor will continue his investigations into the distribution and turnover of sodium and potassium in acute infections by proceeding along the following lines of endeavor:

"a. Standardization of methods

"Though much time and effort has gone into development of techniques in the past year and a half some of the techniques still must be standardized to be sure they are absolutely dependable. No data are available on normal values for some techniques and these must be established before definitive experiments can be attempted or the data on experiments in progress interpreted.

"The radiopotassium work in animals has just begun. The technique must be standardized and normal values established for K^{42} space or exchangeable K content in normal rabbits.

"Normal values must be established for the tissue content of total potassium and K^{42} in normal rabbits.

"Since potassium is found almost entirely intracellularly in association with tissue proteins, the interpretation of data in abnormal states becomes extremely difficult. In addition to the control values for normal animals not under stress, a second type of control experiment must be done. It has been

shown that simply putting normal persons to bed will increase the nitrogen excretion in the urine, presumably from destruction of tissue protein. It might be presumed that the potassium excretion would be increased under such circumstances and the total tissue potassium correspondingly reduced. The validity of this thesis must be established in experimental animals under some stress which is different from that to be induced later in definitive experiments. Therefore, a second group of animals will be starved to induce tissue breakdown under reasonably normal physiologic conditions and the above studies performed in order to determine the effect of this stress alone - without infection or immune reaction - on the total exchangeable potassium content or potassium space and the tissue content of potassium. This control should be valid since animals ill with an infection or serum disease are not likely to eat as much as would normal animals.

"In order to determine whether the correlation between radiopotassium content and urinary creatinine excretion reported in normal human males will hold in rabbits, urinary creatinine should be determined at the same time the potassium excretion is measured in both normal and starved animals.

"Normal values must be established for rabbits by the tagged serum protein technique utilizing I^{131} as a marker. The range of normal values in animals, utilizing not only rabbit albumin but rabbit globulin and perhaps even large protein molecules such as fibrinogen, must be done.

"Depending upon the relative alteration of Na^{24} , K^{42} and I^{131} values as determined in the above experiment, autoradiography of the organs should be attempted in order to locate the tissues into which ions and proteins leak in the course of infections and immune reactions. Though potassium and sodium are soluble, it is hoped that a technique utilizing plastic fixation without dehydration will prove feasible so that the soluble ions will not be reached out. The problem should be less technically difficult with iodine tagged proteins which may be precipitated and left in situ.

"Preliminary experiments in human beings have given interesting and often unexpected results indicating a relationship between urinary creatinine and κ^{42} excretion. These experiments should be considerably extended in a wide range of pathological conditions in order to serve as a control on the alterations in permeability in specific infectious diseases and in known demonstrable immune reactions. Experiments should be run particularly on disease processes which are known to affect the permeability of capillary or cellular membranes - such as acute rheumatic fever, glomerulonephritis and myxedema.

"Comparison of blood volumes, utilizing human albumin and human globulin tagged with I^{131} and the Evans blue techniques, should be done.

"b. Intracellular infections

"Since the experimental techniques to be utilized have not yet been completely standardized, it was not possible during the past year to evaluate experimental infections in animals. It will be necessary to standardise an infection in rabbits, preferably with an experimental Rocky Mountain spotted fever strain, which is at present established in guinea pigs. The guinea pig is not a suitable animal for the experiments contemplated and our techniques are all standardized for rabbits.

"As soon as a standardized dose is determined and a dependable reproducible infection induced, the techniques, utilizing Na^{24} , κ^{42} , and I^{131} labeled rabbit serum fractions, developed will be applied. Serial studies at as close intervals as technical problems - such as rate of decay of isotopes - will permit will be done.

"If satisfactory autoradiographic techniques are developed, such studies will be done in fatal instances and representative animals sacrificed at appropriate intervals as a check on the physiologic method by an anatomic one.

"If time permits, an attempt will be made to tag the rickettsias with P^{32} by introduction of the isotope into the chick egg during growth of the rickettsias. The labeled organisms will then be injected into normal rabbits and rabbits previously immunised against the same strain of rickettsias, in order to study more accurately the localization of the parasite.

"In all of the experiments the physiologic measurements will be correlated with the immunologic responses and the data compared with the previous findings in clinical instances of Rocky Mountain spotted fever in human beings.

"c. Extracellular infections

"The experiments now in press on fluid changes in trichinosis - an extracellular infection - should be repeated with the application of the techniques now being standardized. Rabbits will be fed trichinous rat meat; the Na²⁴, K⁴² and I¹³¹ labeled protein fraction studies will be done at appropriate intervals. The physiologic data will be correlated with the immunologic response and the findings compared with the small amount of data available in clinical cases of trichinosis in human beings.

"The difficulty in reproducing standardized extracellular interstitial infections in rabbits with the pneumococcus, as compared with the difficulty in trichinella infections, is so much greater that it seems more profitable to return to the parasitic infestation and to abandon, at least temporarily, the bacterial infection.

"d. Immune reactions without infections

"Further attempts will be made to standardize a dependable passive transfer method for induction of serum sickness in rabbits.

"If these attempts are unsuccessful, the experiments completed and in press in which serum sickness was induced actively by injection of human albumin should be repeated and the techniques under standardization be applied. Sodium-24, potassium-42, and iodine-131 labeled protein fraction alterations should be determined in rabbits.

"e. Auto-antibody studies

"The limitations of time and available technical assistance have so far postponed the inauguration of antibody studies. If the above outlined studies with

experimentally induced intracellular and extracellular infections and immune reactions without infections can be completed, this year the following study should be started.

"An attempt will be made to produce auto-antibody to rabbit heart using as antigen a mixture of group A beta hemolytic Streptococcus somatic group specific fractions which have been combined with normal rabbit heart. If the attempt is successful, the immunologic and physiologic methods, utilizing Na^{24} , K^{42} , and I^{131} labeled rabbit serum fractions, will be applied to the animals. In an additional group of animals the antibody itself can be tagged with I^{131} for studies on the distribution of the antibody in normal and sensitized animals. The histologic lesions could be correlated with the physiologic changes by autoradiography.

"As a control, the effect of repeated sensitization of rabbits with the bacterial fractions alone would be studied, utilizing the same techniques, and the results compared with those obtained by the auto-antibody technique.

"f. Clinical studies

"The techniques developed and standardized in human beings are being applied to the study of infectious diseases in human patients. The development of more potent antibiotics, such as terramycin, continues to reduce the number of clinical instances of rickettsial spotted fever or other acute infectious diseases admitted to the hospital. Such cases as are appearing for study have almost invariably been treated with at least one antibiotic before admission so that the cases are hardly suitable for study. In such cases as are admitted before treatment, baseline studies can be obtained but the infection is usually arrested so quickly by therapy with antibiotics that the physiologic changes observed in prior years do not develop to the extent previously seen or do not develop at all. It is for this reason that emphasis is being shifted to the experimental animal. Clinical studies will still be conducted in human beings when at all feasible.

"In order to utilize personnel and facilities in the intervals between suitable cases of infection, the techniques developed and standardized will be applied to various pathologic states which are known to induce

alteration in permeability of membranes, as well as to some which at present are not thought to induce changes in permeability.

Observations will continue to be made measuring the exchangeable potassium content in human beings. Up to the present only survey studies with single determinations have been possible. An attempt will be made to do serial studies during the acute phase of disease. Permission has been obtained from the Isotopes Division to repeat studies at relatively short intervals. The limiting factor in K^{42} experiments is the chemical toxicity of the potassium administered because of the relatively low specific activity, rather than the cumulative radiation dose.

Studies on sodium- 24 space, utilizing the technique already published, will be continued and expanded. The same types of disease processes will be studied as described in the preceding paragraphs. The specific activity of Na^{24} is so high that no problem in chemical sodium intoxication has been encountered or is anticipated. Permission has been received from the Isotopes Division to enable repeating these studies serially at relatively short intervals in acute instances of disease. Heretofore, only single isolated observations have been done.

Determination of blood volume and permeability of membranes to I^{131} labeled human serum fractions will be continued and expanded. The extravasation of protein fractions into serous cavities, cerebrospinal fluid space, or interstitial spaces, in instances where edema fluid collects, will be continued.

The type of disease process so far studied by the above techniques includes myxedema, rheumatic fever, glomerulonephritis, exogenous obesity, hyperthyroidism, diabetes, syphilis, psychoneurosis, chronic ulcerative colitis, and others. Most of these have been chronic forms of the disease where the pathologic physiologic situation is reasonably stabilized. Attempts will be made to obtain more acute instances of disease for serial studies, for example, diabetic acidosis with coma and dehydration, acute congestive heart failure, and acute glomerulonephritis.

"2. BUDGET - Third Period: July 1, 1951 - June 30, 1952

"a. The Contractor will furnish as its contribution to the Title I project:

- (1) Salaries of staff members, including the project leader, and other personnel engaged in the work in excess of the Government's payment under b (1) below.
- (2) Use of laboratory work space, and equipment, materials and facilities on hand as needed for the work.
- (3) Clerical, administrative and overhead costs in excess of the Government's payment under b (7) below.

"b. The Government will pay to the Contractor the sum of fifteen Thousand Nine Hundred Thirty and 59/100 Dollars (\$15,930.59) which, together with the unexpended amount of Twenty-One and 1/100 Dollars (\$21.01) remaining from the Government's payments under the second period of performance, will cover the Contractor's other expenses, estimated as follows, in the performance of the contract during the third period:

(1) <u>Salaries</u>	
J. F. Aikawa	\$2,400.00
Technician, E. Rhoades	2,400.00
Technician, C. Taylor	2,250.00
House officer for clinical studies	400.00
Electronic engineer	300.00
(2) Permanent equipment	870.00
(3) Isotopes	2,750.00
(4) Animals	1,800.00
(5) Supplies	1,300.00
(6) Travel	300.00

(7) Overhead at 8% \$1,181.60

Total \$15,951.60

"c. Items of property procured or manufactured by the Contractor during this period, title to which will vest in the Government (see Article VI): None.

"TITLE II

"1. PROJECT

"In the preceding years, the formation of phospholipides has been studied on both intact animals and isolated tissues with the aid of P^{32} . The results have given indications on the synthesis of whole phospholipide molecule starting from the inorganic phosphate and on the dependence of this process upon the composition of the diets.

"All phospholipides contain phosphorus, but the various phospholipides differ in their nitrogenous constituents. The most important type of phospholipides, the lecithins, contains choline. This substance is also an essential dietary factor, the deficiency of which leads to serious disturbances (such as fatty infiltration of the liver). The Contractor has used a preparation of choline (labeled in the methyls with C^{14}) in order to study the synthesis of lecithins, as well as other metabolic pathways of choline in the liver. More specifically, during the past year, the investigations have progressed along the following lines: 1) lipid composition of liver mitochondria; 2) incorporation of inorganic P^{32} into the phospholipides of liver slices from rats on various diets; 3) incorporation of labeled choline into the lipides of isolated liver tissue; 4) metabolic pathways of choline in liver slices; 5) synthesis of C^{14} -methyl labeled dimethylethanolamine (a possible choline precursor); 6) disposal of formaldehyde in tissues. During this period the Contractor will continue and extend the above mentioned groups of investigations. The following seem the most promising and the Contractor will concentrate on them:

"a. Incorporation of the nitrogenous constituents into the phospholipides of the liver.

"The data obtained thus far indicate that the incorporation of choline into the phospholipides might proceed independently from the incorporation of the inorganic phosphate. It is therefore suggested that phosphatidic acids (= phospholipides less their nitrogenous moieties) may represent important intermediates in the synthesis of the complete phospholipide molecule as well as in the conversion of one kind of phospholipide into another. The results of experiments in which various substances were added to liver tissue in vitro seem to be in line with the interpretation that a competition occurs between choline and the other nitrogenous components of the phospholipides (or analogues of these components). Such type of experiments will be continued and extended further. It is also hoped to synthesise or obtain from other sources a preparation of C^{14} -labeled ethanolamine (the nitrogenous constituent of the cephalins). Thus the formation of the two main types of phospholipides, lecithins and cephalins could be followed together and with similar techniques, and perhaps it will be possible also to attack the problem of their biochemical relationships.

"b. Incorporation of labeled dimethylethanolamine into the phospholipides of the liver.

"On the basis of its chemical constitution, dimethylethanolamine is likely to represent the immediate precursor of choline. Methyl labeled dimethylethanolamine has been synthesized and added to surviving liver slices. Preliminary results indicate that the compound is incorporated into the phospholipides at approximately the same rate as labeled choline. The future experiments should decide whether the compound is incorporated directly into the phospholipides or, if a preliminary methylation to choline must occur. The possibility of a methylation of the compound after its incorporation into the phospholipides can also be visualized. Methylation of dimethylethanolamine (either free or as a phospholipide moiety) would represent the final step in the synthesis of choline by the tissue, and should be investigated in detail from various points of view, such as oxygen requirement, nature of the methyl donors, characteristics of the enzymes involved, etc. The labeled

dimethylethanolamine will also be used in certain phases of the study of the metabolism of choline in tissues (see below).

"c. Metabolism of choline in isolated liver.

"In spite of its important roles, very little is known about the metabolic products and pathways of choline in the body. When choline is administered to animals or humans, only minimal amounts are excreted in the urine. In order to simplify the problem, the metabolism of methyl labeled choline has been studied with liver slices or homogenates. Preliminary experiments have suggested the following major pathways (in addition to the incorporation of the intact compound into the phospholipides): 1) oxidation of the methyl group presumably to formaldehyde, formic acid and CO₂; 2) formation of trimethylamine and trimethylamine oxide; 3) formation of compounds highly resistant to hydrolysis.

"The Contractor is of the opinion that the last mentioned compounds are organic esters of choline (such as choline phosphate ester) but it is planned to obtain a more convincing evidence of their identity. At the same time the Contractor will try to identify other likely products of choline metabolism such as betaine, betaine aldehyde and dimethylglycine. The separation of these products will not be easy because of the similarity in their chemical and physical properties. Consequently it is expected that much time and effort will be required for the elaboration of a satisfactory scheme of analysis. If attempts will be successful, a balance sheet of choline metabolism in the isolated liver could be prepared. A further step in the investigations will be the study of the changes in the relative importance of these various pathways under the influence of several physiological and pharmacological agents. Besides labeled choline and labeled dimethylethanolamine it is presumed that in these experiments, other methyl-labeled compounds, such as dimethylglycine, betaine, and methionine, could be used advantageously. If the compounds could not be obtained from other sources, the Contractor will attempt to prepare these materials with the proper labels.

"d. Metabolism of formaldehyde.

"The importance of one carbon compounds as intermediates in a number of metabolic reactions, including methylations, is growing rapidly. In recent experiments it was discovered that the enzymatic disappearance of formaldehyde is greatly accelerated in the presence of pyruvic acid. Isotopic techniques confirm the hypothesis of the formation of a condensation product. It seems probable that the product, formed initially, is later changed to other compounds susceptible to oxidation by periodic acid. These investigations will be continued in an attempt to attain a definitive identification of the compound or compounds formed.

"2. BUDGET - Third Period: July 1, 1951 - June 30, 1952

"a. The Contractor will furnish as its contribution to the Title II project:

- (1) Salaries of staff members, including the Project Leader, and other personnel engaged in the work in excess of the Government's payment under b (1) below.
- (2) Use of laboratory work space, and equipment, materials and facilities on hand as needed for the work.
- (3) Clerical, administrative and overhead costs in excess of the Government's payment under b (9) below.

"b. The Government will pay to the Contractor the sum of Eight Thousand Nine Hundred Forty-Three and $\frac{34}{100}$ Dollars (\$8,943.34) which, together with the unexpended amount of Two Thousand One Hundred Sixty-Nine and $\frac{86}{100}$ Dollars (+2,169.86) remaining from the Government's payments under the second period of performance, will cover the Contractor's other expenses, estimated as follows, in the performance of the contract during the third period:

(1) <u>Salaries</u>	
Technician, C. Terhune	\$2,160.00
Two part-time technicians	2,160.00
Investigator, M. Crowder	960.00
(2) Warburg apparatus and accessories	1,100.00
(3) Permanent equipment	360.00
(4) Isotopes	1,700.00
(5) Animals	200.00
(6) Supplies	1,000.00
(7) Travel	300.00
(8) Maintenance of radio-activity apparatus	350.00
(9) Overhead at 8%	831.20
	<hr/>
Total	\$11,113.20

"c. Items of property procured or manufactured by the Contractor during this period, title to which will vest in the Government (see Article VI):
None.

"TITLE III

"1. PROJECT

"In the past two years a systematic study has been undertaken of the toxicity of radioactive phosphate in mice maintained on various diets. The acute toxicity (as measured by the LD₅₀ at the 21st day) is lowest with diets low in fat and protein, and is not modified by fatty infiltration or toxic damage of the liver. A significant degree of protection was obtained by enriching the diets with inorganic phosphate. In experiments of longer duration the role of certain vitamins on the recovery of the damaged tissues has been studied. The importance of an adequate supply

of both vitamin B₁₂ and folic acid could be demonstrated in animals receiving sulfasuxidine (in order to reduce the synthesis of the vitamins in the gastro intestinal tract).

The investigations will be continued essentially along the following main lines during this period:

"a. Effects of vitamins and hormones on the recovery from damage by P³².

"In a continuation of the studies mentioned above, the influence of other vitamins will be studied. Since several of these vitamins are synthesized by the intestinal flora, an acute deficiency is not likely to occur in ordinary conditions. However, one may visualize the possibility that vitamin deficiencies develop as a result of the continued administration of antibiotics (such as it has been suggested precisely in the treatment of radiation injury). Moreover, a limited synthesis of at least certain vitamins occurs also in animal tissues: such a synthesis can probably be encountered by the administration of vitamin analogues. Accordingly, the Contractor will compare the toxicity of P³² in animals receiving either antibiotics, or vitamin analogues (e.g., desoxy pyridoxin) with the toxicity of the isotope in animals generously supplied with the natural vitamins (e.g., pyridoxin).

"It is planned also to investigate if, and to what extent the administration of certain hormones (e.g., corticosterone or ACTH) might favor the recovery of the tissues from the damage induced by the radioactive isotope.

"b. Alkalotic and acidotic diets.

"Preliminary data indicate that acid-producing substances tend to decrease the survival of mice injected with P³². In an extension of these experiments, the effects of the addition of alkaline salts to the diets are being studied. If significant differences will become apparent, an attempt will be made to correlate the data on the survival with the changes in pH and isotope content of the urine.

"c. Increased mobilization of P^{52} from the skeleton.

"Among the various experimental dispositions tested, only the enrichment of the diets with phosphate appeared clearly effective in this respect. To date, attempts to cause a simultaneous mobilization of calcium and phosphate from the skeleton by the admixture of citrate in the diet or by injection of parathyroid hormone were not successful. However, additional experiments are needed before definite statements on this point can be made.

"In addition, the Contractor will test the effects of the administration of other "chelating" agents (such as "arsenes"), which are known to markedly reduce the concentration of calcium ions in blood. Polyphosphates which are also effective in this respect could possibly be beneficial by another mechanism (hydrolysis by pyrophosphatase with increased concentration of non-isotopic phosphate on the surface of the bones). It seems likely that in experiments of this type larger animals should be used, in order to make possible the intravenous injection of large volumes of solutions and to determine calcium and phosphorus levels in blood.

"d. Distribution and toxicity of P^{32} injected as pyrophosphate.

"As a collateral investigation, it is planned to compare the distribution and the toxicity of radioactive pyrophosphate with those of the orthophosphate. Since pyrophosphate does not exchange directly with the inorganic phosphate, it seems likely that differences in the behavior of these two forms of P^{32} will chiefly depend upon the rate of hydrolysis of pyrophosphate to inorganic phosphate under the action of the pyrophosphatases in the various tissues. The results of such a study might even suggest some practical applications for the use of P^{32} in therapy.

"2. BUDGET- Third Period: July 1, 1951 - June 30, 1952

"a. The Contractor will furnish as its contribution to the Title III project:

- (1) Salaries of staff members, including the Project Leader, engaged in the work.
- (2) Use of laboratory work space, and equipment, materials and facilities on hand needed for the work.
- (3) Clerical, administrative and overhead costs in excess of the Government's payment under b (7) below.

"b. The Government will pay to the Contractor the sum of Five Thousand Nine Hundred Eighteen and 3/100 Dollars (\$5,918.03) which, together with the unexpended amount of Three Hundred Forty-Five and 97/100 Dollars (\$345.97) remaining from the Government's payments under the second period of performance, will cover the Contractor's other expenses, estimated as follows, in the performance of the contract during the third period:

(1) Salaries

Technician ($\frac{1}{2}$ time)	\$1,200.00
Technicians (part-time)	2,100.00
(2) Permanent equipment	700.00
(3) Isotopes	500.00
(4) Animals	500.00
(5) Supplies	600.00
(6) Travel	200.00
(7) Overhead at 8%	464.00

Total \$6,264.00

"c. Items of property procured or manufactured by the Contractor during this period, title to which will vest in the Government (see Article VI): None."

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement on the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

WITNESSES:

Jane Lineback

BY: C. Vanden Bulck
C. Vanden Bulck, Acting Manager, ORO
TITLE: Contracting Officer

Bowman Gray School of Medicine
(Address)

BOWMAN GRAY SCHOOL OF MEDICINE
OF WAKE FOREST COLLEGE

Katherine Davis

BY: Harry O. Faxon

Winston-Salem, NC.
(Address)

TITLE: Controller

ACCEPTANCE BY PROJECT LEADERS:

I have read the foregoing Supplemental Agreement and agree to be bound by its provisions to the extent they are applicable to the project for which I am responsible.

George Howell
Project Leader, Title I

Dr. Camille Arton
Project Leader, Title II

Dr. Camille Arton
Project Leader, Title III

TYPED _____
PREPARED *[Signature]*
APPROVED *[Signature]*

Contract No. AT-(40-1)-288
Modification No. 1

SUPPLEMENTAL AGREEMENT

RETURN TO
CONTRACT SECTION

THIS SUPPLEMENTAL AGREEMENT, entered into this 26th day of June, 1950, effective as of the 1st day of July, 1950, by and between the United States of America (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission") and THE BOWMAN GRAY SCHOOL OF MEDICINE of Wake Forest College (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the Government and the Contractor entered into a Contract No. AT-(40-1)-288, dated June 22, 1949, for the performance of research work by the Contractor, and the parties desire to extend the term of the contract under the revised terms and conditions hereinafter set forth; and

WHEREAS, this Supplemental Agreement is authorized by and executed pursuant to the Atomic Energy Act of 1946;

NOW, THEREFORE, the parties hereto mutually agree that said Contract No. AT-(40-1)-288 is hereby modified in the following particulars, but in no others:

1. The following Section 4 is added to Article I - Purpose and Scope:

"4. The Contractor shall furnish all services, facilities, equipment, supplies and materials (except such services, equipment, supplies and materials as the Government has agreed to furnish herein) required for the performance of the research program described in Section 2 above."

2. Delete Article II - Term of Contract, and substitute therefor the following Article II:

"Article II - Term of Contract

"The period of performance for the research projects covered by this contract will commence on July 1, 1949, and will end on June 30, 1951. It is recognized that completion of the research work under this contract may involve a period of several years and that the term of this contract may be extended by mutual agreement."

3. Delete Article III - Program Development and Financing, and substitute therefor the following Article III:

"Article III - Program Development and Financing

"1. Consideration. In consideration of the performance of the research activities described in Article I, the Government shall pay to the Contractor the sum of Fifty-Three Thousand Seven Hundred Forty-Eight Dollars (\$53,748.00) for the period July 1, 1949, through June 30, 1951.

"2. Payment.

a. Prior to June 1, 1950, the Government has paid to the Contractor the sum of Twenty-Four Thousand Seven Hundred Ninety-Nine Dollars and Ninety-Four Cents (\$24,799.94), which represents the initial payment of the lump-sum consideration stated in Section 1 above.

b. As soon as practicable after July 1, 1950, the Government shall pay to the Contractor, upon submission by the Contractor of a properly certified voucher, the sum of Fourteen Thousand Four Hundred Seventy-Four Dollars and Three Cents (\$14,474.03); and, on or before January 1, 1951, the Government shall pay to the Contractor, upon submission by the Contractor of a properly certified voucher, the sum of Fourteen Thousand Four Hundred Seventy-Four Dollars and Three Cents (\$14,474.03).

c. In the event that the term of the contract is further extended, the Government shall pay to the Contractor, upon submission of properly certified vouchers, each six months in advance, an amount equal to one-half the annual agreed consideration for the project as mutually agreed upon by the parties hereto.

"3. Program and Budget for Subsequent Periods. On or before April 1, 1951, and April 1 of each year thereafter, the Contractor will submit to the Commission a current statement of its expenditures for the projects, an estimate of expenses to be incurred during the remainder of the then current term of the contract, and a proposed program and budget for the succeeding year, showing the proposed work to be financed by the Commission and the Contractor. The Contractor and the Commission shall then negotiate as to the amount to be paid by the Commission to the Contractor for the services to be performed during the ensuing period, taking into consideration any portion of payments theretofore made which will remain unexpended at the end of the preceding period. The extended program, budget and the additional amount to be paid to the Contractor shall be incorporated into a formal modification of this contract."

4. Delete Sections 2 to 6 inclusive of Article V - Reports, Records and Inspection, and substitute therefor the following Sections 2 and 3:

"2. The Contractor shall make progress and other reports in such manner and at such times as specified in Appendix "C" which is attached hereto and hereby made a part of this contract. Progress reports shall include a list of personnel working on the project. Names appearing for the first time should be accompanied by a brief statement of the individual's background, training, and experience.

"3. The Commission shall at all times be afforded access to the premises and to all technical records, correspondence, instructions, drawings, and memoranda of record value of the Contractor pertaining to said work."

5. Delete Article VI - Property Furnished To Contractor - Liability, and substitute therefor the following Article VI:

"Article VI - Title To Property Acquired by Contractor

In consideration of the Contractor's contribution to the research project described in Appendix "A" of this contract, title to all materials, tools, machinery, equipment and supplies, acquired from any source including the Commission, or manufactured by the Contractor under this contract, and specifically all of that property itemized in Transfer Invoice No. 201172, Item # 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 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747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, shall vest in the contractor, except that title to items of property described in Section 2, c, of Appendix "A" shall vest in the Government."

6. The attached Supplement to Appendix "A" is made a part of Appendix "A" of this contract.

7. Delete b. Term, under a. Project, of Titles I, II and III of Appendix "A".

8. Delete item 3, Progress Reports, of Titles I, II and III of Appendix "A".

9. The following new Section 12 is added to Appendix "B":

"12. Fellowships. It is understood by the Contractor that none of the funds supplied by the Commission under this contract shall be used in any way to pay the stipend of any appointment for which commensurate services are not rendered under this contract; nor shall any of the funds be used to confer a fellowship, or to pay any part of the stipend of a fellowship, of any kind."

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement on the day and year first above written.

UNITED STATES OF AMERICA

BY: U. S. ATOMIC ENERGY COMMISSION

BY: C. Vanden Bulek
C. Vanden Bulek
Contracting Officer
(Title)

BOWMAN GRAY SCHOOL OF MEDICINE
OF WAKE FOREST COLLEGE

BY: Mary O. Foster
Controller
(Title)

Acceptance by Project Leader

I have read the foregoing Supplemental Agreement and agree to be bound by its provisions.

G. T. Howell (Title I)
Project Leader

H. Camille Astor (Title II)
Project Leader

G. T. Howell (Title III)
Project Leader

SUPPLEMENT NO. 1 TO APPENDIX "A"

This Supplement No. 1 describes the research program and Budget for Contract No. AT-(40-1)-288 for the period July 1, 1950, through June 30, 1951.

TITLE I

1. Research Program. Continues unchanged.

2. Budget

A. Contractor will furnish:

(1) Salary of Project Leader, and major portion of salaries of Dr. Jerry K. Aikawa and Dr. Ernest H. Yount.

(2) Laboratory space and facilities.

B. Commission will furnish:

(1) The additional sum of \$13,858.00 to cover the following approximate requirements:

a. Salaries of Personnel:

Dr. Yount (part-time)	\$1,800.00
Dr. Aikawa (part-time)	1,800.00
Technician	2,100.00
Technician	2,100.00
Electronic engineer (part-time)	300.00
Total	<u>\$8,400.00</u>

b. Permanent Equipment:

Dipping tube horizontal shield housing	\$. 200.00
Bacteriologic incubator	120.00
Water bath	100.00
Microscope lamp	49.00
Storling hand pipette	42.00
Animal cages	120.00
Internal sample counter	300.00
Microscope attachments	200.00
Total	<u>\$1,131.00</u>

c. Dependable Supplies:

Geiger-Muller tubes	\$ 300.00
Supplies for Egg Work	100.00
Bottled gas and chemicals	200.00
Isotopes - cost, shipping charges	300.00
Glassware	500.00
Animals	<u>1,500.00</u>
Total	<u>\$2,900.00</u>

d. Travel 200.00

e. Miscellaneous 200.00

f. Overhead 1,027.00

GRAND TOTAL \$13,858.00

It is understood and agreed that the Contractor, in expending the funds provided by the Government, shall be guided by, but not bound to conform to, the details of the program and budget set forth above.

c. Items of property acquired or manufactured by the Contractor under this contract, title to which will vest in the Government (see Article VI of this supplementary Agreement): None.

TITLE II

1. Research Program. Continues unchanged.

2. Budget

A. Contractor will furnish:

(1) Salary of Project Leader (Dr. Artom), Dr. L. A. Swanson, and Marietta Crowder, a graduate student.

(2) Laboratory space and facilities.

B. Commission will furnish:

(1) The additional sum of \$11,437.00 to cover the following approximate requirements:

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a. Salaries of personnel:

Full-time technician	\$2,160.00
Two part-time technicians	2,160.00
Total	<u>\$4,320.00</u>

b. Permanent equipment:

Sealing unit, Model 163	\$ 600.00
Timer, T-10250	120.00
Freezing cabinet for the high speed centrifuge	300.00
Van Slykes manometric carbon apparatus	300.00
Total	<u>\$1,320.00</u>

c. Consumable supplies:

Radioactive phosphorus	\$ 250.00
Radioactive compounds ^{all} labeled	1,250.00
Expense for synthesizing new ^{all} labeled compounds	600.00
Animals	500.00
Chemicals	600.00
Glassware	600.00
Organic Solvents	300.00
Total	<u>\$4,100.00</u>

d. Travel 250.00

e. Other expenses:

Maintenance, repairs and replacements of radio- activity apparatus	\$ 350.00
Incidentals	250.00
Total	<u>\$ 600.00</u>

f. Overhead 87.00

GRAND TOTAL \$11,137.00

It is understood and agreed that the Contractor, in expending the funds provided by the Government, shall be guided by, but not bound to conform to, the details of the program and budget set forth above.

C. Items of property acquired or manufactured by the Contractor under this contract, title to which will vest in the Government (See Article VI of this Supplementary Agreement): None.

TITLE III

1. Research Program. Continues unchanged.

2. Budget

A. Contractor will furnish:

- (1) Salaries of the three principal investigators, Drs. Artom, Cayer and Harrell.
- (2) Use of laboratory space and equipment.

B. Commission will furnish:

(1) Additional sum of \$6,153.00 to cover the following approximate requirements:

a. Salaries of personnel:

Technician	\$2,100.00
Technician (part-time)	1,500.00
Total	<u>\$3,600.00</u>

b. Permanent equipment:

Metabolism cages	\$ 250.00
Refrigerator for diets	300.00
Scales for diets	200.00
Shielding-bricks	100.00
Minometers	100.00
Total	<u>\$ 950.00</u>

c. Expendable supplies:

Radioactive phosphorus	\$ 400.00
Dietary components	300.00
Animals	100.00
Glassware	200.00
Total	<u>\$1,300.00</u>

d. Miscellaneous 125.00

e. Overhead 478.00

GRAND TOTAL \$6,153.00

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It is understood and agreed that the Contractor, in expending the funds provided by the Government, shall be guided by, but not bound to conform to, the details of the program and budget set forth above.

- C. Items of property acquired or manufactured by the Contractor under this contract, title to which will vest in the Government (See Article VI of this Supplementary Agreement): None.

APPENDIX "C"

DISTRIBUTION AND SCHEDULING OF REPORTS
FOR DIRECT AEC RESEARCH CONTRACTS

	Date	Copies and Distribution	Remarks
CONTRACTOR REPORTS			
1. Progress	On one of following: March 15 June 15 Sept. 15 Dec. 15	(2) Appropriate Washington Division (See note) (2) Oak Ridge Operations Office (See note)	To be received on date listed which is nearest to end of nine month period from effective date of contract and annually thereafter on the same date
2. Summary 200 words on scope and purpose	1. On completion of contract negotiation 2. With progress reports	Prepared as a part of contract negotiations (2) Same as Progress Reports	1. Distribution by Oak Ridge Operations Office with Contract copies 2. Revised Summary to be included as part of Progress Report
3. Manuscripts	As available	(1) Patent Branch, Washington (1) Technical Library, Washington (1) Appropriate Washington Division (1) Oak Ridge Operations Office	
Reprints	As available	(2) Appropriate Washington Division (2) Technical Information Branch, Washington (1) Oak Ridge Operations Office	
5. Complete Scientific Report	On Contract Termination	(1) Same (1) as (1) for (1) manuscripts	Manuscripts prepared for publication may in some cases take the place of this report
6. Brief Reports	As desired by investigator	(1) Appropriate Washington Office (1) Oak Ridge Operations Office	Covering significant results or developments.

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NOTE: Full Addresses as follows:

Washington Offices:

Atomic Energy Commission
(Add name of Division or Branch)
1901 Constitution Avenue, N. W.
Washington, D. C.

Oak Ridge Operations Office

Atomic Energy Commission
Office of Research and Medicine
Post Office Box E
Oak Ridge, Tennessee

The appropriate Washington Divisions are:

Division of Biology and Medicine - for contracts in Biology and Medicine.

Division of Research - for contracts in physical research.

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APPENDIX "C"

DISTRIBUTION AND SCHEDULING OF REPORTS
FOR DIRECT AEC RESEARCH CONTRACTS

	Date	Copies and Distribution	Remarks
CONTRACTOR REPORTS			
1. Progress	On one of following: March 15 June 15 Sept. 15 Dec. 15	(2) Appropriate Washington Division (See note) (2) Oak Ridge Operations Office (See note)	To be received on date listed which is nearest to end of nine month period from effective date of contract and annually thereafter on the same date
2. Summary 200 words on scope and purpose	1. On completion of contract negotiation 2. With progress reports	Prepared as a part of contract negotiations (2) Same as Progress Reports	1. Distribution by Oak Ridge Operations Office with Contract copies 2. Revised Summary to be included as part of Progress Report
3. Manuscripts	As available	(1) Patent Branch, Washington (1) Technical Library, Washington (1) Appropriate Washington Division (1) Oak Ridge Operations Office	
Reprints	As available	(2) Appropriate Washington Division (2) Technical Information Branch, Washington (1) Oak Ridge Operations Office	
5. Complete Scientific Report	On Contract Termination	(1) Same (1) as (1) for (1) manuscripts	Manuscripts prepared for publication may in some cases take the place of this report
6. Brief Reports	As desired by investigator	(1) Appropriate Washington Office (1) Oak Ridge Operations Office	Covering significant results or developments.

NOTE: Full Addresses as follows:

Washington Offices:

Atomic Energy Commission
(Add name of Division or Branch)
1901 Constitution Avenue, N. W.
Washington, D. C.

Oak Ridge Operations Office

Atomic Energy Commission
Office of Research and Medicine
Post Office Box E
Oak Ridge, Tennessee

The appropriate Washington Divisions are:

Division of Biology and Medicine - for contracts in Biology and Medicine.

Division of Research - for contracts in physical research.

STATEMENT AND CERTIFICATE OF AWARD

No. AT-(40-1)-288
(Contract)

Date June 22, 1949

U. S. Atomic Energy Commission

Oak Ridge, Tennessee

(Department or establishment)

(Bureau or office)

(Location)

METHOD OF OR ABSENCE OF ADVERTISING

(Section 3709 of the Revised Statutes)

FOR USE BY G. A. O. ONLY

Indexed	Card	Reviewed

- After advertising in newspapers.
- (a) After advertising by circular letters sent to _____ dealers.
(b) And by notices posted in public places.
(If notices were not posted in addition to advertising by circular letters sent to dealers, explanation of such omission must be made. The notation on the certificate below must be "2 (a) (i)" or "2 (a)," depending on whether or not notices were posted.)
- Without advertising, under an exigency of the service which existed prior to the order and would not admit of the delay incident to advertising.
- Without advertising in accordance with the Atomic Energy Act of 1946
- Without advertising, it being impracticable to secure competition because of _____

(Here state circumstances under which the securing of competition was impracticable)

AWARD OF CONTRACT

- To lowest bidder as to price (Expenditures).
- To other than the lowest bidder as to price (Expenditures).
- To highest bidder as to price (Receipts).
- To other than the highest bidder as to price (Receipts).

CERTIFICATE

I CERTIFY that the foregoing statement is true and correct; that the agreement was made in consequence of No. 4 of the method of or absence of advertising and in accordance with award of contract lettered -----, as shown above; that the total number of bids received is -----, and that where lower bids (expenditure contracts) or higher bids (receipt contracts) as to price were received a statement of reasons for their rejection, together with an abstract of bids received, including all lower than that accepted in case of expenditure contracts and all higher in case of receipt contracts, is given below or on the reverse hereof or on a separate sheet attached hereto; that the articles or services covered by the agreement (expenditure) are necessary for the public service, and that the prices charged are just and reasonable.

C. Vanden Bulck

(Signature of contracting officer)

C. Vanden Bulck

Acting Deputy Manager

(Title)

NOTE.—This statement and certificate will be used to support all agreements, both formal contracts and less formal agreements of whatever character, involving the expenditure or receipt of public funds. It must be executed and signed by the contracting officer (unless the award is made by or is subject to approval by an officer other than the contracting officer, when execution and signature may be made by such officer).

UNITED STATES ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
POST OFFICE BOX E
OAK RIDGE, TENNESSEE

RESEARCH CONTRACT

TYPED _____
PREPARED [Signature]
APPROVED [Signature]
[Signature]

CONTRACT NO.: AT-(40-1)-288
CONTRACTOR: THE BOWEN GRAY SCHOOL OF MEDICINE
OF WAKE FOREST COLLEGE
ADDRESS: Winston-Salem 7, North Carolina

RETURN TO
CONTRACT SECTION

AMOUNT OF CONTRACT: \$25,000.00

CONTRACT ASSIGNED TO:

FOR TECHNICAL ADMINISTRATION
(ORGANIZATIONAL UNIT NAMED IN APPENDIX "A")

Atomic Energy Commission
1901 Constitution Avenue, N. W.
Washington 25, D. C.

FOR BUSINESS ADMINISTRATION

Office of Research and Medicine
U. S. Atomic Energy Commission
Oak Ridge Operations
Post Office Box E
Oak Ridge, Tennessee

THIS CONTRACT, entered into this 22nd day of June, 1949, by the UNITED STATES OF AMERICA (hereinafter called the "Government"), acting through the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission") and THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE (hereinafter called the "Contractor");

ARTICLE I - PURPOSE AND SCOPE

1. The Commission, in furtherance of its policy of assisting and fostering private research, desires to support the Contractor's fundamental research in the field of atomic energy.

2. The work under this contract will involve one or more research problems. A description of the problem, plan of approach, agreed upon program and budget for each project is described in Appendix "A" which is hereby made a part of this contract.

3. The work will be carried out by the Contractor under the direction of the Project Leader(s) named in Appendix "A".

ARTICLE II - TERM OF CONTRACT

The period of performance for each research project covered by this contract is set forth in Appendix "A". It is recognized that completion of the research work under this contract may involve a period of several years and that the term or terms of this contract may be extended by mutual agreement.

ARTICLE III - FINANCING AND PROGRAM DEVELOPMENT

1. Payment

a. The combined total of the agreed upon budgets for the projects described in Appendix "A" is in the amount of \$25,000.00 and the Commission has obligated funds in this amount for this contract. However, payments to the Contractor by the Government under this contract with respect to each project described in Appendix "A" shall not exceed the amount of the agreed upon budget for each such project.

b. On or shortly after the effective date of this contract the Commission shall pay to the Contractor a sum which shall represent

the combined total of a mutually agreed upon estimate of the Contractor's cost of operations during the first two quarters under each project described in Appendix "A". As soon as practicable after the end of the first quarter, and after the end of each succeeding quarter during the term of this contract, the Contractor shall submit to the Commission a certified voucher supported by a certified schedule of the Contractor's expenditures under each project described in Appendix "A", and the Commission shall promptly pay all such vouchers. However, the initial payment relating to any one project together with all quarterly payments relating to the same project shall not exceed the agreed upon budget for such projects as set forth in Appendix "A", hereto.

2. Program and Budget for Subsequent Periods

At least three months before the end of the term established in Appendix "A" the Contractor will submit to the Commission a proposed program and budget for the succeeding year showing the proposed work to be financed by the Commission and the Contractor. The Contractor and the Commission shall negotiate as to the amount to be paid by the Commission for the services to be rendered by the Contractor during the next period. Such additional programs and agreed upon budgets shall be incorporated in a formal modification to this contract. In negotiating the new budget for said period the unobligated balance of funds paid to the Contractor covering the budget(s) for the preceding period shall be applied in reduction of funds required to cover the new budget(s). Upon completion of the contract work or upon earlier termination of this contract, the Contractor shall return to the Commission the unobligated portion of all payments made by the Commission to the Contractor under this contract.

3. New Problems

It is contemplated that the parties hereto may, from time to time, agree upon new research problems to be included in the work under this contract. The parties will thereupon prepare a description of the problem, plan of approach, agreed upon program and budget for the new project, which will be incorporated in Appendix "A" hereto, by means of a formal modification of this contract. All such new projects hereafter incorporated in Appendix "A" shall be subject to all the terms and conditions of this contract.

ARTICLE IV - ADMINISTRATION OF CONTRACT BY COMMISSION

The Commission has assigned the responsibility for administering the technical and scientific aspects for each project to the Washington organizational unit set forth in Appendix "A" hereto, to be addressed as follows:

U. S. Atomic Energy Commission
1901 Constitution Avenue, N. W.
Washington 25, D. C.

Responsibility for administering the business aspects of this contract, including contract negotiations, budget, payment, audit, etc., has been assigned by the Commission to:

Office of Research & Medicine
Oak Ridge Operations Office
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee

The Contractor may, as necessary, communicate directly with the appropriate office, as indicated above. The Contractor shall furnish information copies of communications, memoranda of telephone conversations, or other contacts to Oak Ridge Operations Office on all direct dealings with the Washington Office.

ARTICLE V - REPORTS, RECORDS AND INSPECTION

1. The Commission shall have the right to inspect in ~~any~~ manner and at such times as it deems appropriate all activities of the Contractor arising in the course of the work under this contract.

2. The Contractor shall make progress reports quarterly (unless a different reporting period is specified in Appendix "A") to the Commission on all its activities under this contract, including a list of personnel working on the project. Names appearing for the first time should be accompanied by a brief statement of the individual's background, training and experience. As soon as practicable after the end of the term of this contract and any renewal thereof the Contractor shall make a technical report to the Commission of all its activities under this contract. In the interest of reducing the effort required in preparing these reports the Contractor may include as a part of such reports copies of pertinent technical papers prepared for publication in customary scientific publication channels. At the time technical papers prepared by the Contractor relating to the work hereunder are submitted for publication in customary scientific publication channels the Contractor shall furnish the Commission with information copies of such papers.

3. If, during the course of the Contractor's activities under this contract, any technical findings are made which, in the opinion of the Contractor, would be of special interest to the Commission, the Contractor shall immediately make a report of such technical findings to the Commission.

4. The Commission will require five (5) copies of all reports and papers. Two (2) copies shall be sent to Washington and three (3) copies to Oak Ridge, addressed as shown in Article IV of this contract. The Commission shall have the right to reproduce and distribute at its discretion all such reports and technical papers. Appropriate credit lines will be included in all such reproductions.

5. The Contractor agrees to keep records and books of account showing the manner of expenditures of all funds received by it pursuant to this contract.

6. The Commission shall at all times be afforded access to the premises and to all books, records, correspondence, instructions, drawings, receipts, vouchers, and memoranda of record value of the Contractor pertaining to said work.

ARTICLE VI - PROPERTY FURNISHED TO CONTRACTOR - LIABILITY

1. RESERVATION BY GOVERNMENT

The Government reserves the right to furnish any materials, equipment or supplies which may be required in the performance of this contract. Except as provided in paragraph 3 of this Article, all property so furnished shall be and remain the property of the Government. The Contractor shall, to the extent practicable, cause all capital items of Government property so furnished to be suitably marked with an identifying symbol indicating Government ownership and the uses and disposition of such items shall be made a matter of record.

2. LIABILITY FOR GOVERNMENT-OWNED PROPERTY

Except as otherwise specifically provided, the Contractor shall not be liable for loss or destruction of or damage to property of the Government in the possession or control of the Contractor in connection with this contract (hereinafter called "Government property") unless such loss, destruction or damage results from wilful misconduct or failure to exercise good faith on the part of the Contractor's corporate officers, Executive Director, or Director of any program administered by the Contractor in the performance of this contract.

3. TITLE TO PROPERTY PURCHASED BY CONTRACTOR

Notwithstanding any other provisions of this Article VI and in consideration of the Contractor's contribution to the research project described in Appendix "A" of this contract, title to all materials, tools, machinery, equipment and supplies, acquired from sources other than the Government, or manufactured by the Contractor under this contract (including items manufactured in whole or in part from property furnished by the Government but only to the extent the Government has not designated such property as capital), shall vest in the Contractor, except that title to items of property described in Section 2.c. of each Title of Appendix "A" shall vest in the Government.

ARTICLE VII - PURCHASE OF RADIOISOTOPES

The Contractor shall purchase, to the extent available in appropriate form, all radioisotopes irradiation services and cyclotron time required in the performance of the work hereunder, through the Commission's Isotope Division, Post Office Box E, Oak Ridge, Tennessee.

ARTICLE VIII - GENERAL PROVISIONS

The provisions of Appendix "B", attached hereto, are hereby made a part of this contract.

ARTICLE IX - AUTHORIZATION

This contract is authorized by and has been executed under the Atomic Energy Act of 1946.

ARTICLE X - ALTERATIONS

The following alterations to this contract were made by mutual agreement of the parties prior to its execution:

IN WITNESS WHEREOF, the parties hereto have executed this contract the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: *C. Vanden Bulck*
C. Vanden Bulck, Acting Deputy Manager
THE BOWMAN GRAY SCHOOL OF MEDICINE OF
WAKE FOREST COLLEGE
(Contractor)

WITNESSES:

Harry C. Parker
Katherine Harris

BY: *Al B. Spent*

TITLE: *Dean*

APPENDIX "A"

Contract No. AT-(40-1)-288
(The Bowman Gray School of Medicine
of Wake Forest College)

TITLE I

1. PROJECT

a. Project Leader

The work under this Title I of Appendix "A" will be carried out by the Contractor under the direction of Dr. George T. Harrell as Project Leader.

b. Term

The performance of work under this Title I of Appendix "A" shall commence on July 1, 1949 and continue until June 30, 1950. It is understood, however, that completion of the research project described herein may involve a period of several years. Accordingly, the work under this Title I may be extended by mutual agreement.

c. Program

(1) Outline of the proposed work and the plan of attack.

Studies in human beings with Rocky Mountain spotted fever have shown a drop in the blood volume and a rise in the thiocyanate extravascular space during the second week of the disease. Rabbits with serum sickness and trichinosis have shown similar responses. Clinical edema develops with the rise in thiocyanate space; apparently the permeability of membranes is altered. It is not known whether capillary and cellular walls are both altered or whether the edema is within or between cells. It is known that water is retained during acute infections and that diuresis occurs during recovery. It is also known that chloride and water are retained during the acute phase of serum sickness. Water is held in tissue by ions; chloride ions are not held without corresponding anions - usually sodium and potassium. It is of immediate practical importance in therapy to know which ions traverse the membranes and whether they go into cells or remain in interstitial spaces. The turnover of radio sodium in the blood and interstitial edema fluid has been followed in heart failure. This technique could be applied to our problem in the following fashion:

- (a) Serum sickness could be induced in animals; when edema developed, radio sodium and thiocyanate would be given. The levels in plasma, urine and interstitial fluid for total sodium - as determined by the

flame photometer - would be compared with the radio sodium - as determined by a Geiger-Muller tube - and correlated with the thiocyanate space. A similar experiment would be done administering radioactive potassium.

(b) The experiments in animals would be repeated using an interstitial infection - trichinosis - and an intercellular infection - a rickettsia.

(c) After facility in the methods has been attained, the experiments would be repeated in human beings with infections and with serum sickness. It would be highly desirable to take radioautographs of tissue for comparison with stained histologic sections. The technique for determining deposition of insoluble radio phosphorus in bone might be modified for use on frozen sections.

2. BUDGET - PERIOD JULY 1, 1949 - JUNE 30, 1950

a. The Bowman Gray School of Medicine of Wake Forest College will furnish as its contribution to the project described in this Title I, the following:

- (1) Salary of Project Leader.
- (2) Overhead costs allocable to the contract work.

b. The Commission will furnish a sum not to exceed \$11,000.00 to be spent roughly as follows:

(1) Personnel

Part-time salary of Dr. Yount.....	\$1800.00	
Technician.....	2400.00	
Electronic engineer, part-time.....	500.00	
		\$4,700.00

(2) Permanent Equipment

Shielded sample changer.....	200.00
Scaling circuit.....	450.00
Flame Photometer.....	725.00
Timer.....	60.00
Geiger tubes.....	100.00
Time recorder.....	150.00
Centrifuge.....	250.00
Balance.....	230.00

Deep Freeze Unit.....	160.00	
Metabolism cages.....	350.00	
Vacuum pump.....	75.00	
		\$2,750.00
 (3) <u>Expendable Supplies</u>		
Glassware.....	750.00	
Purchase of radioisotopes.....	400.00	
Chemicals.....	500.00	
Animals.....	1500.00	
		\$3,150.00
 (4) Travel.....		
		200.00
 (5) Miscellaneous.....		
		200.00
TOTAL.....		\$11,000.00

It is understood and agreed by and between the parties hereto, that the Contractor in expending the funds provided by the Government shall be guided by, but not bound to conform to, the details of the program and budget set forth above.

- c. Items of property procured or manufactured by the Contractor under this contract, title to which will vest in the Government. See Article VI, Section 3.

QUANTITYDESCRIPTION

None

3. PROGRESS REPORTS

The Contractor shall make progress reports at 6 months intervals in the manner described in Article V of this contract.

4. TECHNICAL ADMINISTRATION BY COMMISSION

The Commission has assigned the responsibility for administering the technical and scientific aspects of this Title I of Appendix "A" to:

Medical Branch
 Division of Biology and Medicine
 U. S. Atomic Energy Commission
 1901 Constitution Avenue, N. W.
 Washington 25, D. C.

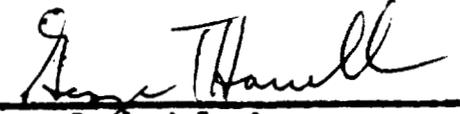
Appendix "A" (Cont'd)

TITLE I

Contract No. AT-(40-1)-288

5. ACCEPTANCE BY PROJECT LEADER

I have read the foregoing Title I of Appendix "A" and the basic contract to which it relates and I agree to be bound by the provisions of said documents.

SIGNED 
Project Leader

DATE: 7/6/49

TITLE II

1. PROJECT

a. Project Leader

The work under this Title II of Appendix "A" will be carried out by the Contractor under the direction of Dr. Camillo Artom as Project Leader.

b. Term

The performance of work under this Title I of Appendix "A" shall commence on July 1, 1949, and continue until June 30, 1950. It is understood, however, that completion of the research project described herein may involve a period of several years. Accordingly, the work under this Title II may be extended by mutual agreement.

c. Program

Phospholipides are universal constituents of living cells and while their exact roles are not yet well defined, a basic knowledge of the mechanism of formation of phospholipides in tissues and of the various intrinsic and extrinsic factors involved seems to be essential for an adequate understanding of many physiological and pathological processes. This knowledge is still very incomplete. Results obtained recently in this laboratory showed changes in the rate of synthesis of phospholipides under the action of drugs, some of which, such as phlorizin, are believed to poison certain enzyme systems in tissues, while others, such as thiourea and thiouracil, may act more or less as specific hormone inhibitors. These results suggest several possibilities for further investigation, such as the following: (1) that the formation of phospholipides, at least in the liver, may be controlled directly or indirectly by hormones; (2) that the effects observed may instead be due to a close relationship between the metabolism of phospholipides and that of carbohydrates or fats; (3) that by the use of inhibitors of specific enzyme systems, compounds, which are intermediates in the synthesis of phospholipides, may accumulate in tissue, so that their identification will become easier.

Two types of experiments are planned (a) in intact animals and, (b) in isolated tissue slices. In both conditions the synthesis of phospholipides will be followed with the aid of radioactive

phosphorus as a tracer for the phosphate part of the molecule. By labeling the methyl group of choline with C¹⁴, the formation of lecithins after administration of choline could also be studied. The concentration of either isotope will be determined in the phospholipides as well as in other phosphorus containing fractions which might presumably include intermediate products for the synthesis of phospholipides.

In the experiments on intact animals, rats will be maintained on a choline deficient diet, then radioactive phosphorus (with or without isotopic choline) will be administered. Various pharmacological and hormonal agents will then be given and their effect on the rate of lipide phosphorylation will be investigated in the liver, probably also in other tissues. We are tentatively contemplating the use of phlorizin, thiourea, alloxan, urethan, B.A.L., insulin, thyroxine and anterior pituitary extracts. On the basis of the results obtained, other substances and different experimental conditions will be tested, such as the surgical removal of the thyroid, diets containing various amounts of fats and carbohydrates, etc. Parallel experiments will be made on the isolated tissues in the presence of isotopic phosphate and choline, with or without direct addition of drugs and hormones to the medium.

While it is anticipated that only part of the above program can be carried out in one year's work, it is hoped that interesting results will be obtained early, and give an indication along what lines it will be most profitable to concentrate the investigative effort. The possibility that as soon as definite results have been obtained on normal tissues, the investigation might be extended to neoplastic tissues is also contemplated.

2. BUDGET - PERIOD JULY 1, 1949 - JUNE 30, 1950

a. The Bowman Gray School of Medicine of Wake Forest College will furnish as its contribution to the project described in this Title II the following:

- (1) Salaries of following personnel:
Dr. Camillo Artom as Project Leader
~~Dr. W. E. Crowder~~
Dr. M. A. Swanson
Marietta Crowder, Graduate Student

- (2) Overhead allocable to the contract work.

b. The Commission will furnish a sum not to exceed \$11,000.00 to be spent roughly as follows:

(1) Personnel

Full time technician (M. L. Haigler)...	\$2160.00	
2 Part time technicians.....	2160.00	
		\$4,320.00

(2) Permanent Equipment

High speed centrifuge.....	650.00	
Two carbon Combustion apparatus.....	600.00	
Direct reading balance for animals.....	250.00	
Geiger-Muller counter.....	450.00	
Shielded manual sample changer with amplifier.....	200.00	
Accessories for Warburg apparatus.....	350.00	
		\$2,500.00

(3) Consumable Supplies

Radioactive phosphorus.....	250.00	
Radioactive compounds (C ¹⁴ labelled)...	1250.00	
Animals.....	500.00	
Glassware.....	600.00	
Chemicals.....	500.00	
Organic Solvents.....	300.00	
		\$3,400.00

(4) Travel..... 200.00

(5) Miscellaneous (Maintenance, repairs and replacements of radioactivity apparatus)...	350.00	
Incidentals.....	230.00	
		580.00

TOTAL..... \$11,000.00

It is understood and agreed by and between the parties hereto, that the Contractor in expending the funds provided by the Government shall be guided by, but not bound to conform to, the details of the program and budget set forth above.

c. Items of property procured or manufactured by the Contractor under this contract, title to which will vest in the Government. See Article VI, Section 3.

Appendix "A" (Cont'd)

TITLE II

Contract No. AT-(40-1)-288
(The Bowman Gray School of Medicine
of Wake Forest College)

IDENTITY

DESCRIPTION

None

3. PROGRESS REPORTS

The Contractor shall make progress reports at 6 months intervals in the manner described in Article V of this contract.

4. TECHNICAL ADMINISTRATION BY COMMISSION

The Commission has assigned the responsibility for administering the technical and scientific aspects of this Title II of Appendix "A" to:

Medical Branch
Division of Biology and Medicine
U. S. Atomic Energy Commission
1901 Constitution Avenue, N. W.
Washington 25, D. C.

5. ACCEPTANCE BY PROJECT LEADER

I have read the foregoing Title II of Appendix "A" and the basic contract to which it relates and I agree to be bound by the provisions of said documents.

SIGNED: *E. Camille Arson*
Project Leader

DATE: 7/6/49

APPENDIX "A"

Contract No. AT-(40-1)-288
(The Bowman Gray School of Medicine
of Wake Forest College)

TITLE III

1. PROJECT

a. Project Leader

The work under this Title III of Appendix "A" will be carried out by the Contractor under the Direction of Dr. George T. Harrell as Project Leader associated with Drs. C. Artom and D. Cayer.

b. Term

The performance of work under this Title III of Appendix "A" shall commence on July 1, 1949 and continue until June 30, 1950. It is understood, however, that completion of the research project described herein may involve a period of several years. Accordingly, the work under this Title III may be extended by mutual agreement.

c. Program

(1) Description of Project

Toxicity of P^{32} as related to the functional capacity of the liver.

(2) Plan of approach

Radio isotopes can enter the cell and be incorporated into protoplasmic constituents, exerting a radiation effect in immediate proximity to the enzyme systems in the cells. Accordingly, the results of internal radiation may not necessarily duplicate those of external radiations such as X-rays. While cells altered by malignant changes are known to be more susceptible to radiation than normal cells, the possibility may also exist of increased effects of radiation on cells previously damaged by factors other than malignancies such as infectious diseases, dietary inadequacies or exposure to toxic substances. The additive effect of radiation from isotopes introduced in the body (perhaps even only in tracer amounts) may possibly harm cells already partially damaged, this reducing their functional capacity below the level required for life. Since the liver is especially susceptible to damage even from mild agents and since P^{32} is synthesized very actively into various organic compounds in the liver, this tissue seems to offer considerable interest for

such a study. Of special importance would be the role of lipotropic substances since these have been shown to exert beneficial effects in several conditions with liver damage such as in cirrhosis. A possible approach to preventive or corrective therapy can thus be visualized. Preliminary experiments have already been made on the toxicity of P³² in mice. It is planned to extend further this study by varying the proportion and the nature of the protein, fat and carbohydrate components of the diet. The possible effects of various vitamins will also be investigated. Additional experiments will be done on animals in which anatomical and functional changes of the liver have been induced either by partial hepatectomy or by exposure to toxic agents.

2. BUDGET - PERIOD JULY 1, 1949 - JUNE 30, 1950

a. The Bowman Gray School of Medicine of Wake Forest College will furnish as its contribution to the project described in this Title III the following:

- (1) Salaries of three principal investigators, Drs. G. Anton, C. T. Harrell and D. Cayer.
- (2) Overhead costs allocable to the contract work.

b. The Commission will furnish a sum not to exceed \$3,000.00 to be spent roughly as follows:

(1) Salaries

Technical help.....	\$1500.00	
		\$1,500.00

(2) Permanent Equipment

Metabolism cages for animals.....	250.00	
One homogenizer for the preparation of diets.....	35.00	
		285.00

(3) Expendible Supplies

Radioactive phosphorus.....	300.00	
Dietary components and animals.....	500.00	
Glassware and containers.....	150.00	
		950.00

(4) Miscellaneous.....	265.00	
		265.00

TOTAL.....	\$3,000.00
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It is understood and agreed by and between the parties hereto, that the Contractor in expending the funds provided by the Government shall be guided by, but not bound to conform to, the details of the program and budget set forth above.

- c. Items of property procured or manufactured by the Contractor under this contract, title to which will vest in the Government. See Article VI, Section 3.

QUANTITY

DESCRIPTION

None

3. PROGRESS REPORTS

The Contractor shall make progress reports at 6 months intervals in the manner described in Article V of this contract.

4. TECHNICAL ADMINISTRATION BY COMMISSION

The Commission has assigned the responsibility for administering the technical and scientific aspects of this Title III of Appendix "A" to:

Medical Branch
Division of Biology and Medicine
U. S. Atomic Energy Commission
1901 Constitution Avenue, N. W.
Washington 25, D. C.

5. ACCEPTANCE BY PROJECT LEADER AND ASSOCIATE PROJECT LEADERS

I have read the foregoing Title III of Appendix "A" and the basic contract to which it relates and I agree to be bound by the provisions of said documents.

SIGNED: *Gene Howell*
Project Leader

H. Cornelius Arson
Associate Project Leader

David Cayer
Associate Project Leader

DATE: 7/6/49

APPENDIX "B"

GENERAL PROVISIONS

1. PATENTS

a. Whenever any patentable invention or discovery is made or conceived by the Contractor or its employees in the course of any of the work under this contract, the Contractor 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 rights under any application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

b. No claim for pecuniary award under the provisions of the Atomic Energy Act of 1946 shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of any of the work under this contract.

c. Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs a. and b. of this Article from all persons who perform any part of the work under this contract, except clerical and manual labor personnel who will not have access to technical data.

d. Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts provisions making paragraphs a., b., and c. of this Article applicable to the subcontractor and its employees.

2. PUBLICATIONS

The Contractor shall have full freedom of publication of the results of the research under this contract and the Contractor is urged to disseminate the results of the work through customary scientific publication channels, except that "restricted data" as defined in the Atomic Energy Act of 1946 shall be governed by the provisions of Paragraph 3 of this Appendix "B". All publications shall include a reference that the results were developed under a Commission sponsored project.

3. DISCLOSURE OF INFORMATION

a. It is understood that the work under this contract will not involve restricted data and the Contractor will perform such work as unclassified work. However, if in the course of such work any discoveries are made or any data used or developed that constitute restricted data, the Contractor shall promptly inform the Commission and shall classify and safeguard all

discoveries and data in accordance with the requirements of the Commission. It is understood that the person directing research work under this contract shall have been cleared by the Commission for access to restricted data. The Contractor agrees that it will not permit any individual to have access to restricted data until the Federal Bureau of Investigation shall have made an investigation and report to the Commission of the character, associations and loyalty of such individual and the Commission shall have determined that permitting such person to have access to restricted data will not endanger the common defense or security. If doubt exists as to whether any discovery or data developed constitute restricted data, prior to the release of these data and before permitting any individual who has not received clearance from the Commission to have access to such data, the Contractor shall seek guidance from the Commission. Furthermore, the Commission reserves the right to require the classification of work whenever in its opinion restricted data are involved.

b. The continuation by the Contractor of work found to involve restricted data will be subject to mutual agreement of the Commission and the Contractor and shall be covered by a modification of this agreement. The phrase "restricted data" as defined in the Atomic Energy Act of 1946 and employed in this section shall mean "all data concerning the manufacture or utilization of atomic weapons, the production of fissionable material, or the use of fissionable material in the production of power, but shall not include any data which the Commission from time to time determines may be published without adversely affecting the common defense and security".

4. DISPUTES

Except as otherwise specifically provided in this contract, all disputes which may arise under this contract and which are not disposed of by mutual agreement shall be decided by a representative of the Commission duly authorized to supervise and administer performance under this contract, who shall reduce his decision to writing and cause a copy thereof to be mailed to the Contractor, said decision shall be final and conclusive, subject to the provisions of the sentence next following. Within thirty (30) days from the date of such mailing, the Contractor may appeal in writing to the Commission, whose written decision thereon, or that of its duly authorized representative, representatives, or board not including the representative mentioned in the preceding sentence, shall be final and conclusive. Pending decision of a dispute hereunder, the Contractor shall proceed with the performance of its undertakings under this contract.

5. SAFETY AND ACCIDENT PREVENTION - INSPECTIONS

The Contractor will comply with health and safety regulations of the Commission required for work of this nature, and permit the Commission and its designees to inspect the work conducted under this agreement.

6. OFFICIALS NOT TO BENEFIT

No member of or Delegate to Congress, or Resident Commissioner shall be admitted to any share or part of this contract or to any benefit that may arise therefrom, but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

7. ANTI-DISCRIMINATION

The Contractor, in performing the work required by this contract, shall not discriminate against any employee or applicant for employment because of race, creed, color, or national origin.

8. CONVICT LABOR

The Contractor shall not, in the performance of this contract, employ any person undergoing sentence of imprisonment at hard labor.

9. TERMINATION

a. The Commission may at any time upon 120 days written notice terminate this contract in whole or in part.

b. In the event of termination pursuant to subsection a., the Contractor will be paid for the portion of the contract work already performed, together with reasonable costs of termination.

10. EIGHT-HOUR LAW

No laborer or mechanic doing any part of the work contemplated by this contract, in the employ of the Contractor or any subcontractor contracting for any part of said work contemplated, shall be required or permitted to work more than eight (8) hours in any one calendar day upon such work at the site thereof, except upon the condition that compensation is paid to such laborer or mechanic in accordance with the provisions of this Article. The wages of every laborer and mechanic employed by the Contractor or any subcontractor engaged in the performance of this contract shall be computed on a basic day rate of eight (8) hours per day and work in excess of eight (8) hours per day is permitted only upon the condition that every such laborer and mechanic shall be compensated for all hours worked in excess of eight (8) hours per day at not less than one and one-half ($1\frac{1}{2}$) times the basic rate of pay. For each violation of the requirements of this Article a penalty of Five Dollars (\$5.00) shall be imposed upon the Contractor for each laborer or mechanic for every calendar day in which such employee is required or permitted to labor more than eight (8) hours upon said work without receiving compensation computed in accordance with this Article, and all penalties thus imposed shall be withheld for the use and benefit of the Government; provided, that this stipulation shall be subject in all respects to the exceptions and provisions of U.S. Code, Title 40, Sections 321, 324, 325, and 326, relating to hours of labor, as modified by the provisions of Section 303 of Public Act No. 781, 76th Congress, approved September 9, 1940, relating to compensation for overtime.

11. DEFINITIONS

As used in this contract the terms "United States Atomic Energy Commission", "Atomic Energy Commission" and "Commission" shall mean the United States Atomic Energy Commission or its duly authorized representative or representatives.