1139 R

Office Memorandum • UNITED STATES GOVERNMENT

TO : J. W. Ould, Jr., Assistant General Counsel DATE: May 18, 1954

FROM : R. G. Humphries, Assistant Director, Contract Division 717198

SUBJECT: REQUEST FOR MODIFICATION OF CONTRACT NO. AT-(40-1)-288 - BOWMAN GRAY SCHOOL OF MEDICINE

SYMBOL: ADA:ARB

It is requested that you prepare an appropriate modification to the subject contract to show that the work under the contract was terminated as of December 31, 1953. Provisions should be included to cover expenses incurred in connection with showing an exhibit prepared by Dr. Harrell, the Project Leader, which expenses were not incurred until March 31, 1954. The amount of the total cost for the last period of performance under the contract should be reduced from $8,576.52 to $2,504.98.

A Request for Contract Action, dated May 14, 1954, from the Research and Medicine Division, asking for the above modification, is enclosed.

R. G. Humphries

Enclosures:
1. Request for Contract Action
2. Attachment "A"
3. Cy Ltr fm Parker dtd 4/6/54
4. Cy Ltr fm Kasschau dtd 3/4/54
5. Cy Ltr fm LeFevre dtd 11/23/53
6. Cy Report of Expenditures
7. Cy Report of Receipts and Expenditures

CC: C. S. Shoup
L. D. MacKay
Ed Ziegler, w/Encls. 1 and 2
J. Nicholson

Brown:arb

REPOSITORY Oak Ridge Operations
Records Holding Area
COLLECTION Documents 1944-94
Contracts AT-(40-1)-266-288
BOX No. 2 of 2 Bldg. 2714-H
Record of Negotiations
FOLDER & Awards - Backup

135

1111911

J. W. Ould, Jr., Assistant General Counsel May 18, 1954

R. G. Humphries, Assistant Director, Contract Division

REQUEST FOR MODIFICATION OF CONTRACT NO. AT-(40-1)-888 - BOWMAN GRAY SCHOOL OF MEDICINE

SYMBOL: ADA:ARB

It is requested that you prepare an appropriate modification to the subject contract to show that the work under the contract was terminated as of December 31, 1953. Provisions should be included to cover expenses incurred in connection with showing an exhibit prepared by Mr. Harrell, the Project Leader, which expenses were not incurred until March 31, 1954. The amount of the total cost for the last period of performance under the contract should be reduced from $8,576.52 to $2,504.98.

A Request for Contract Action, dated May 14, 1954, from the Research and Medicine Division, asking for the above modification, is enclosed.

R. G. Humphries

Enclosures:
1. Request for Contract Action
2. Attachment "A"
3. Cy Ltr fm Parker dtd 4/6/54
4. Cy Ltr fm Kassahn dtd 3/4/54
5. Cy Ltr fm LaFevre dtd 11/23/53
6. Cy Report of Expenditures
7. Cy Report of Receipts and Expenditures

CC: G. E. Shoup
L. B. MacKay
Ed Ziegler, w/Encls. 1 and 2
J. Nicholson

Brown:arb

1111912

5-14-54

Form OR-569 (2/53) REQUEST FOR CONTRACT ACTION (submit in duplicate)

1. TO: J. R. Moore Chairman Contract Board. From: Research & Medicine Div.

It is requested that the Contract Board take the necessary action to process the following described contract action in accordance with the provisions of Bulletin OR-O&M-19:

2. Nature of Action Requested

☐ Selection of New Contractor and Negotiation of Contract.

☒ Modification of Contract No. AT-(40-1)-288
Contractor: Bowman Gray School of Medicine
Winston-Salem, North Carolina

☐ Review and approval of Contract, Subcontract or Purchase Order.
Number:
Name:

☐ Other (Explain)

3. Nature of Services to be Covered by Contract

Construction ☐ Architect-Engineer ☐ Other ☒ (Explain) Research

4. Funding Amount to be Obligated by this Contract Action $ None

Source of Funds

Approved ORO Financial Plan, _____ Quarter, Fiscal Year 19__
Project No. _____ or, Activity No. _____
Funds to be Obligated: Allotment No. _____ (F.Y. 19__ Funds)
Procurement Directive No. _____ Dated _____
Issuing Office _____

Concurrence in Funding Statement: (signed) _____
Chief, Budget Branch

5. Project or Activity to be Covered by Contract Action:

Location of Work: _____ Construction Directive No. _____
Estimated Cost of Work to be Covered by this Contract Action $ _____
Schedule: Date Work to Start _____ Estimated Completion Date _____
Description of Project or Activity:

(If more space is required use separate sheets and attach hereto:)

Bulletin OR-O&M-19

Exhibit I

1111913

6. Contract Board Docket No. _____ (To be assigned by Board Secretary)	7. Request Submitted By: (signed) Norman M. Roth Date: 5/14/54 Title: RESEARCH AND MEDICINE DIVIST

8. Complete Description of Services to be Furnished by Contractor:

Washington designated research contract.

Title: Distribution and Turnover of Sodium and Potassium in Acute Infections.

(If more space is required use separate sheets and attach hereto:)

9. Description of other changes to be covered by Modification:

See Attachment "A"

(If more space is required use separate sheets and attach hereto:)

10. Negotiated Contracts. (Show why it appears desirable to negotiate new contract or to negotiate modification to existing contract)

See Attachment "A"

(If more space is required use separate sheets and attach hereto:)

11. Contracts, Subcontracts, or Purchase Orders Submitted for Review and Approval: (Furnish brief description of action in this space and attach pertinent documents)

None

12. Disputes:

Attach a statement summarizing the dispute together with pertinent documents and Background Material.

None

1111914

Attachment "A"

Contract No. AT-(40-1)-288 was extended on July 1, 1953, for a period of one year with new funds in the amount of $10,000. On December 8, 1953, we were advised that the Project Leader, Dr. George T. Harrell had been elected Dean of the University of Florida Medical School and that work under the contract should be terminated as of December 31, 1953. We advised the College of our approval of the termination by a letter dated December 31, 1953, to Mr. Harry O. Parker, a copy of the letter was furnished your office. The Washington Office authorized the College to incur expenditures in showing an exhibit prepared by Dr. Harrell. The expenses, however, were not incurred until the last of March. A copy of the letter from Washington to Dr. Harrell regarding the exhibit is enclosed.

The College has submitted an expenditure statement indicating an unexpended balance of $3,576.52 on December 31, 1953. Also, $5,000 of the new funds provided are still held by the Finance Division. The contractor has submitted a check to the Finance Division to refund the unexpended balance.

It is requested that the contract be modified to indicate the termination date of December 31, 1953, with mention of the exhibit showing. Also, funds in the amount of $8,576.52 should be withdrawn from the contract to indicate the total cost for the last period of performance to be $2,504.98. This figure is made up of $1,081.50 unexpended from the previous period and $1,423.48 of the new funds.

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WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
Winston-Salem, North Carolina

April 6, 1954

U. S. Atomic Energy Commission
Oak Ridge Operations
Oak Ridge, Tennessee

Subject: Contract No. AT-(40-1)-288
OR:JER

Gentlemen:

Reference is made to your letter to us dated March 4, 1954, in regard to termination of the subject contract. There is enclosed a statement of receipts and expenditures, by years, under this contract from July 1, 1949 to June 30, 1953. There is also enclosed a report of expenditures as compared with contract amounts for the subject contract and contract no. AT-(40-1)-1638, which shows expenditures through March 31, 1954 together with estimated expenditures to June 30, 1954.

It will be noted on the statement of receipts and expenditures for contract No. AT-(40-1)-288 that the cash balance for Title I at June 30, 1953 amounted to $1,081.50. During the current year we received $5,000.00 and we have expended $2,504.98 which leaves a balance on hand of $3,576.52. The disbursements shown include the cost of travel expense and transportation charges for showing the exhibit in Cleveland, Ohio in March.

According to your instructions in your letter of March 4, 1954, we are enclosing our check in the amount of $3,576.52 representing the balance on hand for Title I of this contract. We trust that this is in accordance with your records.

Very truly yours,

/s/ Harry O. Parker

Harry O. Parker
Controller

HOP:ahc

Encl. (3)

C
O
P
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1111916

In Reply
Refer to: OR:JFR

Oak Ridge, Tennessee
March 4, 1954

Mr. Harry O. Parker
Controller
Wake Forest College
The Bowman Gray School of Medicine
Winston-Salem, North Carolina

Subject: CONTRACT NO. AT-(40-1)-268

Dear Mr. Parker:

Reference is made to your letter of February 25, 1954.

We agree with your proposal to delay action on refunding the balance of funds that remain unexpended under the contract until the end of March. As soon as you have the necessary information on the exact balance we shall appreciate your cooperation in submitting to us a check made payable to the Treasurer of the United States to cover the unexpended balance. At that time we will initiate action to terminate the contract.

Your cooperation in this matter is appreciated.

Very truly yours,

Kenneth Rasschau
Director
Research and Medicine Division

Roumesville:ce

1111917

C O P Y

BMM:PGL

November 23, 1953

Dr. George T. Harrell
Department of Internal Medicine
Wake Forest College
The Bowman Gray School of Medicine
Winston-Salem, North Carolina

Dear Doctor Harrell:

We were pleased to receive the photograph of your prize-winning exhibit on cation turnover, and would appreciate receipt of one or two colored prints. I expect to be in Winston-Salem on Monday, December 7, and can pick up the prints at that time, if they will be available. I would also like to spend a few hours with you and your group and hear of the status of your research project and your immediate plans.

With respect to your expenses in exhibiting at Cleveland in March, I believe there need be no specific authorization from this office concerning the transfer of funds, if this can be worked out within your present budget. The contract budget is taken as a general guide, rather than a strict stipulation of the allotment of the funds. Reasonably small transfers within the several categories may be made at any time. If fairly large transfers are required, you should consult the Oak Ridge Operations Office and indicate the necessity for the changes desired.

Please let me know whether you will be available on December 7, and if so, what hours would be most convenient for my visit.

Sincerely yours,

Paul G. LeFevre
Assistant to Chief (Research)
Medical Branch
Division of Biology and Medicine

CC: to OROO - Att: K. Kasschau

LEFEVRE:rmk

Medical

1111918

Office Memorandum • UNITED STATES GOVERNMENT

TO J. W. Culd, Jr., Assistant General Counsel DATE: June 3, 1953

FROM John R. Moore, Director, Contract Division

SUBJECT: RENEWAL OF CONTRACT NO. AT-(40-1)-288 - THE BOWMAN-GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

SYMBOL: AD:ARB

Enclosed is an approved proposal for renewal of subject contract for one year beginning July 1, 1953. This approval action is covered by Procurement Directive No. BM-53-270, dated May 15, 1953, in the amount of $10,000.00.

It is requested that an appropriate modification be prepared to renew this contract for a period of one year beginning July 1, 1953, and provide for payment of $10,000.00.

John R. Moore

Enclosures:
1. Request for Contract Action
2. Memo fm LeFevre dtd 5/15/53
3. Ltr fm Harrell dtd 4/4/53
4. Proposal
5. Report of Expenditures
6. Cy Ltr fm Harrell dtd 5/22/53
7. Cy Ltr fm LeFevre dtd 5/15/53
8. Resume
9. Budget
10. Ltr fm Harrell dtd 5/22/53

CC: C. S. Shoup
L. D. MacKay
Ed Ziegler, w/Encl. 1
J. Nicholson

/arb

1111919

Form OR-569 (2/53) REQUEST FOR CONTRACT ACTION (submit in duplicate)

1. John R. Moore, Director Chairman
TO: Contract Division Contract Board. From: Research & Medicine Div.

It is requested that the Contract Board take the necessary action to process the following described contract action in accordance with the provisions of Bulletin OR-O&M-19:

2. Nature of Action Requested

☐ Selection of New Contractor and Negotiation of Contract.

☐ Review and approval of Contract, Subcontract or Purchase Order.
Number: _____
Name: _____

☒ Modification of Contract
No. AT-(40-1)-288
Contractor: Wake Forest College
The Bowman-Gray School of Medicine
Winston-Salem, North Carolina

☐ Other (Explain) _____

3. Nature of Services to be Covered by Contract

Construction ☐ Architect-Engineer ☐ Other ☒ (Explain) Research

4. Funding Amount to be Obligated by this Contract Action $10,000

Source of Funds

Approved ORO Financial Plan, _____ Quarter, Fiscal Year 19__
Project No. _____ or, Activity No. _____
Funds to be Obligated: Allotment No. _____ (F.Y. 19__ Funds)
Procurement Directive No. BM-53-270 Dated 5-15-53
Issuing Office Division of Biology and Medicine Washington

Concurrence in Funding Statement: (signed) _____
Chief, Budget Branch

5. Project or Activity to be Covered by Contract Action:

Location of Work: _____ Construction Directive No. _____
Estimated Cost of Work to be Covered by this Contract Action $ _____
Schedule: Date Work to Start _____ Estimated Completion Date _____
Description of Project or Activity:

(If more space is required use separate sheets and attach hereto:)

Bulletin OR-O&M-19

Exhibit I

Procurement Directive
1 BM-53-270 5/15/53
$10,000.00

1111920

6. Contract Board Docket No. _____ (To be assigned by Board Secretary)

7. Request Submitted By: (signed) _____
Date: _____ Title: _____

RESEARCH AND MEDICINE DIVISI...

8. Complete Description of Services to be Furnished by Contractor:

Washington designated research contract
Title: Distribution and Turnover of Sodium and Potassium in Acute Infections

(If more space is required use separate sheets and attach hereto:)

9. Description of other changes to be covered by Modification:

Renewal of Contract for period of one year, beginning July 1, 1953

(If more space is required use separate sheets and attach hereto:)

10. Negotiated Contracts. (Show why it appears desirable to negotiate new contract or to negotiate modification to existing contract)

Memo P. G. LaFevre to Kenneth Kasschau dated May 15, 1953

(If more space is required use separate sheets and attach hereto:)

11. Contracts, Subcontracts, or Purchase Orders Submitted for Review and Approval: (Furnish brief description of action in this space and attach pertinent documents)

None

12. Disputes:
Attach a statement summarizing the dispute together with pertinent documents and Background Material.

None

1111921

UNITED STATES ATOMIC ENERGY COMMISSION
DIVISION OF BIOLOGY AND MEDICINE
WASHINGTON, D. C.

DATE: MAY 15 1953

TO : Kenneth Kassohau, Director, Office of Research and Medicine, Oak Ridge Operations Office

FROM : Paul G. LeFevre, Assistant to Chief (Research), Medical Branch

SUBJECT: TRANSMITTAL OF RESEARCH PROPOSAL FOR CONTRACT NEGOTIATION

SYMBOL : BMM:PGL

This letter with enclosure, in triplicate, is sent in accordance with the procedure described in a letter from the General Manager to all Managers of Operations dated January 27, 1949.

1. Institution: Wake Forest College

2. Investigator (s): G. T. Harrell, Jr.

3. Title: "Distribution and Turnover of Sodium and Potassium in Acute Infections"

4. ( ) New Contract or (x) Renewal of Contract No. AT(40-1)288, Project I

5. Duration - From: July 1, 1953 to June 30, 1954

6. AEC Technical Supervision: Medical Branch

7. Recommended Support: $10,000.00, including overhead at 8%

Authorized by Procurement Directive No. BM53-270

Issued _____ $ 10,000.00

Activity No. 6300

8. Other Comments:

1111922

8. **Comments** (Continued)

9. **Security Requirements:**

In accordance with the provisions of GM-93 (Revised March, 1950), and the requirements of the Declassification Guide, the Division of Biology and Medicine has determined that the following security precautions should be taken in connection with the proposed research contract.

Since there is essentially zero chance that restricted data will be required or developed, no personnel security requirements should be imposed.

10. **Reports:** (x) Reports are to be required as provided for by Memorandum Instruction of November 9, 1949, on subject "Direct Research Contract Reports".

( ) Special Reports Instructions are as follows:

Enclosures:

( ) "A" - Proposal, dated Copy sent to OROO by investigator
( ) "B" - Notification letter, dated _____
( ) "C" - Other correspondence, _____ letters
(x) "D" - Procurement Directive RM53-270

Distribution:

Addressee:	Original (w encl.)	**Division File:**	Yellow Copy (w encl.)
	1st Copy (w encl.)		Pink Copy (w/o encl.)
	2nd Copy (w encl.)		
Program Analysis Branch:	White Copy (w/o encl.)	**Branch File:**	White Copy (w encl.)

1111923

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

DEPARTMENT OF
INTERNAL MEDICINE

May 22, 1953

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

Gentlemen:

Confirming my phone conversation yesterday with Mr. Shoup of the Oak Ridge Operations Office, we would like to submit the following revised budget for Title I of our contract AT-(40-I)-288 for the next year beginning July 1, 1953. This revised budget will replace the one included in our proposal of April 4, 1953.

(1) Salaries			
Technician (not selected	$2700		
Animal technician (Brooks)	2250		
Electronic Engineer, part-time	300		
		Total Salaries	$5250
(2) Equipment			502
(3) Isotopes			1850
(4) Animals			1800
(5) Supplies			
Geiger-Mueller tubes	200		
Glassware	300		
Chemicals	300		
		Total Supplies	800
(6) Travel			300
			$ 10502
(7) Overhead @ 8% on $9259			741
		Total	$ 11243
1952-3 unexpended balance	1243		
1953-4 new funds	9259		
working budget	10502		
overhead	741		
	$ 11243		
1952-3 unexpended balance			1243
1953-4 working budget	9259		
overhead	741		10000
	10000		$ 11243

MAY - 195

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C.3303

I believe these figures in the revised budget are practical in light of our expenditures through May 5, as given to us by categories by the Controller. If there is any additional information or any further changes which we can make, please command us.

Please let me express to you, again, our deep appreciation for the support of our research. Were it not for these funds, it would be impossible for us to conduct the experiments.

Respectfully yours,

George T. Harrell

George T. Harrell, M.D.
Research Professor of Medicine

GTH:vs

1111925

May 22, 1953

Atomic Energy Commission
Medical Branch
Division of Biology and Medicine
Washington 25, D.C.

Attn: Paul G. LeFevre
Assistant to Chief (Research)

Gentlemen:

Following a phone conversation with Oak Ridge Operations Office, as noted in your letter of May 15, we have prepared the enclosed revised budget. If there is any additional information or any further changes we should make in our proposal, we would be most happy to do so.

We note the remarks about further support and will adjust our program accordingly.

Respectfully yours,

George T. Harrell

George T. Harrell, M.D.
Research Professor of Medicine

GTH:vs
Encl:

COPY

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1111926

OAK RIDGE OPERATIONS
U.S. AEC

BUDGET

WAKE FORREST COLLEGE
BOWMAN-GRAY SCHOOL OF MEDICINE
Contract No. AT-(10-1)-2[illegible]

1) Salaries and Wages:		$5,250.
Technician	$2,700.	
Animal Technician	2,250.	
Electronic Engineer, (part time)	300.	
Total Salaries and Wages		
2) Equipment:		502.
3) Isotopes:		1,850.
4) Animals:		1,[illegible]00.
5) Supplies:		900.
Geiger-Mueller Tubes	$ 200.	
Glassware	300.	
Chemicals	300.	
Total Supplies		
6) Travel:		300.
Total		$10,502
Less unexpended balance under Title I		1,243
		9,259.
7) Overhead		741.
Total		$10,000.

1111927

WAKE FOREST COLLEGE,
BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
Dr. G. T. Harrell, Project Leader.

Formerly Title I to Contract AT-(40-1)-2[illegible].

RESUME'

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 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.

C. S. Shoup

1111928

RRM:PGL

MAY 15 1959

Dr. George T. Harrell
Department of Internal Medicine
Wake Forest College
Bowman Gray School of Medicine
Winston-Salem 7, North Carolina

Dear Doctor Harrell:

Your proposal for continuation of Atomic Energy Commission support of the project on iodide distribution and turnover in acute infections was considered at the last session of our Research Contracts Committee. It was agreed to renew this contract for an additional year, but at a somewhat reduced level, and with the understanding that this will almost certainly be the terminal year of support.

As indicated by Mr. James F. Haggerty of this office at the time of last year's renewal, the Atomic Energy Commission would probably be able to continue support of projects deriving from Titles II and III (of the older joint contract) at about the previous level, but is forced to reduce its support of research in the field covered by the former Title I.

We regret that it will be necessary to delete or reduce some of the budgetary items proposed for this coming year. No specific objections have been made to any of the listed items, and the requisite modifications are left to your discretion in conference with the Oak Ridge Operations Office. You should soon hear from that office regarding these negotiations.

Sincerely yours,

Paul S. LeFevre
Assistant to Chief (Research)
Medical Branch
Division of Biology and Medicine

Copy to OROO - att: K. Kasschau

LEFEVRE:rmk

Medical

1111929

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

DEPARTMENT OF
INTERNAL MEDICINE

April 4, 1953

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

Gentlemen:

Enclosed you will find two carbon copies of the proposal for renewal of Title I of our contract AT-(40-1)-288 which has been forwarded today to the Division of Biology and Research in Washington.

We have already forwarded to you, under separate cover, the progress report and summary of the scope and purpose of the investigation along with reprints. The report of expenditures through March 31 and projection of the estimated expenditures through June 30, 1953 will go forward to you under separate cover directly from the Controller.

Please let me express to you the deep appreciation of all of the people concerned with this project for the very helpful and cooperative attitude taken by your office in the administration of this project. It has been a pleasure to be relieved of the harassment of many unnecessary administrative details which has permitted us to place our energy primarily on the scientific aspects of the project.

If there are any additional questions about the progress report, reprints, summary or the proposal for next year which we can answer, please do not hesitate to phone or write us.

Cordially,

George T. Harrell

George T. Harrell, M.D.
Research Professor of Medicine

GTH:vs
Encl:

APR 6 1953

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(1) Salaries

	Technician (full time, [illegible])	$24[illegible]
	Research Associate (part time, [illegible])	1500.00
(2)	Permanent equipment	300.00
(3)	Isotopes	600.00
(4)	Supplies	500.00
(5)	Animals	250.00
(6)	Travel	250.00
(7)	Overhead at 8%	~~[illegible]~~ 464.00
	TOTAL	$6284.00

D. Camillo Artom
Gregory T. Hamill, Jr.

1111931

Contract No. AT-(40-1)-268
The Bowman Gray School of Medicine
of Wake Forest College

TITLE I

PROJECT: PERMEABILITY OF MEMBRANES IN INFECTIONS

Project leader: George T. Harrell, Jr.

A. Scope and Plan of Approach

Patients with acute infections retain fluids during the acute stage and excrete them during convalescence from the disease. Edema often develops, indicating that the permeability of capillary and cell membranes has been altered. Alterations in permeability can be visualized as a change in the size of pores in the membranes, increasing progressively as the severity of the disease increases. In mild instances, only crystalloids would leave the blood stream; in more severe instances, protein molecules or even red cells may leave the circulation.

In normal individuals, sodium is the predominant ion in the extracellular space and potassium in the intracellular space. Studies in previous years have indicated that the metabolism of these ions is upset in the course of infections. Disturbances in the distribution and turnover of sodium and potassium have been found in acute infections where the organisms may be either extracellular or intracellular; in disease that results from an antigen antibody reaction without actual infection as with serum sickness; or in diseases of collagenous tissue such as rheumatic fever which frequently appear several weeks after the acute phase of an infection.

Alterations in the content and turnover of ions or molecules may result from defects in absorption, distribution, excretion or utilization. Recovery from infection or other human disease is a complicated process involving many mechanisms and sites of action. If the mechanisms can be established by which increased amounts of water, electrolytes, or protein are passed across capillary or cell membranes, it may be possible to devise means of correcting the physiologic abnormality in acute infections or in diseases in which antigen-antibody reactions are thought to play a part.

The studies on the movement of ions, begun with Na_{24} and K_{42} which are both positively charged, should be extended with other ions. Ions naturally occurring in the body are preferable for study since foreign material, such as thiocyanate ions or the colloidal complexes of Evans blue dye, may not be handled in an identical fashion to normal body constituents of similar size. In addition to anions and cations, it would be desirable to study human protein molecules of various sizes tagged with isotopes I_{131}.

1. Standardization of Methods

Should it become necessary to utilize dogs for certain experiments instead of the guinea pigs and rabbits used previously, micro methods for blood volumes by various techniques, Na_{24} and K_{42} spaces and Na and K content of tissues will have to be developed and standardized.

Serial determinations of Na_{24} and K_{42} spaces in normal older human beings should be determined.

Bone, which is a storehouse for an appreciable amount of sodium in the human being, should be investigated further in animals to determine the extent to which it participates in the readily available pool of this ion.

1111932

2. Intracellular Infections

Further attempts should be made to increase the virulence of the spotted fever rickettsias or to obtain another strain which will induce greater physiologic changes in rabbits. If this can be achieved, the studies on experimentally induced Rocky Mountain spotted fever will be continued. The effect of antibiotics alone in normal animals; antibiotics in animals infected with rickettsias; animals infected with rickettsias treated with cortisone; and animals infected with rickettsias treated with both antibiotics and cortisone will be studied.

3. Extracellular Infections

The experiments previously reported on fluid changes in trichinosis, an extracellular infection inducing high degrees of antigen-antibody reaction and studied by non-isotopic techniques, should be repeated with the appli- of the tracer methods developed.

Time permitting, further attempts should be made to standardize an extracellular interstitial infection in the skin and subcutaneous tissues of rabbits with virulent type 1 pneumococci.

4. Metabolic Factors Apart from Infection

In order to determine the effect of the normal secretion of the thyroid gland on the distribution of ions and protein molecules, rabbits or dogs should 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} and K_{42} tissue content will be determined. The reversibility of the changes under replacement therapy with thyroid hormone will be studied.

Other hormones, such as adrenocorticotrophic hormone (ACTH) or cortisone, or drugs, such as salicylate or its degradation products, should be studied to determine the effect of their administration to normal animals, as has been done in the past with purified derivatives of digitalis. Studies using these substances in treatment of diseased animals could then be attempted.

5. Clinical Studies

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

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

The preliminary observations on the Na_{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.

BUDGET - Fifth Period: July 1, 1953 - June 30, 1954

"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

1111933

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 Twelve Thousand Five Hundred Eighty two Dollars ($12582.00) (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		
	Technician (not selected)	$2700.00	
	Animal technician (Breeks)	2250.00	
	Electronic Engineer, part-time	300.00	
	Total Salaries		$ 5250.00
(2)	Equipment		500.00
(3)	Isotopes		3000.00
(4)	Animals		1800.00
(5)	Supplies		
	Geiger-Mueller tubes	200.00	
	Glassware	300.00	
	Chemicals	300.00	
	Total Supplies		800.00
(6)	Travel		300.00
			$11650.00
(7)	Overhead @ 8%		932.00
	TOTAL		$12582.00

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

WINSTON-SALEM, NORTH CAROLINA

Contract No. AT(40-1)[illegible] Contractor: Bowman Gray School of Medicine of Wake Forest College

REPORT OF EXPENDITURES

TITLE I

	Contract Amount	Actual Expenditures to 6-30-52	Unexpended Balance 6-30-52
7-1-49 - 6-30-52	$41,809.60	$41,698.11	$ 111.49

7-1-52 - 6-30-53	Contract Amount	Actual Expenditures to 3-31-53	Unexpended Balance 3-31-53	Estimated Expenditures 4/1/53-6/30/53	Estimated Balance 6-30-53
Salaries	$ 8,450.00	$ 6,051.60	$2,398.40	$2,135.00	$ 263.40
Equipment	505.00	200.00	305.00	54.00	251.00
Isotopes	3,380.00	2,380.73	999.27	-	999.27
Animals	1,800.00	571.81	1,228.19	650.00	578.19
Travel	300.00	-	300.00	300.00	-
Supplies	1,300.00	1,798.39	(498.39)	350.00	(848.39)
Overhead	1,258.80	1,258.80	-	-	-
TOTALS	$16,993.80	$12,261.33	$4,732.47	$3,489.00	$1,243.47

TITLE II

	Contract Amount	Actual Expenditures to 6-30-52	Unexpended Balance 6-30-52
7-1-49 - 6-30-52	$33,550.20	$23,858.00	$9,692.20

7-1-52 - 6-30-53	Contract Amount	Actual Expenditures to 3-31-53	Unexpended Balance 3-31-53	Estimated Expenditures 4/1/53-6/30/53	Estimated Balance 6-30-53
Salaries	[illegible],600.00	$ 4,273.37	$2,326.63	$1,250.00	$1,076.63
Equipment	1,100.00	104.70	995.30	995.30	-
Isotopes	1,2[illegible]0.00	4[illegible]5.00	735.00	400.00	335.00
Animals	200.00	60.15	139.85	100.00	39.85
Supplies	1,350.00	1,928.20	321.80	550.00	(228.20)
Travel	300.00	-	300.00	300.00	-
Overhead	3[illegible]	3[illegible]	-	-	-
TOTALS	$11,510.00	$ 6,791.42	$4,818.58	$3,595.30	$1,223.28

TITLE III

	Contract Amount	Actual Expenditures to 6-30-52	Unexpended Balance 6-30-52
8-1-49 - 6-30-52	$15,717.00	$13,356.14	$2,360.86

7-1-52 - 6-30-53	Contract Amount	Actual Expenditures to 3-31-53	Unexpended Balance 3-31-53	Estimated Expenditures 4/1/53-6/30/53	Estimated Balance 6-30-53
Salaries	$ 3,900.00	$ 2,085.00	$1,815.00	$ 540.00	$1,275.00
Equipment	300.00	153.00	147.00	50.00	97.00
Isotopes	600.00	96.00	504.00	224.00	280.00
Animals	250.00	187.55	62.45	350.00	(2[illegible]7.55)
Supplies	500.00	562.75	(62.75)	100.00	(162.75)
Travel	250.00	-	250.00	250.00	-
Overhead	464.00	464.00	-	-	-
TOTALS	$6,264.00	$3,548.30	$2,715.70	$1,514.00	$1,201.70

1111935

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO : J. Wallace Ould, Jr., Assistant General Counsel DATE: June 12, 1952

FROM : R. G. Humphries, Chief, Contract Coordination Branch

SUBJECT: REQUEST FOR RENEWAL OF CONTRACT AT-(40-1)-288 - BOWMAN GRAY SCHOOL OF MEDICINE

SYMBOL: DC:LW

Enclosed is an approved proposal for extension of subject contract for one year beginning July 1, 1952. This approval action is covered by Procurement Directive BM-52-262 dated May 23, 1952, in the amount of $28,370.

The contractor asked for a budget of $34,867.80 for the Titles I, II and III combined with an available balance of $5,628.23 for use in partially funding the new period. Deducting this amount from the proposed budget of $34,867.80 leaves a total of $29,239.57 for the new period, as shown on the hand written work papers attached. The note from Alice Corley, also attached, indicates that Dr. Hardy, Washington, promised this office a revised procurement directive for $869.57 more funds to cover this contract.

Accordingly, it is requested that you prepare an appropriate modification to extend this contract for another year and provide for the payment of $29,239.57.

Dr. C. S. Shoup will act as technical advisor on this contract action.

R. G. Humphries

Enclosures:
1. Note fm Corley 6-9-52
2. Handwritten notes by RGH
3. Memo fm Kasschau 6-3-52
4. Memo fm Haggerty 5-23-52
5. Contractor's proposal

CC: Dr. C. S. Shoup
Mr. L. D. MacKay
Mr. Ed. Ziegler
Mrs. J. Nicholson

/lw

The mod. will not be mailed to the contractor until the revised P.D. is received.

PD BM-52-262-A
6/16/52 & 1177

1111936

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

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

TO (Name and unit)	INITIALS / DATE	REMARKS
Lois		Tell Alice Carley that Cook will have to issue a revision of the P.D. for $869.51 more funds to cover Bowman-Gray. They took credit for more balance than actually exists. See work papers attached.
FROM (Name and unit): Glenn	DATE	

USE OTHER SIDE FOR ADDITIONAL REMARKS

16—66667-1 U. S. GOVERNMENT PRINTING OFFICE

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

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

TO (Name and unit)	INITIALS / DATE	REMARKS
Glenn Humphries Contract Div.		By phone call this date, Dr. Hardy of the Washington Office informed me that a Procurement Directive in the amount of $869.51 will be forwarded for the Bowman Gray Contract AT(40-1)-288.
FROM (Name and unit): Carley	PHONE NO. 4278 / DATE 9 Mar 52	Lois: Carley Tell we can proceed with the put in process and be sure and Legal that this go out and get signed. The PD go out and get in.

USE OTHER SIDE FOR ADDITIONAL REMARKS

16—66667-1 U. S. GOVERNMENT PRINTING OFFICE

1161931

re: operation 288

Boorman - Gray

		Net Balance	Net Payment
Title I	16,993.80	85.18 ~~26.85~~	$16,908.12 16,966.95
" II	11,610.00	3797.33	7,812.67
" III	6,264.00	1804.05	4,459.95
	$34,867.80	$5,628.33 5,687.06 *	$~~29,239.57~~ 29,180.74

Amt. of Procurement Directive 28,370.00

Short in funds $ 810.74 869.57

need revised PD in this amt to cover.

looking for took credit for $6500.00 balance. actual balance was.

2923957

1111938

Bowman - Troy adjusted

~~orig. adjust~~ [redacted]

		~~Govt. amt.~~			
Title I.	1st year	11,000.00			
	2nd year	13,858.00	Estimated balance 6/30/51	actual Balance 6/30/51	Net adjustment required
(add)	3rd year	1,000.00			
		25,858.00	$21.01	(100.85)	179.84
		Est. Balance 6/30/52		106.69 / 21.01 / 85.68	106.69
		Net Bal. 6/30/52			86.85
Title II.	1st year	8,000.00 ~~11,000.00~~			
	2nd year	11,437.00	Est. Balance 6/30/51	actual Balance 6/30/51	Net adjustment required
		19,437.00	3,169.86	$1,265.89	(903.97)
		Est. Balance 6/30/52			4701.30
		Net Bal. 6/30/52			3,797.33
Title III,	1st year	3,000.00	Est Bal. 6/30/51	act. Bal. 6/30/51	Net. adjust required
	2nd year	6,453.00			
		$9,453.00	345.97	448.38	102.41
		Est. Bal. 6/30/52			1701.64
		Net. Bal 6/30/52			1,804.05

1111939

Office Memorandum • UNITED STATES GOVERNMENT

TO : John Moore, Chief, Contract Division DATE: June 3, 1952

FROM : Kenneth Kasschau, Director, Office of Research and Medicine

SUBJECT: RENEWAL OF LUMP-SUM CONTRACT NO. AT-(40-1)-288, WITH THE BOWMAN GRAY SCHOOL OF MEDICINE, WINSTON-SALEM, N. C. DRS. G. T. HARRELL, JR, AND C. ARTOM, PROJECT LEADERS

SYMBOL: ORB:CSS

We are in receipt of approval from the Medical Branch, Division of Biology and Medicine, for renewal of the above contract for one year. Procurement Directive No. BM-52-262 in the amount of $28,370.00, provides for the new funds required on the three titles listed amounting to $34,870.00 less $6,500.00 of estimated unobligated balance.

Dr. C. S. Shoup will serve as Technical Advisor for this office.

Kenneth Kasschau

Encls.:
1. Pro. Dir. BM-52-262
2. Memo JFH to KK dtd 5/23/52
3. Cy ltr HOP to AEC dtd 4/10/52 w Encls.

Shoup:ec

PD BM-52-262 5/23/52

1111940

UNITED STATES ATOMIC ENERGY COMMISSION
DIVISION OF BIOLOGY AND MEDICINE
WASHINGTON, D. C.

DATE: MAY 2 3 1952

TO : Kenneth Kasschau, Director, Office of Research and Medicine
Oak Ridge Operations Office

FROM : James F. Hagan, Jr., Medical Branch

SUBJECT: TRANSMITTAL OF RESEARCH PROPOSAL FOR CONTRACT NEGOTIATION

SYMBOL : BMM:JFH

This letter with enclosures, in triplicate, is sent in accordance with the procedure described in a letter from the General Manager to all Managers of Operations dated January 27, 1949.

1. Institution: Wake Forest College, Bowman Gray School of Medicine

2. Investigator (s): See comments

3. Title: See comments

4. ( ) New Contract or (X) Renewal of Contract No. AT(40-1)288

5. Duration - From: July 1, 1952 To: June 30, 1953

6. AEC Technical Supervision: Medical Branch

7. Recommended Support: $28,370.00 ($34,870.00 less $6,500.00 unexpended balance)

Authorized by Procurement Directive No. BM52-262

Issued _____ 1952 $ 28,370.00

Activity No. 6300

8. Other Comments:

Project I: Investigator: G. T. Harrell, Jr.
Amount: $16,995.00
Title: "Distribution and Turnover of Sodium and Potassium in Acute Infections"

Project II: Investigator: C. Artom
Amount: $11,610.00
Title: "Formation of Tissue Phospholipides"

Project III: G. T. Harrell, Jr., et al - Investigators
Amount: $6,265.00
Title: "Toxicity of Radiation as Related to Previous Damage and the Functional Capacity of an Organ: the Effect of P-32 and X-rays on Liver and Marrow"

3269 1952

1111941

8. **Comments** (Continued)

In approving this contract the Committee indicated that support next year would be at a lower level.

9. **Security Requirements:**

In accordance with the provisions of GM-93 (Revised March, 1950), and the requirements of the Declassification Guide, the Division of Biology and Medicine has determined that the following security precautions should be taken in connection with the proposed research contract.
Since there is essentially zero chance that restricted data may be required or developed, no personnel security requirements should be imposed.

10. **Reports:** (X) Reports are to be required as provided for by Memorandum Instruction of November 9, 1949, on subject "Direct Research Contract Reports".

( ) Special Reports Instructions are as follows:

Enclosures:
(X) "A" - Proposal, dated April 10, 1952
( ) "B" - Notification letter, dated _____
( ) "C" - Other correspondence, _____ letters
(X) "D" - Procurement Directive BM52-262

Distribution:

Addressee:	Original (w encl.)	**Division File:**	Yellow Copy (w encl.)
	1st Copy (" ")		Pink Copy (w/o encl.)
	2nd Copy (" ")		Green Copy (" ")
Program Analysis Branch:	White Copy (w/o encl.)	**Branch File:**	White Copy (w ")

1111942

April 10, 1952

Atomic Energy Commission
Division of Biology and Medicine
1901 Constitution Avenue, N.W.
Washington, D. C.

Gentlemen:

Enclosed you will find the statement of expenditures on our contract AT-(40-1)-238 Titles I, II and III for bills paid through March 31, 1952. As you can see from this statement, some materials have been received and used by the principal investigators, but the suppliers have been slow in billing. You will also find enclosed an estimate of projected expenditures from April 1 through June 30, 1952. The estimated expenditures include the items for March as yet unpaid and the unbilled materials already used in the experiments.

Enclosed you will also find the proposals for renewal of the contract for Titles I, II and III for next year beginning July 1, 1952. I have examined the budgets and administrative portions of these proposals as the contracting officer of the school and find them to be in order. The school is very happy to endorse and approve these proposals for renewal in this form, and will provide the services called for as the school's contribution to the research. If there is any additional detailed information we can give to assist in the review and processing of these proposals, we would be most happy to furnish it.

Please let me express to you our regret that these proposals were not sent in earlier. Dr. George T. Harrell, our coordinator for this contract, informs me of his phone conversations with the Office of Research and Medicine in Oak Ridge yesterday. We have searched the files in this office and in those of both principal investigators and can find no trace of the letter of February 28 requesting us to send in these proposals earlier. We would have been most happy to comply with this request had we received it.

Please let me express to you our appreciation for your continued support of this research. Some of us in the administration division of the school have been impressed with the scientific interest shown in these investigations. We sincerely hope support can be continued at this level, since it would be impossible to continue support from any other funds now available to us.

Respectfully yours,

Harry O. Parker

Harry O. Parker
Controller

HOPrpl
Enclos.

1111943

PERIOD

of Wake Forest College

REPORT OF EXPENDITURES

TITLE I

	Contract Amount	Actual Expenditures to 6/30/51	Balance Unexpended as of 6/30/51
Adjusted 7/1/49-6/30/51	$25,858.00	$25,958.85	$ (100.85)

7/1/51-6/30/52	Contract Amount	Actual Expenditures to 3/31/52	Balance Unexpended as of 3/31/52	Estimated Expenditures 4/1/52-6/30/52	Estimated Balance Unexpended 6/30/52
Salaries	$ 7,750.00	$ 5,502.00	$ 2,248.00	$ 2,248.00	-
Supplies & Animals	3,100.00	2,447.91	652.09	650.00	2.09
Isotopes	2,750.00	1,277.00	1,473.00	1,400.00	73.00
Travel	300.00	177.98	122.02	122.02	
Equipment	870.00	588.40	281.60	250.00	31.60
Overhead	1,181.60	1,181.60	-	-	-
TOTALS....	$15,951.60	$11,174.89	$ 4,776.71	$ 4,670.02	$ (106.69)

TITLE II

	Contract Amount	Actual Expenditures to 6/30/51	Balance Unexpended as of 6/30/51
Adjusted 7/1/49-6/30/51	$19,437.00	$18,171.11	$ 1,265.89

7/1/51-6/30/52	Contract Amount	Actual Expenditures to 3/31/52	Balance Unexpended as of 3/31/52	Estimated Expenditures 4/1/52-6/30/52	Estimated Balance Unexpended 6/30/52
Salaries	$ 5,280.00	$ 1,700.00	$ 3,580.00	$ 540.00	$ 3,040.00
Supplies & Animals	1,550.00	372.70	1,177.30	550.00	627.30
Isotopes	1,700.00	430.00	1,270.00	1,050.00*	220.00
Equipment	1,460.00	446.00	1,014.00	200.00	814.00
Travel	300.00	-	300.00	300.00	
Overhead	823.20	823.20	-	-	
TOTALS....	$11,113.20	$ 3,771.90	$ 7,341.30	$ 2,640.00	$ 4,701.30

*Approx. $600.00 is represented by Material used but not paid for as of 3/31/52.

TITLE III

	Contract Amount	Actual Expenditures to 6/30/51	Balance Unexpended as of 6/30/51
7/1/49-6/30/51	$ 9,453.00	$ 9,004.62	$ (448.38)

7/1/51-6/30/52	Contract Amount	Actual Expenditures to 3/31/52	Balance Unexpended as of 3/31/52	Estimated Expenditures 4/1/52-6/30/52	Estimated Balance Unexpended 6/30/52
Salaries	$ 3,300.00	$ 1,255.00	$ 2,045.00	$ 510.00	$ 1,535.00
Supplies & Animals	1,100.00	1,047.81	52.19	350.00	(297.81)
Isotopes	500.00	224.00	276.00	200.00	76.00
Equipment	700.00	111.55	588.45	200.00	388.45
Travel	200.00	120.84	79.16	79.16	-
Overhead	464.00	464.00	-	-	-
TOTALS....	$ 6,264.00	$ 3,223.20	$ 3,040.80	$ 1,339.16	$ 1,701.64

1111944

April 10, 1952

Atomic Energy Commission
Division of Biology and Medicine
1901 Constitution Avenue, N. E.
Washington, D. C.

Gentlemen:

Enclosed you will find an original and one carbon of the proposals for renewal of Titles I, II and III of our contract AT-(40-1)-206 for the next year beginning July 1, 1952. We have prepared a recapitulation of the budgets of the three titles for your ready reference.

Please let me express to you our regret that these proposals did not reach you as soon as you wished. I talked yesterday with the Office of Research and Medicine at Oak Ridge, and discovered only at that time that a letter had been written in late February requesting us to forward these proposals as quickly as possible. Presumably, this request was sent to the administrative offices of the college, which are located in the town of Wake Forest a hundred and ten miles east of us, instead of to the medical school in Winston-Salem. Neither the Controller, Dean or project leaders, Dr. Camilo Artom and myself, can find any trace of this correspondence. We would most certainly have complied at your request had we received it.

Please let me express to you the deepest appreciation of all the members of our staff working on these projects for your help in our research program. It would have been completely impossible to have undertaken any of these studies without your support. We would like particularly to emphasize the pleasure it has been to work administratively with the Commission and its research divisions on these projects.

We should like to call attention again to the difficulty in obtaining suitable scientific assistance above the level of technician with the relatively modest funds at our disposal. The diminishing return from endowments in the small private educational institutions is imposing an increasingly great strain on principal investigators and their scientific associates who would like to devote the major portion of their time to such research as is conducted under this contract. As you can see from the financial report, two of the projects have not completely expended their budget since the scientific supervision of experiments on which we insist could not be provided because of unfilled vacancies in our professional staff. We earnestly hope that provision can be made in this or future contracts for some measure of financial support to principal and associate investigators.

If there is any additional information we can give or if we can clarify any points which are not clear, please command us. Any of us would be most happy to meet with you here, in Washington, or in Oak Ridge at your convenience to negotiate further the details of the contract should you so desire. If you wish a separate 200 word summary of the scope and purpose of this investigation, we would be delighted to prepare it. We did not include a separate one since the phone conversation with Oak Ridge indicated that the short orientation and progress report at the beginning of

1111945

each proposal would serve that purpose.

By a coincidence, we have just today received in the mail the enclosed copy of the publication by the Abbott Laboratories circulated to all the medical profession in this country. We were highly pleased and surprised to find on page 17 reproduced almost half of one of the papers published under Title III of this contract. We thought you would be interested in the recognition afforded this research.

Respectfully yours,

George T. Harrell

George T. Harrell, M. D.
Professor of Medicine and
Director of the Department

GTH:pl
Encl.

1111946

Contract No. AF-(AO-)-248
(The Bowman Gray School of
Medicine of Wake Forest Colle
April 10, 1952

Proposal for Renewal

July 1, 1952 - June 30, 1953

Budgets

	Title I	Title II	Title III
1. Salaries	$8450.00	$6950.00	3900.00
2. Permanent equipment	505.00	1100.00	300.00
3. Isotopes	3380.00	1200.00	600.00
4. Animals	1800.00	200.00	250.00
5. Supplies	1300.00	1000.00	500.00
6. Travel	300.00	300.00	250.00
Subtotal	$ 15735.00	$10750.00	$5800.00
7. Overhead at 8%	1258.80	860.00	464.00
Total	$ 16993.80	11610.00	6264.00

Titles I, II, III combined $ 34,867.80

1111947

Contract No. AT-(40-1)-288 - Title I
(The Bowman Gray School of Medicine
of Wake Forest College)
April 2, 1952

1. PROJECT

Distribution and turnover of sodium and potassium in acute infections.

Project leaders: Dr. George T. Harrell, Jr. Time: July 1, 1952 - June 30, 1953
Dr. Jerry K. Aikman

Orientation

In the acute phase of certain human infections, such as Rocky Mountain spotted fever and tuberculosis, edema develops. With the alterations in distribution of fluid, peripheral circulatory collapse often develops and leads to the death of the patient. Patients recovering from infectious diseases have a diuresis during recovery in which water and salt are excreted. Similar physiologic disturbances take place during serum sickness, an antigen-antibody reaction which occurs without infection.

From studies of the blood volume and extravascular thiocyanate space, it is not known whether the fluid lost from the blood and accumulated as edema goes into cells or between them. The increase in permeability of capillary and cell membranes can be visualized as a graded series of pores. In mild instances of disease, only crystalloids leave the blood stream; in more severe instances protein molecules leak out. A small defect should be detectable by the extent to which radioactive tracer ions such as Na^{24} and K^{42} leave the blood after injection and are diluted in extravascular spaces. A larger defect should be detectable by the diffusion from the blood of protein molecules such as albumin tagged with a tracer such as I^{131}.

If the mechanism can be established by which increased amounts of water, electrolytes and protein are passed across capillary or cell membrane, it may be possible to devise means of correcting the physiologic abnormality in infections or in diseases in which antigen-antibody reactions are thought to play a part.

Progress to date

A progress report covering the experiments conducted March 16, 1951 to March 15, 1952 has already gone forward.

Techniques have been developed for the determination of plasma volume, thiocyanate, Na^{24} and K^{42} spaces for use in rabbits and human beings. Techniques for analysis of stable and isotopic content of sodium and potassium in tissues of experimental animals have been developed.

After standardization of the methods control data have been collected for Na^{24}, K^{42} and I^{131} tagged albumin spaces in human beings in the absence of disease for comparison with experimental data collected in diseased states. Control values for Na^{24}, K^{42} spaces and tissue K^{42} content in normal rabbits have been determined. The effect of starvation on K^{42} space and tissue content in normal rabbits has been determined.

A lantern slide method has been developed for autoradiography of organs of normal rats following injection of I^{131} or I^{131} tagged human serum albumin.

Intracellular infections with the Rocky Mountain spotted fever strain of rickettsiae have been established in fertile hen's eggs, guinea pigs and rabbits. Preliminary groups of animals with some analyses of alterations in water and

potassium content have been run.

Immune reactions without infection have been studied by inducing serum sickness in rabbits by (1) the injection of whole human plasma; (2) the injection of albumin or globulin fractions of human plasma; (3) a passive transfer technique, utilizing the injection of antihuman immune serum previously prepared in other rabbits.

Clinical studies of alterations in Na^{24}, K^{42} and I^{131} tagged albumin spaces have been started in various disease processes, such as acute rheumatic fever, glomerulonephritis, cirrhosis, diabetes, myxedema, and congestive heart failure.

<u>Proposed Plan of Experiments for 1952-53</u>

a. <u>Standardization of methods</u>

In view of the difficulty so far encountered in establishing a fatal or severe rickettsial infection in rabbits and the relative ease of inducing it in guinea pigs, it may become necessary to utilize guinea pigs for the study of intracellular infections. If such proves to be the case, it will be necessary to develop and standardize micromethods for blood volume, Na^{24}, K^{42} spaces and Na and K content of tissues in guinea pigs. If a suitable technique for serial determinations in living animals—similar to that developed in rabbits—cannot be found, a method will have to be developed involving sacrifice of the guinea pigs at predetermined times after infection.

In order to determine the reliability of the procedure and the reproducibility of results, serial determinations of the K^{42} space in normal young women will be done. The data obtained will give information on normal physiologic variations and on the stability of the K^{42} space as a basis for interpretation of experimental data to be obtained in diseased states. Similar serial data should be obtained in normal men. It would be advisable to determine the effect of age on the K^{42} space, since the normal values established so far have been determined only in normal young men and women.

It would be highly desirable 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. This experiment should parallel those done last year in rabbits. The data would be useful as a basis for comparison with those in normal persons and interpretation of experimental results in disease processes. The limited number of hospital beds available to us makes it most unlikely that this experiment can be performed here. It may be possible to do these experiments in another hospital out of the city.

If time permits, the normal physiologic variations in the Na^{24} space could be determined in normal young and old men and women; the Na content of normal young women is thought to vary appreciably with the menstrual cycle.

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

1111949

Contract No. AT-(40-1)-288
(The Bowman Gray School of
Medicine of Wake Forest College)
April 2, 1952

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. These data will be useful in interpreting experimental data in infections and immune reactions where the metabolism is known to be increased, presumably through stimulation of the thyroid gland.

b. Intracellular Infections

The studies on experimentally induced Rocky Mountain spotted fever in rabbits and guinea pigs will be continued. In guinea pigs the effect on the temperature curve, weight and survival of animals at the peak of experimental rickettsial infection of large doses of cortisone or ACTH with and without antibiotics—such as aureomycin or chloramphenicol—will be determined. These data will be compared with the previous data obtained following the larger administration of small doses of cortisone from the beginning of the infection. The effect of Na^{24} and K^{42} spaces will be determined utilizing techniques to be developed as outlined above. The physiologic changes will be correlated with the immune response as determined by the complement fixation reaction using as antigen the same strain of rickettsiae grown in fertile hen's eggs.

Further attempts will be made to increase the virulence of the rickettsiae for rabbits and to induce greater physiologic changes than were obtained last year. Since our methods are already standardized for rabbits, the use of this animal would be preferable if the experiments are feasible. Serial studies at as close intervals as technical problems—such as the rate of decay of isotopes—permit will be done.

Autoradiographic studies by the technique previously developed will be done on representative animals as a check on the physiologic method by an anatomic one. Further attempts will be made to develop a method for fixation in tissue of soluble ions such as Na^{24} and K^{42} which would permit autoradiographic studies following injection of those isotopes.

c. 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. Rabbits will be fed trichinous rat meat and the Na^{24}, K^{42} and I^{131} labeled protein studies will be done at appropriate intervals. The physiologic data will be correlated with the immunologic response as determined on blood serum by the flocculation or complement fixation technique.

If time permits, further attempts should be made to standardize an extracellular interstitial infection with virulent type I pneumococci in the skin and subcutaneous tissue of rabbits. Preliminary experiments with this "dermal pneumonia" have been variable, but extravascular edema has been produced in a sufficient number of animals to warrant continuation of the study.

d. 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. It is hoped that by hyperimmunization a higher titer of immune bodies will be produced in the serum and greater physiologic disturbances produced. The alteration in Na^{24}, K^{42} and I^{131} tagged protein fractions will be determined.

c. 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 antibiotics has reduced the number of untreated instances of clinical infections with rickettsiae or other etiologic agents 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 patients are hardly suitable for our studies. In such cases as are admitted before treatment, base line studies can be obtained, but the infection is then usually arrested by therapy so quickly that the physiologic changes observed in later years do not develop to the extent previously seen or do not develop at all. It is for this reason that emphasis in infections is being shifted to the experimental animal. Clinical studies will be conducted in human beings with any type of infection 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. Disease processes which are thought to be concerned in some manner with antigen-antibody reactions, but which have not definitely been proved to be due to any single infection, will be studied. As a control, similar studies will be conducted on those processes which at present are not thought to induce changes in permeability, or which are not known to be connected with immune reactions.

The preliminary observations on the Na^{24} space in rheumatic fever will be extended and data on K^{42} space will be obtained. The effect of therapy with salicylates (or their degradation products) and with hormones (ACTH or cortisone) on the distribution of Na^{24} and K^{42} will be studied carefully. The changes in Na^{24} and K^{42} spaces occurring in the natural course of diseases where no specific therapy is available, will be continued and expanded. The type of process which will be studied further includes glomerulonephritis, nonnotic obesity, psychoneurosis, chronic ulcerative colitis, and others. Attempts will be made to obtain acute instances of disease in preference to the chronic form where the pathologic physiologic situation is more stabilized.

Other types of disease processes which are amenable to specific therapy—such as myxedema, hyperthyroidism, diabetes, congestive heart failure, syphilis and others—will be studied before and after the institution of specific therapy. Particular attention will be paid to allergic reactions such as serum sickness or drug idiosyncrasy. Observations will be made with Na^{24}, K^{42} and I^{131} tagged human protein fractions.

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 leaders, 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.

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(3) Clerical, administrative and overhead costs in excess of the Government's payment under b (7) below.

b. The Government is requested to pay the Contractor the sum of $16,993.80 for the performance of the contract during the fourth period for the expenses estimated as follows:

(1) Salaries		
J. K. Aikens	3,000.00	
Technician, E. Rhoades	2,400.00	
Technician, W. Brooks	2,250.00	
House Officers for clinical studies	500.00	
Electronic engineer	300.00	
		8,450.00
(2) Permanent equipment		
Beta-gamma survey meter	275.00	
Sample storage unit	30.00	
Steel lockers	200.00	
		505.00
(3) Isotopes		
Na^{24} and K^{42}, handling charge and transportation of weekly shipments of each	3,120.00	
Indirect Effects	260.00	
		3,380.00
(4) Animals	1,800.00	
		1,800.00
(5) Supplies		
Geiger-Mueller tubes	400.00	
Glassware	500.00	
Chemicals and other supplies	400.00	
		1,300.00
(6) Travel	300.00	
		300.00
(7) Overhead at 8%	1,258.80	1,258.80
TOTAL		$16,993.80

Approved: George T. Harrell, Jr.

1111952

Contract No. AF-(40-1)-256 - Title II
(The Bowman Gray School of Medicine
of Wake Forest College)
April 8, 1952

1. PROJECT

Formation of phospholipides in tissues.

Project leader: Dr. Camillo Artom

Terms: July 1, 1952 to June 30, 1953

Orientation and progress to date

Since phospholipides are universal constituents of all living structures, it appears that the maintenance of a constant composition of these compounds in the tissues is essential to the effective functioning and to the well being of the body. Moreover, it is believed that certain phospholipides (especially those of the liver) play an important role in the metabolism and perhaps in the transportation of fats.

In the first phase of our investigations, the formation of phospholipides in the liver has been studied on intact animals receiving isotopic phosphate. The action of a number of factors, especially changes in the supply of dietary choline and related substances, was investigated. The results obtained indicate that the synthesis of phospholipides in the liver takes a high priority among other metabolic processes. It appears that the liver has a very extensive functional reserve in this respect, since in intact animals phospholipides are formed in the organ at a rate about normal, even under adverse conditions.

In subsequent experiments we have studied the formation of phospholipides in slices and homogenates of the liver, incubated with various labeled compounds. Indeed since most phospholipides are made up of at least five constituent parts (nitrogenous substance, phosphate, glycerol, 2 fatty acids), a complete elucidation of the mechanisms involved in the biological synthesis of such compounds would require a systematic study of the incorporation of each constituent in the complex phospholipide molecule. We have investigated first the incorporation of phosphate, then the incorporation of choline. The latter substance is the nitrogenous component of the most important type of phospholipides (lecithins) and presents also a special interest because of its well established action in preventing and curing the fatty infiltration of the liver. For these reasons, our studies have been extended to a probable metabolic precursor of choline (dimethylethanolamine = DME). Several other metabolic pathways of choline in the liver (in addition to its incorporation into the phospholipides) have also been explored.

The results obtained in the various groups of experiments have been summarized in our progress reports. It is felt that these results not only represent substantial contributions to the problems studied, but also give definite promise for a successful continuation of the investigations essentially along the lines followed thus far. More precisely, in the coming year, we are planning to concentrate our activity to the specific problems indicated below.

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Contract No. AF-(600-1)-200 - Title II
(The Bowman Gray School of Medicine
of Wake Forest College)
April 5, 1952

Proposed Plan of Investigations for 1952-53

a. Intermediate stages in the synthesis of the phospholipide molecule.

In most of our previous experiments, liver slices have been used for the study of the incorporation of choline into the phospholipides. However, under proper conditions, the process did occur, though at a reduced rate, also in cell-free homogenates of the liver. In such materials differences in the permeability of the cell membranes toward various substances are abolished or at least minimized. Thus it seems now possible to approach the study of the intermediate steps in the synthesis of phospholipides by isotope dilution methods applied to liver homogenates (unfractioned or fractioned). As an illustration, we are describing the following experiment, designed to investigate whether or not phosphoryl-choline is an intermediate stage in the incorporation of choline into the phospholipides. Liver homogenates will be incubated with C^{14} labeled choline in the presence or in absence of non labeled phosphoryl-choline. If this compound is actually an intermediate stage in the process, its addition should result in a corresponding dilution of the isotope in the phospholipides isolated from the tissue at the end of the incubation. Similar experiments could also give us some information on the pathways followed in the incorporation of the other phospholipide components, and perhaps also on the order, according to which the various reactions arrange themselves.

b. Incorporation of nitrogenous constituents (other than choline) in the phospholipides.

For these experiments we hope to be able to synthesize (or obtain from other sources) a preparation of ethanolamine labeled with C^{14}. The incorporation of this compound into the phospholipides will be studied in experiments similar to those in which the incorporation of labeled choline or DME in the phospholipides has been investigated.

c. Metabolic pathways of choline in isolated liver.

These investigations will be a direct continuation of those carried out in previous years. It is planned first to attempt to improve the procedures for the separation and characterization of the probable products of choline metabolism. If this attempt will be successful, we shall try to identify certain products of choline metabolism which, on the basis of the indirect evidence obtained previously, appear to be quantitatively important. This would be a decisive step toward our final goal to draw a complete balance sheet of the metabolism of choline in the liver.

d. Oxidation of fatty acids in the liver of choline-deficient animals.

Until recently, the action of choline and of its precursors in preventing and curing fatty liver, was generally interpreted by assuming that choline promotes the mobilization of fatty acids from the liver and their transportation in blood plasma. A number of recent data including those obtained by us, makes this interpretation rather doubtful. It seems possible instead that choline may act by enhancing the degradation of fatty acids in the liver itself. We are planning to test the latter hypothesis by studying the oxidation of isotopic fatty acids in the isolated liver from animals in choline deficiency. C^{14} labeled stearic or palmitic acid will be incubated with slices or homogenates of the liver from rats on

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choline-rich, or choline-deficient diets, respectively, and the amounts of isotopic CO_2 and acetoacetic acid produced from the added fatty acid will be determined. The results of preliminary experiments in this direction seem rather promising.

e. Other investigations

If limitations in time and personnel will not be too serious, it is hoped that it will be possible to continue certain collateral investigations, such as that on the enzymatic condensation of formaldehyde with pyruvate. This study has some relationship also with the other problems of choline metabolism, since it is not unlikely that formaldehyde is an intermediate stage in the synthesis and/or in the oxidation of the methyl groups of choline.

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

In our progress report of the work done for this project from March 16, 1951 to March 15, 1952, it was pointed out that during the past months the research work has been hampered by serious deficiencies in both professional and technical personnel. The writer is confident that it will be possible in the near future to make up for such deficiencies provided that adequate compensation could be offered to secure the cooperation of qualified workers. Because of this consideration, the amount requested for the salaries of the personnel during 1952-53 has been increased. Since, however, corresponding decreases in the other expenditures appear feasible, the total sum for the 1952-53 is only slightly higher than that requested in the previous year.

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 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 cost in excess of the Government's payment under b (7) below.

b. The Government is requested to pay the contractor the sum of $11,010 for the performance of the contract during the fourth period for the expenses estimated as follows:

(1) Salaries

Dr. C. Artom	None
Dr. M. A. Swanson	None
Research associate (unselected)	1500.00
Graduate student (L. Pollard)	1500.00
Technician, full time, 12 mos. (unselected)	2400.00
Technician, part time, 6 mos.	1200.00
	$6,600.00

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(2) Permanent equipment		
New cooling unit	800	
Additional equipment	300	
		1,100.00
(3) Isotopes (C^{14}- labeled compounds)		1,200.00
(4) Animals		200.00
(5) Supplies		
Glassware	500	
Chemicals	500	
		1,000.00
(6) Travel		300.00
(7) Maintenance, replacements of, and repairs to, radioactivity apparatus		350.00
(8) Overhead at 8%		800.00
TOTAL		$11,810.00

M. Camille Artom

1111956

Contract No. AT-(40-1)-2[illegible] - Title [illegible]
(The Bowman Gray School of Medicine
of Wake Forest College)
April 9, 1952

1. [illegible]

Toxicity of P^{32} related to various extrinsic and intrinsic factors

Project leaders: Dr. Camillo Artom and Dr. George T. Harrell, Jr.

Terms: July 1, 1952 - June 30, 1953

Orientation and progress to date

During the past few years, we have systematically studied the effects of internal radiation by P^{32} in animals and a number of extrinsic factors which might modify those effects. Changes in the quantitative composition of the diet definitely affected the survival of the animals receiving the isotope. Among the specific dietary factors which were tested, lipotropic factors, such as choline, were ineffective. On the other hand, certain B vitamins, such as pyridoxin and the combination of folic acid plus B_{12}, were shown to cause a significant increase in the number of survivors and in the survival time, at least under conditions in which a more or less severe vitamin deficiency developed.

In parallel studies, the possibility of increasing by various means the mobilization of P^{32} initially deposited in the bones (thus decreasing the effective time of exposure to radiation) was investigated. A significant protection was obtained by the administration of diets with a high content of inorganic [illegible]. A number of other attempts were made with the reasonable expectation that a greater mobilization of the calcium from the bones might be accompanied by a corresponding mobilization of P^{32}. Until now these attempts have not been successful.

In spite of several failures it appears therefore that in the past few years certain definite indications have been obtained which we believe are of both theoretical and practical interest. We are planning to continue the investigations essentially along the lines followed thus far and, in addition, to explore certain other possibilities. While these possibilities may seem at present rather remote, some trial experiments in their direction appear worthwhile.

Protective role of vitamins

It is planned to extend to other factors of the [illegible] and a great deal of systematic study on the protective role of vitamins against P^{32}. As in previous experiments, the administration of generous amounts of the vitamin to animals without obvious signs of vitamin deficiency will first be tested. The experiments will then be repeated on animals, in which a deficiency has been induced or enhanced by various experimental procedures (such as dietary deficiency, increased metabolic demands, metabolic antagonists, antibiotics).

Protective role of certain hormones and drugs.

The only hormonic preparation which we have tested thus far was a parathyroid extract. The results of these experiments were not encouraging. It is possible, however, that the short duration of the action and the rapid development of an antibody were responsible for our failure. We are planning to repeat similar experiments with dihydro-tachysterol (DHT) the action of which has some similarity

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with that of the parathyroid hormone but is more prolonged. A study of the effects of cortical and other steroid hormones is also on our agenda.

Attempts to increase the mobilization of P^{32} from the bones.

Thus far most of these attempts have given only negative or equivocal results. As mentioned above the only experiments in which a significant increase in the survival of the animal injected with P^{32} was found, were those experiments in which the diet had been enriched with phosphate. This effect was interpreted as due to an increased exchange of the radioactive phosphate deposited in the bone with the non isotopic phosphate present in blood plasma. In this respect, we are planning to explore now the effects of the introduction of inactive pyrophosphate. It seems reasonable to expect that, as a result of the action of the pyrophosphatase of the bone, a local increased concentration of exchangeable orthophosphate may occur in the bone layers closest to the blood supply.

The effects of repeated exposure to internal radiation.

Mice will first receive a sublethal dose of either P^{32} or of another bone seeking radioisotope. Then, after periods varying from 2 to 16 weeks, a larger dose of P^{32} in the sublethal range will be injected. Controls run simultaneously will receive the larger dose of P^{32} only. The possibility that changes in the resistance toward radiation may develop as a result of the initial radioactive dose, will thus be explored.

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

In the past year, our experiments have been somewhat slowed down, since Dr. Dornbrzer, one of the members of our group, left this institution. It is felt that this may be compensated and the scope of the future investigations broadened considerably, if it were possible to obtain the cooperation of a competent hematologist. To secure such a cooperation we have included in the salary a sum to be used as a part time compensation for the work done in behalf of this project.

Permissible reductions in the other estimated expenditures, allow us to maintain the total requested for this project at the same level as that granted in the contract for 1951-52.

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 connection with the Government's payment under b (7) below.

b. The Government will pay to the Contractor the sum of [illegible], which will cover the contractors other expenses, estimated as follows, in the performance of the contract during the fourth period:

1111958

PROGRESS REPORT

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

Distribution and turnover of sodium and potassium in acute infections.

Dr. George T. Harrell, Jr., Project leader July 1, 1951 to March 15, 1952

Facilities: The laboratory as originally constructed has proved to be very satisfactory. No major changes in the design or arrangement of the facilities have been made. No difficulty has been experienced with the major items of equipment with the exception of a drying oven which has worn out and is being replaced. Additional shields for tubes, cabinets, and other relatively minor items of equipment have been purchased during the year.

Personnel: Dr. Jerry K. Aikman has continued to work almost full time on the project with the principal investigator. His fellowship with the American Heart Association will terminate July 1, 1952. We have been able to obtain continuing support for part of his time from funds donated by the American Heart Association, which we hope will permit him to continue on the project for five more years. It will be necessary to continue supplementation of these funds from the grant in order to retain him at the present level of activity.

Miss Eloise Rhoades, technician, has proved entirely satisfactory and is continuing enthusiastically in her work.

Our former negro technician, Claude Taylor, has resigned and has been replaced by William Brooks, another negro, who has completed a technician's course at the Kate Bitting Reynolds Memorial Hospital in Winston-Salem. Though he is yet incompletely trained in our techniques, he is proving to be thoroughly reliable and dependable. He has worked seven days weekly throughout the spring without complaint in order to assure that the experiments ran smoothly.

We have been extremely fortunate this year in being able to utilize, intermittently throughout the year, two excellent house officers, Drs. Malcolm Tyer and John H. Felts. As you can see from the bibliography, these men have been invaluable in pursuing the experiments with patients on the wards of the hospital. We are still losing men to military service and the shortage of personnel at this level is critical for the coming year. Our human work may suffer during the next years unless personnel are released from military service or returned to civilian training, or unless we can obtain financial support for one of these two men, both of whom have seen military service.

Isotopes: After much consultation with the airlines, including a conference with the presidents of Capital and Piedmont Airlines, we are obtaining our isotopes more regularly. We have redesigned our experiments so that we utilize sodium 24 and potassium 42 starting early Tuesday mornings. We are not encountering as much chemical toxicity with potassium 42 as in the past year.

Animals: We have discontinued trying to breed the strain of animals obtained from Oak Ridge. Animals are in better supply from commerical breeders in the vicinity. We have been able to establish our rickettsial strain in guinea pigs without difficulty, but have not yet been able to adapt the technical methods to guinea pigs. We have been unable to establish the rickettsial strain in rabbits at sufficient virulence to give us statistically satisfactory changes. We are continuing to pursue experiments in both species of animals. No difficulty has been encountered in maintaining virulence in fertile hen's eggs.

1111959

Results of Experiments

Concept of Membrane Permeability Defect

The discussion of our concept of the effect of infections and immune processes on alterations in membrane permeability has been published: Harrell, G.T. and Aikawa, J.K.: Alterations in the Permeability of Membranes During Infections, J.A.M.A. 147: 232-237 (Sept. 15) 1951.

Standardization of Methods

Studies on the normal values for the radiosodium space in rabbits have been completed and published as reported last year.

The values for radiosodium space and the comparison with the extracellular fluid space as measured by thiocyanate technique in normal individuals and in some disease processes has been published: Aikawa, J.K.: The Significance of Radiosodium Space in Human Disease, South. Med. J. 44:656-661 (July) 1951.

Data on radiopotassium space and tissue radiopotassium content in normal rabbits has been completed and published: Aikawa, J.K.: The Effect of Starvation on the Exchangeable Potassium in Tissue K^{42} Content in Rabbits, Proc. Soc. Exper. Biol. & Med. 78:524-528 (Nov.) 1951.

A study on the exchangeable radiopotassium space in twenty normal young women has been completed and the results compared with the previously known data in normal young men: Aikawa, J.K., Harrell, G.T. and Eisenberg, B.: The Exchangeable Potassium Content of Normal Women, J. Clin. Invest. Accepted for publication and scheduled for April, 1952. In these normal women, the mean K^{42} space was 31 milliequivalents per kilogram with a range of 25 to 35. No variation was detected with different stages of menstrual cycle, though serial determinations in the same individual have not been done. The lower value in women was interpreted as reflecting the relatively smaller proportion of muscle and greater proportion of fat in females as compared with males.

In order to study the effect of stress different from that to be included later in definitive experiments on the breakdown of cells with the liberation of potassium, normal rabbits were starved and the effect on the exchangeable radiopotassium space and tissue content of radiopotassium were determined: Aikawa, J.K.: The Effect of Starvation on the Exchangeable Potassium in Tissue K^{42} Content in Rabbits, Proc. Soc. Exper. Biol. & Med. 78:524-528 (Nov.) 1951.

No significant correlation between the radiopotassium content and urinary creatinine excretion was detected in starved, normal male rabbits: reference cited.

Comparison of the blood volume by the human serum albumin technique tagged with radioactive iodine 131 and the non-isotopic Evans blue dye (T-1824) technique has been completed in normal human beings and the values found to run parallel.

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Time did not permit this year comparison of normal values for blood volume in rabbits by the tagged serum protein technique utilizing I^{131} as a marker.

Autoradiography of organs of normal rats following the injection of I^{131} and iodinated human serum albumin. A suitable technique for fixation of tissues after the injection of soluble ions of potassium and sodium has not yet been developed. An attempt to localize iodinated albumin molecules in the liver of rats was unsuccessful. These data were desired to serve as a basis for localization of antigen-antibody reactions. The lantern slide technique is proving satisfactory.

Intracellular Infections

Uniform experimental infections with Rocky Mountain spotted fever strain of rickettsias has been established in guinea pigs. Experimental infections in rabbits have been established but the disease is mild and the fatality rate so far has been low. Preliminary experiments in the initial groups have just been completed but are not yet analyzed.

Preliminary experiments on rickettsial spotted fever infection in guinea pigs treated with cortisone have shown no significant alteration in mortality. This experiment was performed to determine whether cortisone would increase the spread of an intracellular infection as it has been reported to do with extracellular infections such as those with staphylococci, streptococci and tubercle bacilli. Alterations in the height and duration of fever in guinea pigs treated with cortisone are not as striking as have been reported in human beings with naturally acquired Rocky Mountain spotted fever simultaneously treated with antibiotics. The comparable experiment combining cortisone and antibiotic therapy in guinea pigs has not been done.

Since we have not yet been able to step up the virulence of the rickettsias for rabbits, a preliminary group was run at the present virulence to detect alterations in the sodium 24 and potassium 42 spaces, but the data have not been analyzed. The tissue values have not been completed. The immunologic response as determined by complement fixation reaction has not been entirely dependable in rabbits and the titers have been low, so that data comparing alterations in permeability with immune responses are so far felt to be not entirely reliable.

No experiments were attempted this year tagging rickettsias with P^{32}.

Extracellular Infections

Time did not permit this year experiments on fluid changes in Trichinosis, an extracellular infection, applying the techniques for radioisotopic studies.

Immune Reactions Without Infections

The initial studies on active sensitization of rabbits with human plasma have been published: Aikman, J.K. and Harrell, G.T.: The Immunophysiology of Serum Sickness. Alterations in the Blood Volume and Thiocyanate Space in Relation to the Development of Humoral Antibodies in the Rabbit, J. Clin. Invest. 30:360-368 (April) 1951. The continuation experiments utilizing different fractions of plasma have been published: Aikman, J.K., Yount, E.H., Harrell, G.T. and Jennings, T.M.: Immunophysiology of Serum Sickness. Alterations in the Blood Volume and Thiocyanate Space in Relation to Humoral Antibodies in Rabbits Sensitized with Human Albumin or Globulin, J. Allergy 22:508-517 (Nov.) 1951.

1111961

Experiments with a passive transfer method for induction of serum sickness in rabbits have been published: Aikawa, J.K. and Rhoades, E.L.: Immunophysiology of Immune Reactions. Alterations in the Thiocyanate Space in Quantitative Passive Transfer Experiments in Rabbits, J. Allergy 23:123-129 (March) 1952.

An attempt to localize the site at which fluid accumulates in the extravascular spaces as a result of immune reactions has been completed and published: Aikawa, J.K. and Rhoades, E.L.: Immunophysiology: Increase in Radiosodium Space of Adrenal Glands in Rabbits Sensitized with Human Plasma, Proc. Soc. Exper. Biol. & Med. 79:233-235 (Feb.) 1952. The findings in this study are compatible with the thesis that the adrenal gland plays a role in immune reaction and is compatible with the clinical experience that cortisone is efficacious in the treatment of diseases of allergic etiology.

Rabbits have been actively sensitized by the injection of human plasma and the effect on external potassium balance and radiopotassium exchangeable space determined. Preliminary examination of the data do not reveal much alteration but the analysis is yet incomplete. This experiment is at present being repeated by hyperimmunizing a group of rabbits in an attempt to obtain more striking results.

Autoantibody Studies

The limitations of time and available technical assistance have not permitted inauguration of autoantibody studies.

Clinical Studies

The results of a preliminary survey of alterations in permeability to radiosodium in various disease states has been reported: Aikawa, J.K.: The Significance of Radiosodium Space in Human Disease, South. Med. J. 44:651-661 (July) 1951. Additional data collected in the past year have, in general, followed the results previously obtained.

The usefulness of the radiosodium technique as a tool in the study of the abnormal physiology of rheumatic fever was reported briefly at the meeting of the Southern Society for Clinical Research, Atlanta, Georgia, January, 1952. An abstract of these studies is in press in the AMERICAN JOURNAL OF MEDICINE. The data indicate that the radiosodium space is increased in untreated acute rheumatic fever and that therapy with salicylates will decrease the available exchangeable radiosodium space without greatly altering the body weight of the individual. These data have been interpreted as indicating an increased permeability of cells to sodium which is reversible with salicylates and which recurs on withdrawal of the drugs. We would like to extend these studies to a larger series of cases, but admission of acute instances of the disease has been rare during the past year.

An initial preliminary survey of the exchangeable radiopotassium content in human beings with various disease states has been submitted for publication. The results were interpreted as indicating that the radiopotassium method is more accurate and more sensitive than the external balance method for assaying changes in body potassium content. The radiopotassium method is particularly applicable to the study of such disease states as diabetes, myxedema, cirrhosis, congestive heart failure, and individuals with any disease under treatment with ACTH and cortisone.

1111962

The magnitude of the deficiency of the body content of potassium as measured by the exchange of radiopotassium induced by the administration of adrenocorticotropic hormone (ACTH) or cortisone has been reported: Aikawa, J.K. and Felts, J.H.: Body Potassium Loss During Therapy with ACTH and Cortisone, N. C. Med. J. 13:22-24 (Jan.) 1952. These data seem also to indicate that the renal tubules do not handle sodium and potassium entirely independently, at least under the influence of these hormones.

The radiopotassium space has been determined in a group of 50 diabetic patients. Diabetes is known to affect integrity of arterioles and capillaries producing hemorrhages in the eye grounds, albuminuria and hematuria in poorly regulated cases. The magnitude of the body deficiency of potassium and the ease of replacement as measured by serial determinations while supplementary potassium salts were being given, has been studied. An abstract of this study will appear in the program of the American Society for Clinical Investigation, Atlantic City, New Jersey, May 5, 1952, and will be subsequently published in the JOURNAL OF CLINICAL INVESTIGATION.

The exchangeable potassium space has been determined in patients with cirrhosis of the liver, a disease in which the permeability of capillaries in the portal system is altered. These studies are being analysed and the results correlated with studies on protein metabolism using human serum albumin tagged with I^{131}.

Studies have been done in patients with cirrhosis of the liver following the injection of human serum albumin tagged with I^{131} and the results reported: Tyor, M.P. and Cayer, D.: Studies with Iodine Tagged Albumin in Cirrhotic Patients, South. Med. J. 45:141-145 (Feb.) 1952 and Tyor, M.P., Aikawa, J.K. and Cayer, D.: The Plasma Disappearance and Urinary Excretion Rate of I^{131} Albumin in Patients with Cirrhosis, Gastroenterology, accepted for publication. In the course of these studies the rate of appearance of iodinated albumin in ascitic fluid and its rate of metabolism by the liver as determined by the appearance of inorganic iodine in the urine have been determined.

Studies utilizing I^{131} tagged human serum albumin and K^{42} are continuing as clinical material becomes available on the wards of the hospital. So far most patients studied have been instances of the chronic form of the disease process where the pathologic physiologic situation is reasonably stabilized. The number of instances of acute disease suitable for our studies has been limited this year.

Studies of Digitalis

The study of previously completed has now been published: Aikawa, J.K., Knight, V.H. and Tyor, M.P.: Effective Intravenous Digitoxin on Fluid Distribution in Hospitalized Males Without Cardiovascular Disease, Proc. Soc. Exper. Biol. & Med. 76:250-252 (Feb.) 1951. No new experiments in this field have been undertaken this year.

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Articles published or in press summarizing the investigation conducted under the contract with the Atomic Energy Commission.

1. Aikawa, J.K.: Fluid Volumes and Electrolyte Concentrations in Normal Rabbits, Am. J. Physiol. 162: 695-702 (Sept.) 1950.

2. Aikawa, J.K., Knight, V.H. and Tyer, M.P.: Effect of Intravenous Digitoxin on Fluid Distribution in Hospitalized Males Without Cardiovascular Disease, Proc. Soc. Exp. Biol. & Med. 76:250-252 (Feb.) 1951.

3. Aikawa, J.K. and Harrell, G.T.: The Immunophysiology of Serum Sickness. Alterations in the Blood Volume and Thiocyanate Space in Relation to the Development of Humoral Antibodies in the Rabbit, J. Clin. Invest. 30:360-368 (April) 1951.

4. Aikawa, J.K.: The Significance of the Radiosodium Space in Human Disease, South. Med. J. 44:65[illegible]-66[illegible] (July) 19[illegible].

5. Harrell, G.T. and Aikawa, J.K.: Alterations in the Permeability of Membranes During Infections. J.A.M.A. 147:230-237 (Sept.) 1951.

6. Aikawa, J.K., Yount, E.H., Harrell, G.T. and Jennings, T.M.: Immunophysiology of Serum Sickness. Alterations in the Blood Volume and Thiocyanate Space in Relation to Humoral Antibodies in Rabbits Sensitized with Human Albumin or Globulin. J. Allergy 22:508-517 (Nov.) 1951.

7. Aikawa, J.K.: The Effect of Starvation on the Exchangeable Potassium and Tissue K^{42} Content in Rabbits, Proc. Soc. Exp. Biol. & Med. 78:524-526 (Nov.) 1951.

8. Aikawa, J.K. and Felts, J.H.: Body Potassium Loss During Therapy with ACTH and Cortisone, N. C. Med. J. 13:22-24 (Jan.) 1952.

9. Aikawa, J.K. and Rhoades, E.L.: Immunophysiology. Increase in Radiosodium Space of Adrenal Glands in Rabbits Sensitized with Human Plasma, Proc. Soc. Exper. Biol. & Med. 79:233-235 (Feb.) 1952.

10. Tyer, M.P. and Cayer, D.: Studies with Iodine-Tagged Albumin in Cirrhotic Patients, South. Med. J. 45:141-145 (Feb.) 1952.

11. Aikawa, J.K. and Rhoades, E.L.: Immunophysiology of Immune Reactions. Alterations in the Thiocyanate Space in Quantitative Passive Transfer Experiments in Rabbits, J. Allergy 23:123-129 (March) 1952.

12. Aikawa, J.K., Harrell, G.T., and Eisenberg, B.: The Exchangeable Potassium Content of Normal Women, J. Clin. Invest. Scheduled for April, 1952, issue.

13. Tyer, M.P., Aikawa, J.K. and Cayer, D.: The Plasma Disappearance and Urinary Excretion Rate of I-131 Albumin in Patients with Cirrhosis, Gastroenterology, accepted for publication.

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Progress report on the research project

FORMATION OF PHOSPHOLIPIDES IN TISSUES

sponsored by the Atomic Energy Commission, Division of Biology and Medicine under contract No. AT-(40-1)-288, Title II, with the Bowman Gray School of Medicine of Wake Forest College.

Project leader: Dr. Camillo Arton

The present report covers the work done from March 16, 1951, through March 15, 1952. This work is a direct continuation of that previously done with the aid of the Atomic Energy Commission and summarized in my progress report of March 15, 1951. In addition to the writer, the following investigators participated in the research work for various periods of time: M. A. Swanson, Ph.D., M. Crowder, M.S., P. Mitchell, M.S. Technical assistance was given by C. Torhune, and H. Pollard.

A. General outline of the work.

The experiments on the Incorporation of C^{14} labeled choline in the lipides of isolated liver tissue have been completed and our previous findings (already presented in a preliminary form) have been confirmed and extended. Both groups of results are now being organized for presentation in two complete papers.

The study on the Incorporation of labeled dimethylethanolamine (a likely precursor of choline) into the lipides of the isolated liver has been carried out actively. The data will be reported shortly in a summarized form and it is believed that only a limited number of additional experiments will be required for completion of this study. The labeled compound has been synthesized by a method which presents some unusual features. These have been described in a note which is now in press.

Some progresses have been made in the investigation of the metabolic pathways of choline in the isolated liver. It is felt, however, that on several points definite conclusion can not yet be drawn and that the present data represent merely an indication for future work.

Studies on the metabolism of formaldehyde have been continued. Previous findings on the occurrence in most tissues of an enzyme condensing formaldehyde with pyruvic acid have been confirmed. While the products of this reaction have been only partially characterized, it appears that the reaction might be of a considerable importance in various phases of the intermediary metabolism (including the formation and transfer of methyl groups). The preliminary report has been published and another will appear shortly.

Further details on each group of investigations are given below:

B. Incorporation of labeled choline into the phospholipides of isolated liver slices.

Definitive evidence has been obtained [illegible] that the whole molecule of choline is incorporated as a unit into the phospholipides of the isolated liver. Some of the recent experiments made for such a purpose are: (a) Incubation of slices from the same liver with choline labeled either in the methyl-, or in the ethylene moiety; (b) Hydrolysis of the isotopic lipides

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synthesised in vitro and determination of the radioactivity in various fractions of the lipide hydrolysates; (c) degradation of the choline separated from these hydrolysates and localization of the isotope in the [illegible] as in the choline added to the tissue slices.

In other experiments a direct comparison has been made between the incorporation of labeled phosphate and labeled choline into the lipides of slices or homogenates prepared from the same liver. The results have confirmed our previous statement that the two processes are affected in quite different manners by a number of factors, such as homogenisation of the tissue, substitution of nitrogen for oxygen or air, addition of respiratory inhibitors, previous dietary history of the animals. It may now be stated definitely that the synthesis of the ester bond between choline and the remaining part of the lecithin molecule has a relatively low requirement of energy and can proceed independently from the formation of the other three ester bonds present. This would make possible a "rejuvenation" of the choline end of the molecule without destruction of the whole compound. The findings also suggest that one phospholipide may be easily converted into another with a different nitrogenous constituent, possibly as the result of a change in the concentrations of the nitrogenous components within the cells. The results of the experiments with labeled DME (see below) give further indications in the same direction.

[illegible]. Incorporation of labeled dimethylethanolamine (DME) into the phospholipides of liver tissue.

The labeled compound (synthesised by our method) was added to slices or homogenates of liver from rats maintained on various diets. A notable part of the added compound was incorporated directly into the phospholipides. The isotopic values in slices from rats on adequate stock diets were smaller than in those from animals on choline-deficient diets. Under both conditions, DME incorporation in the lipides was greater in nitrogen than in oxygen or air. Homogenization of the tissue reduced but did not suppress the process. Addition of non-isotopic choline inhibited the incorporation of DME, whereas addition of non isotopic DME inhibited the incorporation of isotopic choline into the phospholipides.

Only a minor proportion of the isotope added as DME is found as choline in the lipides extracted after incubation. Furthermore, the amounts of labeled choline in the lipides of the incubated tissue are not significantly increased by the addition of methionine or betaine to slices from normal rats (although the formation of DME containing lipides is depressed under such a condition). When, however, the liver slices were obtained from choline-deficient animals and methionine was added to the tissue, the proportion of C^{14} in the lipide choline was definitely increased at the expense of the C^{14} of the DME present in the lipides.

These results indicate that choline and DME are incorporated into the phospholipides under conditions which are essentially similar, and probably by the activity of the same enzymatic system for which the two compounds compete. Accordingly the relative proportion of DME and choline in the phospholipides will depend upon their respective concentrations in the cell. DME is methylated to choline, but since the choline thus formed is rapidly oxidized to betaine aldehyde and betaine by liver slices of normal rats, notable amounts of labeled choline formed from DME are found only under

conditions in which the methylation of DME is enhanced and the activity of choline oxidase is depressed (slices from fatty livers incubated in the presence of methionine and labeled DME).

. Metabolic Pathways of choline in isolated liver.

The data obtained thus far give definite information on the following points: (a) labeled trimethylamine (TMA) and TMA oxide were found after incubation of liver slices with labeled choline. It can now be stated that the formation of such compounds is due to the activity of liver and not to a bacterial contamination since the results were not affected by the addition of antibiotics (penicillin, streptomycin, penicillin plus streptomycin, aureomycin) (b) a considerable portion of the labeled choline added to the liver slices can be recovered at the end of the incubation by a strong hydrolysis of the aqueous extract. These findings suggested to us the possibile formation of a choline-phosphate ester as one of the major pathways of choline metabolism in the liver. A comparison between the hydrolytic curves of the unknown compound and phosphoryl-choline had now been made, with results which do not favor our hypothesis. Analysis of the fractions separated by absorption suggest some other possibilities. Before these possibilities can be explored, it is felt that the separation procedures used thus far should be considerably refined. (c) Addition of DME to liver slices causes a moderate increase in the oxygen consumption, but no such increase is found when DME is added to liver homogenates which oxidize added choline very actively. It seems therefore, that DME is actually a likely precursor of choline, and that methylation to choline is the main metabolic pathway of DME in the liver, little or no DME being oxidized directly to dimethylglycine. (d) On the other hand, it was further confirmed that partial demethylation of choline with formation of DME does not occur in the liver, the major products of choline degradation in the isolated liver being betaine aldehyde and betaine.

E. Metabolism of Formaldehyde in Tissues

The widespread occurrence in animal tissue of a formaldehyde-pyruvate condensing enzyme was described by us in a previous report. Most of our preliminary data have been already confirmed in investigations, carried out independently in other laboratories. We have now studied further the properties of the enzyme in a partially purified preparation (mitochondria of rat liver). Additional experiments with C^{14} labeled formaldehyde have confirmed and amended our previous data on the characteristics of the addition product. The more recent information indicates that the enzyme is not a carboxylase leading to the formation of acyloins. Since no CO_2 is produced in the reaction, and at least part of the added formaldehyde can be recovered by oxidation with HIO_4, it appears now that the initial product of the reaction is a four carbon compound which contains a free OH adjacent to a COOH group. Other compounds are probably formed from this initial product, either enzymatically or not enzymatically.

F. Remarks

It is believed that the results summarized above represent a definite advancement in the development of our investigations. This has been accomplished in spite of adverse circumstances which have reduced considerably the efficiency of our group. Two full members of the department of Biochemistry (Dr. . . . Cornatzer and Miss M. Crowder) resigned, thus increasing the teaching load of the remaining professional workers. The trained technician who had been working

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on this project during 1950-1951, also left in July, and could be replaced only with a less skillful person who had to be trained for our specialized type of work. It is hoped that we will be able in the near future to make up for the present deficiencies in both professional and technical [illegible] and thus speed up the investigative effort on this project.

• Bibliography

From March 16, 1951, through March 15, 1952, the following papers, based on the results of the investigations of this project, have been published:

1. "Incorporation of Labeled Phosphate into the Lipides of Liver Slices", By [illegible] and M.A. Swanson, J. of Biol. Chem., Vol. 193, pgs. 473-[illegible] (1951)

2. "The Synthesis of Choline (Methyl-C^{14}) Chloride", By A. Roe, J. of Biochem. Mitchell Soc., Vol. 77, pgs. 54-[illegible] (1951)

3. "Mechanism of Action of Lipotropic Factors in Animals", By J. Artom, Transaction of the Tenth Conference on Liver Injury, J. Macy, Jr. Foundation, pgs. 58-60 (1951)

4. "Incorporation of Labeled Choline in Phospholipides of Isolated Liver Tissue", By J. Artom, M. Crowder, and M.A. Swanson, Federation Proc., Vol. 10, pgs. 157-158 (1951)

5. "Enzymatic Disappearance of Formaldehyde in the Presence of Pyruvate", [illegible] Mitchell and J. Artom, Federation Proc., Vol. 10, pgs. [illegible] (1951)

The following paper is presently in press:

6. "Preparation of C^{14} Methyl Labeled Dimethylaminoethanol", By J. Artom and M. Crowder, J. of Amer. Chem. Soc., Vol. 74

The following preliminary reports [illegible] program of scientific meetings:

7. "Incorporation of Labeled Dimethylethanolamine in Phospholipides of Isolated Liver Tissue", By M. Crowder and J. Artom, Am. Soc. of Biol. Chemists, New York, April 1952.

8. "[illegible]-pyruvate dehydrogenase complex", By [illegible] Mitchell and J. Artom, Amer. Soc. of Biol. Chemists, New York, April 1952.

Comprehensive surveys of the results obtained in the past and more recent investigation on this subject will be presented by J. Artom at a Symposium on Phosphorus Metabolism (John Hopkins University, Baltimore, Maryland, June 1952) and at the Second International Congress of Biochemistry, ([illegible], [illegible], 1952).

D. Camillo Artom

Camillo Artom, M.D.

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Progress report on the research project.

TOXICITY OF P^{32} AS RELATED TO THE DIET

sponsored by the Atomic Energy Commission under direct contract AT-(40-1)-2[illegible], Title III, with the Bowman Gray School of Medicine of Wake Forest College

Principal Investigators: Drs. C. Arten and G. T. Harrell, Jr.

The present report covers the work done from March 16, 1951 to March 15, 1952. In addition to the principal investigators, Dr. W. S. Cormatzer and Dr. E. M. Stevens participated for short periods in the research work. Technical assistance was given by J. Giles and C. Downs.

A. General outline of the work:

During the past year the experiments have been carried along two main parallel lines: (a) continuation of our systematic study of the dietary factors which might protect against, or favor the recovery from, the effects of internal radiation by P^{32}, (b) continuation of our attempts to modify by various means the deposition of the isotope in the bones or its mobilization from the bones.

Until now, the latter group of investigations did not yield satisfactory results. On the contrary, the experiments on the role of pyridoxin in the protection against the injury by P^{32} were quite conclusive. Our recent findings in this respect parallel those previously obtained by us with the combined administration of vitamin B_{12} and folic acid. In both cases a significant protection against the effects of internal radiation could be demonstrated only in animals in which the vitamin deficiency was clearly developed. Since damage to the blood-forming tissues probably plays a dominant role in the toxicity by radioactive phosphate, it seems possible that the protective action of B_{12}+ folic acid and of pyridoxin is related to the high requirement for these vitamins of rapidly regenerating structures, such as the erythro- and lymphopoietic tissues. Future work on this aspect of the problem is contemplated and in this respect, the results of a collateral investigation on the uptake of P^{32} by the nucleic acids of developing chick embryo, may perhaps be of some interest.

B. Protective role of Pyridoxin against P^{32}

Two series of experiments were made on a total of about [illegible] mice. In preliminary experiments the animals were maintained on a low protein diet without pyridoxin and injected with mid-lethal doses of P^{32}. Administration of large amounts of pyridoxin to these animals did not change the survival figures.

Since in these experiments the mice did not show symptoms of vitamin deficiency, the experiments were repeated on animals in which the deficiency of pyridoxin was enhanced by the administration of a pyridoxin analog (desoxypyridoxin (DOP)). Symptoms of a severe deficiency developed rapidly and many deaths occurred even in the [illegible] groups. By reducing to the first few days of the experiment the period in which DOP was added to the diet, it was possible to slow down the rapidity of the deficiency and permit the survival of most of the controls not receiving the DOP. Under these conditions a marked reduction in the number of deaths

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and a definite prolongation of the survival time of the mice injected with P^{32} was observed, when pyridoxin was added to the diet together with its metabolic antagonist. For instance, in one of our series (5% casein diet with [illegible] g. 1 [illegible] g. of diet - P^{32} injected: 5 microcuries per g. of body weight), supplementation of the diet with pyridoxin (2 mg / 1[illegible] g.) shifted the day of 50% deaths from the 14th to beyond the 42nd, the average time of survival from 19 to 33 days and the proportion of survivors (at the 21st day after the introduction of the isotope) from 19% to 77%.

In subsequent experiments a relative deficiency of pyridoxin was induced by increasing the metabolic demands for this vitamin. Mice placed on a high protein diet to which either cystine or methionine was added, developed obvious symptoms of pyridoxin deficiency. In these animals also pyridoxin administration exerted a quite significant protection against the injurious action of P^{32}. For instance, in animals maintained on a 32% casein diet supplemented with 0.5% cystine and injected with 5 microcuries of P^{32} per g. of body weight, the administration of pyridoxin (1 mg / 100 g. of diet) shifted the day of 50% deaths from the 18th to beyond the 42nd day, the average time of survival from 21 to 36 days and the proportion of survivors (at the 21st day) from 22% to 83%.

A statistical analysis of the results obtained in the various series of experiments indicates that the differences observed have a high degree of significance and are much larger than those which might be ascribed to a simple additive effect of internal radiation and vitamin deficiency.

The results of these experiments have been reported at the winter meeting of the Southeastern Section of the Society for Experimental Biology and Medicine. A complete report is now in press in the Proceedings of the Society for Experimental Biology and Medicine.

C. Effects of the administration of "chelating" agents.

A fairly large number of experiments have been made on the effects of the introduction of "Versene", a preparation which is known to bind calcium ions in blood plasma. It was thought that this effect would be followed by a mobilization of both calcium and phosphorus from the bones and thus decrease the amount of ionizing radiation received by the bone marrow. In various series of experiments mice injected with P^{32} received versene (1-2 injections daily), and the amounts of the isotope in the urine were determined. Differences in the P^{32} excretion between the experimental and the control groups were observed, but the effects on the survival figures of the animals were often slight and not consistent. The experiments are now being continued on mice maintained on a phosphate-rich diet. If these experiments will not be clearly successful, it is planned to make some further attempt, using larger animals in which versene will be introduced by continuous instillations in the veins.

D. Experiments with pyrophosphate - P^{32}.

In various series of experiments the effects of the same radioactive dose introduced in the form of either pyrophosphate, or ordinary phosphate were compared. Here again differences in the rate of elimination of the isotope were observed, but up to now these differences did not cause consistent or significant changes in the survival of the animals. It seems likely that the

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variability in the results may be due to variations in the activity of the tissue enzymes which convert pyrophosphate to inorganic phosphate.

Experiments with introduction of comparatively large amounts of non isotopic inorganic pyrophosphate shortly after the injection of P^{32} are presently under way.

E. Uptake of P^{32} by nucleic acids of developing chick embryo.

Fertile chicken eggs at various days of incubation (9 to 18) were injected with radioactive phosphate. Six hours later the embryos were dissected, desoxyribose - and ribose-nucleic acids were isolated, and their content in P^{32} and P^{31} was determined. In both nucleic acids the uptake of P^{32} increased rapidly to a peak on the 13th day, then fell abruptly. At its peak value the turnover rate of phosphorus in the nucleic acids of the embryo is much greater (10 to 20 times) than the corresponding values obtained by others on the bone marrow (which shows the highest turnover among the tissues of adult animals.)

F. Bibliography

In the period covered by the present report, the following complete papers have been published.

1. "Beneficial Effects of Vitamin B_{12} and Folic Acid on Recovery from Internal Radiation by P^{32}". By A. E. Cornatzer, C. Artom, G. T. Harrell, Jr., [illegible], Proc. Soc. Exp. Biol. and Med., Vol. 76, pgs. 552-554 (1951)

2. "Relation of Uptake of Radiophosphorus into Nucleic Acids to Age of Developing Chick Embryo." By F. M. Stevens. Cancer Res., Vol. 12, pgs. 62-64 (1952).

The following complete paper is presently in press:

3. "A Protective Role of Pyridoxin Against the Toxic Effects of P^{32}". By C. Artom, A. E. Cornatzer and G. T. Harrell, Jr., Proc. Soc. Exp. Biol. and Med. (1952).

C. Camillo Artom

Camillo Artom, M.D.

George T. Harrell, Jr.

George T. Harrell, Jr., M.D.

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Beneficial Effects of Vitamin B_{12} and Folic Acid on Recovery from Internal Radiation by P^{32}

W. [illegible] [illegible], [illegible] [illegible], GEORGE T. HA[illegible]ELL, JR., AND [illegible] CARTER.

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1951, v76, 552-554

Beneficial Effects of Vitamin B_{12} and Folic Acid on Recovery from Internal Radiation by P^{32}.* (18553)

W. E. CORNATZER, CAMILLO ARTOM, GEORGE T. HARRELL, JR., AND DAVID CAYER.
From the Departments of Biochemistry and Internal Medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.

In a previous paper the toxicity of P^{32} has been investigated in relation to the content of lipotropic factors, protein, fat and phosphate in the diets(1). In a continuation of such a study, the effect of varying the supply of certain vitamins has now been tested. Damage to the bone marrow is a constant occurrence in radiation injury and should be of even greater importance after administration of radioactive compounds, such as isotopic phosphate which is deposited preferentially in the skeleton. Under this condition, one might expect that the recovery of the animals will be affected markedly by a deficiency of hematopoietic factors such as folic acid and vit B_{12}. Some beneficial effects of folic acid on the anemia and leukopenia following radiation therapy in human beings have been reported(2,3). An increase in the % of survivors and in the survival time of x-ray irradiated mice receiving generous amounts of either pyridoxine or folic acid has also been described(4). However, no significant effect of these vitamins on the hematological changes of the animals was detected. Folic acid also failed to prevent such changes after total body irradiation with x-rays of rats(5), cats(6), and swine(7), and after introduction of P^{32} in human beings, or Sr^{89} in rats(8). Likewise, vit B_{12} failed to modify the anemia and leukopenia of rats exposed to x-rays(9).

To our knowledge, no study has yet been reported concerning the effectiveness of the combined administration of folic acid and vit B_{12} on the recovery from radiation injury: a point which is directly suggested by the close relationships in the biological actions of these two compounds. Moreover, since large amounts of these and other vitamins are synthesized by the intestinal flora, an attempt to reduce such a synthesis by the ingestion of poorly absorbed antibacterial agents, would tend to give a more accurate estimation of the value of the vitamins.

Experimental. Four series of experiments were carried out on a total of 525 mice under conditions identical to those of our previous experiments(1), except as indicated below. In series I and II, 172 mice were maintained on experimental diets without added sulfasuxidine and injected with 6 $\mu c/g$ of P^{32}. Large doses of folic acid (20 mg/100 g of diet) or of a mixture of folic acid (20 mg/100 g) and vit B_{12} (0.75 mg) were added to the diet of part of these animals. In Series III and IV the low fat, low protein diet (Diet No. 34) (1) contained 5% sulfasuxidine and a basal mixture of B vitamins (Thiamine HCl 0.5 mg, riboflavin 0.5 mg, pyridoxine HCl 0.5 mg, Ca

* Technical assistance was given by A. H. Smith, Jr. This work was performed under a contract (No. AT-40-1-288, Title III) between the U. S. Atomic Energy Commission and the Bowman Gray School of Medicine. The P^{32} was obtained from the Oak Ridge National Laboratories, Oak Ridge, Tenn. Part of the vitamins was graciously supplied by Merck and Co., Rahway, N. J.

1. Cornatzer, W. E., Harrell, G. T., Jr., Cayer, D., and Artom, C., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 492.
2. Watson, C. J., Sebrell, W. H., McKelvery, J. L., and Daft, F. S., *Am. J. Med. Sci.*, 1945, v210, 463.
3. Davis, P. L., *Am. J. Med.*, 1946, v1, 634.
4. Goldfeder, A., Cohen, L., Miller, C., and Singer, M., PROC. SOC. EXP. BIOL. AND MED., 1948, v67, 272.
5. Stearner, S. P., PROC. SOC. EXP. BIOL. AND MED., 1948, v69, 518.
6. Adams, W. S., and Lawrence, J. S., *Am. J. Med. Sci.*, 1948, v216, 656.
7. Cronkite, E. P., Tullis, J. L., Tessmer, C., and Ullrich, F. W., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 496.
8. Jacobson, L. O., Stearner, P., and Simmons, E., *J. Lab. a. Clin. Med.*, 1947, v32, 1425.
9. Carter, E. R., Busch, E., and Strang, V., *J. Hematol.*, 1950, v5, 753.

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TABLE I. Effects of Certain Vitamins on Survival of Mice Injected with P^{32} (5 μc/g) and Maintained on a Sulfasuxidine Containing Diet.*

Supplements	No. of mice	Avg food consumption, g/day	Avg change in wt/g	Time of 50% deaths, days	% of survivors 21st day	% of survivors 56th day	Avg time of survival,† days
0	73	3.5	−1.6	27	58	16	29 ± 2.0
FA	39	4.1	−5.0	29	49	31	30 ± 3.3
B_{12}	24	3.7	−3.8	34	58	46	36 ± 4.0
FA + B_{12}	34	4.1	−0.1	>56	76	56	42 ± 3.5
FA, B_{12}, K, Bio.	67	4.0	−1.1	54	72	49	41 ± 2.5
0‡ (controls)	18	4.1	−6.7	>56	100	83	55 ± 0.8

* Diet No. 34(1) containing 5% sulfasuxidine. A basal B vit. mixture (see text) was incorporated daily in the diet.

† In the calculation of the avg time of survival, a survival time of 56 days was ascribed to the mice still alive at the end of the experiments. Values preceded by ± are the standard errors of the means.

‡ Not injected with P^{32}.

TABLE II. Statistical Comparison of the Survival of Mice Injected with P^{32} (5 μc/g) and Maintained on a Sulfasuxidine-containing Diet.

Supplements	Avg time of survival: n	t	P	No. of survivors at 56th day: χ^2	P
FA	110	0.23	>.05	2.32	>.05
B_{12}	95	1.67	>.05	7.56	<.01
FA + B_{12}	105	3.19	<.01	15.70	<.01
FA, B_{12}, K, Bio.	138	3.85	<.01	15.92	<.01

* n = Degrees of freedom; t = According to Fisher(10); P = Probability for a chance occurrence.

pantothenate 2 mg, inositol 2 mg). In addition, some groups received also, as "supplements" to each 100 g of the diet: folic acid alone (FA = 1.5 mg), or vit B_{12} alone (B_{12} = 0.45 μg), or both folic acid and B_{12} (FA + B_{12}; 1.5 mg and 0.45 μg, respectively), or a mixture (FA,B_{12},K,Bio) of folic acid (1.5 mg), vit B_{12} (0.45 μg), 2,methyl-1,4-naphthoquinone (Menadione, 15 μg), and biotin (1.2 μg). Three groups of 6 mice each were maintained for the whole period of the experiments on the sulfasuxidine-containing diet without supplements and were not injected with the isotope. All other animals were maintained on the diets, unsupplemented or supplemented, for 10 days before the introduction of P^{32}, and for 56 more days thereafter. Each of these mice received a single injection of P^{32} (5 μc/g): from our previous data this dose was estimated to be slightly below the LD_{50} (at the 21st day and for a low-protein, low-fat diet)(1). In the experiments of Series IV, one animal in each group was sacrificed by decapitation immediately before and at regular intervals after the introduction of P^{32}, so that blood could be obtained for determinations of the hemoglobin content, red blood cell and white blood cell counts, and hematocrit.

Results. In the experiments of Series I and II the diets did not contain sulfasuxidine, and therefore notable amounts of vitamins were probably still available to the animals through synthesis in the intestine. Supplementation of such diets with folic acid, or folic acid and vit B_{12}, did not appear to cause any significant effect on the survival of mice injected with a dose of P^{32} in the higher range of the LD_{50} (at the 21st day)(1). Data of the experiments of these series (and of Series IV also) are omitted for brevity. Only the data on the survival of mice on the diets containing sulfasuxidine and the results of a statistical treatment of these data are recorded in Tables I and II, respectively. A few of

10. Fisher, R. A., *Statistical Methods for Research Workers*, London, 1936, 6th Edition.

1111974

the mice not injected with P^{32} died after several weeks on the low protein diet with added sulfasuxidine. On the other hand, in the groups of mice injected with 5 μc g of P^{32}, the % of survivors at the 21st day and the time of 50% deaths were the same as, or greater than the values previously observed in mice injected with a smaller dose of P^{32} (4 μc g) and maintained on a diet without added sulfasuxidine (Diet 31, which differed from Diet 34 only in a higher fat content) (1). It seems therefore that the inclusion of sulfasuxidine in the diet did not enhance the susceptibility of the animals to the injurious action of the isotope.† Supplementation of the sulfasuxidine-containing diet with folic acid alone increased the % of survivors at the 56th day, but the increase was not statistically significant ($P>0.05$). Vit B_{12} seemed more effective, however only the increase in the % of survivors was significant. On the other hand, the combined administration of folic acid and vit B_{12} offered a marked protection with a high degree of significance for both % of survivors and survival time. The further addition of menadione and biotin did not enhance the beneficial action of the mixture of folic acid and vit B_{12}. Altogether our results suggest that none of the vitamins tested modify appreciably the damage caused by the introduction of P^{32}, but that an adequate supply of both vit B_{12} and folic acid may be an important factor for the recovery of the damaged tissues.

† Several recent reports suggest that antibiotics may even be beneficial in the treatment of radiation injury by preventing general or localized infections. For example, streptomycin and penicillin effectively reduced the mortality or prolonged the survival of rats injected with P^{32} (11).

11. Koletsky, S., and Christie, J. H., Proc. Soc. Exp. Biol. and Med., 1950, v75, 363.

The hematological changes following the introduction of P^{32} in mice on the sulfasuxidine-containing diet showed approximately the same general behavior in all groups of Series IV. After an initial fall, the values rose progressively and often declined again at the longest intervals. However, between the 12th and the 36th day, that is, during the recovery period after the initial fall, the % hemoglobin and the red and white cell counts in the blood of mice on the diet supplemented with both folic acid and vit B_{12} were all higher than in the other groups. Because of the limited number of determinations, the differences observed can only be taken as a suggestive indication for a relationship between the improved hematological picture and the prolonged survival of mice receiving the mixture of the two vitamins.

Summary. The addition of generous amounts of folic acid, or folic acid and vit B_{12}, to experimental diets had no significant effect on the survival of mice injected with a dose of P^{32} in the higher range of the LD_{50} (21st day). On the other hand, when sulfasuxidine was added to the diet and the mice were injected with a dose of P^{32} slightly below the LD_{50} (21st day), the administration of vit B_{12} and folic acid increased significantly the time of 50% deaths, the average time of survival and the % of survivors (at both the 21st and the 56th day).

Received February 26, 1951. P.S.E.B.M., 1951, v76.

1111975

RELATION OF UPTAKE OF RADIOPHOSPHORUS INTO NUCLEIC ACIDS TO AGE OF DEVELOPING CHICK EMBRYOS

KINGSLEY M. STEVENS

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1111976

Relation of Uptake of Radiophosphorus into Nucleic Acids to Age of Developing Chick Embryos*

KINGSLEY M. STEVENS†

(Department of Internal Medicine of the Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina)

While much work has been done on the turnover rates of nucleic acids in young and adult animals, especially the rat (5), little is to be found on their turnover in embryonic tissue. Since the relative rate of growth of tissue is much greater during embryonic development than during adult life, it was felt that a study of the changes in turnover rates of desoxyribonucleic acid (DNA) and pentosenucleic acid (PNA) in relation to age would be of interest. When mature animals are used, separate organ analyses can be made, but such analyses are not generally feasible on embryonic material. With the use of radiophosphorus,[1] we have demonstrated high turnover rates with large differences in these rates at different ages.

MATERIALS AND METHODS

Fertile chicken eggs were incubated for from 9 to 16 days at 38° C. In each experiment from four to eleven eggs were used, the larger number being used for the younger embryos. Five-tenths ml. of a solution containing 5 μc. of carrier-free $Na_2HP^{32}O_4$, 25 units of penicillin, and 250 μg. of streptomycin was injected into the yolk sac of each egg. After 6 hours' further incubation at 38°, the embryos were dissected free, observed for viability, pooled, weighed, and blended. The nucleic acids were then extracted by the method of Hammarsten (4), with the modification that the PNA was precipitated by the neutralization of the acid lanthanum after the DNA was removed. Although a great deal of PNA is lost by this technic, the loss does not alter the specific activity. Phosphorus determinations on aliquots of the DNA and PNA were made by the method of Allen (2) and DNA determinations by the method of Stumpf (9). When a value of DNA phosphorus of 9.1 per cent was assumed, the DNA values as determined by the two methods checked within 10 per cent. DNA analyses were made on the PNA to detect possible contamination. Only one experiment showed contamination of over 6 per cent for which appropriate corrections were made. Counts were made on the entire dried sample brought to constant mass with sodium chloride. Over 10,000 counts in duplicate were taken in all cases.

Since the administered $Na_2HP^{32}O_4$ equilibrated with the total inorganic P of the egg, it was necessary to multiply the "raw" specific activity values by the quantity of inorganic P per egg. These data for eggs of varying ages were secured from Kugler (6). The term "relative specific activity" as used here refers to the product of counts/minute/milligram nucleic acid P × the milligrams of inorganic P per egg. Since the same quantity of P^{32} was injected in all experiments, this term is proportional, though not equal, to the more conventional definition of "relative specific activity."

RESULTS

The results are shown in Chart 1.

The "relative specific activities" of both PNA and DNA are seen to rise rapidly from the ninth day, reach a peak on the thirteenth day, and then drop precipitously. The DNA remains low through the sixteenth day, while the PNA begins to rise moderately. The ratio of PNA/DNA "relative specific activities" remains essentially constant until the fourteenth day, and then rises.

DISCUSSION

Novikoff and Potter (8) studied the changes in PNA and DNA concentrations in the developing chick embryo. Their data are shown in Chart 2, along with data from Needham (7), showing changes in protein concentrations.

In our study only 9–16-day embryos were in-

*Supported, in part, by a contract between the Atomic Energy Commission and the Bowman-Gray School of medicine.

† Atomic Energy Commission postdoctoral fellow in the Medical Sciences, 1948–50. Present address: Surgical Research Unit, Brooke Army Hospital, Fort Sam Houston, Texas.

[1] It has been demonstrated that inorganic P^{32}- and C^{14}-labeled purines give similar nucleic acid turnover rates (1).

Received for publication October 6, 1951.

1111977

vestigated. Younger embryos required a larger number of eggs than were available, while older ones could not be extracted satisfactorily by this technic.

The similarity of the position of the peaks in Charts 1 and 2 is apparent. Chart 2 represents concentrations of these substances, while Chart 1

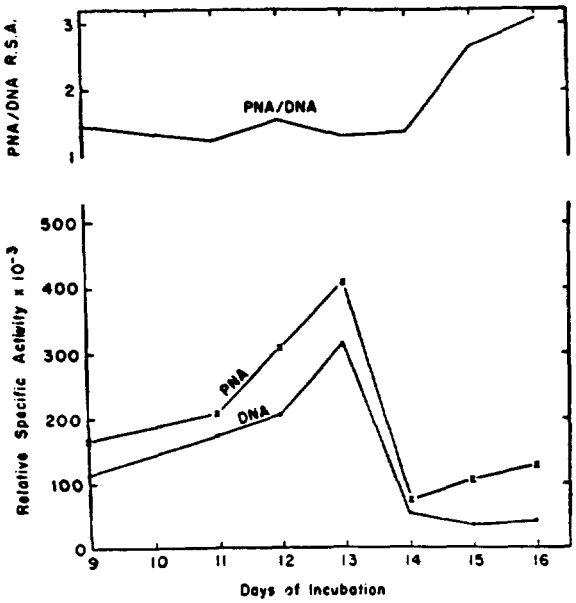

CHART 1.—Changes in PNA and DNA relative specific activities (counts/min/mg nucleic acid P×mg inorganic P/egg) with increasing age. No values were obtained for the tenth day. Days 9 through 13 represent single experiments. Day 14, three experiments, standard deviation PNA, 24,300; DNA, 18,000. Day 15, four experiments, s.d. PNA, 19,600; DNA, 11,200. Day 16, two experiments, s.d. PNA, 1230; DNA, 1520.

presents the pattern of change in turnover rates. Hence, not only do the concentrations but also the turnover rates increase greatly about the thirteenth day. Since it is difficult to determine accurately just how long an egg has been incubating, the difference of 1 day in the peak is probably not significant. If both the turnover rates and the amounts of nucleic acids are important factors in the rate of protein synthesis, then around the thirteenth or fourteenth day the product of the two is at a level several times higher than at earlier or later periods between 9 and 16 days.

A rough estimation of the absolute turnover rates can be calculated.[2] For the peak value of the thirteenth day, a rate of 148 per cent per 24 hours is found for PNA and 116 per cent for DNA. This contrasts strongly with the rate for adult animals, since the highest nucleic acid turnover rates in rabbits, found in bone marrow, were only 13 per cent for PNA and 4 per cent for DNA per day.[3] Even the lowest rates in the embryo, found on the fourteenth day, are 28 per cent and 20 per cent per day for PNA and DNA, respectively.

After the thirteenth day the DNA activity drops and then remains constant, while the PNA activity drops but quickly begins rising. This may reflect a continued high rate of cytoplasmic protein synthesis in contrast to a relative decrease in cell division.

Since these studies were made on whole embryos, the particular organs responsible for the increase remain unknown. Davidson and Leslie (3) could demonstrate no marked increase in the amounts of nucleic acids in the heart or liver of chick embryos in the twelfth- to sixteenth-day period. However, in adult animals, the nucleic acid turnover rates are much higher in lymphoid tissue, spleen, bone marrow, and intestinal mucosa (5).[3] Study of these tissues in embryos would be preferable if sufficient quantities of tissues could be secured.

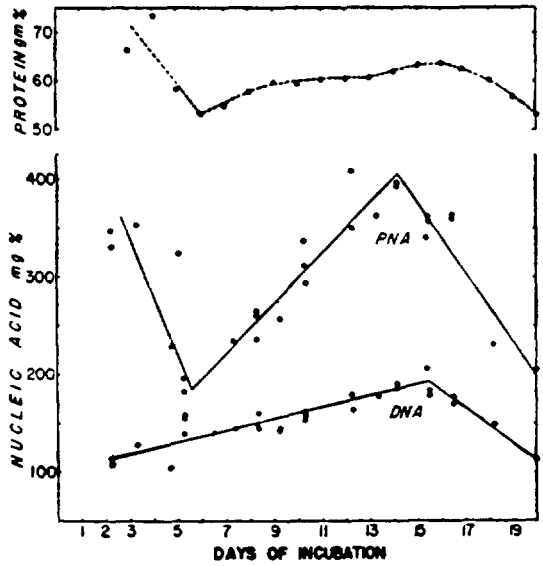

CHART 2.—Changes in PNA and DNA concentrations with age, from Novikoff and Potter (8). Top curve: changes in protein concentration, from data of Needham (7). Dry weight basis.

It is clear that, about the thirteenth or fourteenth day, the chick embryo undergoes drastic changes in its nucleic acid metabolism. Further study of this period may reveal important information concerning normal growth.

[2] Method of calculation: 5 μc. P^{32} injected which produce 11×10^6 disintegrations per minute. The counter efficiency for P^{32} was 9.9 per cent. Hence, 5 μc. would produce 10.9×10^6 counts per minute. There are 17.2 mg. of inorganic P in a 13-day egg. This will give a specific activity of 6.3×10^4 counts/min, mg P. The PNA-P specific activity was 23.6×10^3 counts/min/mg PNA-P. Hence, the turnover rate would be 37 per cent for 6 hours, or 148 per cent per day.

[3] K. M. Stevens, unpublished data.

1111978

SUMMARY

1. The uptake of radiophosphorus into desoxyribonucleic acid (DNA) and pentosenucleic acid (PNA) in 9–16-day chick embryos has been determined.

2. The "relative specific activities" of both DNA and PNA rise rapidly to a peak on the thirteenth day, then fall abruptly to about 20 per cent of this peak value. The DNA activity then continues constant, while the PNA begins to rise again.

3. The turnover rates of both nucleic acids, but especially DNA, appear to be much higher in embryos than in adult tissues.

REFERENCES

1. Abrams, R., and Goldinger, J. M. Utilization of Purines for Nucleic Acid Synthesis in Bone Marrow Slices. Arch. Biochem., **30**:261–68, 1951.
2. Allen, R. J. L. The Estimation of Phosphorus. Biochem. J., **34**:858–65, 1940.
3. Davidson, J. N., and Leslie, I. Nucleic Acids in the Development of the Chick Embryo: Changes in Ribonucleic Acid Phosphorus (RNAP) and Desoxyribonucleic Acid Phosphorus (DNAP) in Heart and Liver. Biochem. J., **43**: 266, 1948.
4. Hammarsten, E. On the Extraction of Nucleotides from Cells. Acta Med. Scandinav. (Suppl.), **196**:634–45, 1947.
5. Hevesy, G. Advances in Enzymology, **7**:173–82. New York: Interscience, 1947.
6. Kugler, O. E. Acid Soluble Phosphorus in the Developing Hen's Egg. J. Cell. & Comp. Physiol., **23**:69–75, 1944.
7. Needham, J. Chemical Embryology. New York and Cambridge: Macmillan, 1931.
8. Novikoff, A. B., and Potter, V. R. Changes in Nucleic Acid Concentration during the Development of the Chick Embryo. J. Biol. Chem., **173**:233–38, 1948.
9. Stumpf, P. K. A Colorimetric Method for the Determination of Desoxyribosenucleic Acid. J. Biol. Chem., **169**:367–71, 1947.

1111979

RECORD OF NEGOTIATIONS AND AWARD

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

CONTRACTOR: THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

ADDRESS: WINSTON-SALEM 7, NORTH CAROLINA

I - N - D - E - X

ITEM	DESCRIPTION
1.	RECORD FOR PROPOSED AWARD OF CONTRACT
2.	MEMORANDUM RECORD OF NEGOTIATIONS (HUMPHRIES TO FILES) JULY 5, 1949
3.	RESEARCH PROJECT PROPOSAL SUBMITTED BY CONTRACTOR AND REQUEST FROM WASHINGTON FOR PREPARATION OF CONTRACT
4.	ROUGH AND FINAL DRAFTS OF CONTRACT
5.	BACK-UP FOR MODIFICATION NO. 1
6.	BACK-UP FOR MODIFICATION NO. 2

1111980

[illegible] AT-(LO-1)-268

Research

price, cost or cost-plus-fee: Cost.

c. Whether contract was negotiated or awarded on competitive basis: Negotiated.

d. Name and address of contractor:
The Bowman Gray School of Medicine of Wake Forest College
Winston- Salem 7, North Carolina.

e. Description of work covered under the contract:
Title I - Project Leader: Dr. George T. Harrell - Distribution and turnover of sodium and potassium in acute infections.
Title II - Project Leader: Dr. Camillo Artom - Hormonal and Pharmacological actions on formation of tissue phospholipides
Title III - Project Leader: Dr. George T. Harrell, Associate Project Leaders: Dr. C. Artom and Dr. D. Cayer - Toxicity of P^{32} as related to the functional capacit the liver.

[illegible] consideration [illegible], estimated total estimated cost of contract, etc., as appropriate): Estimated combined cost for all titles during first period is in the amount of $25,000.00. Two quarters estimated operating cost will be advanced to the Contractor at the start of the contract. Reimbursement of actual expenditures will be made thereafter on quarterly basis.

Brief description of any unusual or unique [illegible] relating to the work to be performed [illegible] unusual contract provisions or [illegible] from normal prices or fees:
The work will be performed in Contractor-owned facilities and will be administered by the Contractor in accordance with his normal procedure and policy as a part of the institutions regular program. In addition to furnishing the use of his facilities without cost there will be no charge made for the institutions general and administrative (executive) expenses.

h. Description of such unusual or important contract provisions:
In consideration of the Contractor's contribution (overhead use of facilities) title to all property acquired under the contract will vest in the contractor, unless listed as an exception under Appendix "A". Funds will be advanced to the Contractor but he will not be required to establish a separate bank account since bills will be paid under his regular procedures. Also, reimbursement vouchers will be supported only by a simple certified listing of expenditures, in lieu of invoices, payrolls, etc., which are usually required. The budget article provides for recoupment of funds advanced but not obligated upon termination or expiration or for application of unobligated balances on the next years budget.

1111981

RECORD FOR PROPOSED AWARD OF CONTRACT

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

NAME OF CONTRACTOR: The Bowman Gray School of Medicine of Wake Forest College

ADDRESS: Winston-Salem 7, North Carolina

PROJECT LEADERS: Title I - Dr. George T. Harrell
Title II - Dr. Camillo Artom
Title III - Project Leader - Dr. George T. Harrell, Associate Project Leaders: Dr. C. Artom and Dr. D. Cayer

BACKGROUND

The Commission's General Manager issued a policy statement on January 27, 1949, to the effect that the Commission would greatly expand Commission support of research projects in the fields of biology, medicine and biophysics. The Washington Division of Biology and Medicine was assigned the responsibility for approval of research proposals in these fields and for technical supervision of the resulting research contracts. The several operations offices were assigned the responsibility under an interim procedure for negotiating the contracts and for handling all phases of business administration. In this connection the Washington Division of Biology and Medicine recommends a budget but the Operations office is responsible for, and is authorized to negotiate the details of the budget in accordance with sound business judgment and in harmony with the requirements of the research project.

By memorandum dated May 23, 1949, Dr. L. W. Tuttle, Assistant Chief, Medical Branch, Division of Biology and Medicine, forwarded the approved research program with Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina, consisting of the continuation of two projects initiated with AEC funds and administered during Fiscal Year 1949 under Office of Naval Research Contracts Nos. N8onr-63701 and N8onr-63702, respectively. Also included in the approved research program is a new project to be carried out under the joint direction of Drs. Artom, Harrell and Cayer.

The budget ceiling recommended by the Washington Division for the two projects to be renewed is in the amount of $11,000 for each project; the budget ceiling approved for the new project is in the amount of $3,000. The memorandum requested Oak Ridge Operations to negotiate an appropriate contract with Bowman Gray School of Medicine in accordance with the interim procedure approved by the General Manager.

BRIEF DESCRIPTION OF THE WORK

Title I - Distribution and turnover of sodium and potassium in acute infections.

1111982

Record for Proposed Award of Contract No. AT-(40-1)-288

Title II - Hormonal and Pharmacological actions on formation of tissue phospholipides.

Title III - Toxicity of P^{32} as related to the functional capacity of the liv

AMOUNT OF CONTRACT

It is estimated that the combined cost of the three project titles under this contract will be $25,000.00 during the fiscal year beginning July 1, 1949. Funds in this amount have been obligated from the allotment by the Washington Division of Biology and Medicine under Appropriation 8990100.001 Allotment 903-101, Program 620.

TIME OF COMPLETION

The work under this contract will probably continue for a number of years, however, funds will be made available after the initial period of the contract on a year to year basis.

SPECIAL CONTRACT PROVISIONS

Every effort has been made to develop a contract which will require a minimum of administrative effort commensurate with sound business practice and which will permit the contractor to conduct his research with the necessary latitude of action for work of this nature and with only slight interference with his normal procedures. The unusual provisions which have been incorporated in the contract are described below:

a. Property

In consideration of the contractor's contribution to the project the contract provides for vesting of title of all property acquired under the contract in the contractor. The contractor will furnish space, use of his facilities already on hand to the extent that such use will not interfere with programs already in progress, and all general and administrative overhead activities. Estimated equipment purchases for the initial period beginning July 1, 1949, are in the amount of $5535. and represent items of property of very little future value to the Commission's program. Items of property which may arise in future budgets and which are deemed to be of sufficient value to the Commission in its other programs after work under this contract has been completed will be listed in Section 2 c. of Appendix "A" as an exception to this provision of the contract which vests title to property in the contractor.

1111983

b. Advances and Reimbursement

Provisions have been made to advance funds to the Contractor at the start of the contract. The contractor will estimate his requirements for the first two quarters. The amount of this estimate will be paid as an advance of funds. The contractor will not be required to establish a separate bank account. After the end of each quarter the contractor will submit a voucher supported by a simple certified listing of his expenditures during the preceding quarter. Invoices, payrolls, and other normal types of supporting documents will not be required, however, the contractor agrees to keep records showing his expenditures and these records are open to AEC inspection at any time. The substitution of a certified schedule of expenditures for usual supporting documents is agreeable to the local General Accounting Office since the Comptroller General has previously approved this procedure for use on similar OSRD Research and Development contracts. Provision is also made in the contract for recouping any portion of the advance not actually obligated by the Contractor in the performance of the contract. This adjustment will be made on an annual basis and the unobligated balance will either be recouped or applied on the next year's budget.

1111984

Office Memorandum • UNITED STATES GOVERNMENT

TO The Files

DATE July 5, 1949

FROM R. G. Humphries, Office of Special Assistant to the Manager

SUBJECT NEGOTIATION OF RESEARCH CONTRACT WITH THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

REFER TO SYMBOL: SA:RGH

Dr. Harry Stoeckle and the undersigned met with Dr. George T. Harrell and Dr. Camillo Artom on June 22, at the Bowman Gray School of Medicine, in Winston-Salem, North Carolina, for the purpose of negotiating a contract to cover the three research projects which had been proposed by Bowman Gray and which had been approved, with some limitations, by the Washington Division of Biology and Medicine and forwarded to Oak Ridge Operations Office for negotiation, by memorandum dated May 23, 1949, from Dr. L. W. Tuttle, Assistant Chief, Medical Branch.

In order to secure a better understanding of the Contractor's proposed budget, Dr. Harrell conducted the Commission representatives on an inspection tour of the facilities where the contract work will be carried on. The new laboratory which will be utilized by the Contractor in carrying out most of the work under this contract will be located on the 5th floor of the main laboratory building of the school and has been completely altered to fit it for work of this nature. The Contractor was in the process of moving [redacted] of his equipment into the Laboratory during our visit.

Dr. Stoeckle and the undersigned then met with Dr. Artom to go over the budget for the project that he will serve as Project Leader and which is designated as Title II of the contract.

The budget as originally submitted by the Contractor is in the proposed amount of $12,120.00 to which had been added a proposed overhead allowance of 8% to cover the school's administrative costs. The Washington Division in approving this project, limited the amount of funds to cover the work to $11,000. The contractor had proposed to furnish the salaries of staff members without charge to the project, leaving the requested labor charges to cover one full time technician and two part-time technicians with a total amount of $4,320.00. This amount was accepted by the Commission representatives.

In going over the list of permanent equipment proposed to be purchased, a question was raised as to whether or not Dr. Artom would be able to utilize an analytical balance already on hand in the laboratory. Dr. Artom stated that he could use the existing balance and it was agreed to eliminate this item from the equipment portion of the budget, leaving a sum of $2500.00 to be expended for equipment as itemized.

As requested by the Washington Division, the proposed purchase of a Geiger-Muller counter with a gas chamber was discussed with Dr. Artom.

1111985

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO: The Files

DATE: July 5, 1949

FROM: R. G. Humphries.

SUBJECT: NEGOTIATION OF RESEARCH CONTRACT WITH THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

REFER TO SYMBOL: SA:RGH

It was explained that there was some feeling that he might find this particular type of counter unsatisfactory for his work and it was thought advisable, before actually making the purchase, that he investigate the possibility of utilizing another type counter. This Dr. Artom agreed to do.

The consumable supplies outlined in the contractor's proposal were reviewed and agreed to as reasonable items in the total amount of $3400.00.

The elimination of the proposed trip to the First International Congress of Biochemistry, in Cambridge, England, was explained to Dr. Artom and he agreed to limit his travel expenditures to $200.00.

Miscellaneous and incidentals in the total amount of $580.00 was agreed to as covering the last item in the budget, rounding out a total of $11,000 for Title II work.

Dr. Stoeckle and the undersigned then met with Dr. George Harrell to review the budgets for Titles I and III.

Under Title I the Contractor had proposed a charge for salaries in the amount of $4700. There was some discussion of the item of part-time salary of Dr. Yount since we felt that Dr. Yount, being a member of the school staff, should be part of the Contractor's contribution to the project. Dr. Harrell pointed out that, due to the school's poor financial condition, they were unable to pay Dr. Yount a salary commensurate to his ability and that he had previously been permitted to spent one or two days each week seeing patients at the school's hospital to augment the salary paid him by the School to make a livable salary. That in order to secure the services of Dr. Yount for this project it will be necessary for the school to pay him the amount that he would otherwise earn seeing patients and since the school was unable to pay the additional salary he had asked for this salary as a part of the contract cost. Dr. Harrell pointed out that this project would not be able to make the proper progress without the services of Dr. Yount. It was then agreed to include the item in the budget.

1111986

STANDARD FORM NO. 64

Office Memorandum - 3 - UNITED STATES GOVERNMENT

TO The Files DATE: July 5, 1949

FROM R. G. Humphries

SUBJECT NEGOTIATION OF RESEARCH CONTRACT WITH THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

REFER TO SYMBOL: SA:RGH

In the permanent equipment portion of the budget the Contractor had proposed a flame photometer in the amount of $2000.00 and a chemical hood in the estimated amount of $1200 to be used with the flame photometer. Since the total budget of the contractor in the amount of $13,075 had been cut back by Washington to $11,000, it was necessary to eliminate these items from the permanent equipment budget. In lieu of the type of flame photometer originally proposed by Dr. Harrell there was substituted in the budget a flame photometer of another type with an estimated cost of $725.00 since, from a review of the laboratory facilities, Dr. Stoeckle felt that the contractor would be unable to carry forward the work properly without the use of such equipment. The adjusted equipment portion of the budget was in the amount of $2750.

In reviewing the consumable supplies portion of the budget it was noted that the contractor had failed to include an item for the purchase of radioisotopes which would be needed in the work and a sum of $400 was included in the budget for this purpose, making an adjusted total of $3,150 for consumable supplies.

Travel and contingency funds were allowed in the proposed amount of $200 each, rounding the budget out in the approved amount of $11,000 for Title I work.

In reviewing the budget for Title III, the salary item of $1500 was accepted as proposed.

One item of proposed permanent equipment, one direct reading balance for animals, in the amount of $250 was eliminated since Dr. Harrell indicated he could use similar equipment in another part of the laboratory. The adjusted equipment budget item was in the amount of $285.00.

Expendable supplies was accepted as proposed with the addition of animals to the item described as dietary components which now reads "dietary components and animals - $500.00". The total for expendable supplies is $950.00.

Balance of available funds was listed under miscellaneous as $265.00 completing the budget in the total amount of $3000.00.

1111987

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO The Files DATE: July 5, 1949

FROM R. G. Humphries

SUBJECT: NEGOTIATION OF RESEARCH CONTRACT WITH THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

REFER TO SYMBOL: SA:RGH

A draft of the contract which had been prepared by the Commission prior to the meeting was then discussed with Dr. Harrell, going over the draft point by point, and met with no objection from the school representatives.

Since the budgets described above do not include any of the proposed overhead allowance of 8% on each project made by the contractor, the question of ove head was then discussed with Mr. Parker, Controller. Mr. Parker was very adamant in his stand almost to the point of insisting that the overhead allowance, as proposed, be included in the budget. It was explained that the Commission representatives had already agreed to items in the working budget to the full extent of funds provided by the Washington office and that any allowance for overhead would result in a cut back of some of the essential items to be used by the scientific personnel.

The question was not resolved before the Commission representatives left to catch a plane back to Oak Ridge. Dr. Harrell stated before the meeting adjourned that he would refer the question of accepting the contract without the overhead provision to Dr. C. C. Carpenter, Dean of the School. Dr. Harrell made the trip back to Oak Ridge with the Commission representatives for purposes not connected with contract negotiations.

At 11:00 a.m., June 23, the undersigned received a telephone call from Dr. Harrell in Oak Ridge indicating that he had just talked to Dr. Carpenter, in Winston-Salem, and Dr. Carpenter was agreeable to accepting the contract without including an overhead allowance in the budget. On this basis the Commission proceeded with preparation of a contract for signature.

R. G. Humphries

Humphries:lm

1111988

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DEPARTMENT OF THE NAVY
OFFICE OF NAVAL RESEARCH
WASHINGTON 25, D.C.

Contract Administrator, SW Area
EXOS:CNR:N269:brg
N8onr-63701 and N8onr-63702

June 23, 1949

Mr. Harry O. Parker, Controller
Wake Forest College
The Bowman Gray School of Medicine
Winston-Salem, North Carolina

Subject: Research Contracts N8onr-63701 and N8onr-63702 - Payment After 30 June 1949 for Equipment Ordered Prior thereto but Undelivered by that Date, etc.

Dear Mr. Parker:

In my letter to you dated 9 June 1949, concerning the subject matter, you were advised that it was desired that the subject contracts be cleaned up by the terminating date, June 30, 1949, and that payment for equipment ordered under these contracts prior to June 30, 1949, but undelivered by that date should be charged to the Atomic Energy Commission contracts when delivered.

On the basis of the representation made by Mr. Stanwood of the Atomic Energy Commission, Washington, D.C., on behalf of the Atomic Energy Commission facility at Oak Ridge that it would facilitate the negotiation of the new AEC contract if some equipment delivered after June 30, 1949, under the subject contracts could be paid thereunder and charged thereto when delivered. The procedure outlined in my letter of June 9, 1949, is hereby modified to eliminate the item of fume hood equipment. Therefore, the cost of this item may be charged to the applicable subject contract and reimbursement claimed therefor and delivery, which is understood to be on or about 17 July 1949.

Very truly yours,

R. F. Lynch, Contract Administrator
Southeastern Area, Office of Naval Research, Navy Department

cc: AAA, Duke
Dr. G.T. Harrell, Wake Forest
Dr. C. Artom, Wake Forest
Mr. H.A. Stanwood, Jr. AEC

JUN 29 1949

RM-5540

Glen
Thought you might want this for your file.
Best.

1111989

M. L. Price, Assistant General Counsel June 27, 1960

G. Vandem Bulek, Chairman, Contract Board

REQUEST FOR PREPARATION NEGOTIATED RESEARCH CONTRACT (BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE)

REFER TO SYMBOL: SA:RSH

Attached is a draft of a research contract which has been negotiated with the Bowman Gray School of Medicine of Wake Forest College. It is requested that you prepare this contract in final form for execution. In preparing this contract it is requested that you include the new clauses which you have recently developed covering security classified procedures.

Since the contracts have been negotiated to permit the description of projects in Appendix "A" under separate titles, Article [illegible] in the basic contract form has been revised to provide that the period of reports will be that set forth in Appendix "A". This was necessary since the Washington Division approving the projects is in some cases specifying reporting periods different from the standard quarterly reports required by Article V.

The Record of negotiation will be furnished to you as soon as possible. I hope [illegible] will be able to go ahead with the contract preparation before you receive the record of negotiation, since time is running short between now and June 30, the end of the fiscal year.

W Key RSH
G. Vandem Bulek

Attach.:
Cont. draft (AT-(40-1)-[illegible])

CC: Dr. A. E. Bellami, Jr.
Mr. [illegible] Watson

Humphries:lm

1111990

In Reply Refer To:
RHS:MB

Oak Ridge, Tennessee
July 19, 1949

Dr. C. C. Carpenter, Dean
Wake Forest College
Bowman Gray School of Medicine
Winston-Salem, North Carolina

Dear Dr. Carpenter:

I want to thank you for your letter of July 13, explaining the School's position in signing Contract No. AT-40-1-288.

We are happy to learn that there was no reluctance on the part of the School to accept the Contract as written.

Your cooperation in this matter is deeply appreciated.

Sincerely yours,

Harry Steeckle, M.D.
Chief
Biology and Medicine Division

cc: Dr. George T. Harrell,
Bowman Gray School of Medicine

Steeckle:cc

cc: Mr. R. G. Humphries, AEC, w/ltr.
fm. Dr. Carpenter, dtd. 7-13-49.

5086

1111991

AT-40-1-288

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7
OFFICE OF THE DEAN

July 13, 1949

Dr. Harry Stoeckle, Chief
Division of Biology and Medicine
Atomic Energy Commission
Oak Ridge, Tennessee

Dear Dr. Stoeckle:

Dr. George Harrell has just telephoned me the substance of the telephone conversation between you two relative to the letter of "protest" sent you by Mr. Harry O. Parker, Controller of this institution, in connection with the signing of Contract No. AT-(40-1)-288.

As I understand it to have been explained to you by Dr. Harrell, Mr. Parker's letter was written in accordance with usual government contract language, as a means of protecting the institution from having created a precedent in case future legislation allows overhead for institutions entering into contracts with the Atomic Energy Commission. I have before me a copy of Mr. Parker's letter to you, in which that point is mentioned, as follows:

> "In order that the signing of these contracts with this stipulation contained therein, may not jeopardize the negotiation of future contracts, we wish to go on record as signing contracts under protest insofar as stipulation 2a (2) Titles I, II, and III of Appendix 'A' is concerned."

Of course, I am not as well informed on language usage in government contracts as Mr. Parker, who is a well trained Certified Public Accountant, with several years' experience, but I can understand the reasoning behind such usage.

I signed the contracts as the official representative of this school, and there was no reluctance on the part of the school officially to accepting the contract, as written, for the year specified.

I hope this clarifies the matter to your satisfaction.

Very truly yours,

C. C. Carpenter, M. D., Dean

JUL 18 1949

R-7160

CONTRACTS
Bowman Gray

CCC/kd
CC: Dr. George T. Harrell

1111992

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO H. L. Price, Assistant General Counsel DATE June 27, 1949

FROM C. Vanden Bulck, Chairman, Contract Board

SUBJECT: REQUEST FOR PREPARATION NEGOTIATED RESEARCH CONTRACT (BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE)

REFER TO SYMBOL: SA:RGH

Attached is a draft of a research contract which has been negotiated with the Bowman Gray School of Medicine of Wake Forest College. It is requested that you prepare this contract in final form for execution. In preparing this contract it is requested that you include the new clause which you have recently developed covering security clearance procedures.

Since the contracts have been negotiated to permit the description of projects in Appendix "A" under separate titles, Article V, Section 2, in the basic contract form has been revised to provide that the period of reports will be that set forth in Appendix "A". This was necessary since the Washington Division approving the projects is in some cases specifying reporting periods different from the standard quarterly reports required by Article V.

The Record of negotiation will be furnished to you as soon as possible. I hope that you will be able to go ahead with the contract preparation before you receive the record of negotiation, since time is running short between now and June 30, the end of the fiscal year.

C. Vanden Bulck

C. Vanden Bulck

Attach.:
Cont. draft (AF-(__-1)-288

CC: Dr. A. H. Holland, Jr.
Mr. F. C. Watters

Humphries:lm

RECEIVED JUN 27 1949 Office of Assistant General Counsel

1111993

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO John C. Franklin, Area Manager
Office of Oak Ridge Operations

DATE May 23, 1948

FROM L.W. Tuttle, Asst. Chief, Medical Branch
Division of Biology and Medicine

SUBJECT REQUEST TO NEGOTIATE RESEARCH CONTRACT WITH BOWMAN GRAY SCHOOL OF MEDICINE, WINSTON-SALEM, NORTH CAROLINA

REFER TO SYMBOL: BEM:LWT

This Division has approved A.E.C. support of a joint research project submitted by Dr. George T. Harrell covering three research projects as listed below:

I. "Distribution and Turnover of Sodium and Potassium in Acute Infections," with Dr. George Harrell as principal investigator. The level of support requested is $13,075.

II. "Hormonal and Pharmacological Actions on the Formation of Tissue Phospholipides", with Dr. Camillo Artom as principal investigator. The level of support requested is $12,120.

III. "Toxcity of P-32 as Related to the Functional Capacity of the Liver," with Drs. Artom, Harrell and Cayer as principal investigators. Level of support requested is $3,135.

Under the provisions of the General Manager's "Interim Procedure for Handling Research Proposals and Contracts in the Field of Biology and Medicine and Biophysics," dated January 27, 1947, the Office of Oak Ridge Operations is requested to negotiate an appropriate contract.

Comments on the Budget

With reference to the budget of Project I, this office has indicated to Dr. Harrell that the flame photometer item would not be forthcoming under the contract. It is believed that the remaining items in the budget are sound. Support of this portion of the work is authorized at a level of $11,000.

With reference to the budget of Project II under Dr. Artom, it appears that the expenditure of $650. for a trip to England cannot be justified. Concerning items of permanent equipment in the budget, we questioned the inclusion of an analytical balance since this is standard equipment which should be available from other funds. With respect to the "Q" gas counter, it is believed that this particular counter has not proven satisfactory in other laboratories, and the question of the desirability of supplying this or other type of counter is left to the discretion of

MAY 26 1948
Rm-4939

CONTRACTS
Bowman Gray Sch

Encl 9
1111994

the Office of Oak Ridge Operations. It appears that the high speed centrifuge, carbon combustion apparatus and warburg apparatus are necessary. Support is authorized at a level of $11,000.

With reference to the budget of Project III, the inclusion of a direct reading animal balance is questioned, inasmuch as a similar item was included in Project II and may represent an undersirable duplication. Support is authorized at a level of $3,000.

Wake Forest College is one of the participating institutions under the A.E.C. fellowship program, and this work has been supported by the A.E.C. during the past year under a contract administered by the Office of Naval Research.

In the opinion of this office, restricted data is not likely to be used or developed in this investigation. The investigator is expected to publish his scientific results in the appropriate journals.

Progress report at 6 month intervals (3 copies) sent to this office, with informal letter reports at the ~~investi~~gators discretion or when significant results accrue, are desired.

The Medical Branch of the Division of Biology and Medicine will have responsibility for technical supervision of the program and liaison with the Operations Office.

By copy of this memorandum the Budget Branch is requested to allot funds in the amount of $25,000. to the Office of Oak Ridge Operations for the above purpose. Copies of the proposals and pertinent correspondence are enclosed.

Attachments: [illegible]
2 cpys. of Proposal I
2 cpys. of Proposal II
2 cpys. of Proposal III
2 cpys of ltr. from Carpenter to Dir., 5/2/49
2 cpys. of ltr. from Harrell to Dir., 5/2/49
2 cpys. of ltr. from Artom to Bowers, 4/27/49
2 cpys. of "Coordinated Summary of Research Grants and Proposals"

1111995

Coordinated Summary of Research Grants and Proposals

WAKE FOREST COLLEGE
Bowman Gray School of Medicine

(at present designated contract N8onr - 63701)

Principe Investigator		7/1/48 - 6/30/49 Budget Approved		7/1/49 - 6/30/50 Budget Requested	
Artom: (project NR-171 678) Dept. Biochemistry "Phospholipide"	Personnel	$ 3600		$ 4320	
	Equipment	2100		2850	
	Supplies	2100		3400	
	Other	700		1550	
			$ 8500		$12120
Harrell: (project NR-171 677) Dept. Medicine "Na and K"	Personnel	4200		4700	
	Equipment	3350		5225	
	Supplies	1250		2750	
	Other	700		400	
			9500		13075
Isotope Laboratory (project NR-171 678)	Construction	6250		-	
	Equipment	-		-	
			6250		
Training Program (project NR-171 678)	Travel	900		-	
			900		
Artom, Harrell, Cayer (New project) D s. Biochemistry and Medicine	Personnel			1500	
	Equipment			535	
	Supplies			950	
	Other			150	
					3135
TOTAL			25150		28330
Overhead at 8% (none on lab. and training)			1440		2266
			$ 26590		$ 30596

996

Encl 1d

Wake Forest — ATOMIC ENERGY COMMISSION — Harrell — P13,075

PHS-3-6 (Rev. 7-48) — ~~FEDERAL SECURITY AGENCY~~ — Budget Bureau No. 68-R249.1. Expiration date Nov. 30, 1948.

~~PUBLIC HEALTH SERVICE~~

RENEWAL OF

APPLICATION FOR/GRANT FOR RESEARCH PROJECT

(previously designated N8onr-63702, Project NR-171 677)

Director, Division Biology and Medicine
Atomic Energy Commission
~~Fran Sencenge Building,~~
~~U. S. Public Health Service,~~
Washington 25, D. C.

Date April 30, 1949

Application is hereby made for a grant-in-aid in the amount of $ 13075 for the period from 7-1-49 to 6-30-50, inclusive,* for the purpose of conducting a research project on the following subject:

Distribution and turnover of sodium and potassium in acute infections.
(Give only brief statement of nature of project: details on pages 2 and 3)

George T. Harrell, Professor of Medicine and Director of the Department of Internal Medicine.
(Principal investigator) (Title)

Bowman Gray School of Medicine, Winston-Salem 7, North Carolina
(Address of principal investigator)

Harry O. Parker, Comptroller
(Title of financial officer to whom check should be mailed)

Bowman Gray School of Medicine, Winston-Salem 7, N. C.
(Address of this officer)

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant-in-aid may be revoked in whole or in part at any time by the ~~Surgeon General~~ provided that a revocation shall not include any amount obligated previous to the effective date of the revocation if such obligations were made solely for purposes set forth in this application; (3) that all reports of original investigations supported by any grant-in-aid made as a result of this request shall acknowledge such support; and (4) that if any patentable discoveries or inventions are made in the course of the work aided by any grant received as a result of this application, the applicant will, in consideration of such grant, refer to the ~~Surgeon General of the Public Health Service~~ for determination, the question of whether such patentable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

Name of institution Bowman Gray School of Medicine of Wake Forest College

(Type name and title of official authorized to sign for institution) C. C. Carpenter, Dean

Signature of this official C C Carpenter

* This period is not to exceed 1 year.

16-47427-8

Enclosed

1111997

1. Outline the proposed work and the plan of attack. (Use a continuation sheet for details, if necessary.)

See attached Progress Report and Proposal for Renewal

2. Estimated total number of years of project duration five years

3. Has any work been done on this project by principal investigator (named on page 1)? Yes ☒ No ☐
If yes, what are the significant results and publications to date? If possible, please enclose reprints.

16—47487-6 U. S. GOVERNMENT PRINTING OFFICE

Harrell, G. T., Aikawa, J.K., and Kelsey, W.M.: Rocky Mountain Spotted Fever, Am. Pract. 1:425-435 (April) 1947.

Harrell, G.T. and Aikawa, J.K.: The Pathogenesis of Circulatory Failure in Rocky Mountain Spotted Fever. Alterations in the Blood Volume and the Thiocyanate Space at Various Stages of the Disease, Arch. Int. Med. 83:331-347 (March) 1949. (enclosed).

Harrell, G.T. and Yount, E.H.: Plasma Volume and Extravascular Thiocyanate Space in Experimental Serum Sickness in Rabbits, (To be published), (Abstract). (enclosed).

Wolff, Ned. and Harrell, G.T.: Liver and Kidney Function in Rocky Mountain Spotted Fever, (Submitted for publication).

Other reprints have been previously submitted.

1111998

4. What pertinent results bearing on this project have been obtained by other investigators?

P[illegible]emann, F.M., Longcope, W. T. and Peters, J. F.: The Excretion of Chloride and Water and the Renal Function in Serum Disease, Arch. Int. Med. 18:498, 1916.

Hawn, C.V.Z. and Janeway, C.A.: Histological and Serological Sequences in Experimental Hypersensitivity, J. Exper. Med. 86:571, 1947.

Burch, G., Reaser, P. and Cronvich, J.: Rates of Sodium Turnover in Normal Subjects and in Patients with Congestive Heart Failure, J. Lab. & Clin. Med. 32:1169, 1947.

Elkinton, J.R., Winkler, A.W. and Danowski, T.S.L.: Transfers of Cell Sodium and Potassium in Experimental and Clinical Conditions. J. Clin. Invest. 27:74, 1948.

Pressman, D, Hill, R.F., and Foote, F.W.: The Zone of Localization of Anti-Mouse-Kidney Serum as Determined by Radioautographs, Science, 109:65, 1949.

Turner, J. C. and Mulliken, B.: Parasitization of Mouse Sarcoma 180 by Vaccine Virus and its Effect on Tumor Growth, J. Clin. Invest. 26:1198, 1947.

5. (a) What financial support has been received for this or related research by the principal investigator or his associates?

SOURCE	AMOUNT	YEARS OF SUPPORT (From ____ to ____)
John and Mary R. Markle Foundation for	$ 7,000	July 1, 1945 to July 1, 194
trichinella and rickettsial research.	3,500	July 1, 1947 to July 1, 194
N8onr - 63702, project NR-171 677	9,500	July 1, 1948 to June 30, 19
U.S.P.H.S. RG-1334	4,266	July 1, 1948 to July 1, 194

(b) Does the principal investigator have other requests for assistance on this or related research projects pending with governmental agencies, or with public or private foundations? Yes ☒ No ☐

If yes, give significant data, including title of project, name of agency, and amount of requested funds.

Renewal of U.S.P.H.S. RG-1334 for the second of two years. This grant is now numbered H129 (C), $4320, 7-1-49 to 7-1-50.

1111999

BUDGET FOR PROPOSED PROJECT FROM 7-1-49 TO 6-30-50

ITEM	FUNDS REQUESTED FROM THE ~~PUBLIC HEALTH SERVICE~~ Atomic Energy Commission	FUNDS FROM OTHER SOURCES
Personnel (Itemize):		
Chief Investigator (George T. Harrell)		Bowman Gray Sch. of Med
Substitute for teaching, part-time (Dr. E. Yount)	$ 1900	Bowman Gray Sch. of Med
Research Fellow (Dr. Jerry Aikawa)		AEC Fellow
Technician (unselected)	2400	
Electronic engineer, part-time	500	
	4700	
Permanent Equipment (Itemize):		
Shielded sample changer	200	
Scaling circuit	450	
Timer	60	
Geiger tubes	100	
Time recorder	150	
Centrifuge	250	
Balance	230	
Deep Freeze	160	
Metabolism cages	350	
Vacuum pump	75	
Flame Photometer	2000	
Chemical Hood	1200	
	5225	
Consumable Supplies (Itemize):		
Glassware	750	
Chemicals	500	
Animals	1500	
	2750	
Travel:		
Travel	200	
Other Expense (Itemize):		
Contingency fund	200	
TOTAL	13075	

112000

PROGRESS REPORT AND PROPOSAL FOR RENEWAL

Distribution and Turnover of Sodium and Potassium in Acute Infections
(Contract N8onr-63702, Project NR-171 677)

George T. Harrell, Wake Forest College
Bowman Gray School of Medicine, Winston-Salem, N. C.

1. Scope and Present Status

It has been known for many years that patients recovering from acute infections have a diuresis during recovery. It has also been known for some time that patients with serum sickness during the recovery stage will have a diuresis in which water and chloride are lost. Observation of cases of Rocky Mountain spotted fever have shown that edema develops during the acute phase of the disease. Measurements of the extent of edema have been made utilizing the thiocyanate technique. Generalized edema is also seen in patients with trichinosis, an interstitial infection, as well as in the intracellular infection with rickettsias of spotted fever, and the pure antigen-antibody system without infection of serum disease. It is known that the blood chlorides will drop during the acute phase of pneumonia and of Rocky Mountain spotted fever. No studies are available on the distribution of fluid or changes in electrolytes in trichinosis; in the rare cases in which they have been done, the serum proteins have been reported to drop. In Rocky Mountain spotted fever serum proteins are known to drop during the acute phase of the disease. It appears then that water and chlorides, and perhaps protein molecules, leave the blood stream at a greater rate in some cases of infectious diseases than in normal individuals. Extravasation of proteins or ions into interstitial tissues would tend to retain fluid outside the blood vessels. The retention of water outside the vascular tree by sodium ions is now recognized as a factor in the production of edema in heart failure.

The process in infections can be visualized as a graded series of pores, as in a seive, so that in instances of mild disease only crystalloids leave the blood stream. In more severe instances the pores are larger and protein molecules, such as albumin, will leave the blood stream; in most severe cases even red cells will be lost. It is not known whether the fluid which leaves the blood stream in infections and which is measured as an increase in thiocyanate space is found between cells or within them.

In the proposal made last year, we planned to induce serum sickness in rabbits; when the edema developed, radio-sodium and thiocyanate would be given. The level of the two ions in plasma, urine, and interstitial fluid would be determined - total sodium by the flame photometer, radiosodium by isotope techniques and thiocyanates by a colorimetric procedure; the values would then be correlated. A similar experiment would be done substituting radio potassium for radiosodium. It was then proposed that similar experiments be repeated using an interstitial infection - trichinosis - and an intracellular infection - rickettsiosis. Since the radiations of sodium are somewhat dangerous, we did not feel it advisable to begin any experiments until protection of personnel could be assured by construction of the isotope laboratory.

Because the negotiations on the contract and the construction of the laboratory have delayed the application of radio isotope techniques to our studies, we have this year extended our previous studies on serum sickness with additional groups of animals, utilizing whole human plasma as well as purified albumin and globulin fractions. We have borrowed the use of a flame photometer to familarize personnel with the technique; an unexpected administrative obstacle was encountered in the purchase of an instrument. We have not, up to the present, been able to arrange for the use of the flame photometer for determination of levels in material containing radioactive isotopes, because of the danger of contamination of the instrument and of the room where the instrument

1112001

is being housed and used by another department for other studies.

In order to utilize personnel trained last summer, some preliminary experiments were conducted with the Department of Biochemistry on the toxicity of radio phosphorus. Clinical observations of patients with acute liver disease, given radiophosphorus as a tracer in studies of phospholipide turnover, suggested the possibility that the addition of a small amount of a harmful factor - radiation - to cells already damaged by the underlying liver disease of both toxic and dietary nature might have been sufficient to induce considerable further liver damage. Since the problem posed fundamental questions on the biologic effects of radiation in tissue, preliminary experiments were conducted in animals in conjunction with Dr. Artom; these are discussed in the enclosed abstract. Continuation of the experiments seems justified and a proposal for continuation is separately enclosed.

Dr. Camillo Artom has kindly made available the facilities and equipment in his laboratory in the Biochemistry Department in the basement for use by one of the AEC Fellows who is interested in problems concerning radioactive phosphorus. This man will continue to use Dr. Artom's facilities in his study on enzyme systems concerned in antibiotic chemotherapy until the new school isotope laboratory can be completed on the fifth floor.

2. Scientific Motivation

If the mechanism by which increased amounts of electrolytes are passed across capillary and cell membranes can be established, it may be possible to devise measures to correct the physiologic abnormality. In infectious diseases the harmful effects of excessive hydration might be combatted. If the mechanism is established, it may be possible eventually to apply the technique in reverse to therapy of human disease. An increase in permeability might be induced so that radioisotopes could be encouraged to enter tissue and there exert their radiation effect. Some evidence has accumulated from our experiments outlined above that an antigen-antibody reaction may be responsible for the increase in permeability of membranes. Evidence has been presented that certain types of malignancies in animals are caused by filterable viruses; other evidence indicates that certain types of malignant tissue can concentrate viruses such as vaccinia which have been well studied. If an immune serum could be made against either virus, and the virus be introduced into an animal with cancer, a local antigen-antibody reaction might be induced; a radioisotope introduced when the reaction was at its maximum would be concentrated in cancerous tissue since the antigen-antibody reaction would take place in or on cancer cells. If it becomes possible through the application of the autoantibody technique to develop an antiserum against cancerous tissue, the same principle would hold and the antigen-antibody reaction would take place only on malignant cells. We are attempting to determine whether the ions which leave the blood stream in antigen-antibody reactions go between or within cells and in studying the mechanism by which the transfer is effected. We will attempt to make direct measurements on the distribution of ions, as well as to calculate the site of action by indirect evidence. Confirmatory experiments utilizing the radioautograph technique will be done for comparison with stained histologic sections. The radioautographs will probably have to be done on frozen sections of unfixed tissue; no recognized technique meeting these requirements is known at present.

3. Materials, Equipment and Facilities

The grant was to have begun July 1, 1948. Negotiations on the contract were not begun by the Navy until October 7 and the contract was not made effective until

1112002

December. The College was unwilling to begin construction of the laboratory until the contract was made effective and reimbursement was assured. Permission of the College authorities was finally obtained to enclose a portion of the roof on the east end of the medical school building, adjacent to the fifth floor animal quarters, and permission of ONR was granted to utilize funds in the AEC grant for this purpose. Plans were drawn according to the enclosed blueprint and a contract was let. The partitions, ceiling, plumbing, and heating are now being installed and the contractor expects to turn the laboratory over to us by June 15. A radioactive fume hood of the design recently approved at Oak Ridge is promised for delivery about June 15; the installation of the fume hood and of a stainless steel sink will be made out of funds earmarked for equipment on our grant this year. Photographs of the completed laboratory can be forwarded about July 1 for your records. We have ordered Geiger tubes, scaler, sample holder, monitoring equipment, balance, centrifuge, refrigerator and so forth from our research funds this year to equip the school isotope laboratory. Funds are insufficient this year and we are not requesting in our renewal budget funds for chemical benches or other fixed equipment. We are requesting only such specific equipment as is necessary for our experiments. For the reasons outlined above we need a flame photometer and an ordinary chemical hood in which to operate it. We do not believe a radioactive hood would be necessary for these experiments, because of the short half life of sodium and potassium hence contamination should not be a problem.

4. Scientific Personnel

The principle investigator, Dr. George T. Harrell, is already known to the Commission through the original application. Dr. Ernest H. Yount will be employed part time on the project; it has been feasible to release him from a portion of his teaching duties to participate in these experiments. Dr. Yount's curriculum vitae is enclosed. Dr. Jerry K. Aikawa and Dr. Kingsley Stevens are already known to the Commission; both hold AEC fellowships administered through the National Research Council. Aikawa will be utilized full time on this project; Dr. Stevens will continue his enzyme studies until he transfers to Chicago in the fall. We are losing through marriage our technician who has been partially trained in isotope technique; a new technician is being sought and will have to be trained. It will be possible to hire on an hourly part time basis the electronic engineers from the Western Electric Radio Shops located in the city for maintenance of equipment.

5. Proposed Budget

The exact figures and the detailed breakdown by categories of the proposed budget are found on the enclosed sheet. The amount requested for salary of a technician and to release Dr. Yount from teaching duties are the same as last year; the item for part time electronic engineering help for maintenance of equipment is new since equipment has not yet been installed; this year such services were not necessary. The current equipment budget has been extended for purchase of isotope equipment to provide the minimum necessary for conducting experiments; the major item was the radioactive fume hood which will cost $2125 plus installation. As discussed above it will be necessary to purchase a flame photometer and a fume hood in which to operate it - items which make up the major part of the equipment category this year. The increase in consumable supplies is due almost entirely to the great increase in the cost of animals purchased locally which has occurred in the past year. Some increase is due to the high cost of gas and oxygen for satisfactory operation of the flame photometer. The other items have been reduced. The College will furnish heat, light, water, janitor service, up keep of the building, as well as the salary of the principle investigator and the major portion of the salary for Dr. Yount.

1112003

6. Other Responsibilities

The principle investigator is obligated with Dr. Ernest Yount for continuation of U.S.P.H.S. grant H129-C for the amount of $4320; this is the second year on a two-year grant. The principle investigator is obligated to U.S.P.H.S. grant 643 (C-2) in the amount of $5929 for continuation of antibiotic research as co-investigator with Dr. Manson Meads of this department. The principle investigator is concluding through a close-out grant of the Markle Foundation in the amount of $3500 studies on trichinosis and alteration of body function in rickettsial diseases which has been previously supported by them over a periods of years.

7. Administrative Information

A copy of the latest catalog of the Bowman Gray School of Medicine is enclosed. Other information is found on the first page of the enclosed application.

Respectfully submitted,

George T. Harrell, M.D.
Professor of Medicine and
Director of the Department

GTH:mfc

1112004

TOXICITY OF RADIOACTIVE PHOSPHORUS IN MICE ON VARIOUS DIETS

By W. E. Cornatzer, David Cayer, George T. Harrell, Jr. and Camillo Artom. (From the Departments of Biochemistry and Medicine, Bowman Gray School of Medicine, Winston-Salem, North Carolina).

The present investigation is a part of a more extended study undertaken with the idea that the resistance of the organism to the toxic effects of radioactive isotopes introduced into the body may be decreased by alterations in the functional capacity of the liver. This point would, of course, be of practical interest for the use of radioactive isotopes as diagnostic and therapeutic agents in patients with liver diseases since in these individuals even small doses of radioactivity could exert an additive harmful action.

To our knowledge, the only data on the toxicity of P^{32} are those of Anthony and Snyder (Atomic Energy Commission, Document MDDC-881). On the basis of a few experiments on mice (presumably maintained on a stock diet), these authors suggest that the LD_{50} after one injection of P^{32} is around 4 microcuries per gram of body weight. With this dose 4 out of 6 mice died between 16 to 21 days.

In the present experiments we have studied the mortality and survival time of mice, maintained on diets of known composition and injected with radioactive phosphorus as sodium diphosphate. We have investigated the possible role of a deficiency of lipotropic factors in the diets, such a deficiency leading to a fatty infiltration of the liver. If in this condition the toxicity of the isotope were increased, supplementation of the diet with choline should give a more or less marked protection.

Several groups of mice (approximately 20 gm. body weight) were transferred from a stock diet to a low protein, high fat diet (Diet 31, containing casein 10 parts, Crisco 30, cod liver oil 2, sucrose 29, dextrin 23, roughage, salts and B vitamins). The animals were maintained for five days on the diets, then they were injected with a single dose of radioactive phosphorus and kept under observation for three weeks. To date, a total of 120 mice have been used.

There were no deaths among mice not injected with radioactive P and maintained for 25 days on the unsupplemented diet. Of the animals injected with 2 microcuries per gram of body weight and maintained on either the unsupplemented or supplemented diet none died in 21 days. With 4 microcuries per gram of body weight the mortality at the twenty-first day was 16% and the average survival time was 20 days for both the controls on the unsupplemented diet and the mice of the choline supplemented diet. With 6 microcuries per gram of body weight the mortality has been 72% and 86% and the average survival time 16 and 12 days, respectively. With 8 microcuries per gram of body weight the mortality was 89 and 89 per cent and the average survival time 12 and 13 days respectively.

In another group of rats injected with 6 microcuries per gram of body weight the level of the fat in the diet was decreased from 32 to 5 per cent (Diet 34). There was a slight decrease in mortality but no change in the survival time after injecting 6 microcuries per gram. Likewise, no significant

1112005

protection was observed when the protein content of the low fat, low protein diet was increased from 10 to 25% (Deit 29).

This work was supported by the U. S. Atomic Energy Commission under a contract between the Bowman Gray School of Medicine and the Office of Naval Research, U.S. Navy Department. The P^{32} used was supplied by the National Laboratory, Oak Ridge, Tennessee, on allocation from the U. S. Atomic Energy Commission.

1112006

ABSTRACT

Plasma Volume and Extravascular Thiocyanate Space in Experimental Serum Sickness in Rabbits. George T. Harrell and (by invitation) Ernest H. Yount, Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

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Patients with Rocky Mountain spotted fever develop clinical edema during the acute phase of the disease. Frequently the plasma volume is reduced transiently and peripheral circulatory failure may ensue. The maximum changes usually occur just before the temperature begins to fall. The time relationships suggest the possibility that an antigen-antibody reaction may explain the pathogenesis of the alteration in capillary permeability. To test this thesis 12 rabbits were injected intravenously with 8 cc. per kilogram of human plasma. The plasma volume was measured by the Evans blue technique and the thiocyanate space simultaneously determined by the loss of thiocyanate from the plasma. Three baseline determinations were done before injection; three additional determinations were done on successive days, beginning with the appearance of precipitins for human plasma in the rabbit's blood, usually on the seventh or eighth day after injection. A final determination was done one week later. A significant rise in the thiocyanate space was observed and was accompanied by clinical manifestations of serum sickness - edema, fever, listlessness. The drop in the plasma volume was small, but was statistically significant for the group. The changes reverted to normal in convalescence. Similar results were obtained in a second group after the injection of purified human serum albumin.

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PATHOGENESIS OF CIRCULATORY FAILURE IN ROCKY MOUNTAIN SPOTTED FEVER

Alterations in the Blood Volume and the Thiocyanate Space at Various Stages of the Disease

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PERIPHERAL circulatory failure is an important complication of Rocky Mountain spotted fever. Previous studies have shown that the collapse occurs usually in the second week of rash and that the disturbance can be alleviated by the administration of preformed protein.[1] The mechanism responsible for the circulatory changes is obscure, but the peripheral collapse is accompanied with a drop in serum proteins and with the development of visible generalized edema.[2] The resemblance of the clinical picture to "shock" suggests that a drop in the circulating blood volume occurs.

The present studies were undertaken to determine whether the blood volume is altered, to observe the time at which the changes develop and to correlate the magnitude of the alterations with the clinical picture and other pertinent laboratory data. Determinations of the plasma volume and the thiocyanate space were done serially in a group of patients with rickettsial spotted fever, and the effects of supportive and specific therapy on the altered distribution of the fluid were observed.

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Presented before the American Society for Clinical Investigation, Atlantic City, May 5, 1947.

From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital.

1. Harrell, G. T.: Wolff, W. A.: Venning, W. L., and Reinhart, J. B.: The Prevention and Control of Disturbances of Protein Metabolism in Rocky Mountain Spotted Fever, South. M. J. **39**:551-558 (July) 1946.

2. Harrell, G. T.: Venning, W. L., and Wolff, W. A.: The Treatment of Rocky Mountain Spotted Fever, with Particular Reference to Intravenous Fluids: A New Approach to Basic Supportive Therapy, J.A.M.A. **126**:929-934 (Dec. 9) 1944.

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CLINICAL STUDY

Material.—The 13 cases presented were studied between June and October 1946. Seven of the patients were adults, and 6 were children; most of them were in the North Carolina Baptist Hospital, but several were in hospitals in nearby towns.[3] Additional patients have been similarly studied, but these 13 cases have been selected for presentation because each one illustrates some principle we wish to bring out.

The diagnosis of Rocky Mountain spotted fever was made on the basis of the history and the physical signs and was later confirmed by serologic tests. The cases are classified roughly according to the clinical severity of the disease and are further subdivided according to the type of treatment received. Seven patients received supportive therapy only, and 6 received, in addition, specific therapy. The distribution of cases according to clinical severity was approximately the same in the two groups.

CLASSIFICATION OF CASES

Therapy	Clinical Severity* Mild	Moderate	Severe	Fatal	Total Cases
Supportive only*	2	4, 7	1, 8	3, 12	7
Specific and supportive*	5, 6	11	9, 10	13	6
Total cases	3	3	4	3	13

*The figures indicate the case number in the text.

Cases were classified as mild if the result of the tourniquet test was negative throughout the illness, if edema was minimal or absent and if the pulse and blood pressure remained stable. Moderate cases were those in which the patients exhibited a positive reaction to the tourniquet test, slight clinical edema, tachycardia and toxic symptoms. The disease was considered severe if severe purpura, moderate to pronounced clinical edema, delirium and other signs of severe infection were present. Cases were classified as fatal whether death resulted directly from the infection itself, from a complication or as a result of unwisely selected therapy.

Method.—Studies were done serially in each case. The initial studies were done as soon as possible after the patient's admission to the hospital regardless of the duration of the infection; they were repeated at the clinical peak of the disease and during convalescence in the hospital. Whenever feasible, additional studies were done during the acute phase and after complete recovery from the disease.

3. The Pediatrics Service of the North Carolina Baptist Hospital and Physicians in the Sternberger Hospital, Greensboro, and in the Rowan Memorial Hospital, Salisbury, assisted in the clinical management of some of the patients.

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The plasma volume was determined by the T-1824 dye (Evans blue) method as modified for the Evelyn photoelectric microcolorimeter.[4] Two cubic centimeters of a solution containing 3 mg. of the dye per cubic centimeter was injected, and at least three samples were taken at ten minute intervals on each patient; the first was obtained ten minutes after the injection of the solution. The standard value for each adult, indicated by the normal base line in the graphs, was calculated as 5 per cent of the body weight immediately prior to the onset of the illness. If the weight was unknown, the expected weight was calculated from height and age.[5] In children the plasma volume was calculated at 6 to 7 per cent of the body weight prior to the onset of illness, depending on the age.

The hematocrit value was determined on venous blood collected without stasis in bottles containing potassium and ammonium oxalate; the tubes were centrifuged for thirty minutes at 3,000 revolutions per minute. The standard hematocrit value was considered as 38 volumes per cent in females and 40 volumes per cent in males, regardless of age. The total blood volume was calculated from the hematocrit reading and the plasma volume. The total circulating red cell volume was calculated from the plasma and total blood volumes.

Determinations of the thiocyanate space were performed simultaneously with those of the plasma volume.[4] Eight cubic centimeters of a solution containing 50 mg. of sodium thiocyanate per cubic centimeter was injected with the dye; at least three blood samples were obtained at ten minute intervals. The standard thiocyanate fluid space was calculated as 20 per cent of the standard body weight in adults and as 25 to 30 per cent of the body weight in children, depending on the age of the patient. The scale on the graph was adjusted so that the standard falls opposite the horizontal base line.

In our hands, the values obtained from duplicate determinations of the plasma volume and the thiocyanate space on these patients and serial determinations on normal persons have not varied more than 10 per cent; therefore, only values which deviated more than 10 per cent from the standard base line for the patient were considered significant in the interpretation of data.

Chemical examinations of the blood were done by standard methods. The total serum protein contents were determined by the Kjeldahl, falling drop and copper sulfate specific gravity methods; usually at least two methods were employed each time as a check. The carbon dioxide—combining power and the blood levels of nonprotein nitrogen, chloride and para-aminobenzoic acid are not included in the data, although determinations of these were made in each case. The results of hematologic studies, which were done with certified pipets and counting chambers, are likewise omitted; the hemoglobin content was determined with the photoelectric colorimeter by the alkaline hematin method.

Results.—Because of the considerable variations in the severity of the disease, it is extremely difficult, if not impossible, to summarize the data. For that reason, brief case summaries are presented to illustrate the

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4. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determination of Plasma Volume with T-1824, and "Available Fluid" Volume with Sodium Thiocyanate, Am. J. Physiol. **125**:142-152 (Jan.) 1939. Gibson, J. G., and Evelyn, K. A.: Clinical Studies of the Blood Volume: IV. Adaptation of the Method to the Photoelectric Microcolorimeter, J. Clin. Investigation **17**:153-158 (March) 1938.

5. Duncan, G. G.: Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment, Philadelphia, W. B. Saunders Company, 1942, p. 935.

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principles involved. The supportive therapy administered was based on the principles outlined in previous publications.[6] Specific therapy consisted of administration of para-aminobenzoic acid (PABA) or hyperimmune rabbit antiserum.[7] The latter was administered intramuscularly or intravenously in doses of 1 cc. per kilogram of body weight daily for a maximum of three days.[1] No serum was administered if the initial dose could not be given by the third day of rash. Para-aminobenzoic acid was administered by mouth or stomach tube on a two hour schedule day and night; the individual dose ranged from 0.5 to 2 Gm. per kilogram of body weight.

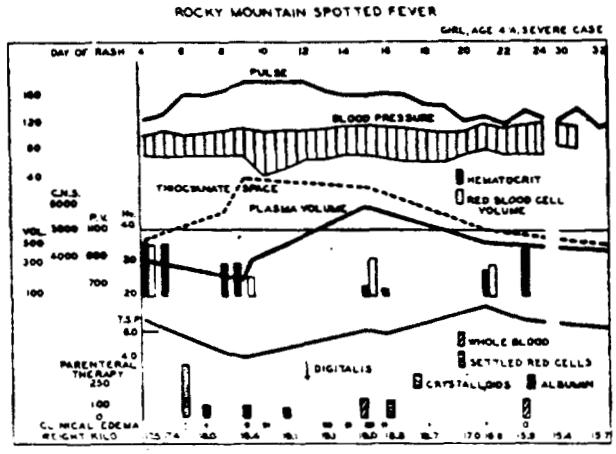

Fig. 1.—Severe Rocky Mountain spotted fever in a girl aged 4½.

SUMMARY OF CASES

CASE 1.—*Supportive therapy; typical severe case* (*fig.* 1).

Note the gradual rise in pulse rate and increase in thiocyanate space accompanied with a fall in diastolic blood pressure and in plasma volume and total serum protein content. After the administration of serum albumin, the plasma volume rose 6 cc. for every gram of albumin injected. With the increase in plasma volume and the return of capillary integrity, central (myocardial) circulatory failure, requiring the administration of digitalis, developed.

CASE 2.—*Supportive therapy; typical mild case* (*fig.* 2).

Note that the rise in pulse rate, drop in diastolic blood pressure and increase in thiocyanate space were minimal. The plasma volume rose with the development of immunity. The total serum protein content was never low, and no edema was

6. Harrell, G. T.; Wolff, W. A., and Venning, W.: A New Approach to Basic Supportive Therapy in Rocky Mountain Spotted Fever, South. M. J. 38: 367-371 (June 1945. Harrell, Wolff, Venning and Reinhart.[1] Harrell, Venning and Wolff.[2]

7. The hyperimmune rabbit antiserum was furnished by Lederle Laboratories, Pearl River, N. Y.

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present. The changes are qualitatively the same as those in more severe cases but quantitatively much less marked.

CASE 3.—*Supportive therapy; fatal case; patient overloaded with crystalloids* (*fig.* 3).

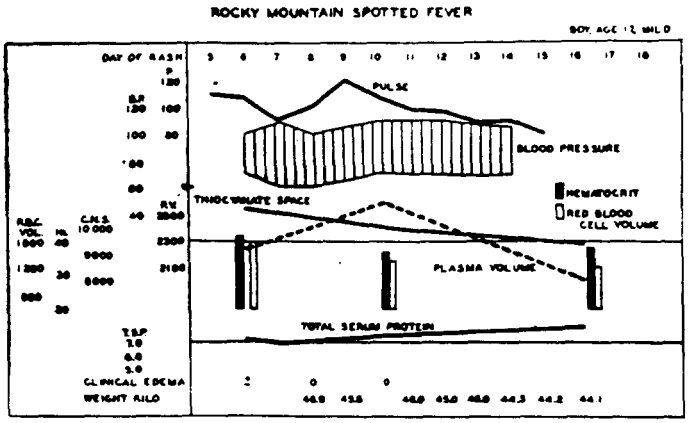

Fig. 2.—Mild Rocky Mountain spotted fever in a boy aged 17.

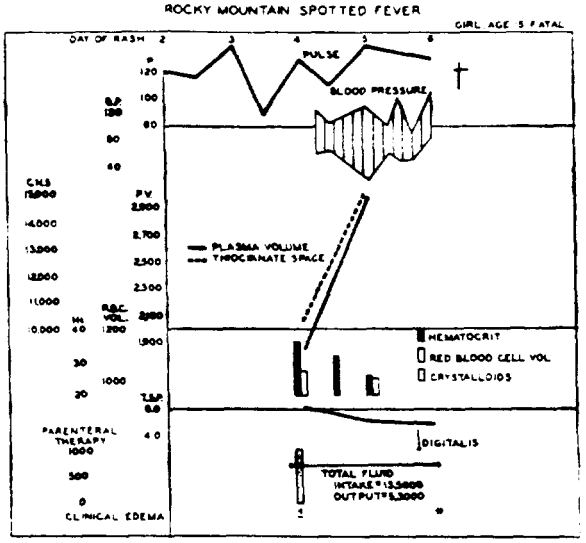

Fig. 3.—Fatal case involving a girl aged 15.

On the patient's admission to the hospital, the condition was classified as mild or moderately severe. The pulse rate was increased, but no change in blood pressure, plasma volume, thiocyanate space or serum proteins was found. Excessive amounts of crystalloids were administered orally to overcome dehydration. The pulse rate showed little change, but the diastolic blood pressure dropped, the plasma volume and the thiocyanate space increased markedly and the serum pro-

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tein content fell slightly. The clinical picture of rapidly developing medullary edema with respiratory arrest resembled bulbar poliomyelitis; peripheral edema rapidly increased, and the patient died.

CASE 4.—*Supportive therapy; moderately severe case; unnecessary use of preformed protein (fig. 4).*

On admission to the hospital, the patient had a low serum protein content and edema, with a lowered diastolic blood pressure, but was not in shock. The plasma

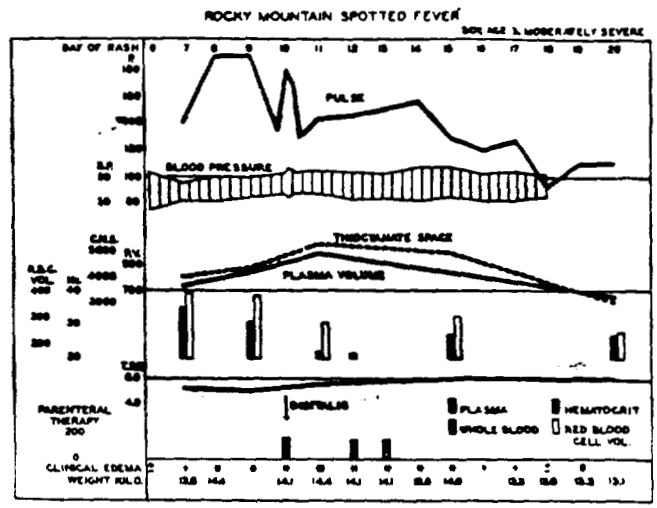

Fig. 4.—Moderately severe case involving a boy aged 3.

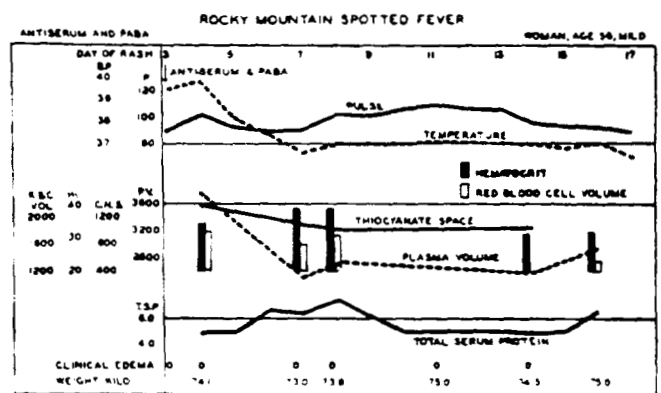

Fig. 5.—Effect of administration of antiserum and para-aminobenzoic acid in a woman, aged 56, with a mild form of the disease.

volume was not lowered, but the thiocyanate space was increased. The plasma volume was increasing as recovery began, and the pulse was dropping when plasma was administered. Gallop rhythm with central (myocardial) circulatory failure was precipitated. With rapid digitalization and a decrease in fluid intake, the abnormality was corrected.

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CASE 5.—*Specific therapy with antiserum and para-aminobenzoic acid; mild case (fig. 5).*

The administration of both antiserum and para-aminobenzoic acid early in the course of the patient's mild illness did not prevent a drop in plasma volume. There was no increase in thiocyanate space, and edema did not develop. It was felt that the mildness of the infection was a greater factor in the prevention of edema, maintenance of serum proteins and failure of the thiocyanate space to increase than was the specific therapy.

CASE 6.—*Specific therapy with para-aminobenzoic acid; mild case (fig. 6).*

The patient presented an increased pulse rate, a lowered blood pressure, a lowered serum protein content and a slight increase in the thiocyanate space but no change in the plasma volume. The course was mild, and clinically he appeared

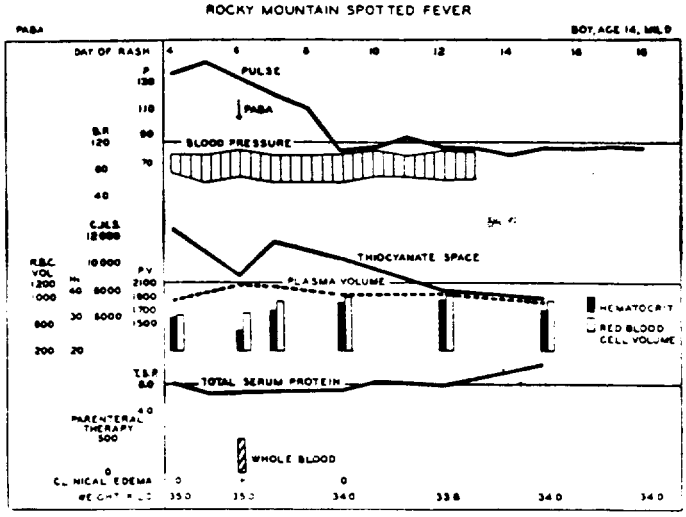

Fig. 6.—Effect of administration of para-aminobenzoic acid in a boy, aged 14, with a mild form of the disease.

to be recovering when specific therapy with para-aminobenzoic acid was initiated on the sixth day of rash. It was felt that the course of the mild infection was unaltered by the late administration of the drug.

CASE 7.—*Supportive therapy; mild case complicated by encephalitis (fig. 7).*

There was no change in plasma volume, thiocyanate space or serum protein content on the patient's admission to the hospital, though the pulse rate was increased and the blood pressure low. Because of encephalitis and coma, he was maintained on an inadequate oral protein intake (1 Gm. per kilogram of body weight daily), and an attempt was made to substitute protein hydrolysate by intravenous administration as a source of protein-building materials. Fifty grams of protein hydrolysate (1 Gm. per kilogram) was given daily. The failure of this therapy is shown by the fact that the thiocyanate space increased later than usual in the course of the disease, after capillary integrity had begun to be restored (as is illustrated by the increase in plasma volume). Gavage feedings were then begun (4 Gm. of protein per kilogram daily). The greater efficacy of preformed proteins in the form of whole blood, as compared with protein hydrol-

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yate, in raising the total serum protein content and decreasing edema is illustrated in the graph. Dehydration developed when parenteral therapy was discontinued, as is shown by the drop in thiocyanate space in the fourth week of rash.

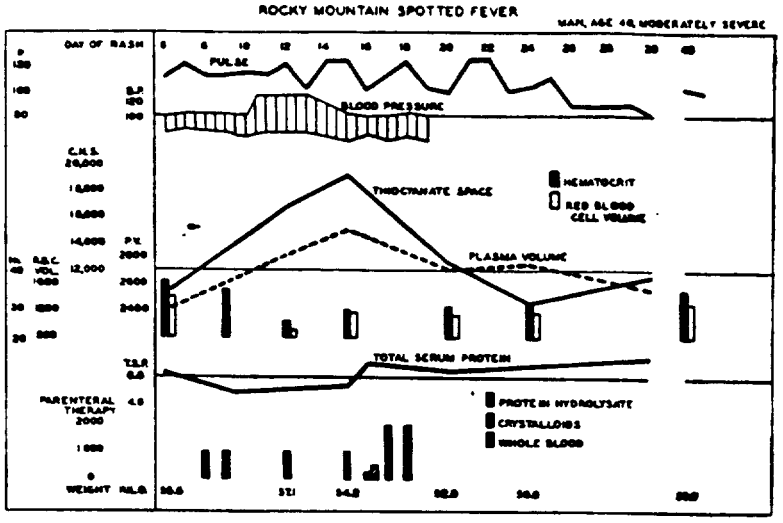

Fig. 7.—Moderately severe Rocky Mountain spotted fever in a man aged 40.

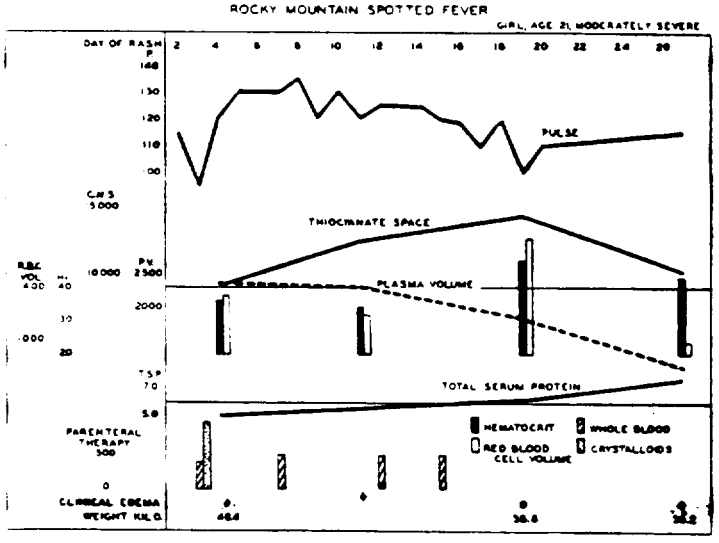

Fig. 8.—Moderately severe Rocky Mountain spotted fever in a woman aged 21.

CASE 8.—*Supportive therapy; moderately severe case in which there was an inadequate protein intake* (*fig.* 8).

Early in the course of the patient's illness there was no change in the thiocyanate space or the plasma volume, though the pulse rate was increased and

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the serum proteins were low. The patient ate little and did not tolerate a gavage tube. The inadequacy of the usual quantity of preformed proteins as the sole source of protein intake is illustrated by the late increase in the thiocyanate space and the drop in plasma volume after capillary integrity should have been restored. The rise in serum protein content and in the hematocrit value toward the end of the hospital stay indicates the necessity for repeated transfusions in such instances. Asthenia was present to a notable degree throughout the entire course of the disease and continued for weeks into convalescence.

CASE 9.—*Specific therapy; severe disease treated with antiserum and para-aminobenzoic acid (fig. 9).*[8]

The patient was severely ill on admission to the hospital. The pulse rate was increased, the blood pressure low and the thiocyanate space increased; the plasma volume and the serum protein content were not altered. With hydration, the thio-

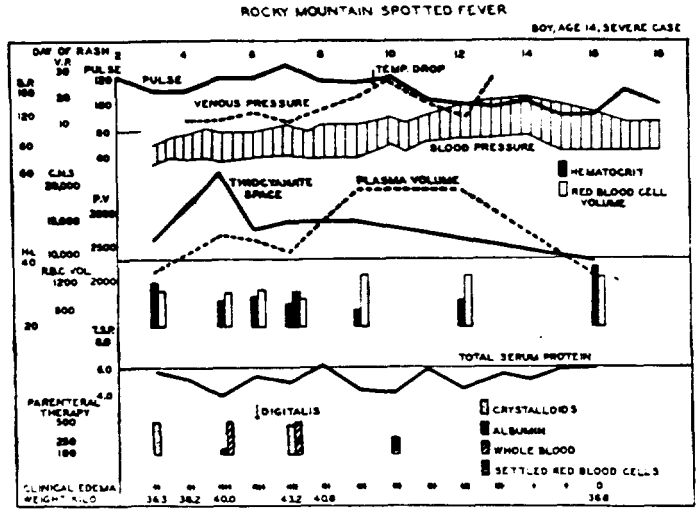

Fig. 9.—Severe case involving a boy aged 14.

cyanate space increased and the serum protein content dropped simultaneously with the development of notable clinical edema. The administration of antiserum from the third to the sixth day of rash caused little improvement. Administration of para-aminobenzoic acid was then started; the peak blood levels were attained between the ninth and eleventh days of rash, when clinical recovery usually begins. With the rise in plasma volume, central circulatory failure developed and was controlled with digitalis. As convalescense progressed, the blood pressure rose, the pulse rate dropped and the plasma volume, thiocyanate space and serum protein content returned to normal. A high oral protein intake (approximately 5 Gm. per kilogram of body weight daily) was maintained. Anti-histaminic drugs were administered but not until the twenty-second day of the rash, after the circulatory

8. This case is reported in greater detail in the American Practitioner 1:425-435 (April) 1947. Photographs of the patient and colored diagrams illustrating the mechanism by which circulatory failure can be precipitated through unwisely chosen parenteral therapy are included.

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changes had reverted to normal. The necessity for meticulous attention to every minor detail of supportive therapy is well illustrated; it was the unanimous opinion of all the physicians up until the tenth day of rash that the patient would die.

CASE 10.—*Specific therapy; patient with severe disease treated with para-aminobenzoic acid (fig. 10).*[9]

The patient was severely ill when first seen by us. The blood pressure was lowered, the thiocyanate space increased and the serum protein content low although the plasma volume was normal. In spite of vigorous supportive therapy and massive doses of para-aminobenzoic acid, circulatory collapse developed; it was corrected by the administration of albumin. With the return of capillary integrity, the thiocyanate space decreased and the plasma volume and serum protein content rose; central circulatory failure developed and was controlled by digitalis. The failure of para-aminobenzoic acid to maintain capillary integrity in severe as well as in mild cases is illustrated.

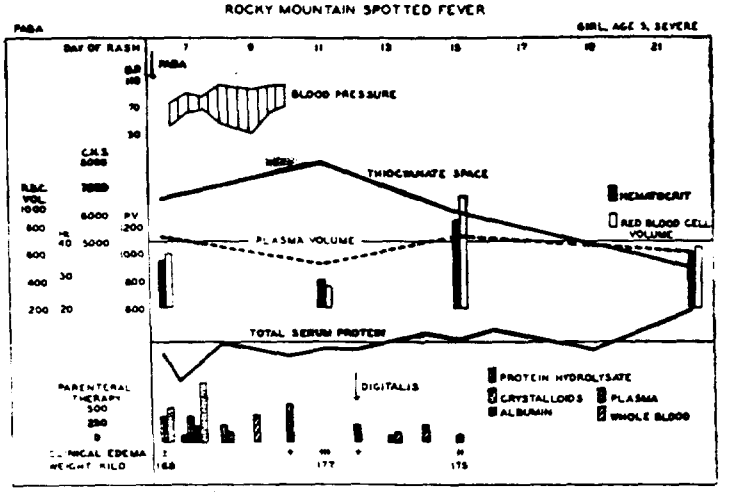

Fig. 10—Effect of administration of para-aminobenzoic acid in a girl, aged 5, with a severe form of the disease.

CASE 11.—*Specific therapy; patient with moderately severe disease treated with antiserum; the reproduction of the physiologic changes of spotted fever during serum sickness (fig. 11).*

The patient showed signs of dehydration and toxemia on admission to the hospital. The administration of antiserum decreased the toxic symptoms but did not prevent the alterations in capillary permeability. The thiocyanate space increased, the plasma volume and the serum protein content dropped and edema developed. With the restoration of capillary integrity during clinical recovery (manifested by the drop in temperature and the decrease in toxic symptoms), the edema disappeared and the thiocyanate space decreased but the plasma volume

9. This case was reported in greater detail in regard to the effect of para-aminobenzoic acid by S. F. Ravenel (Para-Aminobenzoic Acid Therapy of Rocky Mountain Spotted Fever: Outline of Comprehensive Plans of Treatment with Report of Five Cases, [case 5], J.A.M.A. 133:989 [April 5] 1947).

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remained low. When serum sickness developed, edema returned and the thiocyanate space increased markedly but the plasma volume and serum protein content showed little change. Benadryl(R) (beta dimethylaminoethyl benzhydryl ether hydrochloride) was given. After recovery from serum sickness and the disappearance of edema, the thiocyanate space, plasma volume and serum protein content all decreased.

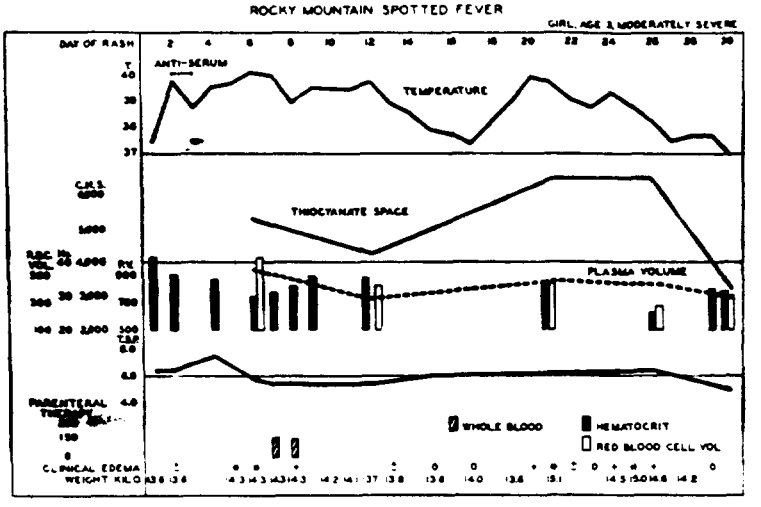

Fig. 11.—Moderately severe Rocky Mountain spotted fever in a girl aged 3

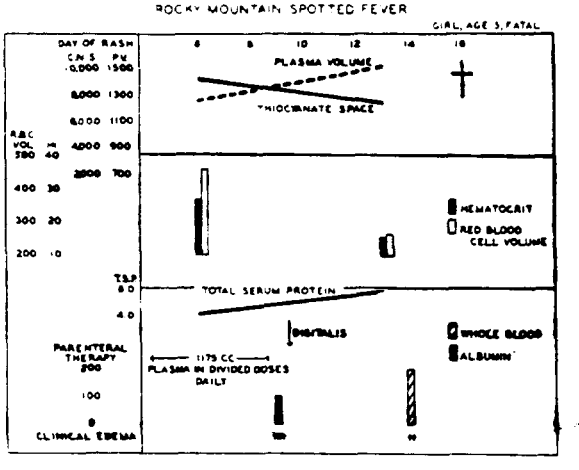

Fig. 12.—Fatal case involving a girl aged 5.

CASE 12.—*Specific therapy with para-aminobenzoic acid; fatal case complicated by pneumonia and myocardial failure* (*fig.* 12).

The patient was severely ill from the beginning. The oral protein intake was low, and an attempt was made to compensate for this deficiency by multiple in-

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fusions of plasma. The thiocyanate space remained high and the serum protein content low, though the plasma volume was maintained in spite of considerable edema. The administration of serum albumin precipitated myocardial failure, which was only partially controlled with digitalis. Lobar pneumonia developed and did not respond to penicillin therapy. Terminally pulmonary edema was present as well. The administration of para-aminobenzoic acid did not prevent the alteration of capillary permeability to crystalloids.

CASE 13.—*Specific therapy with antiserum and para-aminobenzoic acid; fatal case complicated by massive intestinal hemorrhage* (*fig.* 13).

The patient was moderately ill on admission to the hospital. The pulse rate was not increased, and the plasma volume was normal; the thiocyanate space was increased, though no clinical edema was present. Antiserum was administered, but it did not change the character or decrease the rate of spread of the rash. The rise

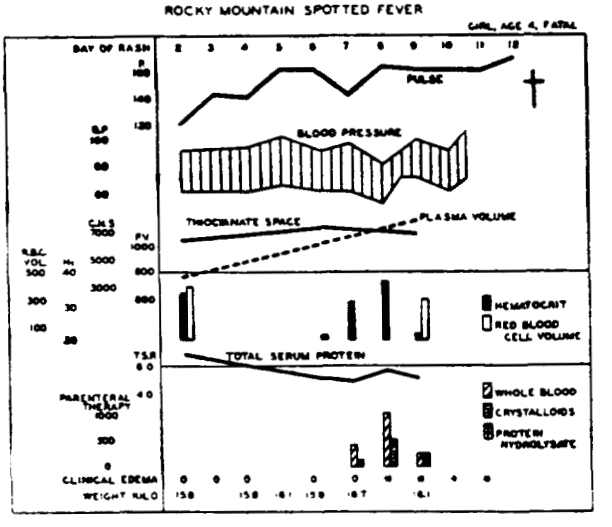

Fig. 13.—Fatal case involving a girl aged 4.

in pulse rate and the drop in blood pressure were due to bleeding from the bowel. At first the plasma volume was unaltered, but in the seventh day of rash the patient was in shock: almost the entire circulating blood volume was replaced intravenously in less than twelve hours, and the blood pressure and the serum protein content rose. Para-aminobenzoic acid was administered late in the course, without producing any alteration in the clinical picture. Clinical edema developed, although there was no decided change in the thiocyanate space. At autopsy, lesions of the small blood vessels resembling periarteritis nodosa were seen in many organs.

From these data several generalizations can be made. Early in the course of the disease, dehydration and lowering of the blood chloride content are common; the dehydration is accompanied with little change in the plasma volume and thiocyanate space unless crystalloids are administered in large quantities. Capillary permeability to crystalloids, protein and red blood cells is altered progressively as the disease increases

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in severity. The alteration is greatest near the clinical peak of the disease, between the tenth and fourteenth days of rash; at this time there is a tendency for the plasma volume and the serum protein content to drop, the thiocyanate space to increase and clinical edema to develop. These alterations can be accelerated by the excessive administration of crystalloids alone. The alteration in capillary permeability is corrected with clinical recovery, which is evidenced by a drop in temperature and a decrease in toxic symptoms.

Under the conditions of these experiments the administration of hyperimmune rabbit antiserum and para-aminobenzoic acid (PABA) did not prevent the alteration in capillary permeability to crystalloids. The data suggest that some decrease in the permeability of capillaries to protein may occur under therapy with para-aminobenzoic acid.

COMMENT

Relation of Capillary and Cellular Permeability to Immunity.—An increase in the capillary permeability occurs in the course of Rocky Mountain spotted fever; the alteration can be detected early in the course of the disease but is most significant during the second week of rash—the time at which immunity and allergy may be expected to develop. Allergy has not been demonstrated in rickettsial diseases, however. That an immune mechanism is involved in the alteration of capillary permeability is suggested by the similarity of the changes observed during serum sickness (case 11) to those observed during the course of rickettsial spotted fever.

It has been known for years that antigen-antibody reactions liberate a histamine-like substance. That histamine and similar substances alter capillary permeability is demonstrated by the production of a wheal when histamine is injected into the skin. In Rocky Mountain spotted fever the maximum changes in capillary permeability occur at the time when immunity is rising rapidly and is beginning to attain ascendency over the infection. Our observations in cases of Rocky Mountain spotted fever suggest that the antigen-antibody effect involves the general circulation and alters the permeability of the entire vascular tree.

Because rickettsias are located intracellularly, one would expect cellular as well as capillary permeability to be increased. The fact that cells participate in the immune process and are affected by allergic manifestations is well known. An antigen-antibody reaction occurring within the cell might be expected to liberate a histamine-like substance which would increase the permeability of the cell membrane. In patients with spotted fever it is difficult to obtain an adequate quantity of interstitial fluid for chemical examination by the insertion of needles subcutaneously. In view of the ease with which fluid can be obtained from patients with

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congestive failure, we are led to suspect that some of the fluid lost from the circulation in spotted fever may be found within cells as well as between them. The disproportion between the changes in weight and the changes in thiocyanate space also suggests that cellular hydration occurs. The observation of stupor, tremor and medullary respiratory arrest (case 3) is clinical evidence that nerve cells are hydrated excessively; the increase in cerebrospinal fluid pressure in such instances is usually less than would be expected if the cerebral edema were interstitial.

Unfortunately, no technic is available at present for the measurement of intracellular fluid. Regardless of whether the fluid goes into tissue space or into cells, the loss from the circulating intravascular fluid lowers the blood volume and precipitates peripheral circulatory collapse.

Since the effect on permeability of membranes is not confined to the cells but presumably affects the capillary wall between cells, one might postulate that at least one antigen involved in the immune reaction is a soluble one. If this hypothesis is correct, the substance produced by the rickettsias inside cells would diffuse out and induce an antibody response in the circulation. Thus, humoral as well as cellular immunity would develop, and antigen-antibody reactions would occur in the circulation on the surface of cells and within them.

In any event, the alterations in permeability are evidently reparable with the establishment of immunity; this conclusion is based on clinical observation alone, however, since no quantitative data on the degree of immune response were obtained. The diuresis which regularly occurs with recovery from infectious diseases has been known to clinicians for years, though the mechanism has never been explained.[10] The restoration of capillary and cellular integrity would enable interstitial and intracellular fluid to be mobilized and excreted through the kidney.

The Similarity of Serum Sickness to Rocky Mountain Spotted Fever.—The observations made in case 11 during the patient's serum sickness led to further experimental studies, which are being reported separately.[11] Serum sickness produced in rabbits by the administration of human plasma caused the increase in thiocyanate space, drop in circulating plasma volume, drop in serum protein content and development of edema seen in cases of Rocky Mountain spotted fever. The recent introduction of antihistaminic drugs raises the interesting possibility of preventing the harmful effects of immune reactions without affecting the

10. Rackemann, F. M.; Longcope, W. T., and Peters, J. P.: The Excretion of Chlorids and Water and the Renal Function in Serum Disease, Arch. Int. Med. 18:496-504 (Oct.) 1916.

11. Aikawa, J. K.: The Immuno-Physiology of Serum Sickness: Alterations in the Blood Volume and Thiocyanate Space in Relation to the Development of Immunity, to be published.

1112023

beneficial ones. The administration of antihistaminic drugs, "benadryl" and "pyribenzamine," in cases 9 and 11 was too late in the course of the disease to enable us to draw definite conclusions. The favorable response following the administration of these drugs to patients with serum sickness suggests that a beneficial effect might be achieved.

The Effect of Therapy on Permeability and Circulatory Failure.—The administration of supportive therapy alone to 7 patients did not prevent the development of circulatory failure in some cases. The necessity for the administration of large amounts of protein to replenish or conserve protein stores and to maintain the circulating plasma and blood volume is well illustrated in cases 7, 8 and 10.

A few observations on the response of the blood volume to the administration of serum albumin (as in case 1) indicate that the rise in the plasma volume was less than would be expected from the experience in other diseases. Usually an increase of 14 cc. for each gram of albumin injected may be anticipated.[12] When this increase does not occur, it is not known whether the albumin is stored or leaks into tissue spaces.

Since immune bodies are found in the globulin fraction of serum, the chance presence of immune bodies to rickettsias might explain the reactions to transfusions of blood and plasma observed occasionally in patients with Rocky Mountain spotted fever.[13] If this explanation is correct, serum albumin should be used to support the circulation when preformed protein is necessary in the treatment of circulatory collapse; if the hematocrit value is low and anemia is simultaneously present, settled or washed red cells should be used in preference to whole blood. Because of the large amounts of plasma necessary to maintain the circulating blood proteins in the face of the pronounced degree of protein destruction and nitrogen excretion observed in the disease, every effort should be made to encourage maintenance of protein stores by feeding rather than by replacement with transfusion.[1]

The administration of specific therapy to 6 patients either early or late in the course of the disease did not prevent the development of peripheral circulatory failure. No evidence was found that the doses of antiserum used raised the antibody titer sufficiently to increase the permeability of membranes; in all likelihood the immune balance was not shifted with this quantity of antibody. Since the rickettsias require several days to become established intracellularly, one would anticipate

12. Cohn, E. J.; Oncley, J. L.; Strong, L. E.; Hughes, W. L., Jr., and Armstrong, S. H., Jr.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: I. The Characterization of the Protein Fractions of Human Plasma, J. Clin. Investigation 23:417-432 (July) 1944.

13. Martin D. W.: Rocky Mountain Spotted Fever in Children, J. Pediat. 16:468-472 (April) 1940.

1112024

that the early administration of adequate quantities of serum might decrease or prevent the parasitization of cells and the subsequent alteration in the permeability of cellular membranes; prevention of an increase in capillary permeability would not necessarily be expected.

The administration of para-aminobenzoic acid early or late in the course of the disease did not prevent circulatory failure. The recurrence of an increase in thiocyanate space without a simultaneous drop in plasma volume in the patients in cases 6 and 12 while they were under therapy with para-aminobenzoic acid suggests that this drug may decrease the extent of capillary permeability so that only slightly increased amounts of crystalloids and no proteins are passed by the capillary membrane. If this hypothesis be true, administration of para-aminobenzoic acid would exert its effect through interference with the product of an antigen-antibody reaction and hence could be classed as supportive rather than specific therapy. This drug is chemically similar to salicylates and procaine, both of which have been used to alleviate the symptoms of serum sickness.

Pathogenesis of Central (Myocardial) Circulatory Failure.—In some instances, such as cases 9 and 10, myocardial failure as well as peripheral circulatory collapse was observed. In other instances (cases 1 and 4) congestive failure was precipitated by therapy. Changes in the electrocardiogram on all patients with spotted fever were not observed, and few electrocardiographic readings have been made during the acute episodes of congestive failure. The changes in the electrocardiogram observed in previous cases are similar to those which occur with edema due to beriberi, myxedema or anasarca of other cause. Pathologically, sections of the myocardium in fatal cases usually show edema of the muscle fibers. In other fatal cases, lesions resembling periarteritis nodosa have been seen in small blood vessels, as in case 13. Two mechanisms may be involved in the myocardial failure, i.e., mechanical interference from edema and anoxia from the involvement of arterioles.

SUMMARY

1. Peripheral circulatory failure in rickettsial spotted fever is accompanied with a drop in serum protein content and the development of edema.

2. The plasma volume is decreased and the thiocyanate space increased in the second week of the disease, when circulatory changes are at a maximum.

3. With the establishment of immunity (or allergy), capillary integrity is restored, diuresis occurs, the edema disappears, the plasma volume increases and the patient recovers.

1112025

4. The fact that the circulatory changes are at a maximum during the second week of the disease, when immunity begins to attain ascendency over the infection, suggests that an antigen-antibody reaction may be responsible for the changes in permeability of the membranes.

5. An alteration in the permeability of membranes was observed in 1 patient during serum sickness induced by the therapeutic administration of Rocky Mountain spotted fever antiserum; the changes resembled those seen during the rickettsial infection and give support to the aforementioned hypothesis.

6. An alteration of permeability probably takes place in cell membranes as well as in capillary walls; the capillary permeability may progressively increase in degree, so that crystalloids, protein and red blood cells are allowed to pass out of the capillaries.

7. Myocardial failure may occur as the direct result of the anoxia induced by vascular lesions of the disease or by interstitial edema, or it may be precipitated by excessive administration of fluids, particularly during the period when capillary integrity is being restored.

8. In 6 cases specific therapy in the form of antiserum or para-aminobenzoic acid, alone or together, early or late in the course of the disease did not prevent circulatory changes.

9. Supportive therapy does not prevent the circulatory changes of spotted fever, but a high protein diet administered from the beginning of therapy reduces the physiologic effects of the disease; serum albumin is probably the best preformed protein for parenteral administration in cases of acute circulatory collapse.

10. In other infectious diseases in which the permeability of membranes may be altered, proper replacement of protein and the avoidance of excessive administration of crystalloids might decrease circulatory failure; the principles of supportive therapy described are probably applicable to these infectious diseases

Printed and Published in the United States of America

1112026

HE-398(NIH) Number NRG-1 (Rev. 9-47)

Budget Bureau No. 68-R249.1.
Expiration date Nov. 30, 1948.

RENEWAL APPLICATION ~~FOR GRANT~~ FOR RESEARCH PROJECT
covered by Contract No. N8-onr-63701 between the Office of Naval Research and the Bowman Gray School of Medicine.

Date ..... March 31, 1948 .....

Director, Division Biology and Medicine
~~Atomic Energy Commission~~
~~[illegible]~~,
~~[illegible]~~, Constitution Ave.
Washington ~~25~~, D.C.

Copy to:
Head, Biophysics Branch
Medical Sciences Division
Office of Naval Research, Navy Dept.
Washington, D. C.

Application is hereby made for a grant-in-aid in the amount of $..12,120.00...

for the period from July 1, 1948 to July 1, 1950., inclusive,* for the purpose of ~~[illegible]~~ continuing ~~[illegible]~~ a research project on the following subject:

..Natural and Pharmacological Actions on the Formation of Tissue Prostaglandins.....
(Give only brief statement of nature of project; details on pp. 2 and 3)

.....Camille Artom, M. D., Professor and Head of the Department of Biochemistry.....
(Principal investigator) (Title)

.....Bowman Gray School of Medicine, Winston-Salem, North Carolina.....
(Address of principal investigator)

Mr. Harry G. Parker, Controller
.....
(Title of financial officer to whom check should be mailed)

.....Bowman Gray School of Medicine, Winston-Salem, North Carolina.....
(Address of this officer)

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant-in-aid may be revoked in whole or in part at any time by the Surgeon General, provided that a revocation shall not include any amount obligated previous to the effective date of the revocation is such obligations were made solely for purposes set forth in this application; (3) that all reports of original investigations supported by any grant-in-aid made as a result of this request shall acknowledge such support; and (4) that if any patentable discoveries or inventions are made in the course of the work aided by any grant received as a result of this application, the applicant will, in consideration of such grant, refer to the Surgeon General of the Public Health Service, for determination, the question of whether such patentable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

Name of institution .Bowman Gray School of Medicine of Wake Forest College...

(Type name and title of official authorized to sign for institution)..C. C. Carpenter, M. D., Dean.....

Signature of this official .....C. C. Carpenter.....

*This period is not to exceed 1 year.

16-47427-3

(COPY)

1112027

1. Outline the proposed work and the plan of attack. (Use a continuation sheet for details, if necessary.)

As shown in the enclosed progress report, a considerable amount of work has been done during the first nine months of operation of the project for which renewal application is made. Some of the results seem to be definite and interesting enough for publication in one complete paper. Other results will be the subject of four different preliminary reports at scientific meetings, but it is felt that further experimental elaboration is needed. It is anticipated that this elaboration will be started during the three months remaining before the expiration of the present contract, but to complete all the groups of experiments several more months of work will be necessary. Work on other points included in our original application has been initiated but progress has been less satisfactory and the results obtained thus far represent merely an indication of the lines along which future investigative efforts should be directed with a greater chance of success. This applies especially to the experiments in vitro. In these experiments the use of compounds labelled with C^{14} should probably be very helpful but, since work with C^{14} has not yet been started, it is suggested that the time required for such experiments will extend beyond July 1, 1949. Accordingly, a renewal of the present contract for one additional year is requested. The work planned will be essentially a continuation and extension along the lines proposed in the initial application. It is planned to devote a large part of the investigators' activity to the in vitro experiments and to use in these experiments both P^{32} and C^{14}. Besides the substances already tested, the action of other drugs and hormones will be studied and experiments made also on animals with altered liver functions and after surgical removal of certain endocrine glands.

2. Estimated total number of years of project duration one or two years

3. Has any work been done on this project by principal investigator (named on page 1)? Yes X, No ...
If yes, what are the significant results and publications to date? If possible, please enclose reprints.

16-4727-2

See initial application and the progress report enclosed herein.

The following papers on related subjects have been published since the initial application was presented:

C. Artom and M. A. Swanson: On the Absorption of Phospholipides, Journal of Biological Chemistry, 175:871, September 1948.

C. Artom and W. E. Cornatzer: The Action of Ethanolamine, Methylethanolamine, and Dimethylethanolamine on Lipide Phosphorylation, Journal of Biological Chemistry, 176:949, November 1948.

W. E. Cornatzer and C. Artom: The Relation of Chemical Structure to the Stimulation of Lipide Phosphorylation, American Chemical Society, 114th Meeting Abstracts, P. 41-C, September 1948. (The complete paper will appear in Journal of Biological Chemistry, April 1949.)

(COPY)

1112028

What pertinent results bearing on this project have been obtained by other investigators? See initial application.

5. (a) What financial support has been received for this or related research by the principal investigator or his associates?

Source	Amount	Years of Support (From ..... to .....)
~~Atomic Energy Commission (Contract No.~~	~~$16,000~~	~~1948-1949~~
N6onr-63701, Office of Naval Research		

(b) Does the principal investigator have other requests for assistance on this or related research projects pending with governmental agencies, or with public or private foundations? Yes ... No .X.

If yes, give significant data, including title of project, name of agency, and amount of requested funds.

I6-47627-2

(C O P Y)

1112029

Budget for proposed project from July 1, [illegible] to [illegible]

Item	Funds Requested From the Public Health Service	Funds from other Sources
Personnel (Itemize):		
Camille Artom, M. D. Professor	None	Salary from Bowman Gray
M. R. Carpenter, Ph. D., Asst. Professor	None	" " " "
M. A. Swanson, Ph. D., Instructor	None	" " " "
Marietta Crowder, Graduate Student	None	" " " "
Full-time technician (M.L. Ziegler)	2,160.00	
2 Part-time technicians (Not selected)	2,160.00	
Permanent Equipment (Itemize):		
High speed centrifuge	[illegible]	
Two carbon combustion apparatus	800.00	
Analytical balance	350.00	
Direct reading balance for animals	250.00	
Geiger-Muller counter with Q gas	450.00	
Modified manual sample changer with amplifier	300.00	
Accessories for Warburg apparatus	[illegible]	
Consumable Supplies (Itemize):		
Radioactive phosphorus	250.00	
Radioactive compounds (C^{14} labelled)	1,250.00	
Animals	600.00	
Glassware	600.00	
Chemicals	600.00	
Organic Solvents	300.00	
Travel:		
First International Congress of Biochemistry, Cambridge, England*	650.00	
Scientific conferences and visits in this country	250.00	
Other Expense (Itemize):		
Books, drawings, reprints	150.00	
Maintenance, repairs and replacements for radioactivity apparatus	350.00	
Incidentals	150.00	
Total	12,120.00	

(COPY) 16-47427-2

*A paper based on the results of the present work is included in the program of the Congress

1112030

March 31, 1949

Progress report on the research project

HORMONAL AND PHARMACOLOGICAL ACTION ON THE FORMATION OF TISSUE PHOSPHOLIPIDES

sponsored by the Atomic Energy Commission, Division of Biology and Medicine, under Contract No. N8onr-63701 between the Office of Naval Research, U. S. Navy Department and the Bowman Gray School of Medicine.

Principal Investigator: Dr. Camille Artom

Research Progress

The present report covers the work done from July 1, 1948 to March 31, 1949. As indicated in the original application, the experiments have been carried out simultaneously on intact animals and on isolated tissues. In both experimental conditions the synthesis of phospholipides has been studied by determining the concentration of radioactive phosphorus in the liver lipides after introduction in vivo or in vitro of sodium phosphate containing P^{32}. In relation to these experiments, a collateral study was also made on the toxicity of radioactive P in mice fed various diets. Because of the delay in the functioning of an isotope laboratory suitable for work with relatively high radioactivities, radioactive carbon as a label for choline or related compounds could not be used as it was originally planned.

A. Experiments on intact animals.

The action of various chemical agents has been studied by comparing the isotope concentrations in the liver lipides of control rats and in those of rats which were maintained under the same experimental conditions, but received also various amounts of the substances to be tested. The results obtained in the various groups of these experiments are here briefly summarized.

(a) Certain drugs which are believed to be rather general poisons for the living cells, such as urethane, Bal and nitrogen mustards, did not affect markedly the rate of phospholipide formation in the liver. These results may be taken as an indication of the considerable ability of the liver to synthesize adequate amounts of phospholipides even under very adverse conditions. On the other hand, it seems likely that if other substances were found to cause changes in this process, these substances should be regarded as acting more or less specifically on the formation of phospholipides in the liver.

(b) Substances which are known as inhibiting the elaboration of thyroid hormone, such as thiourea, thiouracil and propyl-thiouracil caused moderate but significant decreases in the turnover of liver phospholipides. Since these results could not be duplicated in experiments on thyroidectomized rats, it is tentatively suggested that thiourea and the related substances may directly affect phospholipide formation in the liver. The results of this group of experiments will be reported at the future meeting of the N. C. Academy of Science. An abstract of the paper which will be read at this meeting is enclosed.

(c) A few experiments have been made on rats with glucosuria caused by the administration of alloxan or phlorizin. At present, no definite changes in lipide phosphorylation could be ascertained in either experimental condition, but it is felt that much more work is needed on this point.

12031

(d) Several other substances have also been tested which have a chemical constitution more or less closely related to that of the main nitrogenous constituents of phospholipides, choline and ethanolamine. Among these substances, guanidoacetic acid caused a considerable inhibition in the phospholipide turnover. While the action of this substance requires further study, it seems likely that guanidoacetic acid competes for the methyl groups required in the synthesis of choline. A similar marked decrease in the formation of liver phospholipides was observed after prolonged feeding of an analogue of ethanolamine (diethanolamine). The action of the latter compound was studied in detail. The results obtained will be presented and discussed at the next meeting of the Federation of the American Biological Societies in Detroit, Mich. An abstract of the paper to be presented is enclosed. A complete paper on the same subject has also been prepared and submitted for publication. A copy of this completed manuscript is also enclosed.

(e) The results of the last mentioned experiments were of considerable interest for the problem concerning the relation of the lipide phosphorylation to the supply of methyl donors and methyl acceptors in the diet. A number of experiments have been made on this problem. The results of these experiments have been compared with those obtained previously in this and other laboratories and a paper on this subject will be presented at the first International Congress of Biochemistry to be held in Cambridge, England, August 1949. An abstract of this paper is enclosed.

B. In vitro experiments

In these experiments the synthesis of phospholipides have been studied using liver slices, liver homogenates and liver extracts in different stages of purification. Thus far, good results have been obtained only with liver slices in aerobic conditions. The effects of the nutritional state of the animals from which the liver was obtained and the action of various phospholipide components added to the system in vitro have been studied. Further work is required before definite conclusions can be obtained.

C. Toxicity of P^{32} as related to dietary factors

In most of the above experiments radioactive phosphorus has been used as a tracer in animals maintained on inadequate diets which might have caused functional and anatomical changes in the liver. Accordingly, it seemed of interest to investigate the possibility that the toxicity of the radioactive isotope could be increased by dietary deficiencies especially by a lack of lipotropic factors. This possibility was of even greater interest to investigators in this department and in the Department of Medicine who are carrying out experiments with introduction of radioactive phosphorus in patients with liver disease. Accordingly, in collaboration with these investigators, the toxicity of radioactive phosphorus in mice maintained on various diets was studied. No appreciable change was detected by varying the level of proteins and fats in the diets or by supplementing a low protein diet with choline. The results of these experiments will be reported at the next meeting of the N. C. Academy of Science. An abstract of the paper which will be presented, is enclosed.

Personnel

In addition to the principal investigator the following professional workers have collaborated in the experiments: Dr. W. E. Cornatzer (Assistant Professor of Biochemistry), Dr. M. A. Swanson, (Instructor of Biochemistry), M. Crowder and P. Mitchell (Graduate Students), M. L. Haigler (Technician). Part-time technical help has been obtained also by three other individuals. Some experiments were made in collaboration with investigators of the Department of Medicine.

1112032

Equipment

The following permanent equipment has been purchased for work on the present project:

Warburg apparatus with all accessories
Micro Torsion Balance
A deep freeze cabinet and an Angle centrifuge which can be combined for centrifugation at low temperatures.

Travel

With the sums appropriated by the Atomic Energy Commission, three members of this faculty attended the conference on isotopes at the National Laboratory in Brookhaven (July 1948), and three other members attended the course on the use of isotopes at the National Laboratory in Oak Ridge, Tennessee (August 1948). These individuals were members of the Departments of Biochemistry, Medicine, Physiology and Pharmacology.

Isotope Laboratory

The completion of an isotope laboratory to be used by workers from the various departments of this school was delayed, because it was considered expedient to install the isotope laboratory in a new addition to the present building of this school which was under construction. Only recently the construction of this addition has been completed and it is expected that in about three weeks the isotope lab will be ready for use. With the partitions and alterations made possible by the funds included in the present contract, the isotope unit will include one room for chemical work with high radioactivities, one for chemical work at the medium radioactivity level, one room for animals, one room for the study of human patients, one small office, one wash room and one counting room. Safety and protection devices have been purchased with funds shifted from this contract to Contract No. N8onr-63702 of which Dr. G. T. Harrell is the principal investigator. It is believed that the new lab will be adequate for a considerable extension of the work with radioactive isotopes in this school and will also allow the preparation of compounds labelled with C^{14} which will be used in the further development of the present investigations.

Budget

A financial breakdown of the expenditures made or to be made during the first nine month period of the present research project is as follows:

Actual Disbursements:

Salaries	$ 2,250.00
Materials and Supplies	977.75
Travel	990.80
Equipment	1,573.94

Unpaid Commitments:

Alterations and partitions for the isotope lab	6,250.00
Animals, materials and supplies ordered	350.00
TOTAL	$ 12,392.49

1112033

It is believed that the sum remaining from the total appropriation will be completely used during the period from March 31st through June 30, 1949.

K. Camillo Artom

Dr. Camillo Artom

1112034

Bowman Gray [redacted] Contemporary Mgt. N 3135

PHS-398(NIH)
Old number NRG-1
(Rev. 9-47)

[redacted]
Public Health Service

Budget Bureau No.
68-R249.1.
Expiration date June 30,
1948.

III

APPLICATION FOR GRANT FOR RESEARCH PROJECT

Director, Division Biology and Medicine
Atomic Energy Commission
[redacted] Constitution Ave.
[redacted]
[redacted] Public Health Service,
Washington [redacted], D.C.

Date April 27, 1948

Application is hereby made for a grant-in-aid in the amount of $[redacted]
for the period from July 1, 1948 to [redacted], inclusive,* for the purpose of conducting a research project on the following subject:

Toxicity of P[redacted] as Related to the Functional Capacity of the Liver

(Give only brief statement of nature of project; details on pp. 2 and 3)

Drs. G. Artom (Biochemistry), G. T. Merrill (Medicine) and D. Geyer (Medicine)

(Principal investigator) (Title)

Depts. of Biochemistry and Dept. of Medicine, Bowman Gray School of Medicine

(Address of principal investigator) Winston-Salem, N. C.

Harry G. Parker, Controller

(Title of financial officer to whom check should be mailed)

Bowman Gray School of Medicine, Winston-Salem, N. C.

(Address of this officer)

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant-in-aid may be revoked in whole or in part at any time by the Surgeon General, provided that a revocation shall not include any amount obligated previous to the effective date of the revocation is such obligations were made solely for purposes set forth in this application; (3) that all reports of original investigations supported by any grant-in-aid made as a result of this request shall acknowledge such support; and (4) that if any patentable discoveries or inventions are made in the course of the work aided by any grant received as a result of this application, the applicant will, in consideration of such grant, refer to the Surgeon General of the Public Health Service, for determination, the question of whether such patentable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

Name of institution Bowman Gray School of Medicine of Wake Forest College

(Type name and title of official authorized to sign for institution) G. C. Carpenter, M. D., Dean

Signature of this official C. C. Carpenter

*This period is not to exceed 1 year.

16-47427-3

(2 0 3 X)

1112035

1. Outline the proposed work and the plan of attack. (Use a continuation sheet for details, if necessary.)

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 malignancie such as infectious diseases, dietary inadequacies or exposure to toxic substances. The additive effect of radiation from isotopes introduced in the body (radioactive [illegible] in tracer amounts) may possibly harm cells already partially damaged [illegible] 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 [illegible] 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 P^{32} in mice. It is planned to extend further this study by varying the proportion [illegible] of the proteins, fat and carbohydrate components of the diet. The possible [illegible] vitamins will also be investigated. Additional experiments will be made 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. Estimated total number of years of project duration ....Two years....

3. Has any work been done on this project by principal investigator (named on page 1)? Yes ...X... No ...
If yes, what are the significant results and publications to date? If possible, please enclose reprints.

16-4727-2

In preliminary experiments the mortality and survival time of mice maintained on various diets and injected with increasing amounts of P^{32} has been studied. A preliminary report is on the program of the annual meeting of the N. C. Academy of Science, May 7, 1949. Three copies of this report are enclosed.

1112036

(COPY)

What pertinent results bearing on this project have been obtained by other investigators?

The only data on the toxicity of P^{32} are those of Anthony and Snyder (Atomic Energy Commission Document MDDC-[illegible]). On the basis of a few experiments, the LD_{50} for mice on unspecified diets, receiving one injection of P^{32} would be of approximately 4 microcuries per gram of body weight.

5. (a) What financial support has been received for this or related research by the principal investigator or his associates?

Source	Amount	Years of Support (From ..... to .....)
[illegible]		

(b) Does the principal investigator have other requests for assistance on this or related research projects pending with governmental agencies, ow with public or private foundations? Yes ... No .x

If yes, give significant data, including title of project, name of agency, and amount of requested funds.

16-47427-2

The preliminary experiments mentioned above were made as a collateral investigation supported by the grant-in-aid of the project, "Isotopic and Pharmacological Action on the Formation of Tissue Phospholipides."

(C O P Y)

1112037

Budget for proposed project from [illegible] to [illegible].

Item	Funds requested From the Public Health Service	Funds from other Sources
Personnel (Itemize):		
Dr. Aston (Principal Investigator)		Bowman Gray School of Medicine
Dr. Fa. Murphy (Principal Investigator)		Bowman Gray School of Medicine
Dr. Murray (Principal Investigator)		Bowman Gray School of Medicine
Technical Help	$ [illegible]	
Permanent Equipment (Itemize):		
Shielded vault for safely injected radioactive materials	[illegible]	
One homogenizer for the preparation of the diets	[illegible]	
One direct reading balance for animals and diets	[illegible]	
Consumable Supplies (Itemize):		
Radioactive phosphorus	300.00	
Dietary components	[illegible]	
Glassware and containers	150.00	
Travel:		
Other Expense (Itemize):		
Miscellaneous expenses	~~150.00~~ 265.00	
	300.00	
Total	$ [illegible]	

(COPY)

16-47427-2

1112038

CURRICULUM VITAE

Full Name: David Geyer

Born: [redacted] Connecticut

Preliminary education: [redacted]

College education: [redacted].

Medical education: [redacted]

Post Graduate Training: North Carolina State Sanatorium for the treatment of Tuberculosis 1-1-29 to 3-31-39
Duke University Hospital, Intern Medicine, 4-1-39 to 1-1-40.
Assistant resident in Medicine 1-1-40 to 7-1-42.
Resident in Medicine 7-1-42 to 7-1-43.

Assistant in Physiology and Pharmacology of Duke University School of Medicine, 3-3-41 to 6-16-41.

Instructor in Medicine, Duke University School of Medicine, 7-1-42 to 12-30-44.

Research Fellow in Medicine 7-1-43 to 6-30-44.

Fellow in Medicine, Diagnostic Clinic, Duke Hospital, 7-1-44 to 12-31-44.

Assistant Professor of Medicine, Bowman Gray School of Medicine, 1-1-45 to present.

Consultant in Internal Medicine to Veterans Administration, 1948.

Licensed to practice in the following states:
Florida, 1941: North Carolina, 1945.

Certified American Board of Internal Medicine, 1946.

Society Membership:

Phi Beta Kappa, Duke, 1935.
A.O.A., Duke, 1948.
Forsyth County Medical Society, 1-1-45.
North Carolina State Medical Society, 7-1-44.
American Medical Association (Fellow) Sept. 1944.
Trudeau Society, June 1943.
Diplomate National Board, June, 1940.
Tri-State Medical Society, June, 1945.
American College of Physicians (Fellow) 1949.
American Association for the Advancement of Science, 1946.
Southern Society for Clinical Research, 1948.
American Society for Clinical Investigation, 1948.
American Gastroenterologic Association, 1948.

1112039

BIBLIOGRAPHY OF DR. DAVID CAYER

1. Cayer, David: Relative Bradycardia as a Sign of Sulfonamide Fever, North Carolina M. J. 2:486-489 (Sept.) 1941.

2. Cayer, David and Ruffin, Julian M.: The Treatment of Chronic Idiopathic Ulcerative Colitis with Sulfaquanidine, North Carolina M. J. 3:196-197 (April) 1942.

3. Cayer, David and Baylin, George: Duodenal Diverticula, North Carolina M. J. 3:589-591 (Nov.) 1942.

4. Ruffin, Julian M. and Cayer, David: The Present Status of Vitamin Therapy in Deficiency States, North Carolina M. J. 5:37-40 (Feb.) 1944.

5. Ruffin, Julian M., Cayer, David and Perlzweig, William A.: The Relationship Between the Clinical Picture of a Mild or Early Vitamin Deficiency and Laboratory Determinations of Vitamin Levels, Gastroenterology 3:340-356 (Nov.) 1944.

6. Ruffin, Julian M. and Cayer, David: The Effect of Vitamin Supplements on Normal Persons, J.A.M.A. 126:823-826 (Nov.) 1944.

7. Cayer, David and Ruffin, Julian M.: The Clinical Significance of Glossitis and Cheilosis in Deficiencies of the B-Complex, South. M. J. 38:111-117 (Feb.) 1945.

8. Cayer, David and Dubin, I.N.: Case Report, Clinical Pathological Conference, North Carolina M. J. 6:103-106 (Feb.) 1945.

9. Perlzweig, W.A., Ruffin, Julian M., and Cayer, D.: Excretion of Orally Administered B Vitamin in Health and Disease, Fed. Proc., Vol. 4 (March) 1945.

10. Ruffin, Julian M., Baylin, George J. and Cayer, David: The Clinical Significance of Alteration of the Small Intestine Pattern as Demonstrated by X-ray, Gastroenterology 4:289-295 (April) 1945.

11. Cayer, David and Ruffin, Julian M.: Vitamin Levels in Sprue, Am. J. Med. Sc. 210:200-217 (Aug.) 1945.

12. Cayer, David: Case Report, Clinical Pathological Conference, North Carolina M. J. 6:524-527 (Dec.) 1945.

13. Cayer, David: The Diagnosis of Early Vitamin Deficiency Diseases, North Carolina M. J. 7:160-163 (April) 1946.

14. Cayer, David: Case Report, Clinical Pathological Conference, North Carolina M. J. 7:225-228 (May) 1946.

15. Cayer, D., Ruffin, J.M., and Perlzweig, W.A.: Vitamin Levels in Pernicious Anemia, Am. J. Med. Sc. 212:179 (Aug.) 1946.

16. Cayer, David: Case Report, Clinical Pathological Conference, North Carolina M. J. 7:481-483 (Sept.) 1946.

17. Cayer, D.: Diagnosis and Treatment of Early Vitamin Deficiency States, J.A.M.A. 132:558-561 (Nov. 9) 1946.

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18. Taylor, F.R. and Cayer, David: Pellagra Chapter, Oxford Medicine (Feb.) 1947.

19. Jarvis, J.L. and Cayer, D.: Cancer of Caecum, Am. J. D. D. 14:95-99 (March) 1947.

20. Jarvis, J.L. and Cayer, D.: Cholecystography with Priodax, Correlation of X-ray and Pathologic Findings, Gastroenterology 8:461-466 (April) 1947.

21. Abernathy, J. and Cayer, D.: Amoebiasis - Case Reports, N. C. B. N., North Carolina M. J. 8:201-203 (April) 1947.

22. Crescenzo, Victor M. and Cayer, David: Vitamin C Levels in Peptic Ulcer, Gastroenterology 8:754-761 (June) 1947.

23. Cayer, D., and Cody, S.: Nutritional State of Patients with Peptic Ulcer as Determined by Vitamin Levels in Blood and Urine, Gastroenterology 9:84 (July) 1947.

24. Cayer, D., Crescenzo, V., and Cody, S.: Plasma Vitamin A Levels in Pregnancy Relation to Total Lipids, Am. J. Obst. & Gyn. 54:259 (Aug.) 1947.

25. Cayer, D.: Clinical Pathological Conference, Gastroenterology 9:198-204 (Aug.) 1947.

26. Cayer, D., and Nabors, G.C.: A Clinical Evaluation of Total Blood Proteins and Albumin and Globulin Fractions in Hospitalized Patients, South. M. J. 40:744-751 (Sept.) 1947.

27. Taylor, F.R. and Cayer, D.: Anhidrotic Syndromes, Oxford Medicine 1947.

28. Cayer, D.: Case Report, Clinical Pathological Conference, North Carolina M. J. 8:671-674 (Oct.) 1947.

29. Little, J.M., Ogle, B.C., Teagley, J.D., and Cayer, D.: Effect of Tetraethyl Ammonium Chloride in Experimental Gastric Ulceration in the Rat, Science 106:448-449 (Nov. 7) 1947.

30. Cayer, D.: Clinical and Laboratory Observations on the Use of Methionine and Vitamin Supplements in the Treatment of Liver Disease, Arch. Int. Med. 80:644-654 (Nov.) 1947.

31. Cayer, D. and Cody, S.: Urinary Excretion of Niacin and Riboflavin in Acute Infections and Various Chronic Diseases, Am. J. Med. Sc. 215:273-278 (March) 1948.

32. Cayer, D.: Clinical Pathological Conference, North Carolina M. J. 9:210-213 (April) 1948.

33. Gaddy, C.S. and Cayer, D.: Chronic Glomerulonephritis Without Hypertension, Cardiac Enlargement or Retinal Changes, North Carolina M. J. 9:256-260 (May) 1948.

34. Cayer, D.: Modern Concepts in the Medical Treatment of Liver Disease, American Clinica 13:138-141 (Aug.) 1948.

35. Jarvis, J.L. and Cayer, D.: The Effects of Radiation Therapy on the Urinary Excretion of Niacin and Riboflavin in Patients with Malignant Disease, Radiology (in press).

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36. Cayer, D.: Case Report, Clinical Pathological Conference, North Carolina M. J. 9:535-537 (Oct.) 1948.

37. Yeagley, J.D. and Cayer, D.: Changes in Gastric pH Following the Administration of Fruit Juice to Patients with Peptic Ulcer, North Carolina M. J. 9:555-561 (Nov.) 1948.

38. Cayer, D.: Case Report, Clinical Pathological Conference, North Carolina M. J. 9:637-641 (Dec.) 1948.

39. Yeagley, J.D., Cayer, D., and McMillan, R.L.: A Clinical Evaluation of Gastrointestinal Signs and Symptoms in Patients with Coronary Heart Disease and Recent Myocardial Infarction, North Carolina M. J. 10:22-27 (Jan.) 1949.

40. Cayer, D., Little, J.M., and Yeagley, J.: The Use of Tetraethylammonium Chloride in the Treatment of Patients with Peptic Ulcer, Gastroenterology 12:219-224 (Feb.) 1949.

41. Cayer, D.: Chapters in Therapeutics in Internal Medicine Thomas Nelson and Sons, N.Y
Deficiency Diseases
- Vitamin A Deficiency
  - Xerophthalmia
  - Keratomalacia
- Vitamin B Deficiency
  - Beriberi
  - Pellagra
  - Ariboflavinosis
- Vitamin C Deficiency
  - Scurvy
- Vitamin D Deficiency
  - Rickets
- Vitamin K Deficiency

42. Cayer, D., and Cornatzer, W.E.: The Effects of Choline and Methionine on Phospholipide Formation in Patients with Liver Disease as Measured by Radioactive Phosphorus, Science (Accepted for Publication).

43. Cayer, D. and Cornatzer, W. E.: The Effects of Lipotropic Substances on Phospholipide Synthesis in Patients with and Without Chronic Hepatitis, South. M. J. (in press).

1112042

TOXICITY OF RADIOACTIVE PHOSPHORUS IN MICE ON VARIOUS DIETS *

By W. H. Gernatzer, David Gayer, George T. Harrell, Jr. and Camille Artom.

(From the Departments of Biochemistry and Medicine, Bowman Gray School of Medicine, Winston-Salem, North Carolina).

The present investigation is a part of a more extended study undertaken with the idea that the resistance of the organism to the toxic effects of radioactive isotopes introduced into the body may be decreased by alterations in the functional capacity of the liver. This point would, of course, be of practical interest for the use of radioactive isotopes as diagnostic and therapeutic agents in patients with liver diseases since in these individuals even small doses of radioactivity could exert an additive harmful action.

To our knowledge, the only data on the toxicity of P^{32} are those of Anthony and Snyder (Atomic Energy Commission, Document MDDC-881). On the basis of a few experiments on mice (presumably maintained on a stock diet), these authors suggest that the LD_{50} after one injection of P^{32} is around 4 microcuries per gram of body weight. With this dose 4 out of 6 mice died between 16 to 21 days.

In the present experiments we have studied the mortality and survival time of mice maintained on diets of known composition and injected with radioactive phosphorus as sodium diphosphate. We have investigated the possible role of a deficiency of lipotropic factors in the diets, such a deficiency leading to a fatty infiltration

* Presented at the Annual Meeting of the N. C. Academy of Science, May 7, 1949, Chapel Hill, N. C.

1112043

of the liver. If in this condition the toxicity of the isotope were increased, supplementation of the diet with choline should give a more or less marked protection.

Several groups of mice (approximately 20 gm. body weight) were transferred from a stock diet to a low protein, high fat diet (Diet 31, containing casein 10 parts, Crisco 30, cod liver oil 2, sucrose 29, dextrin 25, roughage, salts and B vitamins). The animals were maintained for five days on the diets, then they were injected with a single dose of radioactive phosphorus and kept under observation for three weeks. To date, a total of 120 mice have been used.

There were no deaths among mice not injected with radioactive P and maintained for 25 days on the unsupplemented diet. Of the animals injected with 2 microcuries per gram of body weight and maintained on either the unsupplemented or supplemented diet none died in 21 days. With 4 microcuries per gram of body weight the mortality at the twenty-first day was 16% and the average survival time was of 20 days for both the controls on the unsupplemented diet and the mice of the choline supplemented diet. With 6 microcuries per gram of body weight the mortality has been 72% and 86% and the average survival time 16 and 12 days, respectively. With 8 microcuries per gram of body weight the mortality was 89 and 89 per cent and the average survival time 12 and 13 days respectively.

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In another group of rats injected with 6 microcuries per gram of body weight the level of the fat in the diet was decreased from 32 to 5 per cent (Diet 34). There was a slight decrease in mortality but no change in the survival time after injecting 6 microcuries per gram. Likewise, no significant protection was observed when the protein content of the low fat, low protein diet was increased from 10 to 25% (Diet 29).

This work was supported by the U. S. Atomic Energy Commission under a contract between the Bowman Gray School of Medicine and the Office of Naval Research, U. S. Navy Department. The P^{32} used was supplied by the National Laboratory, Oak Ridge, Tennessee, on allocation from the U. S. Atomic Energy Commission.

1112045

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

DEPARTMENT OF
INTERNAL MEDICINE

June 17, 1949

Mr. Glenn Humphries
Atomic Energy Commission
Oak Ridge, Tennessee

Dear Mr. Humphries:

Thank you for your phone call today. I have arranged with the Robert E. Lee for two single rooms, which will be held in your name. I told them you are arriving on Capital Airlines' Flight 500, 3:57 p.m., so that you should be in the hotel before 6:00. If you find you are delayed, let them know so they will hold the room after that time.

I have arranged for Mr. Parker and Dr. Artom to be available 9:00 a.m. the morning of the 22nd.

Cordially,

George T. Harrell, M. D.

GTH:mjs

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WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

DEPARTMENT OF
INTERNAL MEDICINE

June 11, 1949

Dr. Harry Stoeckle
Chief, Biology and Medicine Division
Atomic Energy Commission
Oak Ridge, Tennessee

Dear Dr. Stoeckle:

Thank you so much for Dr. Belcher's letter of June 8. We have in the same mail gotten a rather disquieting letter from ONR, which indicates that we may have difficulty in paying for equipment ordered under our contract N8onr 63702 if it is delivered after June 30, 1949. We have contacted our suppliers and notified them of this but the major item, the fume hood, is being built by Sheldon and the earliest delivery they had promised was June 30. Also in the same mail, we got a letter from Sheldon indicating that the probable delivery date will be July 17 due to a plant shut-down. The letter received today from Mr. R. F. Lynch, contract administrator, ONR, states as follows: "Since the Atomic Energy Commission will take over the research under the subject Office of Naval Research Contracts by new AEC contracts after June 30, 1949, it is desired that the subject contracts be cleaned up by the terminating date. Therefore, payment for equipment ordered under the subject contracts prior to June 30, 1949, but undelivered by that date should be charged to the new AEC contracts when delivered. It is believed that the necessary record changes to accomplish this presents no problem."

Does this last sentence mean that it will be possible to make some arrangement when you come here June 22 to take care of these items. For instance, one of our problems is that the installation of duct work for the fume hood is on a time and material basis on our present understanding with our local contractor. The plumbing, carpentering, and ventilating contractors have so far been unwilling to make a firm estimate which could be paid now for work to be done, and we did not want to start these things until the major item of equipment was installed so that we could build around it and get tight fits for all the joints and connections.

CONTRACTS
Bowman Gray
Rn- 525:
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Dr. Harry Stoeckle June 11, 1949

I have gone into these problems in some length so that you could think them over and give us an answer as to how to handle it when you come June 22. If there are any other questions you would like to ask me, I will be at Oak Ridge the afternoon of June 15 and morning of June 16. You could contact me through Dr. Brucer.

We certainly are looking forward with a great deal of relief and pleasure to the transfer of our contract to you for administration.

Cordially,

George T. Harrell

George T. Harrell, M. D.

GTH:mjs

1112048

In Reply Refer To:
[illegible]:[illegible]

Oak Ridge, Tennessee
June [illegible]

Mr. George [illegible]
Bowman Gray School of Medicine
Winston-Salem, North Carolina

Dear Mr. Merrill:

This letter will confirm our telephone conversation of yesterday, concerning the date for the negotiations of your contract with the Atomic Energy Commission.

At the present time the exact hour of arrival is not known. As I will be out of town until that time, I have asked Mr. Glenn Humphries, in the office of the Special Assistant to the Manager, to make final arrangements. No doubt, you will hear from Mr. Humphries next week.

I am looking forward to seeing you at that time.

Sincerely yours,

Harry Steeckle, M.D.
Chief
Biology and Medicine Division

cc: Mr. Glenn Humphries

Steeckle:cs

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WAKE FOREST COLLEGE

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THE BOWMAN GRAY SCHOOL OF MEDICINE

Winston- Salem, North Carolina

May 2, 1949

Director
Division of Biology and Medicine
Atomic Energy Commission
Constitution Avenue
Washington 25, D.C.

Dear Sir:

I am very happy to approve on behalf of the Bowman Gray School of Medicine of Wake Forest College the three research proposals for application of isotopes to the study of human disease which are enclosed. A great deal of interest has been aroused among the members of our faculty actively engaged in research of the Fellowship Training Program of the Atomic Energy Commission. As you are aware, the first of the Fellows whose training was begun under this program has progressed sufficiently far to enable him to start out on his own in another institution. We are very happy to continue to train additional Fellows as they are assigned to us by the Commission.

The College is very grateful to the Commission for making available to us facilities to expedite research in the various departments of the School. These research projects could not have been undertaken without your encouragement and financial assistance in helping to make available the necessary facilities. As you are well aware, in the coming years the critical factor will be personnel rather than facilities and equipment. Assistance of the Commission in enabling the investigators to secure and retain adequately trained personnel of the necessary high caliber will be essential to successful prosecution of the research and training.

Please let me express to you on behalf of the College and School of Medicine our appreciation for your help in the past. We have tried to keep our request moderate and sufficient to cover only our immediate need. We believe that the transfer of the administration of our contract to the Operations Office, Oak Ridge, will facilitate the Administration in handling of the details of the contract.

Cordially yours,

G.C. Carpenter, M.D.
Dean

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WAKE FOREST COLLEGE

THE BOWMAN GRAY SCHOOL OF MEDICINE, WINSTON-SALEM

NORTH CAROLINA

ZONE 7

May 2, 1949

Director
Division of Biology and Medicine
Atomic Energy Commission
Constitution Avenue
Washington 25, D.C.

Dear Sir:

In compliance with your letter of April 20, 1949, Dr. Thurman D. Kitchin, President of Wake Forest College, through Dr. C. C. Carpenter, Dean of the Bowman Gray School of Medicine, has designated me to serve as the co-ordinator for the various proposals for the participation of Wake Forest College in the Fellowship Program.

You will find enclosed separate proposals for the continuation of the research of Dr. Camillo Artom on "Hormonal and Pharmacological Actions on the Formation of Tissue Phospholipides"; Dr. George T. Harrell on "Distribution and Turnover of Sodium and Potassium in Acute Infections"; a new proposal by Doctors Artom, Harrell, and David Cayer on "Toxicity of P^{32} as Related to the functional Capacity of the liver." Each proposal is complete with the program report, proposal for the work to be done, and a budget. Also enclosed are a blue print of the isotope laboratory under construction, a copy of the latest catalog of Bowman Gray School of Medicine. Attached is a co-ordinated summary of the research grants and proposals.

By the last of the summer, the equipment requested in the renewals, proposals and that purchased with this year's grants should all be installed in the new isotope laboratory on the fifth floor. These facilities are to be available for all departments in the school. We shall attempt to interest other departments in the application of isotope techniques to their specific research problems.

The needs of the individual investigators for their specific research projects are discussed in each separate proposal. Please let me express to the Atomic Energy Commission for the Administration of the School as well as the individual investigators our appreciation for your gracious support this past year. We all look forward to a long continued, mutually profitable association. If there is any additional detailed information we can forward, please command us.

Respectfully yours,

George T. Harrell, M.D.
Professor of Medicine and
Director of the Department

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WAKE FOREST COLLEGE

THE BOWMAN GRAY SCHOOL OF MEDICINE

Winton-Salem, North Carolina

April 27, 1949

Dr. John Z. Bowers
Assistant to Director
Division of Biology and Medicine
U.S. Atomic Energy Commission
Washington 25, D. C.

Dear Dr. Bowers:

On March 31, 1949 I sent to you an application for one year renewal of the grant-in-aid from the Atomic Energy Commission currently administered by the Office of Naval Research (Contract No. N8onr-63701). This application (in 3 copies) was accompanied by a progress report (3 copies) summarizing the results obtained during the first nine months of work, abstracts of four preliminary papers (3 copies each), the manuscript of a complete paper and reprints of two other recent papers (1 copy each). For your convenience, I am now enclosing three additional copies of this renewal application and also of the progress report.

After receiving the copy of your letter to Dr. Kitchin dated April 20th with the material enclosed and after our telephone conversation of yesterday, I would like to add the following comments concerning the sums requested for the coming year.

You will probably recall that the sum requested in my original application last year amounted to $18,840. The sum was reduced to $16,350, but this figure included the expenses for the participation of several faculty members of this school to training courses at the National Laboratories in Brookhaven and Oak Ridge ($900), and the expenses for alterations, partitions and work required for setting up an isotope laboratory to be used by all departments of this school ($6,250). Thus the actual amount available for the project was limited to $9,200. Accordingly, the original financial plans had to be revised and the work curtailed in order to keep the expenses within this limit. More especially, we omitted the purchase of the equipment, apparatus and compounds required for the experiments with C^{14} and we concentrated our activity on the experiments with radioactive phosphorus.

As shown by the progress report, we believe that our investigations have already given interesting results. However, one or two more years of intensive work will be necessary before more important and more solid conclusions can be reached. Moreover, it is my definite opinion that an extension of the present work by the use of C^{14} labelled compounds will be extremely useful for the correct interpretation of the results obtained thus far and of those which we hope to obtain in the future. On the basis of these considerations for most of the

Cont. 13

1112052

items the sums requested in the renewal application are higher than those which have been available to us this year (although they are much below the amounts listed in the original application of last year).

The increases in the item Technical Assistance (from $3600 to $4320) seems necessary since it does not seem possible to keep the present personnel or to obtain other technicians without somewhat higher salaries.

The expense for Permanent equipment (increased from $2100 to $2850) is intended essentially to cover apparatus necessary for work with C^{14}. In addition we would need one high speed centrifuge in order to fractionate the liver extracts with high speed centrifugation and accessories for the Warburg apparatus to study more intensively the metabolism of phospholipides in isolated liver.

The increase in the item Consumable supplies (from $2100 to $3400) is due chiefly to the cost of the synthesis of C14 labelled compounds.

The item Travel (increased from $300 to $900) includes the sum of $650 for participation of the undersigned to the First International Congress of Biochemistry in Cambridge, England, in the program of which a paper is included based on the results of the present work.

The increases in the Miscellaneous expenses (from $400 to $500) is due chiefly to the increased cost for maintenance, repairs and replacement of radioactivity apparatus. Such increases is to be expected in relation to the aging of these apparatus and to their intensive use.

With many thanks and best personal regards, I am

Sincerely yours,

Camillo Artom, M.D.

Enclosures

Renewal application for grant-in-aid
from the A.E.C. (3 copies)

Progress report (3 copies)

1112053

PHS-396 C
OM-Number
(Rev. 1-2)

ATOMIC ENERGY COMMISSION

Budget Bureau No. 68-R249.1.
Approval Expires Nov. 30, 1948.

RENEWAL OF
APPLICATION FOR GRANT FOR RESEARCH PROJECT
(previously designated N8onr-63702, Project NR-171 677)

Director, Division Biology and Medicine
Atomic Energy Commission
[redacted]
Washington 25, D. C.

Date April 20, 1949

Application is hereby made for a grant-in-aid in the amount of $ 13[redacted] for the period from 7-1-49 to 6-30-50, inclusive,* for the purpose of conducting a research project on the following subject:

Distribution and turnover of sodium and potassium in acute infections.
(Give only brief statement of nature of project; details on pages 2 and 3)

George T. Harrell, Professor of Medicine and Director of the Department of Internal Medicine
(Principal investigator) (Title)

Bowman Gray School of Medicine, Winston-Salem 7, North Carolina
(Address of principal investigator)

Harry O. Parker, Comptroller
(Title of financial officer to whom check should be mailed)

Bowman Gray School of Medicine, Winston-Salem 7, N. C.
(Address of this officer)

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant-in-aid may be revoked in whole or in part at any time by the Surgeon General, provided that a revocation shall not include any amount obligated previous to the effective date of the revocation if such obligations were made solely for purposes set forth in this application; (3) that all re ts of original investigations supported by any grant-in-aid made as a result of this request shall acknowledge such support; and (4) that if any patentable discoveries or inventions are made in the course of the work aided by any grant received as a result of this application, the applicant will, in consideration of such grant, refer to the Surgeon General of the Public Health Service, for determination, the question of whether such patentable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

Name of institution Bowman Gray School of Medicine of Wake Forest College

(Type name and title of official authorized to sign for institution) C. C. Carpenter, Dean

Signature of this official C C Carpenter

* This period is not to exceed 1 year.

16—47427-8

1112054

1. Outline the proposed work and the plan of attack. (Use a continuation sheet for detail.)

See attached Progress Report and Proposal for Research.

2. Estimated total number of years of project duration five years

3. Has any work been done on this project by principal investigator (named on page 1)? Yes ☒ No ☐
If yes, what are the significant results and publications to date? If possible, please enclose reprints.

16—67427-2 U. S. GOVERNMENT PRINTING OFFICE

Harrell, G. T., Aikawa, J.K., and Kelsey, W.E.: Rocky Mountain Spotted Fever, Am. Pract. 1:425-435 (April) 1947.

Harrell, G.T. and Aikawa, J.K.: The Pathogenesis of Circulatory Failure in Rocky Mountain Spotted Fever. Alterations in the Blood Volume and the Thiocyanate Space at Various Stages of the Disease, Arch. Int. Med. 83:331-347 (March) 1949. (enclosed).

Harrell, G.T. and Yount, E.E.: Plasma Volume and Extracellular Thiocyanate Space in Experimental Serum Sickness in Rabbits, (To be published), (Abstract). (enclosed).

Wolff, W.A. and Harrell, G.T.: Liver and Kidney Function in Rocky Mountain Spotted Fever, (Submitted for publication).

Other reprints have been previously submitted.

1112055

4. What pe... results bearing on this project have been obtained by other investigators?

Rachmann, F.H., Longcope, W. T. and Peters, [illegible] The [illegible] and the Renal Function in Serum Disease, Arch. Int. Med. 18:[illegible], 1916.

Raun, C.V.E. and Janeway, C.A.: Histological and Serological Sequences in Experimental Hypersensitivity, J. Exper. Med. 86:571, 1947.

Darsh, G., Reaser, P. and Crowrich, J.: Rates of Sodium Turnover in Normal Subjects and in Patients with Congestive Heart Failure, J. Lab. & Clin. Med. 32:1169, 1947.

Elkinton, J.R., Winkler, A.W. and Danowski, T.S.A.: Transfers of Cell Sodium and Potassium in Experimental and Clinical Conditions. J. Clin. Invest. 27:74, 1948.

Freeman, R, Hill, R.F., and Foote, F.W.: The Zone of Localization of Anti-[illegible]-kidney Serum as Determined by Radiosurtographs, Science, 109:[illegible], 1949.

Turner, J. G. and Halliday, B.: Parasitization of Mouse Sarcoma 180 by Vaccine Virus and its Effect on Tumor Growth, J. Clin. Invest. 26:1198, 1947.

5. (a) What financial support has been received for this or related research by the principal investigator or his associates?

SOURCE	AMOUNT	YEARS OF SUPPORT (From ... To ...)
John [illegible] Harry R. Harris Foundation for	$ 7,[illegible]	[illegible]
trichinella and rickettsial research.	3,500	July 1, 1947 to July 1, 1949
NIcmr - 63708, project NR-171 677	9,[illegible]	July 1, 1948 to June 30, 194[illegible]
U.S.P.H.S. RG-1334	4,266	July 1, 1948 to July 1, 1949

(b) Does the principal investigator have other requests for assistance on this or related research projects pending with governmental agencies, or with public or private foundations? Yes ☒ No ☐

If yes, give significant data, including title of project, name of agency, and amount of requested funds.

Renewal of U.S.P.H.S. RG-1334 for the second of two years. This grant is now numbered [illegible] (C), 14320, 7-1-49 to 7-1-50.

PHS-398-1 (NIH)

111205b

BUDGET FOR PROPOSED PROJECT FROM [redacted] TO [redacted]

ITEM	FUNDS REQUESTED FROM THE PUBLIC [redacted] Atomic Energy Commission	FUNDS FROM OTHER SOURCES
Personnel (Itemize):		
Chief Investigator (George T. Harrell)		Bowman Gray Sch. [redacted]
Substitute for teaching, part-time (Dr. H. Young)	$ 1000	Bowman Gray Sch. [redacted]
Research Fellow (Dr. Jerry Altman)		AMA Fellow
Technician (unselected)	[redacted]	
Electronic engineer, part-time	[redacted]	
	[redacted]	
Permanent Equipment (Itemize):		
Shielded sample changer	[redacted]	
[redacted]	[redacted]	
Timer	80	
Geiger tubes	100	
Time recorder	150	
Centrifuge	[redacted]	
Balance	[redacted]	
Deep Freeze	150	
Metabolism cages	[redacted]	
Vacuum pump	75	
Flame Photometer	[redacted]	
Chemical Hood	1500	
	[redacted]	
Consumable Supplies (Itemize):		
Glassware	[redacted]	
Chemicals	[redacted]	
Animals	1500	
	[redacted]	
Travel:		
Travel	[redacted]	
Other Expense (Itemize):		
Contingency fund	300	
TOTAL	13075	

U. S. GOVERNMENT PRINTING OFFICE 16—47437-2

1112057

PROGRESS REPORT AND PROPOSAL FOR RENEWAL

Distribution and Turnover of Sodium and Potassium in Acute Infections
(Contract NSnr-63702, Project NR-171 677)

George T. Harrell, Wake Forest College
Bowman Gray School of Medicine, Winston-Salem, N.C.

1. Scope and Present Status

It has been known for many years that patients recovering from acute infections have a diuresis during recovery. It has also been known for some time that patients with serum sickness during the recovery stage will have a diuresis in which water and chloride are lost. Observation of cases of Rocky Mountain spotted fever have shown that edema develops during the acute phase of the disease. Measurements of the extent of edema have been made utilizing the thiocyanate technique. Generalized edema is also seen in patients with trichinosis, an interstitial infection, as well as in the intracellular infection with rickettsiae of spotted fever, and the pure antigen-antibody system without infection of serum disease. It is known that the blood chlorides will drop during the acute phase of pneumonia and of Rocky Mountain spotted fever. No studies are available on the distribution of fluid or changes in electrolytes in trichinosis; in the rare cases in which they have been done, the serum proteins have been reported to drop. In Rocky Mountain spotted fever serum proteins are known to drop during the acute phase of the disease. It appears then that water and chlorides, and perhaps protein molecules, leave the blood stream at a greater rate in some cases of infectious diseases than in normal individuals. Extravasation of proteins or ions into interstitial tissues would tend to retain fluid outside the blood vessels. The retention of water outside the vascular tree by sodium ions is now recognized as a factor in the production of edema in heart failure.

The process in infections can be visualized as a graded series of pores, as in a sieve, so that in instances of mild disease only crystalloids leave the blood stream. In more severe instances the pores are larger and protein molecules, such as albumin, will leave the blood stream; in most severe cases even red cells will be lost. It is not known whether the fluid which leaves the blood stream in infections and which is measured as an increase in thiocyanate space is found between cells or within them.

In the proposal made last year, we planned to induce serum sickness in rabbits; when the edema developed, radio-sodium and thiocyanate would be given. The level of the two ions in plasma, urine, and interstitial fluid would be determined - total sodium by the flame photometer, radiosodium by isotope techniques and thiocyanates by a colorimetric procedure; the values would then be correlated. A similar experiment would be done substituting radio potassium for radiosodium. It was then proposed that similar experiments be repeated using an interstitial infection - trichinosis - and an intracellular infection - rickettsiosis. Since the radiations of sodium are somewhat dangerous, we did not feel it advisable to begin any experiments until protection of personnel could be assured by construction of the isotope laboratory.

Because the negotiations on the contract and the construction of the laboratory have delayed the application of radio isotope techniques to our studies, we have this year extended our previous studies on serum sickness with additional groups of animals, utilizing whole human plasma as well as purified albumin and globulin fractions. We have borrowed the use of a flame photometer to familarize personnel with the technique; an unexpected administrative obstacle was encountered in the purchase of an instrument. We have not, up to the present, been able to arrange for the use of the flame photometer for determination of levels in material containing radioactive isotopes, because of the danger of contamination of the instrument and of the room where the instrument

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is being housed and used by another department for other studies.

In order to utilize personnel trained last summer, some preliminary experiments were conducted with the Department of Biochemistry on the toxicity of radio phosphorus. Clinical observations of patients with acute liver disease, given radiophosphorus as a tracer in studies of phospholipide turnover, suggested the possibility that the addition of a small amount of a harmful factor - radiation - to cells already damaged by the underlying liver disease of both toxic and dietary nature might have been sufficient to induce considerable further liver damage. Since the problem posed fundamental questions on the biologic effects of radiation in tissue, preliminary experiments were conducted in animals in conjunction with Dr. Artom; these are discussed in the enclosed abstract. Continuation of the experiments seems justified and a proposal for continuation is separately enclosed.

Dr. Camille Artom has kindly made available the facilities and equipment in his laboratory in the Biochemistry Department in the Basement for use by one of the AEC Fellows who is interested in problems concerning radioactive phosphorus. This man will continue to use Dr. Artom's facilities in his study on enzyme systems concerned in antibiotic chemotherapy until the new school isotope laboratory can be completed on the fifth floor.

2. Scientific Motivation

If the mechanism by which increased amounts of electrolytes are passed across capillary and cell membranes can be established, it may be possible to devise measures to correct the physiologic abnormality. In infectious diseases the harmful effects of excessive hydration might be combatted. If the mechanism is established, it may be possible eventually to apply the technique in reverse to therapy of human disease. An increase in permeability might be induced so that radioisotopes could be encouraged to enter tissue and there exert their radiation effect. Some evidence has accumulated from our experiments outlined above that an antigen-antibody reaction may be responsible for the increase in permeability of membranes. Evidence has been presented that certain types of malignancies in animals are caused by filterable viruses; other evidence indicates that certain types of malignant tissue can concentrate viruses such as vaccinia which have been well studied. If an immune serum could be made against either virus, and the virus be introduced into an animal with cancer, a local antigen-antibody reaction might be induced; a radioisotope introduced when the reaction was at its maximum would be concentrated in cancerous tissue since the antigen-antibody reaction would take place in or on cancer cells. If it becomes possible through the application of the autoantibody technique to develop an antiserum against cancerous tissue, the same principle would hold and the antigen-antibody reaction would take place only on malignant cells. We are attempting to determine whether the ions which leave the blood stream in antigen-antibody reactions go between or within cells and in studing the mechanism by which the transfer is effected. We will attempt to make direct measurements on the distribution of ions, as well as to calculate the site of action by indirect evidence. Confirmatory experiments utilizing the radioautograph technique will be done for comparison with stained histologic sections. The radioautographs will probably have to be done on frozen sections of unfixed tissue; no recognized technique meeting these requirements is known at present.

3. Materials, Equipment and Facilities

The grant was to have begun July 1, 1948. Negotiations on the contract were not begun by the Navy until October 7 and the contract was not made effective until

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December. The College was unwilling to begin construction of the laboratory until the contract was made effective and reimbursement was assured. Permission of the College authorities was finally obtained to enclose a portion of the roof on the east end of the medical school building, adjacent to the fifth floor animal quarters, and permission of ONR was granted to utilize funds in the AEC grant for this purpose. Plans were drawn according to the enclosed blueprint and a contract was let. The partitions, ceiling, plumbing, and heating are now being installed and the contractor expects to turn the laboratory over to us by June 15. A radioactive fume hood of the design recently approved at Oak Ridge is promised for delivery about June 15; the installation of the fume hood and of a stainless steel sink will be made out of funds earmarked for equipment on our grant this year. Photographs of the completed laboratory can be forwarded about July 1 for your records. We have ordered Geiger tubes, sealers, sample holders, [illegible] equipment, balance, centrifuge, refrigerator and so forth from our research funds this year to equip the school isotope laboratory. Funds are insufficient this year and we are not requesting in our renewal budget funds for chemical benches or other fixed equipment. We are requesting only such specific equipment as is necessary for our experiments. For the reasons outlined above we need a flame photometer and an ordinary chemical hood in which to operate it. We do not believe a radioactive hood would be necessary for these experiments, because of the short half life of sodium and potassium hence contamination should not be a problem.

4. Scientific Personnel

The principle investigator, Dr. George T. Harrell, is already known to the Commission through the original application. Dr. Ernest M. Yount will be employed part time on the project; it has been feasible to release him from a portion of his teaching duties to participate in these experiments. Dr. Yount's curriculum vitae is enclosed. Dr. Jerry K. Aikawa and Dr. Kingsley Stevens are already known to the Commission; both hold AEC fellowships administered through the National Research Council. Aikawa will be utilized full time on this project; Dr. Stevens will continue his enzyme studies until he transfers to Chicago in the fall. We are losing through marriage our technician who has been partially trained in isotope technique; a new technician is being sought and will have to be trained. It will be possible to hire on an hourly part time basis the electronic engineers from the Western Electric Radio Shops located in the city for maintenance of equipment.

5. Proposed Budget

The exact figures and the detailed breakdown by categories of the proposed budget are found on the enclosed sheet. The amount requested for salary of a technician and to release Dr. Yount from teaching duties are the same as last year; the item for part time electronic engineering help for maintenance of equipment is new since equipment has not yet been installed; this year such services were not necessary. The current equipment budget has been extended for purchase of isotope equipment to provide the minimum necessary for conducting experiments; the major item was the radioactive fume hood which will cost $2125 plus installation. As discussed above it will be necessary to purchase a flame photometer and a fume hood in which to operate it - items which make up the major part of the equipment category this year. The increase in consumable supplies is due almost entirely to the great increase in the cost of animals purchased locally which has occurred in the past year. Some increase is due to the high cost of gas and oxygen for satisfactory operation of the flame photometer. The other items have been reduced. The College will furnish heat, light, water, janitor service, up keep of the building, as well as the salary of the principle investigator and the major portion of the salary for Dr. Yount.

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6. Other Responsibilities

The principle investigator is obligated with Dr. Ernest Yount for continuation of U.S.P.H.S. grant H129-C for the amount of $4380; this is the second year on a two-year grant. The principle investigator is obligated to U.S.P.H.S. grant 643 (C-2) in the amount of $4029 for continuation of antibiotic research as co-investigator with Dr. Manson Meads of this department. The principle investigator is concluding through a close-out grant of the Markle Foundation in the amount of $3500 studies on trichinosis and alteration of body function in rickettsial diseases which has been previously supported by them over a periods of years.

7. Administrative Information

A copy of the latest catalog of the Bowman Gray School of Medicine is enclosed. Other information is found on the first page of the enclosed application.

Respectfully submitted,

George T. Harrell

George T. Harrell, M.D.
Professor of Medicine and
Director of the Department

GTH:mfc

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ATOMIC ENERGY COMMISSION

[redacted]

[redacted] number NRG-1
(Rev. 9-47)

Budget Bureau No. 68-R249.1.
Expiration date Nov. 30, 1948.

II

RENEWAL APPLICATION [redacted] FOR RESEARCH PROJECT
covered by Contract No. N8-onr-63701 between the Office of Naval Research and the Bowman Gray School of Medicine.

Director, Division Biology and Medicine
Atomic Energy Commission
[redacted],
[redacted], Constitution Ave.
Washington [redacted], D.C.

Copy to:
Head, Biophysics Branch
Medical Sciences Division
Office of Naval Research, Navy Dept.
Washington, D. C.

Date March 31, 1949

Application is hereby made for a grant-in-aid in the amount of $ 12,120.00

for the period from July 1, 1949 to July 1, 1950, inclusive,* for the purpose of [redacted] continuing [redacted] a research project on the following subject:

Hormonal and Pharmacological Actions on the Formation of Tissue Phospholipides
(Give only brief statement of nature of project; details on pp. 2 and 3)

Camillo Artom, M. D., Professor and Head of the Department of Biochemistry
(Principal investigator) (Title)

Bowman Gray School of Medicine, Winston-Salem, North Carolina
(Address of principal investigator)

Mr. Harry O. Parker, Controller
(Title of financial officer to whom check should be mailed)

Bowman Gray School of Medicine, Winston-Salem, North Carolina
(Address of this officer)

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant-in-aid may be revoked in whole or in part at any time by the Surgeon General, provided that a revocation shall not include any amount obligated previous to the effective date of the revocation is such obligations were made solely for purposes set forth in this application; (3) that all reports of original investigations supported by any grant-in-aid made as a result of this request shall acknowledge such support; and (4) that if any patentable discoveries or inventions are made in the course of the work aided by any grant received as a result of this application, the applicant will, in consideration of such grant, refer to the Surgeon General of the Public Health Service, for determination, the question of whether such patentable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

Name of institution Bowman Gray School of Medicine of Wake Forest College

(Type name and title of official authorized to sign for institution) C. C. Carpenter, M. D., Dean

Signature of this official C. C. Carpenter

*This period is not to exceed 1 year.

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1. Outline the proposed work and the plan of attack. (Use a continuation sheet for details, if necessary.)

As shown in the enclosed progress report, a considerable amount of work has been done during the first nine months of operation of the project for which renewal application is made. Some of the results seem to be definite and interesting enough for publication in one complete paper. Other results will be the subject of four different preliminary reports at scientific meetings, but it is felt that further experimental elaboration is needed. It is anticipated that this elaboration will be started during the three months remaining before the expiration of the present contract, but to complete all the groups of experiments several more months of work will be necessary. Work on other points included in our original application has been initiated but progress has been less satisfactory and the results obtained thus far represent merely an indication of the lines along which future investigative efforts should be directed with a greater chance of success. This applies especially to the experiments in vitro. In these experiments the use of compounds labelled with C^{14} should probably be very helpful but, since work with C^{14} has not yet been started, it is expected that the time required for such experiments will extend much beyond July 1, 1949. Accordingly, a renewal of the present contract for one additional year is requested. The work planned will be essentially a continuation and extension along the lines proposed in the initial application. It is planned to devote a large part of the investigators' activity to the in vitro experiments and to use in these experiments both P^{32} and C^{14}. Besides the [illegible] already started, the action of other drugs and hormones will be studied and experiments made also on animals with altered liver functions and after surgical removal of certain endocrine glands.

2. Estimated total number of years of project duration ..one or two years.....

3. Has any work been done on this project by principal investigator (named on page 1)? Yes X.. No ...
If yes, what are the significant results and publications to date? If possible, please enclose reprints.

16-4727-2

See initial application and the progress report enclosed herein.

The following papers on related subjects have been published since the initial application was presented:

C. Artom and M. A. Swanson: On the Absorption of Phospholipides, Journal of Biological Chemistry, 175:871, September 1948.

C. Artom and W. E. Cornatzer: The Action of Ethanolamine, Methylethanolamine, and Dimethylethanolamine on Lipide Phosphorylation, Journal of Biological Chemistry, 176:949, November 1948.

W. E. Cornatzer and C. Artom: The Relation of Chemical Structure to the Stimulation of Lipide Phosphorylation, American Chemical Society, 114th Meeting Abstracts, P. 41-C, September 1948. (The complete paper will appear in Journal of Biological Chemistry, April 1949.)

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[illegible] tinent results bearing on this project have been obtained by other investigators.

See initial application.

5. (a) What financial support has been received for this or related research by the principal investigator or his associates?

Source	Amount	Years of Support (From ..... to .....)
Atomic Energy Commission (Contract No. N8onr-63701, Office of Naval Research	$16,350	1948-1949

(b) Does the principal investigator have other requests for assistance on this or related research projects pending with governmental agencies, ow with public or private foundations? Yes ... No X.

If yes, give significant data, including title of project, name of agency, and amount of requested funds.

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Budget for proposed project from July 1, 1949 to June 30, 1950

Item	Funds requested From the Public Health Service	Funds from other Sources
Personnel (Itemize):		
Camillo Artom, M. D. Professor	None	Salary from Bowman Gray
W. E. Cornatzer, Ph. D., Asst. Professor	None	" " " "
M. A. Swanson, Ph. D., Instructor	None	" " " "
Marietta Crowder, Graduate Student	None	" " " "
Full-time technician (M.L. Haigler)	2,160.00	
2 Part-time technicians (Not selected)	2,160.00	
Permanent Equipment (Itemize):		
High speed centrifuge	650.00	
Two carbon combustion apparatus	600.00	
* Analytical balance	350.00	
Direct reading balance for animals	250.00	
Geiger-Muller counter with Q gas	450.00	
Shielded manual sample changer with amplifier	200.00	
Accessories for Warburg apparatus	850.00	
Consumable Supplies (Itemize):		
Radioactive phosphorus	250.00	
Radioactive compounds (C^{14} labelled)	1,250.00	
Animals	500.00	
Glassware	600.00	
Chemicals	500.00	
Organic Solvents	300.00	
Travel:		
First International Congress of Biochemistry, Cambridge, England*	650.00	
Scientific conferences and visits in this country	250.00	
Other Expense (Itemize):		
Books, drawings, reprints	150.00	
Maintenance, repairs and replacements for radioactivity apparatus	350.00	
Incidentals	150.00	
Total	12,120.00	

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*A paper based on the results of the present work is included in the program of the Congress

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March 31, 1949

Progress report on the research project

HORMONAL AND PHARMACOLOGICAL ACTION ON THE FORMATION OF TISSUE PHOSPHOLIPIDES

sponsored by the Atomic Energy Commission, Division of Biology and Medicine, under Contract No. N8onr-63701 between the Office of Naval Research, U. S. Navy Department and the Bowman Gray School of Medicine.

Principal Investigator: Dr. Camillo Artom

Research Progress

The present report covers the work done from July 1, 1948 to March 31, 1949. As indicated in the original application, the experiments have been carried out simultaneously on intact animals and on isolated tissues. In both experimental conditions the synthesis of phospholipides has been studied by determining the concentration of radioactive phosphorus in the liver lipides after introduction in vivo or in vitro of sodium phosphate containing P^{32}. In relation to these experiments, a collateral study was also made on the toxicity of radioactive P in mice fed various diets. Because of the delay in the functioning of an isotope laboratory suitable for work with relatively high radioactivities, radioactive carbon as a label for choline or related compounds could not be used as it was originally planned.

A. Experiments on intact animals.

The action of various chemical agents has been studied by comparing the isotope concentrations in the liver lipides of control rats and in those of rats which were maintained under the same experimental conditions, but received also various amounts of the substances to be tested. The results obtained in the various groups of these experiments are here briefly summarized.

(a) Certain drugs which are believed to be rather general poisons for the living cells, such as urethane, SH and nitrogen mustards, did not affect markedly the rate of phospholipide formation in the liver. These results may be taken as an indication of the considerable ability of the liver to synthesize adequate amounts of phospholipides even under very adverse conditions. On the other hand, it seems likely that if other substances were found to cause changes in this process, these substances should be regarded as acting more or less specifically on the formation of phospholipides in the liver.

(b) Substances which are known as inhibiting the elaboration of thyroid hormone, such as thiourea, thiouracil and propyl-thiouracil caused moderate but significant decreases in the turnover of liver phospholipides. Since these results could not be duplicated in experiments on thyroidectomized rats, it is tentatively suggested that thiourea and the related substances may directly affect phospholipide formation in the liver. The results of this group of experiments will be reported at the future meeting of the N. C. Academy of Science. An abstract of the paper which will be read at this meeting is enclosed.

(c) A few experiments have been made on rats with glucosuria caused by the administration of alloxan or phlorizin. At present, no definite changes in lipide phosphorylation could be ascertained in either experimental condition, but it is felt that much more work is needed on this point.

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(d) Several other substances have also been tested which have a chemical constitution more or less closely related to that of the main nitrogenous constituents of phospholipides, choline and ethanolamine. Among these substances, guanidoacetic acid caused a considerable inhibition in the phospholipide turnover. While the action of this substance requires further study, it seems likely that guanidoacetic acid competes for the methyl groups required in the synthesis of choline. A similar marked decrease in the formation of liver phospholipides was observed after prolonged feeding of an analogue of ethanolamine (diethanolamine). The action of the latter compound was studied in detail. The results obtained will be presented and discussed at the next meeting of the Federation of the American Biological Societies in Detroit, Mich. An abstract of the paper to be presented is enclosed. A complete paper on the same subject has also been prepared and submitted for publication. A copy of this completed manuscript is also enclosed.

(e) The results of the last mentioned experiments were of considerable interest for the problem concerning the relation of the lipide phosphorylation to the supply of methyl donors and methyl acceptors in the diet. A number of experiments have been made on this problem. The results of these experiments have been compared with those obtained previously in this and other laboratories and a paper on this subject will be presented at the first International Congress of Biochemistry to be held in Cambridge, England, August 1949. An abstract of this paper is enclosed.

B. **In vitro experiments**

In these experiments the synthesis of phospholipides have been studied using liver slices, liver homogenates and liver extracts in different stages of purification. Thus far, good results have been obtained only with liver slices in aerobic conditions. The effects of the nutritional state of the animals from which the liver was obtained and the action of various phospholipide components added to the system in vitro have been studied. Further work is required before definite conclusions can be obtained.

C. Toxicity of P^{32} as related to dietary factors

In most of the above experiments radioactive phosphorus has been used as a tracer in animals maintained on inadequate diets which might have caused functional and anatomical changes in the liver. Accordingly, it seemed of interest to investigate the possibility that the toxicity of the radioactive isotope could be increased by dietary deficiencies especially by a lack of lipotropic factors. This possibility was of even greater interest to investigators in this department and in the Department of Medicine who are carrying out experiments with introduction of radioactive phosphorus in patients with liver disease. Accordingly, in collaboration with these investigators, the toxicity of radioactive phosphorus in mice maintained on various diets was studied. No appreciable change was detected by varying the level of proteins and fats in the diets or by supplementing a low protein diet with choline. The results of these experiments will be reported at the next meeting of the N. C. Academy of Science. An abstract of the paper which will be presented, is enclosed.

Personnel

In addition to the principal investigator the following professional workers have collaborated in the experiments: Dr. W. E. Cornatzer (Assistant Professor of Biochemistry), Dr. M. A. Swanson, (Instructor of Biochemistry), M. Crowder and P. Mitchell (Graduate Students), M. L. Haigler (Technician). Part-time technical help has been obtained also by three other individuals. Some experiments were made in collaboration with investigators of the Department of Medicine.

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Equipment

The following permanent equipment has been purchased for work on the present project:

Warburg apparatus with all accessories
Micro Torsion Balance
A deep freeze cabinet and an Angle centrifuge which can be combined for centrifugation at low temperatures.

Travel

With the sums appropriated by the Atomic Energy Commission, three members of this faculty attended the conference on isotopes at the National Laboratory in Brookhaven (July 1948), and three other members attended the course on the use of isotopes at the National Laboratory in Oak Ridge, Tennessee (August 1948). These individuals were members of the Departments of Biochemistry, Medicine, Physiology and Pharmacology.

Isotope Laboratory

The completion of an isotope laboratory to be used by workers from the various departments of this school was delayed, because it was considered expedient to install the isotope laboratory in a new addition to the present building of this school which was under construction. Only recently the construction of this addition has been completed and it is expected that in about three weeks the isotope lab will be ready for use. With the partitions and alterations made possible by the funds included in the present contract, the isotope unit will include one room for chemical work with high radioactivities, one for chemical work at the medium radioactivity level, one room for animals, one room for the study of human patients, one small office, one wash room and one counting room. Safety and protection devices have been purchased with funds shifted from this contract to Contract No. N8onr-63702 of which Dr. C. T. Harrell is the principal investigator. It is believed that the new lab will be adequate for a considerable extension of the work with radioactive isotopes in this school and will also allow the preparation of compounds labelled with C^{14} which will be used in the further development of the present investigations.

Budget

A financial breakdown of the expenditures made or to be made during the first nine month period of the present research project is as follows:

Actual Disbursements:

Salaries	$ 2,250.00
Materials and Supplies	977.75
Travel	990.80
Equipment	1,573.94

Unpaid Commitments:

Alterations and partitions for the isotope lab	6,250.00
Animals, materials and supplies ordered	350.00
TOTAL	$ 12,392.49

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It is believed that the sum remaining from the total appropriation will be completely used during the period from March 31st through June 30, 1949.

K. Camillo Artom

Dr. Camillo Artom

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number NRG-1
(Rev. 9-47)

ATOMIC ENERGY COMMISSION

Budget Bureau No. 68-R249.1.
Expiration date Nov. 30, 1948.

APPLICATION FOR GRANT FOR RESEARCH PROJECT

Director, Division Biology and Medicine
Atomic Energy Commission
, Constitution Ave.
,
Washington 25, D.C.

Date April 27, 1949

Application is hereby made for a grant-in-aid in the amount of $ 3,135.00 for the period from July 1, 1949 to June 30, 1950 inclusive,* for the purpose of conducting a research project on the following subject:

Toxicity of P^{32} as Related to the Functional Capacity of the Liver

(Give only brief statement of nature of project; details on pp. 2 and 3)

Drs. C. Artom (Biochemistry), G. T. Harrell (Medicine), and D. Cayer (Medicine)
(Principal investigator) (Title)

Depts. of Biochemistry and Dept. of Medicine, Bowman Gray School of Medicine
(Address of principal investigator) Winston-Salem, N. C.

Harry O. Parker, Controller
(Title of financial officer to whom check should be mailed)

Bowman Gray School of Medicine, Winston-Salem, N. C.
(Address of this officer)

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant-in-aid may be revoked in whole or in part at any time by the Surgeon General, provided that a revocation shall not include any amount obligated previous to the effective date of the revocation is such obligations were made solely for purposes set forth in this application; (3) that all reports of original investigations supported by any grant-in-aid made as a result of this request shall acknowledge such support; and (4) that if any patentable discoveries or inventions are made in the course of the work aided by any grant received as a result of this application, the applicant will, in consideration of such grant, refer to the Surgeon General of the Public Health Service, for determination, the question of whether such patentable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

Name of institution Bowman Gray School of Medicine of Wake Forest College

(Type name and title of official authorized to sign for institution) C. C. Carpenter, M. D., Dean

Signature of this official C. C. Carpenter

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*This period is not to exceed 1 year.

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1. Outline the proposed work and the plan of attack. (Use a continuation sheet for details, if necessary.)

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 malignancie 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, thus 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 P^{32} 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. Estimated total number of years of project duration ..... Two years

3. Has any work been done on this project by principal investigator (named on page 1)? Yes X. No ...
If yes, what are the significant results and publications to date? If possible, please enclose reprints.

16-4727-2

In preliminary experiments the mortality and survival time of mice maintained on various diets and injected with increasing amounts of P^{32} has been studied. A preliminary report is on the program of the annual meeting of the N. C. Academy of Science, May 7, 1949. Three copies of this report are enclosed.

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What pertinent results bearing on this project have been obtained by other investigators?

The only data on the toxicity of P^{32} are those of Anthony and Snyder--(Atomic Energy Commission Document MDDC-881). On the basis of a few experiments, the LD_{50} for mice on unspecified diets, receiving one injection of P^{32} would be of approximately 4 microcuries per gram of body weight.

5. (a) What financial support has been received for this or related research by the principal investigator or his associates?

Source	Amount	Years of Support (From ..... to .....)
NONE		

(b) Does the principal investigator have other requests for assistance on this or related research projects pending with governmental agencies, ow with public or private foundations? Yes ... No .X.

If yes, give significant data, including title of project, name of agency, and amount of requested funds.

16-47427-2

The preliminary experiments mentioned above were made as a collateral investigation supported by the grant-in-aid of the project, "Hormonal and Pharmacological Action on the Formation of Tissue Phospholipides."

(C O P Y)

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Budget for proposed project from July 1, 1949 to June 30, 1950

Item	Funds requested From the Public Health Service	Funds from other Sources
Personnel (Itemize):		
C. Artom (Principal investigator)		Bowman Gray School of Medicine
G. T. Harrell (Principal investigator)		Bowman Gray School of Medicine
D. Cayer (Principal investigator)		Bowman Gray School of Medicine
Technical Help	$ 1500.00	
Permanent Equipment (Itemize):		
Metabolism cages for animals injected with highly radioactive materials	250.00	
One homogenizer for the preparation of the diets	35.00	
One direct reading balance for animals and diets	250.00	
Consumable Supplies (Itemize):		
Radioactive phosphorus	300.00	
Dietary components	500.00	
Glassware and containers	150.00	
Travel:		
Other Expense (Itemize):		
Miscellaneous expenses	150.00	
Total	$ 3135.00	

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TOXICITY OF RADIOACTIVE PHOSPHORUS IN MICE ON VARIOUS DIETS *

By W. E. Cornatzer, David Cayer, George T. Harrell, Jr. and Camillo Artom.

(From the Departments of Biochemistry and Medicine, Bowman Gray School of Medicine, Winston-Salem, North Carolina).

The present investigation is a part of a more extended study undertaken with the idea that the resistance of the organism to the toxic effects of radioactive isotopes introduced into the body may be decreased by alterations in the functional capacity of the liver. This point would, of course, be of practical interest for the use of radioactive isotopes as diagnostic and therapeutic agents in patients with liver diseases since in these individuals even small doses of radioactivity could exert an additive harmful action.

To our knowledge, the only data on the toxicity of P^{32} are those of Anthony and Snyder (Atomic Energy Commission, Document MDDC-881). On the basis of a few experiments on mice (presumably maintained on a stock diet), these authors suggest that the LD_{50} after one injection of P^{32} is around 4 microcuries per gram of body weight. With this dose 4 out of 6 mice died between 16 to 21 days.

In the present experiments we have studied the mortality and survival time of mice maintained on diets of known composition and injected with radioactive phosphorus as sodium diphosphate. We have investigated the possible role of a deficiency of lipotropic factors in the diets, such a deficiency leading to a fatty infiltration

*Presented at the Annual Meeting of the N. C. Academy of Science, May 7, 1949, Chapel Hill, N. C.

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of the liver. If in this condition the toxicity of the isotope were increased, supplementation of the diet with choline should give a more or less marked protection.

Several groups of mice (approximately 20 gm. body weight) were transferred from a stock diet to a low protein, high fat diet (Diet 31, containing casein 10 parts, Crisco 30, cod liver oil 2, sucrose 29, dextrin 23, roughage, salts and B vitamins). The animals were maintained for five days on the diets, then they were injected with a single dose of radioactive phosphorus and kept under observation for three weeks. To date, a total of 120 mice have been used.

There were no deaths among mice not injected with radioactive P and maintained for 25 days on the unsupplemented diet. Of the animals injected with 2 microcuries per gram of body weight and maintained on either the unsupplemented or supplemented diet none died in 21 days. With 4 microcuries per gram of body weight the mortality at the twenty-first day was 16% and the average survival time was of 20 days for both the controls on the unsupplemented diet and the mice of the choline supplemented diet. With 6 microcuries per gram of body weight the mortality has been 72% and 86% and the average survival time 16 and 12 days, respectively. With 8 microcuries per gram of body weight the mortality was 89 and 89 per cent and the average survival time 12 and 13 days respectively.

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In another group of rats injected with 6 microcuries per gram of body weight the level of the fat in the diet was decreased from 32 to 5 per cent (Diet 34). There was a slight decrease in mortality but no change in the survival time after injecting 6 microcuries per gram. Likewise, no significant protection was observed when the protein content of the low fat, low protein diet was increased from 10 to 25% (Diet 29).

This work was supported by the U. S. Atomic Energy Commission under a contract between the Bowman Gray School of Medicine and the Office of Naval Research, U. S. Navy Department. The P^{32} used was supplied by the National Laboratory, Oak Ridge, Tennessee, on allocation from the U. S. Atomic Energy Commission.

1112076

CURRICULUM VITAE

Full Name: David Cayer

Born: [redacted] Connecticut

Preliminary education: [redacted]

College education: [redacted]

Medical education: [redacted]

Post Graduate Training: North Carolina State Sanatorium for the treatment of Tuberculosis 1-1-29 to 3-31-39
Duke University Hospital, Intern Medicine, 4-1-39 to 1-1-40.
Assistant resident in Medicine 1-1-40 to 7-1-42.
Resident in Medicine 7-1-42 to 7-1-43.

Assistant in Physiology and Pharmachology of Duke University School of Medicine, 3-3-41 to 6-16-41.

Instructor in Medicine, Duke University School of Medicine, 7-1-42 to 12-30-44.

Research Fellow in Medicine 7-1-43 to 6-30-44.

Fellow in Medicine, Diagnostic Clinic, Duke Hospital, 7-1-44 to 12-31-44.

Assistant Professor of Medicine, Bowman Gray School of Medicine, 1-1-45 to present.

Consultant in Internal Medicine to Veterans Administration, 1948.

Licensed to practice in the following states:
Florida, 1941: North Carolina, 1945.

Certified American Board of Internal Medicine, 1946.

Society Membership:

Phi Beta Kappa, Duke, 1935.
A.O.A., Duke, 1948.
Forsyth County Medical Society, 1-1-45.
North Carolina State Medical Society, 7-1-44.
American Medical Association (Fellow) Sept. 1944.
Trudeau Society, June 1943.
Diplomate National Board, June, 1940.
Tri-State Medical Society, June, 1945.
American College of Physicians (Fellow) 1949.
American Association for the Advancement of Science, 1946.
Southern Society for Clinical Research, 1948.
American Society for Clinical Investigation, 1948.
American Gastroenterologic Association, 1948.

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BIBLIOGRAPHY OF DR. DAVID CAYER

1. Cayer, David: Relative Bradycardia as a Sign of Sulfonamide Fever, North Carolina M. J. 2:486-489 (Sept.) 1941.

2. Cayer, David and Ruffin, Julian M.: The Treatment of Chronic Idiopathic Ulcerative Colitis with Sulfaquanidine, North Carolina M. J. 3:196-197 (April) 1942.

3. Cayer, David and Baylin, George: Duodenal Diverticula, North Carolina M. J. 3:589-591 (Nov.) 1942.

4. Ruffin, Julian M. and Cayer, David: The Present Status of Vitamin Therapy in Deficiency States, North Carolina M. J. 5:37-40 (Feb.) 1944.

5. Ruffin, Julian M., Cayer, David and Perlzweig, William A.: The Relationship Between the Clinical Picture of a Mild or Early Vitamin Deficiency and Laboratory Determinations of Vitamin Levels, Gastroenterology 3:340-356 (Nov.) 1944.

6. Ruffin, Julian M. and Cayer, David: The Effect of Vitamin Supplements on Normal Persons, J.A.M.A. 126:823-825 (Nov.) 1944.

7. Cayer, David and Ruffin, Julian M.: The Clinical Significance of Glossitis and Cheilosis in Deficiencies of the B-Complex, South. M. J. 38:111-117 (Feb.) 1945.

8. Cayer, David and Dubin, I.N.: Case Report, Clinical Pathological Conference, North Carolina M. J. 6:103-105 (Feb.) 1945.

9. Perlzweig, W.A., Ruffin, Julian M., and Cayer, D.: Excretion of Orally Administered B Vitamin in Health and Disease, Fed. Proc., Vol. 4 (March) 1945.

10. Ruffin, Julian M., Baylin, George J. and Cayer, David: The Clinical Significance of Alteration of the Small Intestine Pattern as Demonstrated by X-ray, Gastroenterology 4:289-295 (April) 1945.

11. Cayer, David and Ruffin, Julian M.: Vitamin Levels in Sprue, Am. J. Med. Sc. 210:200-217 (Aug.) 1945.

12. Cayer, David: Case Report, Clinical Pathological Conference, North Carolina M. J. 6:524-527 (Dec.) 1945.

13. Cayer, David: The Diagnosis of Early Vitamin Deficiency Diseases, North Carolina M. J. 7:160-163 (April) 1946.

14. Cayer, David: Case Report, Clinical Pathological Conference, North Carolina M. J. 7:225-228 (May) 1946.

15. Cayer, D., Ruffin, J.M., and Perlzweig, W.A.: Vitamin Levels in Pernicious Anemia, Am. J. Med. Sc. 212:179 (Aug.) 1946.

16. Cayer, David: Case Report, Clinical Pathological Conference, North Carolina M. J. 7:481-483 (Sept.) 1946.

17. Cayer, D.: Diagnosis and Treatment of Early Vitamin Deficiency States, J.A.M.A. 132:558-561 (Nov. 9) 1946.

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18. Taylor, F.R. and Cayer, David: Pellagra Chapter, Oxford Medicine (Feb.) 1947.

19. Jarvis, J.L. and Cayer, D.: Cancer of Caecum, Am. J. D. D. 14:95-99 (March) 1947.

20. Jarvis, J.L. and Cayer, D.: Cholecystography with Priodax, Correlation of X-ray and Pathologic Findings, Gastroenterology 8:461-466 (April) 1947.

21. Abernathy, J. and Cayer, D.: Amoebiasis - Case Reports, N. C. B. H., North Carolina M. J. 8:201-203 (April) 1947.

22. Crescenzo, Victor M. and Cayer, David: Vitamin C Levels in Peptic Ulcer, Gastroenterology 8:754-761 (June) 1947.

23. Cayer, D., and Cody, S.: Nutritional State of Patients with Peptic Ulcer as Determined by Vitamin Levels in Blood and Urine, Gastroenterology 9:54 (July) 1947.

24. Cayer, D., Crescenzo, V., and Cody, S.: Plasma Vitamin A Levels in Pregnancy Relation to Total Lipids, Am. J. Obst. & Gyn. 54:259 (Aug.) 1947.

25. Cayer, D.: Clinical Pathological Conference, Gastroenterology 9:198-204 (Aug.) 1947.

26. Cayer, D., and Nabors, G.C.: A Clinical Evaluation of Total Blood Proteins and Albumin and Globulin Fractions in Hospitalized Patients, South. M. J. 40:744-751 (Sept.) 1947.

27. Taylor, F.R. and Cayer, D.: Anhidrotic Syndromes, Oxford Medicine 1947.

28. Cayer, D.: Case Report, Clinical Pathological Conference, North Carolina M. J. 8:671-674 (Oct.) 1947.

29. Little, J.M., Ogle, B.C., Yeagley, J.D., and Cayer, D.: Effect of Tetraethyl Ammonium Chloride in Experimental Gastric Ulceration in the Rat, Science 106:448-449 (Nov. 7) 1947.

30. Cayer, D.: Clinical and Laboratory Observations on the Use of Methionine and Vitamin Supplements in the Treatment of Liver Disease, Arch. Int. Med. 80:644-654 (Nov.) 1947.

31. Cayer, D. and Cody, S.: Urinary Excretion of Niacin and Riboflavin in Acute Infections and Various Chronic Diseases, Am. J. Med. Sc. 215:273-278 (March) 1948.

32. Cayer, D.: Clinical Pathological Conference, North Carolina M. J. 9:210-213 (April) 1948.

33. Gaddy, C.S. and Cayer, D.: Chronic Glomerulonephritis Without Hypertension, Cardiac Enlargement or Retinal Changes, North Carolina M. J. 9:256-260 (May) 1948.

34. Cayer, D.: Modern Concepts in the Medical Treatment of Liver Disease, American Clinica 13:138-141 (Aug.) 1948.

35. Jarvis, J.L. and Cayer, D.: The Effects of Radiation Therapy on the Urinary Excretion of Niacin and Riboflavin in Patients with Malignant Disease, Radiology (in press).

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36. Cayer, D.: Case Report, Clinical Pathological Conference, North Carolina M. J. 9:535-537 (Oct.) 1948.

37. Yeagley, J.D. and Cayer, D.: Changes in Gastric pH Following the Administration of Fruit Juice to Patients with Peptic Ulcer, North Carolina M. J. 9:555-561 (Nov.) 1948.

38. Cayer, D.: Case Report, Clinical Pathological Conference, North Carolina M. J. 9:637-641 (Dec.) 1948.

39. Yeagley, J.D., Cayer, D., and McMillan, R.L.: A Clinical Evaluation of Gastrointestinal Signs and Symptoms in Patients with Coronary Heart Disease and Recent Myocardial Infarction, North Carolina M. J. 10:22-27 (Jan.) 1949.

40. Cayer, D., Little, J.M., and Yeagley, J.: The Use of Tetraethylammonium Chloride in the Treatment of Patients with Peptic Ulcer, Gastroenterology 12:219-224 (Feb.) 1949.

41. Cayer, D.: Chapters in Therapeutics in Internal Medicine Thomas Nelson and Sons, N.Y
Deficiency Diseases
Vitamin A Deficiency
Xerophthalmia
Keratomalacia
Vitamin B Deficiency
Beriberi
Pellagra
Ariboflavinosis
Vitamin C Deficiency
Scurvy
Vitamin D Deficiency
Ricketts
Vitamin K Deficiency

42. Cayer, D., and Cornatzer, W.E.: The Effects of Choline and Methionine on Phospholipide Formation in Patients with Liver Disease as Measured by Radioactive Phosphorus, Science (Accepted for Publication).

43. Cayer, D. and Cornzater, W. E.: The Effects of Lipotropic Substances on Phospholipide Synthesis in Patients with and Without Chronic Hepatitis, South. M. J. (in press).

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WAKE FOREST COLLEGE

C
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THE BOWMAN GRAY SCHOOL OF MEDICINE

Winston- Salem, North Carolina

May 2, 1949

Director
Division of Biology and Medicine
Atomic Energy Commission
Constitution Avenue
Washington 25, D.C.

Dear Sir:

I am very happy to approve on behalf of the Bowman Gray School of Medicine of Wake Forest College the three research proposals for application of isotopes to the study of human disease which are enclosed. A great deal of interest has been aroused among the members of our faculty actively engaged in research of the Fellowship Training Program of the Atomic Energy Commission. As you are aware, the first of the Fellows whose training was begun under this program has progressed sufficiently far to enable him to start out on his own in another institution. We are very happy to continue to train additional Fellows as they are assigned to us by the Commission.

The College is very grateful to the Commission for making available to us facilities to expedite research in the various departments of the School. These research projects could not have been undertaken without your encouragement and financial assistance in helping to make available the necessary facilities. As you are well aware, in the coming years the critical factor will be personnel rather than facilities and equipment. Assistance of the Commission in enabling the investigators to secure and retain adequately trained personnel of the necessary high caliber will be essential to successful prosecution of the research and training.

Please let me express to you on behalf of the College and School of Medicine our appreciation for your help in the past. We have tried to keep our request moderate and sufficient to cover only our immediate need. We believe that the transfer of the administration of our contract to the Operations Office, Oak Ridge, will facilitate the Administration in handling of the details of the contract.

Cordially yours,

G.C. Carpenter, M.D.
Dean

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WAKE FOREST COLLEGE

THE BOWMAN GRAY SCHOOL OF MEDICINE, WINSTON-SALEM

NORTH CAROLINA

ZONE 7

May 2, 1949

Director
Division of Biology and Medicine
Atomic Energy Commission
Constitution Avenue
Washington 25, D.C.

Dear Sir:

In compliance with your letter of April 20, 1949, Dr. Thurman D. Kitchin, President of Wake Forest College, through Dr. C. C. Carpenter, Dean of the Bowman Gray School of Medicine, has designated me to serve as the co-ordinator for the various proposals for the participation of Wake Forest College in the Fellowship Program.

You will find enclosed separate proposals for the continuation of the research of Dr. Camillo Artom on "Hormonal and Pharmacological Actions on the Formation of Tissue Phospholipides"; Dr. George T. Harrell on "Distribution and Turnover of Sodium and Potassium in Acute Infections"; a new proposal by Doctors Artom, Harrell, and David Cayer on "Toxicity of P^{32} as Related to the functional Capacity of the liver." Each proposal is complete with the program report, proposal for the work to be done, and a budget. Also enclosed are a blue print of the isotope laboratory under construction, a copy of the latest catalog of Bowman Gray School of Medicine. Attached is a co-ordinated summary of the research grants and proposals.

By the last of the summer, the equipment requested in the renewals, proposals and that purchased with this year's grants should all be installed in the new isotope laboratory on the fifth floor. These facilities are to be available for all departments in the school. We shall attempt to interest other departments in the application of isotope techniques to their specific research problems.

The needs of the individual investigators for their specific research projects are discussed in each separate proposal. Please let me express to the Atomic Energy Commission for the Administration of the School as well as the individual investigators our appreciation for your gracious support this past year. We all look forward to a long continued, mutually profitable association. If there is any additional detailed information we can forward, please command us.

Respectfully yours,

George T. Harrell, M.D.
Professor of Medicine and
Director of the Department

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WAKE FOREST COLLEGE

THE BOWMAN GRAY SCHOOL OF MEDICINE

Winton-Salem, North Carolina

April 27, 1949

Dr. John Z. Bowers
Assistant to Director
Division of Biology and Medicine
U.S. Atomic Energy Commission
Washington 25, D. C.

Dear Dr. Bowers:

On March 31, 1949 I sent to you an application for one year renewal of the grant-in-aid from the Atomic Energy Commission currently administered by the Office of Naval Research (Contract No. N8onr-63701). This application (in 3 copies) was accompanied by a progress report (3 copies) summarising the results obtained during the first nine months of work, abstracts of four preliminary papers (3 copies each), the manuscript of a complete paper and reprints of two other recent papers (1 copy each). For your convenience, I am now enclosing three additional copies of this renewal application and also of the progress report.

After receiving the copy of your letter to Dr. Kitchin dated April 20th with the material enclosed and after our telephone conversation of yesterday, I would like to add the following comments concerning the sums requested for the coming year.

You will probably recall that the sum requested in my original application last year amounted to $18,840. The sum was reduced to $16,350, but this figure included the expenses for the participation of several faculty members of this school to training courses at the National Laboratories in Brookhaven and Oak Ridge ($900), and the expenses for alterations, partitions and work required for setting up an isotope laboratory to be used by all departments of this school ($6,250). Thus the actual amount available for the project was limited to $9,200. Accordingly, the original financial plans had to be revised and the work curtailed in order to keep the expenses within this limit. More especially, we omitted the purchase of the equipment, apparatus and compounds required for the experiments with C^{14} and we concentrated our activity on the experiments with radioactive phosphorus.

As shown by the progress report, we believe that our investigations have already given interesting results. However, one or two more years of intensive work will be necessary before more important and more solid conclusions can be reached. Moreover, it is my definite opinion that an extension of the present work by the use of C^{14} labelled compounds will be extremely useful for the correct interpretation of the results obtained thus far and of those which we hope to obtain in the future. On the basis of these considerations for most of the

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items the sums requested in the renewal application are higher than those which have been available to us this year (although they are much below the amounts listed in the original application of last year).

The increases in the item Technical Assistance (from $3600 to $4320) seems necessary since it does not seem possible to keep the present personnel or to obtain other technicians without somewhat higher salaries.

The expense for Permanent equipment (increased from $2100 to $2850) is intended essentially to cover apparatus necessary for work with C^{14}. In addition we would need one high speed centrifuge in order to fractionate the liver extracts with high speed centrifugation and accessories for the Warburg apparatus to study more intensively the metabolism of phospholipides in isolated liver.

The increase in the item Consumable supplies (from $2100 to $3400) is due chiefly to the cost of the synthesis of C14 labelled compounds.

The item Travel (increased from $300 to $900) includes the sum of $650 for participation of the undersigned to the First International Congress of Biochemistry in Cambridge, England, in the program of which a paper is included based on the results of the present work.

The increases in the Miscellaneous expenses (from $400 to $500) is due chiefly to the increased cost for maintenance, repairs and replacement of radioactivity apparatus. Such increases is to be expected in relation to the aging of these apparatus and to their intensive use.

With many thanks and best personal regards, I am

Sincerely yours,

Camillo Artom, M.D.

Enclosures

Renewal application for grant-in-aid
from the A.E.C. (3 copies)

Progress report (3 copies)

1112084

Coordinated Summary of Research Grants and Proposals

WAKE FOREST COLLEGE
Bowman Gray School of Medicine

(at present designated contract N8onr - 63701)

Principle Investigator		7/1/48 - 6/30/49 Budget Approved		7/1/49 - 6/30/50 Budget Requested	
Artom:					
(project NR-171 678)	Personnel	$ 3600		$ 4520	
Dept. Biochemistry	Equipment	- 2100		2000	
"Phospholipids"	Supplies	2100		3400	
	Other	700		1550	
			$ 8500		$12120
Harrell:					
(project NR-171 677)	Personnel	4200		4700	
Dept. Medicine	Equipment	3350		5225	
"Na and K"	Supplies	1250		2750	
	Other	700		400	
			9500		13075
Isotope Laboratory	Construction	6250		-	
(project NR-171 678)	Equipment	-		-	
			6250		
Training Program	Travel	900		-	
(project NR-171 678)			900		
Artom, Harrell, Cayer					
(New project)	Personnel			1500	
Dept. Biochemistry	Equipment			535	
and Medicine	Supplies			950	
	Other			150	
					3135
TOTAL			25150		28330
Overhead at 8% (none on lab. and training)			1440		2266
			$ 26590		$ 30596

1112085

BULLETIN

OF

WAKE FOREST COLLEGE

VOL. XLIII, NO. 7

THE BOWMAN GRAY SCHOOL OF MEDICINE

ROSTER OF FACULTY AND STUDENTS FOR THE ACADEMIC YEAR 1947-1948

ANNOUNCEMENTS FOR THE 1948-1949 SESSION

Winston-Salem, North Carolina

1112086

WAKE FOREST COLLEGE

Wake Forest College, a school of liberal arts, was founded in 1834 by the Baptists of North Carolina primarily to educate men for the ministry; and religious education continued to receive major emphasis in the life of the institution.

In 1879 the first effort toward the addition of other professional schools was made when the Board of Trustees voted to establish a School of Law. It was not until 1894 that the first law students registered, although classes in Law were actually begun in 1893 under private lectures.

Courses primarily designed to prepare students for the practice of medicine were instituted in 1887. A statement in the catalogue of that year announced a course of study "primarily to the study of medicine." Wake Forest College was therefore among the first in the United States to recognize the need for proper premedical training. The two-year School of Medicine was established in 1902.

A "summer school" was developed in 1897, but was not operated continuously until 1921. It was originally established to offer instruction to teachers in the public schools. The summer term now comprises very nearly the same curriculum as that given in the regular session.

Although Wake Forest was founded as a college for men, it now admits women to all classes, including the professional schools.

A seven million dollar enlargement program designed to provide facilities and instruction in keeping with the growth needs of the college was begun in 1943.

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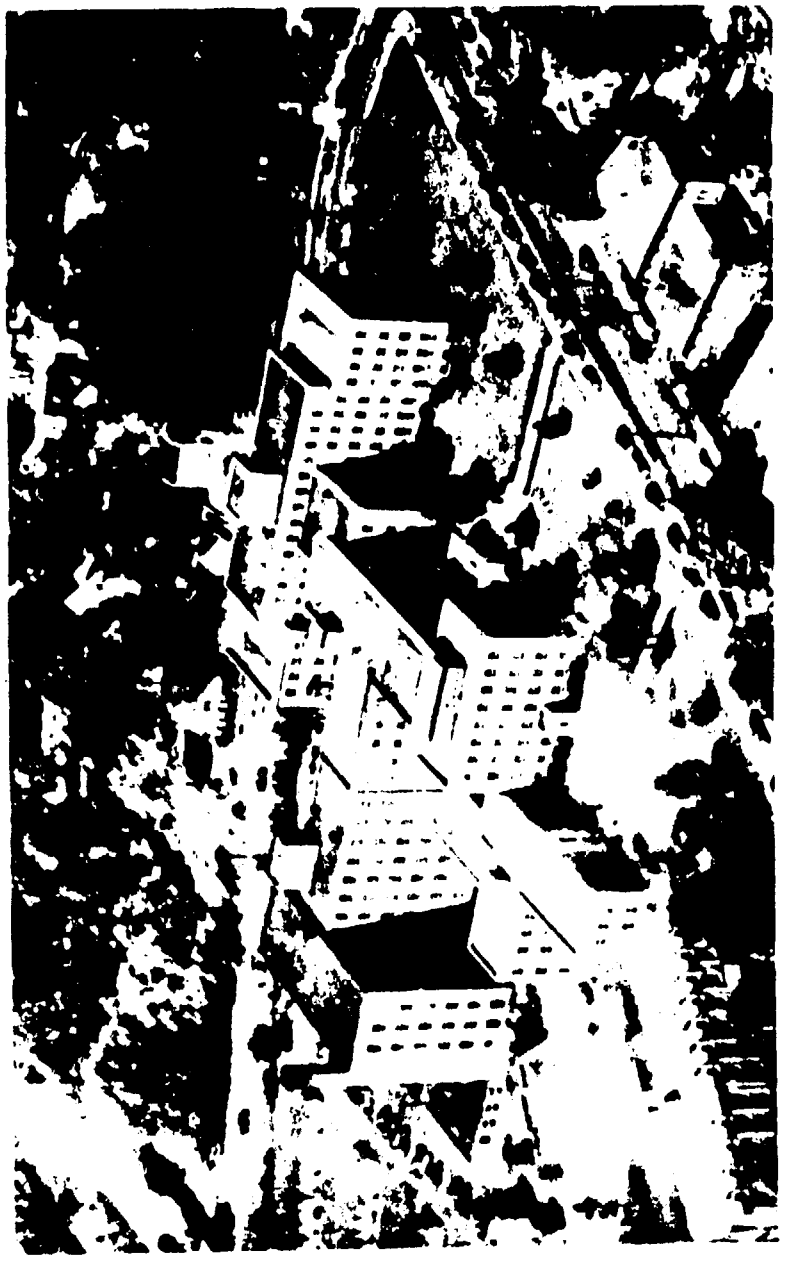
April 1948 Vol. XLIII, No. 2

BULLETIN OF WAKE FOREST COLLEGE

THE BOWMAN GRAY SCHOOL OF MEDICINE

WINSTON-SALEM
NORTH CAROLINA



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SCHOOL CALENDAR

The calendar of the school is planned to serve the greatest convenience of students and to provide an uninterrupted program of education, using the full twelve months of the year.

Freshman students are admitted once a year, in October. At the end of the first academic session of three eleven-week quarters, they are allowed a vacation until the opening of school the following October. On completion of the sophomore year the following spring, the student may go directly into the junior class during the summer quarter. Attendance in school is optional for each quarter of the junior and senior years. Courses in the junior and senior years are offered through the summer months, the same as during the traditional three-quarter academic year. The arrangement of the courses is done in such a manner that a student may drop out any quarter without detriment to his education. By electing to continue in school four quarters of the year without interruption after the sophomore year, the student may complete the entire course and receive the degree of Doctor of Medicine in thirty-nine months. This enables the student to graduate at a younger age and use the extra time for hospital training. He may elect to drop out for as many as two quarters and do research, take courses in other institutions, or work to earn money to continue his education. The plan also allows the slow student an opportunity to take as much as two extra quarters' work and yet graduate in the traditional four calendar years. Others may elect to be out of school two of the eight quarters of the last two calendar years and graduate within four years after entering.

Students who follow the accelerated schedule will have approximately two months vacation during the calendar year: one month in the summer and another month divided between the Christmas vacation and other times.

Details of the calendar are as follows:

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SCHOOL CALENDAR

Monday	Jan. 5, 1948	Winter quarter begins
Saturday	March 20, 1948	Winter quarter ends
Sunday	March 21, 1948	Spring vacation begins
Sunday	March 28, 1948	Spring vacation ends
Monday	March 29, 1948	Spring quarter begins
Saturday	June 12, 1948	Spring quarter ends
Sunday	June 13, 1948	Summer vacation begins
Sunday	July 11, 1948	Summer vacation ends
Monday	July 12, 1948	Summer quarter begins
Monday	Sept. 6, 1948	Labor Day, a holiday
Saturday	Sept. 25, 1948	Summer quarter ends
Sunday	Sept. 26, 1948	Fall vacation begins
Sunday	Oct. 3, 1948	Fall vacation ends
Tuesday	Sept. 28, 1948	Freshman students enroll
Monday	Oct. 4, 1948	Fall quarter begins
Thursday	Nov. 25, 1948	Thanksgiving Day, a holiday
Saturday	Dec. 18, 1948	Fall quarter ends
Sunday	Dec. 19, 1948	Graduation Day
Sunday	Dec. 19, 1948	Christmas vacation begins
Sunday	Jan. 2, 1949	Christmas vacation ends
Monday	Jan. 3, 1949	Winter quarter begins
Saturday	March 19, 1949	Winter quarter ends
Sunday	March 20, 1949	Spring vacation begins
Sunday	March 27, 1949	Spring vacation ends
Monday	March 28, 1949	Spring quarter begins
Monday	April 18, 1949	Easter Monday, a holiday
Saturday	June 11, 1949	Spring quarter ends
Sunday	June 12, 1949	Summer vacation begins
Sunday	July 10, 1949	Summer vacation ends
Monday	July 11, 1949	Summer quarter begins
Monday	Sept. 5, 1949	Labor Day, a holiday
Saturday	Sept. 24, 1949	Summer quarter ends
Sunday	Sept. 25, 1949	Fall vacation begins
Sunday	Oct. 2, 1949	Fall vacation ends
Tuesday	Sept. 27, 1949	Freshman students enroll
Monday	Oct. 3, 1949	Fall quarter begins
Thursday	Nov. 24, 1949	Thanksgiving Day, a holiday
Saturday	Dec. 17, 1949	Fall quarter ends
Sunday	Dec. 18, 1949	Graduation Day
Sunday	Dec. 18, 1949	Christmas vacation begins
Sunday	Jan. 1, 1950	Christmas vacation ends
Monday	Jan. 2, 1950	Winter quarter begins

CALENDARS

1947

JANUARY

S	M	T	W	T	F	S
-	-	-	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	-
-	-	-	-	-	-	-

FEBRUARY

S	M	T	W	T	F	S
-	-	-	-	-	-	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	-
-	-	-	-	-	-	-

MARCH

S	M	T	W	T	F	S
-	-	-	-	-	-	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	-	-	-	-	-

APRIL

S	M	T	W	T	F	S
-	-	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	-	-	-
-	-	-	-	-	-	-

MAY

S	M	T	W	T	F	S
-	-	-	-	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
-	-	-	-	-	-	-

JUNE

S	M	T	W	T	F	S
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	-	-	-	-	-
-	-	-	-	-	-	-

JULY

S	M	T	W	T	F	S
-	-	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	-	-
-	-	-	-	-	-	-

AUGUST

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SEPTEMBER

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OCTOBER

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NOVEMBER

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DECEMBER

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1948

JANUARY

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FEBRUARY

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MARCH

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APRIL

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MAY

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JUNE

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JULY

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AUGUST

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SEPTEMBER

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OCTOBER

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NOVEMBER

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DECEMBER

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1949

JANUARY

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FEBRUARY

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MARCH

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APRIL

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MAY

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JUNE

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JULY

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AUGUST

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SEPTEMBER

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OCTOBER

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NOVEMBER

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DECEMBER

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FEBRUARY

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MARCH

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APRIL

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JUNE

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JULY

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AUGUST

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SEPTEMBER

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OCTOBER

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NOVEMBER

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DECEMBER

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Director of Religious Activities

MCMILLAN, ROBERT L., B.S., M.D.
Associate Professor of Clinical Medicine

MEADS, MANSON, A.B., M.D.
Instructor in Internal Medicine

MONTAGNET, JOSEPH M., B.S., M.D.
Assistant in Obstetrics and Gynecology

MOORE, ROBERT A., M.D.
Assistant Professor of Surgery in Charge of Orthopedics

MOREHEAD, ROBERT P., B.S., M.A., M.D.
Professor of Pathology, Director of Department of Pathology, and Chairman of Division of Structure

MORGAN, RALPH S., B.S., M.D.
Assistant in Internal Medicine

MYERS, RICHARD T., A.B., M.D.
Assistant in Surgery

NORFLEET, CHARLES M., JR., B.S., M.D.
Instructor in Urology

ODOM, ROBERT T., PH.C., M.D.
Instructor in Surgery

OGBURN, LUNDIE C., M.D.
Assistant in Clinical Obstetrics and Gynecology

PATTON, WILLIAM H., M.D.
Assistant in Pediatrics

PHILLIPS, JOSEPH T., JR., B.S., M.D.
Assistant in Surgery

PICKEN, ROBERT L., B.S., M.D.
Assistant in Internal Medicine

PINNEY, CHARLES T., M.D.
Assistant in Internal Medicine

POOL, BENNETTE B., B.A., M.D.
Assistant Professor of Clinical Medicine

POSTLETHWAIT, RAYMOND V., M.D.
Instructor in Surgery

PREVETTE, WILLIAM C., M.D.
Assistant in Surgery

PRICE, HENKEL M., A.B., M.D.
Assistant in Radiology

REID, CHARLES H., JR., B.A., M.D.
Assistant in Clinical Medicine

ROBERTS, R. WINSTON, JR., M.D.
Instructor in Ophthalmology

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ROUSSEAU, JAMES P., M.D.
Professor of Radiology and Director of Department of Radiology

SCHAFER, EARL W., A.B., M.D.
Instructor in Surgery and Orthopedics

SCHRUM, DAVID I., M.D.
Instructor in Pediatrics

SELMAN, JOSEPH, B.S., M.D.
Assistant in Radiology

SHAFFNER, LOUIS, M.D.
Assistant in Surgery

SHEPARD, KARL, B.S., M.D.
Assistant in Clinical Medicine

SMITH, DAVID C., B.S., M.D.
Assistant in Internal Medicine

SPEAS, WILLIAM P., M.D., M.SC.
Assistant Professor of Surgery in Charge of Ophthalmology

SPOON, RILEY E., B.S., D.D.S.
Instructor in Dental Surgery

SPRUNT, WILLIAM H., JR., B.S., M.D.
Professor of Clinical Surgery

STARLING, HOWARD M., M.D.
Instructor in Surgery

STEVENS, JOSEPH B., B.S., M.D.
Assistant in Clinical Medicine

SWANSON, MARJORIE, B.S., M.S., PH.D.
Instructor in Biochemistry

TAYLOR, FREDERICK R., B.S., M.D.
Professor of Medical Literature and Associate Professor of Clinical Medicine

THOMAS, WILBUR C., B.S., M.D.
Assistant Professor of Pathology in Charge of Legal Medicine and Autopsy Pathology

THOMPSON, LLOYD J., A.B., M.D.
Professor of Neuropsychiatry and Director of Department of Neuropsychiatry

TUCKER, THELMA T., A.B.
Research Assistant in Bacteriology

VALK, A. DET., A.B., M.A., M.D.
Professor of Clinical Surgery

VALK, HENRY L., A.B., M.D.
Assistant in Internal Medicine

VANN, HERBERT M., B.S., M.A., M.D.
Professor of Anatomy in Charge of Gross Anatomy

WALL, ROSCOE L., B.S., M.D.
Assistant Professor of Surgery in Charge of Anesthesia

WATKINS, J. CONRAD, B.A., D.D.S., SC.D.
Professor of Periodontia and Clinical Dental Surgery in Charge of Dentistry

WEDDE, THEODORE S., M.D.
Associate in Pathology

WELFARE, CHARLES R., B.S., M.D.
Assistant in Clinical Medicine

WHEELER, RAYMOND F., M.D.
Assistant in Internal Medicine

WHITAKER, J. A., M.D.
Fellow in Urology

WIGGINS, JOHN C., JR., A.B., M.D.
Assistant in Internal Medicine

WILKINS, MCMURRAY, B.S., M.D.
Assistant in Internal Medicine

WILLIAMS, ERNEST H., B.S., M.D.
Assistant in Internal Medicine

WILLIAMS, JEROME O., M.D.
Assistant in Pathology

WOLFF, WILLIAM A., A.B., A.M., PH.D.
Associate Professor of Clinical Chemistry and Toxicology

WRIGHT, ORPHEUS E., M.D.
Assistant in Clinical Medicine

YODER, PAUL A., B.A., M.D.
Assistant Professor of Clinical Medicine

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GENERAL INFORMATION

ORIGIN AND DEVELOPMENT

The School of Medicine, established at Wake Forest in 1902, and renamed the School of Medical Sciences in 1937, operated as a two-year medical school until 1941, when it was moved to Winston-Salem, North Carolina, as a four-year medical college. When the school was expanded to a four-year institution, it was renamed The Bowman Gray School of Medicine of Wake Forest College, in recognition of the benefactor who made the expansion possible, the late Bowman Gray, of Winston-Salem.

The expansion and the enlargement program was made possible on August 3, 1939, when the resources of the Bowman Gray Foundation were awarded to Wake Forst College to be used exclusively for the medical school which is now supported from the general budget of Wake Forest College and from the resources of the Foundation.

ORGANIZATION AND ADMINISTRATION

The control of the medical school is vested in the Board of Trustees of Wake Forest College. The dean of the medical school is responsible for its internal operation. All departments are integrated. In the matter of instruction and evaluation of student accomplishment, each instructor is given complete freedom.

EQUIPMENT

The North Carolina Baptist Hospital constitutes the main teaching hospital of the medical school. All buildings are located on the same campus and adjoin to form a single unit. The clinical and pre-clinical departments are so related physically and the faculty is so constituted that the teaching program is effectively correlated.

In addition, Graylyn, a neuropsychiatric rehabilitation center which provides for several thousand outpatient visits a year and

thirty-five hospital patients, is owned and operated by the medical school. This is completely used for teaching by the Department of Neuropsychiatry.

STANDARDS

The school is a member of the Association of American Medical Colleges and is approved by the Council on Medical Education of the American Medical Association. Academic and professional standards comparable to other leading medical schools in the United States are maintained.

BACHELOR OF SCIENCE DEGREE

The Bachelor of Science degree is awarded by Wake Forest College upon the satisfactory completion of the first year of medicine to students who were enrolled in Wake Forest College for one or more years immediately preceding admission to the School of Medicine. For further information relative to this degree, consult the general catalogue of Wake Forest College.

MEDICAL TECHNOLOGY

The Bachelor of Science degree in Medical Technology is offered by Wake Forest College to students who satisfactorily complete three years of academic work in Wake Forest College and one year of practical training in the laboratories of the medical school. The qualitative requirements effective for other Bachelor's degrees must be met for this degree. Through an affiliation, Salem College students are accepted for training in medical technology, and are awarded the B.S. degree by Salem College on satisfactory completion of laboratory training. The fee for the practical training is $65.00. For requirements and other information, write the Registrar, Wake Forest College, Wake Forest, N. C., or The Registrar, Salem College, Winston-Salem 2, N. C.

No student is eligible for admission to the School of Medical Technology who has not met the minimum standards for admission recommended by the Registry of Medical Technologists. Credentials of applicants are sent to the Registry for approval before the student is admitted. These requirements are:

General biology	8 semester hours
Bacteriology*	3 semester hours
Inorganic chemistry	8 semester hours
Organic chemistry	4 semester hours
Quantitative analysis	4 semester hours

*If this is not available, an advanced course in biology (not botany) may be substituted.

Courses are also available in Radiologic Technique, Dietetics, Anesthesiology, and Nursing.

MASTER OF SCIENCE DEGREE

Graduate students who are not candidates for the M.D. degree may pursue studies in selected fields. Upon the completion of the approved program of graduate study, including a thesis on the subject within the special field of study, the student will be awarded the degree of Master of Science. For further information on this subject, write the chairman of the committee on graduate studies, Bowman Gray School of Medicine.

OTHER GRADUATE TRAINING

Qualified physicians who are interested in internships and residencies in the North Carolina Baptist Hospital, the main teaching hospital of the Bowman Gray School of Medicine of Wake Forest College, should write to Dr. C. C. Carpenter, Dean and Medical Director. Straight internships are available in Medicine, Obstetrics and Gynecology, Pathology, Pediatrics, Radiology, and Surgery.

PREMEDICAL PREPARATION

Students preparing to enter the medical profession are urged not to take up the study of medicine after having completed only those subjects which barely satisfy the minimum requirements. A broad cultural and scientific training is of inestimable value to the medical student, and to the practicing physician.

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A college course which includes thorough training in English, mathematics, biology, chemistry, physics, sociology, psychology, Greek and Latin, and a reading knowledge of German, French, or Spanish is recommended.

Requirements for Admission

Ninety semester hours are the minimum requirements accepted for admission. The required courses are as follows:

Biology	
General biology (not botany)	8 semester hours
Comparative anatomy	4 semester hours
Embryology	4 semester hours
(Courses in histology, bateriology, and physiology may not be substituted for the above requirements in biology since these subjects are included in the medical curriculum.)	
Chemistry	
Inorganic chemistry	8 semester hours
Organic chemistry	4 semester hours
Quantitative analysis	4 semester hours
English	
Freshman English	6 semester hours
Language	
Either French, German, Spanish, Greek, Latin	6 semester hours
Mathematics	
College algebra and trigonometry	6 semester hours
Physics	
General physics	8 semester hours
Social Sciences	
History	6 semester hours
Recommended Electives	
Physical chemistry; elementary bacteriology; advanced courses in French, German, Spanish; advanced mathematics; psychology; logic; advanced courses in English; sociology and economics.	

Admission to the Bowman Gray School of Medicine

Candidates desiring admission will, upon request, be furnished application blanks. The application, properly filled out

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and accompanied by an application fee of five dollars, should be forwarded to the Dean, Bowman Gray School of Medicine, Winston-Salem 7, North Carolina. Upon receipt of transcripts of premedical work the application will be reviewed by the Committee on Admissions, and if favorable action is taken the student will be requested to appear before the committee for a personal interview. A student who is accepted for admission is required to make a fifty dollar tuition deposit within two weeks after the date of his acceptance in order to reserve the place assigned to him. This deposit will not be returned under any condition, but will be credited on tuition and deducted from the payment due when the student matriculates.

Students are selected on the basis of academic records, character, and physical fitness. No student will be admitted who is ineligible, because of scholastic difficulties or misconduct, to re-enroll in any school previously attended. Students more than thirty years of age are seldom admitted.

The school reserves the right to refuse admission to any applicant without assignment of reasons, and also the right to ask a student to withdraw, *for cause*, at any time.

All correspondence should be addressed to the Dean, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem 7, North Carolina.

Admission to Advanced Standing

Applicants in good standing in other accredited medical schools may be admitted to advanced standing. In addition to filing a formal application, such an applicant should also furnish a letter from the dean of the medical school previously attended, giving class standing and other pertinent information. Applicants for admission to advanced standing must also furnish official transcripts of both premedical and medical work.

Credit will not be given for work done in other professional schools, such as schools of dentistry, engineering, public health, and pharmacy.

Fees and Expenses

Statements in this bulletin concerning courses and expenses are not to be regarded as forming an irrevocable contract between the student and the school. The school reserves the right to change without notice requirements for graduation, schedules of classes, and the cost of instruction at any time within the student's term of residence. Changes so made and authorized by the Board of Trustees will become effective at the opening of the next session after enactment.

The tuition is $150 a trimester, payable on the first day of each trimester. No discount is allowed, and no student will be permitted to enter upon the work of a trimester until satisfactory arrangement has been made with the controller for payment of tuition.

Each student is required to pay a breakage deposit of $10.00 on his first registration. If total amounts charged against the breakage deposit exceed the balance on hand, a special asssesment will be made. Any damage or loss of equipment is charged to respective student deposits.[4]

A registration fee of $2.00 is payable on the opening day of each new session. The student health fee (student activities) of $5.00, the library fee of $10.00, the publications fee of $3.00, and the athletic and locker fee of $1.00 are required at the beginning of each trimester. During the first year the cost of textbooks, dissecting instruments, and laboratory coats averages approximately $60.00 to $75.00. In addition, each student is required to provide himself with a standard microscope and substage light. Diagnostic instruments and other equipment must also be purchased as the need for them arises. For detailed information write or consult the dean.

Scholarships and Loan Funds

The following loan funds are available: The Kellogg Loan Fund, the Walter Jerome Moss Loan Fund, the Edna Tyner Langston Loan Fund, and the Senior Loan Fund. The loans made from these funds will be administered by the Winston-Salem Foundation. Loans will be limited to not more than $500.00 to a student during any one session. The interest rate is two and one-half per cent until graduation, after which the rate is six per cent until the loan is paid. For further information, address the Dean, Bowman Gray School of Medicine, Winston-Salem 7, N. C.

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Student Health Program

On entrance, each student is given a complete physical examination, with an x-ray of the chest and examination of the blood and urine. A thorough series of tests for the presence of immunity are given and the indicated immunizations are administered. Each succeeding year the physical examination, chest x-ray, and necessary immunizations are repeated.

A student health physician is employed who has regular office hours each day for the care of minor illnesses in ambulatory students. Ordinary drugs are furnished through the pharmacy. Students with more serious illnesses are admitted to the hospital under the care of the student health physician. Consultations with specialists on the faculty are held when indicated. The cost of special nurses and professional fees for operations are borne by the student.

A comprehensive plan of hospitalization in the Baptist Hospital provides for the use of the operating room and for the cost of room and meals, anesthesia, casts, laboratory procedures, x-ray examinations, and drugs. This plan makes the treatment of illnesses in the students' quarters unnecessary. The student health fee (student activities) covers all these hospital services.

Grades and Promotions

A student whose work is unsatisfactory in any course will, on request, be informed periodically of his standing by the instructor. Only the terms "satisfactory" or "unsatisfactory" will be used, the former designating all passing grades.

A student who fails in two major subjects within the same scholastic year will not be allowed to continue in school. A

student who fails to make a passing grade on one major subject, or who makes a generally poor record, will be required to appear before the promotions committee before being promoted to the next class or allowed to graduate. The student's eligibility to continue the study of medicine shall be determined by a comprehensive oral or written examination, administered by the appropriate promotions committee.

THE CURRICULUM

The curriculum is designed to provide effective correlation of the various subjects that are included in the study of medicine. No attempt is made to follow the traditional pattern of arrangement of subjects or hours of instruction. The science and art of medicine are presented after careful planning in a way that will assure balanced emphasis. This is done by arranging all subjects in the curriculum into four major divisions. These are the Divisions of Structure, Function, Medicine, and Surgery. A knowledge of the structure and function of the body in health and disease is basic medical knowledge. Similarly, all methods used in the practice of medicine have either a medical or a surgical approach.

The divisions and subjects included under each division are as follows:

DIVISION OF STRUCTURE

- Gross Anatomy
- Microscopic anatomy
- Neuroanatomy
- Pathology
- Radiology

DIVISION OF MEDICINE

- Bacteriology
- Internal medicine
- Neuropsychiatry
- Pediatrics
- Preventive medicine

DIVISION OF FUNCTION

- Biochemistry
- Pharmacology
- Physiology

DIVISION OF SURGERY

- General surgery
- Neurosurgery
- Obstetrics and gynecology
- Ophthalmology
- Orthopedics
- Otolaryngology
- Urology

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The plan of horizontal and vertical correlation followed by this school so integrates departments, that the presentation in the catalogue of departmental organization is unnecessary. Instead, the curriculum is arranged by academic years of study. This is followed by a description of courses and a detailed schedule of classes, clinics, and other student exercises. One interested in faculty titles and positions should refer to the alphabetical listing of the faculty on page 9.

CURRICULUM BY YEARS

First Year

	Clock Hours			
	First Trimester	Second Trimester	Third Trimester	Total
Bacteriology			165	165
Biochemistry		253		253
Clinic, Anatomy	11			11
Clinic, Bacteriology			11	11
Clinic, Biochemistry		11		11
Clinic, Physiology			11	11
Gross Anatomy	308			308
Histology	77	33		110
Neuroanatomy		88		88
Physiology			198	198
Psychobiology		11		11
Unassigned Time	33	33	44	110
Total	429	429	429	1287

Second Year

	Clock Hours			
	First Trimester	Second Trimester	Third Trimester	Total
Applied Anatomy			11	11
Clinic, Medical			11	11
Clinic, Pathology	5			5
Clinic, Physiology and Pharmacology	6	11		17
Clinic, Preventive Medicine			11	11
Clinical Laboratory Methods			77	77
Genetics	10			10
Medical Statistics			33	33
Obstetrics, Introduction to			22	22
Parasitology	66			66
Pathology	187	132		319
Physical Diagnosis			99	99
Physiology and Pharmacology	96	220		316
Preventive Medicine			44	44
Psychopathology	11	11		22
Surgery			77	77
Toxicology		22		22
Unassigned Time	48	33	44	125
Total	429	429	429	1287

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Third Year*

	Clock Hours			
	Medical (First)* Trimester	Surgical (Second)* Trimester	Specialties (Third)* Trimester	Total
Allergy			11	11
Anesthesia (repeated each trimester)		11 (SS)		11
Clinic, Medical	11	11	11	33
Clinic, Obstetrics and Gynecology	11	11	11	33
Clinic, Pediatric	11	11		22
Clinic, Preventive Medicine	11	11	11	33
Clinic, Surgical	11	11	11	33
Dentistry	11			11
Dermatology		11	11	22
Dietetics (repeated each trimester)	11 (MS)			11
Family Practice	11	11	11	33
Fractures	11			11
Hereditary Diseases			11	11
Medical Literature	11 (MS)			11
Neurology	11		11	22
Neurosurgery		11		11
Nutrition (repeated each trimester)	11 (MS)			11
Obstetrics-Gynecology (Conference and Rounds)			66	66
Ophthalmology	11			11
Orthopedics		11	11	22
Orthopedics—Rounds and Outpatient Department			38½	38½
Otorhinolargyngology	11	11	11	33
Pediatrics Conferences and Rounds			55	55
Psychiatry	11	11		22
Radiology	11	11	11	33
Splinting and Bandaging			5½	5½
Surgery		11	11	22
Urology	11	11	11	33
Urology Ward Rounds			33	33
Ward Work	187	231	49½	467½
Unassigned Time	55	33	27½	115½
Total	429	429	429	1287

* The Class is divided into three rotating groups designated medical section (MS), surgical section (SS), and specialties section (SpS). The columns are also listed as (first), (second), and (third), in order to indicate what period during the college year a particular course is presented to the entire class. Unless otherwise indicated on the above schedule, courses are attended by the entire class; however, work with patients takes precedence over formal exercises.

FOURTH YEAR*

	Clock Hours			
	Medical (First) Trimester*	*Surgical (Second)* Trimester*	*Specialties (Third)* Trimester*	*Total*
Clinic, Fundamental Sciences	11	11	11	33
Clinic, Medical	11	11	11	33
Clinic, Obstetrics and Gynecology	11	11	11	33
Clinic, Pediatric	11	11	11	33
Clinic, Preventive Medicine	11	11	11	33
Clinic, Surgical	11	11	11	33
Family Practice	11	11	11	33
Hospital Relations	11			11
Neurology	11		11	22
Neurosurgery		11		11
Outpatient Department	165	165	165	495
Psychiatry (repeated each trimester)	33 (MS)			33
Radiology Conference (repeated each trimester)	11 (MS)			11
Tropical Medicine	11			11
Ward Work	110	176	176	462
Total	429	429	429	1287

* The class again rotates through the three trimesters as in the junior year. The specialties trimester is divided into "obstetrical and gynecology period" of five and one-half weeks and "pediatric period" of five and one-half weeks. Unless otherwise indicated in the schedule above, courses are attended by the entire class; however, work with patients takes precedence over formal exercises.

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DESCRIPTION OF COURSES

DIVISION OF STRUCTURE

ANATOMY CLINICS. *First Year*

Clinics are held weekly during the first trimester for first year students. Patients are chosen who illustrate disorders of structures which are being studied in the anatomy laboratory. The clinics are conducted by the Department of Surgery.

GROSS ANATOMY. *First Year*

A systematic dissection of the human body is made under the careful supervision and guidance of members of the staff. Frequent discussion periods are held and the work covered in the laboratory is reviewed and correlated. Students are also given individual instruction at the dissection tables. At the end of the course practical and written examinations on the entire body are given. Osteology is taught in connection with the dissection of each region, every student being furnished with a complete set of bones for home study.

HISTOLOGY. *First Year*

Recognition of parts of the body by the microscopical appearance of histological preparations representing them, plus cognizance of the relationship between microscopical structure and the general subject matter embraced by other fundamental medical sciences including gross anatomy, ontogeny, biochemistry, physiology, and pathology are the two objectives of this course. The principal events of human embryology will be studied concurrently.

NEUROANATOMY. *First Year*

The gross and microscopical anatomy of the entire nervous system will be studied, and functional correlates will be considered in order to establish the significance of structural details.

APPLIED ANATOMY. *Second Year*

A review of the anatomy of the thorax and abdomen and of the female pelvis is offered in conjunction with the courses in physical diagnosis and obstetrics during the third trimester of the sophomore year.

AUTOPSIES. *Second, Third and Fourth Years*

Groups of four men each from the second year class have the privilege of taking active part in the postmortem examinations. The junior or senior students who attended the patient on the wards are required to be present.

The clinical record is summarized, and the problems to be encountered are clearly defined prior to the examination. Emphasis is placed on accurate and detailed methods of observation. The groups are encouraged to review exhaustively the pathological conditions encountered by the judicious use of oral quizzes given by senior members of the department several days after the postmortem examination has been completed. The groups study the microscopic slides from their own cases for a week and then meet for a final consideration of the material.

The gross material is refrigerated, and the cases are reviewed with the second year class during the course in Pathology. The third and fourth year classes are encouraged to attend weekly conferences on the fresh gross material obtained during the preceding week. Microscopical material may be checked out of the slide library by any member of the second, third, or fourth year classes.

CLINICAL PATHOLOGICAL CONFERENCES. *All Years*

The clinical summary of a case is presented and the differential diagnosis is discussed by clinicians. Autopsy material or specimens removed at operation are demonstrated by a pathologist.

GENERAL PATHOLOGY. *Second Year*

The fundamental structural, functional, and chemical changes undergone by the body as a result of disease are studied in this course. Representative gross and microscopic material is issued to each student, who obtains additional material for study by the experimental producton of pathological lesions in animals. There are no formal lectures, but problems of general interest are discussed with the class.

PATHOLOGY CLINICS. *Second Year*

Carefully selected patients are presented once a week during the first trimester to illustrate pathologic processes under study. The symptoms and easily demonstrable physical signs are correlated with the pathologic physiology. An attempt is made to portray disease processes as active and dynamic and to illustrate the systemic effect of pathologic processes in which the lesions may appear predominantly in a single organ.

SPECIAL PATHOLOGY, SPECIAL PHYSIOLOGY AND PHARMACOLOGY.* *Second Year*

Beginning with the sixth week of the first trimester and extending throughout the second trimester, special pathology, special physiology and pharmacology run concurrently. Maximum correlation is provided by considering each organ simultaneously in all three courses.

* For information concerning special physiology and pharmacology, see page 33

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In special pathology, specific diseases are considered and an attempt is made to correlate clinical and pathological findings. The entire class assembles in the large laboratory for the first hour, where the various disease entities are discussed systematically prior to the demonstration of some of these cases in the section laboratories. For the two-hour laboratory period that follows the discussion, the class is divided into sections of twelve, and each group is assigned an instructor who works in conjunction with representatives from the various clinical branches. The material presented in the section laboratories consists of clinical abstracts of the cases, photographs of the autopsy or specimen, gross material and microscopic slides.

TOXICOLOGY. *Second Year*

This course is an introduction to industrial medicine, emphasis being placed on the toxicological aspects of a selected group of agents encountered in small industries and in general medical practice. Their classification, mode of action, treatment, and chemical and biological identification are discussed. Two hours of lecture and practical demonstration are given each week during the second trimester of the second year.

RADIOLOGY. *Third Year*

Weekly lecture and demonstration periods of one hour each on normal and abnormal radiographic findings are held throughout the junior year. Six of these lectures are devoted to the fundamental principles of radiation physics and therapy.

RADIOLOGY CONFERENCES. *Fourth Year*

One hour conference periods and demonstrations are held weekly in the department of radiology for each section on medicine. Each senior student is assigned to observe all work in the department for a period of two weeks. A weekly one-hour radiological conference of the house staff and senior students is conducted throughout the year.

SURGICAL PATHOLOGY. *Third and Fourth Years*

Weekly conferences illustrated with lantern slides and supplemented with notes and an extensive bibliography are given throughout the year. These are further supplemented by groups of microscopic slides arranged according to the various divisions of surgical pathology. Provision has been made for each student to study any material in which he might be interested. Material from about 15,000 cases is added to the collection annually.

FUNDAMENTAL SCIENCES CLINIC. *Fourth Year*

The pathogenesis and pathologic physiology of disorders seen in patients in the hospital are emphasized by clinics and demonstrations. During the first trimester, a chemist selects from the data in the clinical chemistry lab-

oratory cases for discussion. During the second trimester, a physiologist discusses patients from the wards. During the third trimester, a pathologist demonstrates the gross material from autopsies of the preceding week, and a member of the clinical staff correlates the history and physical examination with the pathological findings.

DIVISION OF FUNCTION

BIOCHEMISTRY. *First Year*

Lectures and discussions are devoted to the study of the physico-chemical conditions in blood and tissues; the main organic and inorganic constituents of living bodies; the chemistry of enzymes, vitamins, and hormones; the physico chemical and chemical aspects of cellular activity; the chemical processes of digestion, intermediary metabolism, and excretion in higher animals. Special attention is given each year to one of the subjects. A brief survey of the components of blood, urine, and milk, and their origin and significance concludes the course. Subjects are outlined in the lectures and discussions which the student is expected to pursue by his own systematic reading. The laboratory work consists of the qualitative and quantitative examinations of the substances discussed in the lectures.

It is urged that students review the fundamental laws and theories of chemistry before beginning the course, since their success in this course is largely determined by such knowledge gained in their premedical training.

PHYSIOLOGY, BASIC. *First Year*

This course is devoted to a study of the normal function of the various tissues and organs of the human body and an understanding of their interrelation. Major emphasis is placed upon laboratory experiments, two-thirds of which are performed upon the students themselves, and the remainder upon laboratory animals and upon models. The student is trained to observe and record his own results accurately and to make sound interpretations based on these observations. Special emphasis is given to those laboratory techniques which are useful as diagnostic procedures. The laboratory work is supplemented by conferences and by the preparation of laboratory reports. The work of this course is closely correlated with that in biochemistry and that in neuroanatomy given in the preceding trimester, so as to eliminate excessive overlap and repetition and to assure complete coverage of all important functions. Clinics given during this trimester serve to introduce the student to clinical medicine. They are also used to illustrate many deviations from function which are considered abnormal and to emphasize the necessity of a thorough knowledge of normal function as a basic need before entering upon a study of the disturbances of function seen in disease.

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BIOCHEMISTRY CLINICS. *First Year*

Clinics are held weekly during the second trimester for first year students. Patients are chosen who illustrate disorders of function which are being studied in the course in biochemistry from the theoretic or laboratory point of view. The clinics are conducted by the Departments of Medicine and Surgery.

SPECIAL PATHOLOGY, SPECIAL PHYSIOLOGY AND PHARMACOLOGY.* *Second Year*

In special physiology, the functional disturbances manifested in the various disease entities and their manner of production are presented and analyzed by members of the physiology, biochemistry, and clinical staffs. The student is thus prepared to understand and interpret the deviations from the normal represented by the signs and symptoms and the laboratory findings seen in his patient.

Pharmacology deals with the effects produced by qualitative and quantitative alterations in the chemical environment of cells and tissues. Various physiological and biochemical processes are studied and the manner in which they may be altered by chemical means, whether by drugs or otherwise is shown. Thus a base is established for the later study of modern chemical therapeutics which involves much more than the prescribing of drugs.

The work in special physiology and pharmacology consists of lectures, conferences, and informal discussions, clinics and ward visits, and laboratory experiments. Each student is assigned in rotation to patients on the wards and is expected to study throughout the patient's stay in the hospital, the functional disturbances manifested by the patient, the rationale of the therapeutic procedures utilized and the pharmacodynamic and toxic effect of all the therapeutic agents used on the patient. Observations on these patients are summarized in written reports. At the weekly clinics, patients presenting characteristic examples of disturbance of function are presented and analyzed, and the basis for their therapeutics by pharmacologic and other means is discussed. Laboratory experiments are designed primarily to elucidate the nature of disturbances of function seen in abnormal states and to illustrate the pharmacodynamic and therapeutic possibilities of those drug agents whose functions cannot be readily demonstrated upon patients or upon the students. Throughout these courses, emphasis is placed on encouraging the student to study original literature and near the conclusion of the second trimester, each student prepares a thesis discussing the physiological basis for some normal function, the basis for some disturbance of function presented by a particular disease entity or a review of the pharmacodynamic, therapeutic and toxic properties of some drug agent. The student uses, if possible, one of the patients assigned to him as a basis for the thesis. The more satisfactory of the theses, are presented at one or two seminars near the conclusion of the courses.

* For information concerning special pathology, see page 30.

PHYSIOLOGY AND PHARMACOLOGY CLINICS. *First Year*

Clinics are held weekly during the third trimester for first year students. Patients are chosen who illustrate disorders of function which are being studied in the course in physiology and pharmacology from the theoretic or laboratory point of view. The clinics are conducted by the Departments of Medicine and Surgery.

FUNDAMENTAL SCIENCES CLINIC. *Fourth Year*

The pathogenesis and pathologic physiology of disorders seen in patients in the hospital are emphasized by clinics and demonstrations. During the first trimester, a chemist selects from the data in the clinical chemistry laboratory cases for discussion. During the second trimester, a physiologist discusses patients from the wards. During the third trimester, a pathologist demonstrates the gross material from autopsies of the preceding week, and a member of the clinical staff correlates the history and physical examination with the pathological findings.

DIVISION OF MEDICINE

BACTERIOLOGY AND IMMUNOLOGY. *First Year*

This course is given during the third trimester of the first year. About one-fourth of the total hours is devoted to immunology. Lectures cover all phases of the subject, including morphology, classification, reproduction, growth and death, sterilization, and other biologic and metabolic activities of bacteria. Subsequently all the important disease-producing micro-organisms and viruses are discussed in detail. The principles of immunity and immune reactions are thoroughly discussed. In the laboratory students are required to cultivate and study the important bacteria and fungi. Animals are inoculated for the study of infectious processes and for the purpose of producing antisera. Serum reactions (agglutination, precipitation, complement fixation) are studied in connection with the biology of the micro-organism under study.

CLINICS IN BACTERIOLOGY. *First Year*

Patients with infections caused by organisms under study in the laboratory are presented in weekly clinics during the third trimester. The use of bacteriologic and immunologic methods as tools in the study of individual patients is stressed.

PSYCHOBIOLOGY. *First Year*

The course is designed to give and keep a broad aspect of the integration of the human organism as a whole, functioning in its environment. Normal human behavior, personality structure and development, and emotional responses are discussed and illustrated by case histories.

1112104

CLINICAL LABORATORY METHODS. *Second Year*

The microscopic and chemical examination of blood, urine, sputum, feces, cerebrospinal fluid, gastric contents, transudates and exudates is taught. Lectures and practical laboratory exercises are given. Patients from the wards who illustrate application of the laboratory work are shown regularly.

GENETICS, INTRODUCTORY. *Second Year*

Lectures and demonstrations of the principles of genetics are given for one trimester, concurrently with the course in pathology. The cytologic basis of genetics, the mechanism of and transmission of pathologic genes in man, the penetrance and expressivity of genes, and the interaction of hereditary and environmental factors in the production of disease are covered. Patients and family trees are presented.

MEDICAL PARASITOLOGY. *Second Year*

The important diseases caused by protozoan and metazoan parasites of man are discussed in detail in lectures. Particular emphasis is placed on life cycles of the various parasites as these effect the epidemiology and the host response. The biweekly laboratory exercises are devoted to the study of gross and miscroscopic appearance of the various parasites with special emphasis on those aspects of morphology upon which accurate diagnosis of infection depends. The elements of medical entomology are presented by lecture and demonstration to give the student some perspective of the problems of anthropod transmitted diseases.

MEDICAL STATISTICS. *Second Year*

The course is designed to provide practical instruction in elementary statistical methods essential to the planning of research, evaluation and interpretation of data, and critical analysis of medical literature. The limitations of source material, the effects of forces which determine outcome, and the effects of chance are presented. Instruction will include the characteristics of the normal curve, crude and specific rates, calculation of standard deviation and standard error; the chi square and the T test; correlation; and end point application. The laboratory periods will be devoted to practical application of these methods.

PEDIATRICS—ORIENTATION COURSE. *Second Year*

Second year pediatrics is part of the course in physical diagnosis and is designed to introduce the students to the special techniques employed in the examination of infants and children. After a general discussion of examination methods the students are assigned to hospital cases for practical instruction by members of the clinical staff.

PHYSICAL DIAGNOSIS. *Second Year*

Various methods used in arriving at a clinical impression are discussed and demonstrated. The technique of obtaining the history of a patient's illness is illustrated and practical experience is gained. Emphasis is placed on the importance of the subjective aspects of disease. The methods for general physical examination of the patient are taught; the normal range of variations is discussed, and common errors in elicitation of signs are stressed. Special techniques of examination used in the practice of specialties are covered by instructors from each field. Patients on the wards of the Baptist Hospital, and the Forsyth County Tuberculosis Sanatorium are used regularly. The class is divided into small groups to insure individual instruction.

PREVENTIVE MEDICINE. *Second Year*

The second year course in preventive medicine is designed to present the more important aspects of the ecology of communicable diseases in relation to the individual and the community, stressing the function of the practicing physician in disease control. The respective functions of federal, state, and local health authorities in relation to the practitioner are presented, and the activities of voluntary health agencies are discussed. Particular emphasis is placed upon the air-borne, the food and water-borne, and insect transmitted diseases. Field trips and demonstrations illustrating methods of control of these conditions are a part of the formal curriculum. Such field exercises include inspection of a water purification plant, a sewage disposal plant, a dairy and pasteurization plant, an abattoir, the Forsyth County Tuberculosis Sanatorium, and the City-County Health Department. The essential features of the practice of industrial hygiene and its relation to general community problems are presented. As clinical material is available, illustrative cases are presented in seminar discussion with emphasis upon the preventable aspects.

PSYCHOPATHOLOGY. *Second Year*

Normal and abnormal mental mechanisms, personality deviations and mental disorders are discussed and illustrated. History-taking and methods of psychiatric examinations are covered.

ALLERGY. *Third Year*

The nature of allergy and anaphylaxis, the clinical manifestation of allergy, and the nature and environmental distribution of the allergens are discussed in a series of lectures. Asthma, hay fever, urticaria, eczema, gastrointestinal allergy, allergic migraine, and ocular allergy are discussed. Specific treatment and non-specific or pharmacology therapy are described.

1112105

DERMATOLOGY. *Third Year*

A lecture with lantern slide and case demonstration is given once a week for two trimesters. Emphasis is placed on the diagnosis and simplified management of the common dermatoses. The cutaneous manifestations of syphilis and other systemic diseases are discussed.

HEREDITARY DISEASES. *Third Year*

The hereditary diseases are discussed by systems. Lectures are given weekly for one trimester and illustrative patients are presented in clinics as they are available. Obtaining the pedigrees of patients on the medical wards is part of the work of the clinical clerks.

MEDICINE. *Third Year*

The clinical clerkship of one trimester is designed for intensive study of the group of patients on the medical teaching wards of the hospital. The student is given responsibility for the care of patients assigned to him and his work forms part of the permanent record of the hospital. Histories are meticulously taken and each is carefully checked by a member of the clinical staff. Each physical examination is reviewed at the bedside with a house officer. Three times a week one-hour periods are spent in the demonstration by a student of one patient and a discussion conducted by the instructor, with emphasis on the fundamental principles of the disease process. The nutritional and dietetic aspects of the case are discussed in special exercises (page 38). The therapeutic principles of diet, fluid balance, sedation, activity or rest, and the use of major classes of drugs are discussed in special ward rounds. In another ward round, the interpretation of all laboratory procedures and the alteration of diagnosis or therapy are discussed. The errors inherent in each procedure and the importance of proper collection of specimens for laboratory examination are stressed. All laboratory procedures, including bacteriology studies, which could be done in a practicing physician's office, are performed by the clerk, and all positive findings are checked by the house officers. Oral examinations on the patients seen by the student during his clerkship are given. Attendance at scheduled classes is not compulsory and no roll is taken. Students are to be available at all times for the observation of critically ill patients and the performance of emergency procedures.

MEDICAL LITERATURE. *Third Year*

Each student abstracts articles which have appeared in recent issues of medical journals. The material is critically evaluated and the essentials presented for discussion by the group. The cultivation of insatiable scientific curiosity and habits of study is considered of greater importance than the facts learned. At the end of the exercises, certain highlights of medical *belles lettres* and biography are discussed.

NEUROLOGY. *Third Year*

Clinics devoted to demonstration and discussion of patients with diseases of the nervous system are held weekly. During one trimester each year, the clinics are conducted by the neurosurgeon.

NUTRITION. *Third Year*

During the clinical clerkship on medicine, one ward visit a week is made by the hospital dietitian and a member of the clinical staff. Nutritional disturbances in individual patients and their correction are discussed from the theoretic point of view. On the following day, practical problems in nutrition are demonstrated by the actual preparation of diets discussed the day before. Students may elect to spend one week in the diet kitchen assisting in the planning and preparation of diets for patients on the medical wards.

PEDIATRICS. *Third Year*

Over a period of five and one-half weeks during the specialties trimester of the third year, the students spend part of their time on pediatrics. Rounds are held on the pediatric floors and in the infirmary of the Methodist Children's Home, where the students are introduced to the minor, although common illnesses and contagious diseases of children. This work is correlated by conferences which stress the care of the new-born baby, infant and child feeding and nutrition, growth and development, and preventive pediatric procedures. Diagnosis and treatment of specific diseases are not stressed during this time, for the major emphasis is on the average, "normal" child.

PSYCHIATRY. *Third Year*

Clinics and lectures are devoted to a broad consideration of the various fields of present-day psychiatry. Mental disorders are presented, but emphasis is placed on neurotic reactions, deviating personalities, as well as the reaction of patients to their experiences of various physical diseases.

CLINICAL BACTERIOLOGY. *Third and Fourth Years*

Students serving their clinical clerkships do routine and special bacteriologic studies on patients assigned to them (on the teaching service) under the direction of the staff.

FAMILY PRACTICE. *Third and Fourth Years*

The common problems encountered by physicians in caring for patients at home are discussed and illustrated by actual case histories. Emphasis is put not only on the diagnosis and treatment of major diseases, but on the management of minor complaints and on the physician's relationship to the patient's family and to other physicians.

1112106

MEDICAL CLINICS. *Third and Fourth Years*

Weekly clinics in medicine are held throughout the year. Over a period of two years the various instructors in medicine rotate in conducting the clinics. The major disease processes illustrated by patients are discussed.

PEDIATRICS CLINICS. *Third and Fourth Years*

Each week throughout the year a pediatric clinic is held for the combined third and fourth year classes.

PREVENTIVE MEDICINE CLINICS. *Second, Third and Fourth Years*

Patients are presented weekly throughout the year to illustrate preventive measures which can be taken in individuals. The importance of preventive measures in the various medical specialties as well as in the general practice of medicine is stressed and patients from all services are used. The epidemiology, immunology, and prevention of infectious diseases are emphasized. Problems in which the family unit is important in the transmission or prevention of disease, such as tuberculosis and nutritional deficiencies, are discussed.

MEDICINE. *Fourth Year*

Emphasis is placed on the development of clinical judgment; differential diagnosis and detailed therapy in individual patients are stressed. Students are assigned to a private ward as junior interns, under the supervision of the house officers and an attending physician. Students are on call twenty-four hours a day and are given a considerable degree of responsibility in following diagnostic and therapeutic procedures. Rounds are made with the attending physician at least four days each week. One morning a week is devoted to clinical psychiatry and one morning to radiology (page 31.). For one week each student is assigned to Graylyn as junior intern in residence for intensive practice in the handling of psychiatric patients. For a portion of each trimester, students examine one new patient daily in the outpatient clinic and hold consultations with an attending physician. The importance of speed and accuracy in office practice and its limitations are thus demonstrated.

PEDIATRICS—CLINICAL CLERKSHIP. *Fourth Year*

During this period the students are assigned to the pediatric wards and outpatient department. The major part of the pediatric teaching is done during this period through ward rounds, case presentations, and seminar discussions. The students work both on the wards and in the outpatient department throughout the period, so that an opportunity is given them to follow cases thoroughly.

PSYCHIATRY. *Fourth Year*

Patients are demonstrated and practical instruction is given in the management of psychiatric problems which arise in general practice. Detailed case studies of psychiatric patients at Graylyn are made by junior interns (see Medicine, Fourth Year) and are presented by the student in weekly rounds made by a psychiatric study. A small number of superior students with special interest in psychiatry may elect to take additional work.

TROPICAL MEDICINE. *Fourth Year*

Particular emphasis is placed on those tropical diseases endemic in the United States and certain of the more important of the diseases occurring in other parts of the world are discussed. The epidemiology and the diagnostic criteria presented in the second year course in medical parasitology are reviewed. Attention is directed primarily, however, to the clinical features and to the techniques of treatment. Whenever practicable illustrative cases are presented.

DIVISION OF SURGERY

OBSTETRICS, GYNECOLOGY, AND ENDOCRINOLOGY. *Second Year*

The fundamentals of obstetrics, gynecology, and endocrinology are taught during the third trimester of the second year. The physiology and management of the normal pregnancy, labor, and puerperium are taught by lecture and manikin demonstrations. Special emphasis is placed upon history taking.

An introduction to the known fundamental principles of endocrinology gives the student the background necessary for independent study in relation to the problems of patients.

The normal pelvic anatomy and its relation to clinical obstetrics and gynecology are reviewed while pelvic examination is being taught. Approximately one-third of this course is given by the Department of Anatomy.

SURGERY—PRINCIPLES. *Second Year*

The instruction of surgery begins with an introduction to surgical principles in the third trimester of the second year. Tissue injury, healing, and repair are stressed in lectures and laboratory exercises. Part of the instruction in this course is under the direction of a member of the department of pathology, and reactions to injurious agents and various types of suture material are studied microscopically. Although in this course a few patients are used for demonstration, the student has no intimate contact with patients until his third year.

Part of the course in physical diagnosis is taught by the surgical department.

1112107

ANESTHESIA. *Third Year*

This course consists of a study of the action of anesthetic agents, in health and disease, their danger in various disease conditions, and methods of administration. The fundamentals are considered through correlation with the work in pharmacology and physiology. Clinical clerks are held responsible for a knowledge of the management of anesthesia in their cases that undergo an operation. In addition, formal instruction is given one hour a week during the surgical trimester.

DENTISTRY. *Third Year*

This course is given one hour a week. The more simple dental problems confronted in medical practice are considered. These consist essentially of infections, tumors of the mouth and dental caries.

OBSTETRICS AND GYNECOLOGY. *Third Year*

Four hours each week during the specialties trimester of the third year are spent in the classroom teaching of obstetrics and gynecology. The students have regular assignments in standard textbooks, and these classes are conducted in the form of a quiz conference. An attempt is made to stress the important gynecological lesions, and to emphasize the fundamentals in both obstetrics and gynecology.

These students are also assigned to obstetrical and gynecological patients on the teaching wards, and are expected to be fully acquainted with each case to which they are assigned.

OBSTETRICAL AND GYNECOLOGICAL PATHOLOGY AND PHYSIOLOGY. *Third Year*

This course affords the students of the third year class an opportunity to examine gross pathological material, including all surgical specimens obtained from the hospital that are of teaching value, and also special gross material from the pathological museum. Pathological sections of all important gynecological and obstetrical lesions are discussed from the standpoint of micropathology.

Recent advances in endocrinology as related to obstetrics and gynecology are presented. An attempt is made to apply endocrine therapy to clinical problems. Patients with endocrinopathies are presented.

OPHTHALMOLOGY. *Third Year*

Formal instruction is given one hour a week during the first trimester. This consists of the fundamentals of ophthalmology and a consideration of common eye conditions that should be recognized and understood by the practitioner of medicine who is not a specialist in ophthalmology. In addition to formal instruction, the use of the ophthalmoscope, the study of

visual fields, and other diagnostic methods relating to the eye are taught on the wards and in the outpatient clinics.

ORTHOPEDICS. *Third Year*

Formal instruction is given one hour a week throughout the year. This is supplemented by patient study on the wards and work in the orthopedic outpatient clinic.

OTORHINOLARYNGOLOGY. *Third Year*

Diagnostic procedures, the use of the otoscope, the anatomy and physiology of the ear, and common diseases of the ear, nose, and throat are taught by the use of models, movies, and patient demonstration for one hour a week throughout the year. This instruction is supplemented by ward work and by outpatient department assignments.

SURGERY. *Third Year*

During the third year each student is assigned to the surgical wards of the North Carolina Baptist Hospital for one trimester. The first hour is spent in the conference room adjacent to the ward where cases are presented and discussed from the viewpoint of diagnosis and preoperative and post-operative care. Members of other departments who have studied the cases participate in many of these discussions. One hour each week is devoted to the presentation and discussion of a pertinent topic by the students, the instructor merely acting as referee. Topics discussed are based on cases in the wards, but students may choose any topic allied to surgery such as physiology, bacteriology, or chemistry and discuss its relation to surgery. Three mornings a week are spent in making regular ward visits with the house officers and surgical staff. Students in the surgical section receive one hour of instruction weekly on the administration of anesthetic agents. The whole class is given a one-hour lecture each week for two trimesters.

UROLOGY. *Third Year*

The class meets once a week for a systematic study of the disease conditions affecting the urological system. Clinical clerks assist in cystoscopy and in the operating room after doing a complete work-up of the case. The abundance of clinical material on the wards and in the clinics gives the student a broad experience.

NEUROSURGERY. *Third and Fourth Years*

This course consists of a study of diseases of the nervous system that are commonly treated by surgical methods. The work is correlated with neuro-anatomy, neurophysiology and clinical neurology for a consideration of the nervous system as a whole.

1112108

OBSTETRICAL, GYNECOLOGICAL, AND ENDOCRINOLOGY CLINIC. *Third and Fourth Years*

One hour each week throughout the third and fourth years is used for the demonstration of patients with obstetrical problems and gynecological disease by a member of the obstetrical and gynecological staff. Unusual pathological lesions are shown and each case is discussed from the standpoint of differential diagnosis.

Lectures are given to the entire third and fourth year classes throughout the two-year period, in order to present much fundamental and specialized material to the whole group. One-half of the time is allotted to general endocrinology. Special emphasis is placed upon the endocrine problems of the female; however, a complete course in endocrinology is accomplished in cooperation with the Departments of Medicine and Surgery.

SURGICAL CLINIC. *Third and Fourth Years*

A surgical clinic of one hour is held weekly throughout the third and fourth years. Attendance is not compulsory for the fourth year students. Students are required, however, to be present at operations on patients to whom they have been assigned, and are required to examine and study in the surgical pathology laboratory, material removed at operation.

GYNECOLOGICAL CLERKSHIP. *Fourth Year*

Gynecological patients upon admission are assigned to members of the obstetrical and gynecological section. The student is responsible for preparing a complete record of the case, including the history, physical examination, necessary laboratory procedures, differential diagnosis, and a discussion of suggested treatment. The student goes to the operating room with his patient when a surgical procedure is indicated. The whole group is taken to the operating room only for the demonstration of unusual conditions.

A conference is held each week by the staff of the Department of Obstetrics and Gynecology. Each patient on the gynecological service is presented to the group, a diagnosis is made, and the treatment of choice selected. Following the operation, the pathological material from each patient is shown and the method of treatment is discussed from the post-operative point of view.

GYNECOLOGICAL DISPENSARY. *Fourth Year*

Practical instruction in the etiology, pathology, diagnosis, and treatment of diseases of the pelvic structures is provided in the gynecological out-patient dispensary. The injuries of childbirth receive due attention, and the student is shown the pathological sequelae which result from the neglect of repair. Here patients are examined by groups of students, and the differential diagnosis is made by means of direct questions by the instructor in charge. The course of treatment for each patient is outlined.

OBSTETRICS. *Fourth Year*

Each student receives five and one-half weeks of practical instruction in obstetrics during the specialties trimester of the senior year. This course is a sequel to the course given in the junior year. The work includes giving prenatal care to many patients in the dispensaries, attending them in labor, conducting their delivery, and following them through the puerperium. The deliveries are conducted under the direct supervision of a member of the obstetrical staff. The student is expected to take a careful history and make a physical examination, working out in the presence of an instructor the position and presentation of the fetus, and noting any abnormalities presented by the patient. A detailed record of each confinement must be prepared and filed with the office of the department.

OBSTETRICAL MANIKIN PRACTICE. *Fourth Year*

The mechanism of labor for normal and abnormal obstetrical presentations and positions is studied with the aid of manikin exercises. The student has an opportunity to acquire the technique of each obstetrical operation.

OBSTETRICAL WARD ROUNDS. *Fourth Year*

During the visits on the obstetrical wards normal and abnormal prenatal and puerperal cases are demonstrated. Abdominal palpation and the essentials of pelvimetry are taught. The accidents and complications of labor are discussed.

SURGERY. *Fourth Year*

The surgical trimester during the fourth year is designed to allow a maximum time for students to work with patients in the outpatient department and private patients in the hospital. Each student works in the anesthesia department for a period of two weeks. A two-hour clinical conference is held every week for the presentation of cases.

EXPERIMENTAL SURGERY. *Fourth Year*

Facilities are available for two exceptional students to work in the research laboratories during the surgical trimester.

1112109

FIRST YEAR SCHEDULE

FIRST TRIMESTER

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Gross Anatomy	Gross Anatomy	Histology	Gross Anatomy	Gross Anatomy	Anatomy Clinic
9:30-12:20						Histology
1:30- 4:30	Gross Anatomy	Gross Anatomy	Free	Gross Anatomy	Gross Anatomy	

SECOND TRIMESTER

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Biochemistry	Biochemistry	Biochemistry	Biochemistry	Biochemistry	Biochemistry Clinic
9:30-10:20			Psychobiology			Neuro-anatomy
10:30-12:20			Neuro-anatomy			
1:30- 4:30	Biochemistry	Neuro-anatomy	Free	Histology	Biochemistry	

THIRD TRIMESTER

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Physiology	Bacteriology Laboratory	Physiology	Physiology	Bacteriology	Physiology Clinic
9:30-10:20	Free		Bacteriology			Bacteriology
10:30-11:20	Bacteriology Clinic	Physiology Laboratory	Bacteriology Laboratory	Physiology Conference	Physiology	Bacteriology Laboratory
11:30-12:20						
1:30-2:20	Bacteriology	Physiology Laboratory	Free	Bacteriology		
2:30- 4:20	Bacteriology Laboratory			Bacteriology Laboratory	Physiology Laboratory	

Second Year Schedule

FIRST TRIMESTER

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Pathology* Physiology or Pharmacology†	Pathology	Pathology* Physiology or Pharmacology†	Pathology* Physiology or Pharmacology†	Pathology	Pathology
9:30-10:20	Pathology*		Pathology	Pathology*		
10:30-11:20	Physiology or Pharmacology Laboratory†		Pathology Clinic* Pathology†	Physiology or Pharmacology Laboratory†		
11:30-12:20	Genetics* Physiology or Pharmacology Laboratory†	Free* Physiology or Pharmacology†	Free* Pathology†	Genetics* Physiology or Pharmacology Laboratory†	Psychopathology	Free* Physiology and Pharmacology Clinic†
1:30- 4:30	Pathology* Physiology or Pharmacology Laboratory†	Parasitology	Free	Pathology* Physiology or Pharmacology Laboratory†	Parasitology	

* First five weeks of trimester. † Last six weeks of trimester.

SECOND TRIMESTER

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Physiology or Pharmacology	Pathology	Physiology or Pharmacology	Physiology or Pharmacology	Physiology or Pharmacology	Pathology
9:30-11:20	Physiology or Pharmacology Laboratory	Physiology or Pharmacology	Pathology	Physiology or Pharmacology Laboratory	Pathology	Physiology and Pharmacology Clinic
11:30-12:20						
1:30- 2:20	Physiology or Pharmacology Laboratory	Physiology or Pharmacology Conference	Free	Physiology or Pharmacology Laboratory	Psycho-pathology	
2:30- 4:30					Toxicology	

THIRD TRIMESTER

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Surgery	Introduction to Obstetrics	Applied Anatmoy	Surgery	Surgery Lecture	Free
9:30-10:20	Surgery Laboratory	Medical Statistics	Physical Diagnosis	Introduction to Obstetrics	Surgery Laboratory	Preventive Medicine
10:30-11:20				Medical Statistics		
11:30-12:20	Clinical Laboratory Methods	Medical Clinic		Preventive Medicine	Preventive Medicine Clinic	
1:30- 4:30	Physical Diagnosis	Clinical Laboratory Methods	Free	Physical Diagnosis	Clinical Laboratory Methods	

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Third Year Schedule

MEDICAL (FIRST) TRIMESTER (***)

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Dentistry*	Otorhino-laryngology	Ophthalmology**	Urology	Neurology(†)	Fractures***
9:30-10:20	Ward Class	Therapeutic Ward Rounds	Ward Class	Laboratory Conference	Nutrition Ward Class (MS)	Ward Class
10:30-11:20	Medical Literature		Free		Free	Dietetic Conference
11:30-12:20	Pediatric Clinic	Medical Clinic	Surgical Clinic	Family Practice	Prev. Med. Clinic(**)	Ob.-Gyn. Clinic
1:30- 2:20	Radiology	Psychiatry(*)	Free	Ward Work	Ward Work	
2:30- 4:30	Ward Work	Ward Work				

SURGICAL (SECOND) TRIMESTER (***)

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Surgery*	Otorhino-laryngology	Dermatology**	Urology	Neuro-surgery(†)	Orthopedics***
9:30-11:20	Ward Work	Ward Rounds	Ward Conferences	Ward Rounds	Ward Work	Ward Rounds
11:30-12:20	Pediatric Clinic	Medical Clinic	Surgical Clinic	Family Practice	Prev. Med. Clinic(**)	Ob.-Gyn. Clinic
1:30- 2:20	Radiology	Psychiatry(*)	Free	Ward Work	Ward Work	
2:30- 3:20	Anesthesia (SS)	Ward Work				
3:30- 4:30	Ward Work					

(Footnotes will be found on Page 50)

Third Year Schedule (*Continued*)

SPECIALTIES (THIRD) TRIMESTER (***)

OBSTETRICS, GYNECOLOGY, AND ORTHOPEDICS (5½ weeks)

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
8:30- 9:20	Surgery*	Otorhino-laryngology	Dermatology**	Urology	Neurology(†)	Orthopedics***
9:30-11:20	Obstetrics Conference	Pediatrics Conference	Gynecology Conference	Pediatric Rounds Children's Home	Ob.-Gyn. Pathology Ward Rounds	Orthopedic Ward Rounds
11:30-12:20	Pediatric Clinic	Medical Clinic	Surgical Clinic	Family Practice	Hereditary Diseases(**)	Ob.-Gyn Clinic
1:30- 2:20	Radiology	Allergy(*)	Free	Orthopedics Outpatient Department	Splinting and Bandaging	
2:30- 4:30	Ward Work	Orthopedics Outpatient Department			Ward Work	

(Footnotes will be found on Page 50)

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THIRD YEAR SCHEDULE *(Continued)*

SPECIALTIES (THIRD) TRIMESTER (***)
PEDIATRICS AND UROLOGY (5½ weeks)

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
8:30- 9:20	Surgery*	Otorhino-laryngology	Dermatology**	Urology	Neurology(†)	Orthopedics***
9:30-11:20	Obstetrics Conference	Pediatric Conference	Gynecology Conference	Pediatric Rounds Children's Home	Ob.-Gyn. Pathology Ward Rounds	Urology Ward Rounds
11:30-12:20	Pediatric Clinic	Medical Clinic	Surgical Clinic	Family Practice	Hereditary Diseases(**)	Ob.-Gyn. Clinic
1:30- 2:20	Radiology	Allergy(*)	Free	Ward Work	Pediatric Case Conference	
2:30- 4:30	Urology Ward Rounds	Ward Work		Urology Ward Rounds	Ward Work	
4:30- 5:30	Pediatric Rounds					

(***) The class is divided into three rotating groups, which are designated medical section (MS), surgical section (SS), and specialties section (SpS). The trimesters are also listed as (first), (second), and (third), in order to indicate what period during the college year a particular course is presented. Unless otherwise indicated on the above schedule courses are attended by the entire class.

* Dentistry during first trimester; surgery during second and third trimesters. Entire class.

** Ophthalmology during first trimester; dermatology during second and third trimesters. Entire class.

(*) Psychiatry during first and second trimesters; allergy during third trimester. Entire class.

(**) Preventive medicine clinic during first and second trimester; hereditary diseases during third trimester. Entire class.

(†) Neurology during first and third trimester; neurosurgery during second trimester. Entire class.

*** Fractures during first trimester; orthopedics during second and third trimesters. Entire class.

FOURTH YEAR SCHEDULE

MEDICAL (FIRST) TRIMESTER (*)

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
8:30- 9:20	Medicine Rounds	Psychiatry (MS)	Medicine Rounds	Medicine Rounds	Neurology(†)	Fundamental Sciences Clinic**
9:30-10:20					Hospital Relations	Medicine Rounds
10:30-11:20				Tropical Medicine*	Radiology Conference (MS)	
11:30-12:20	Pediatric Clinic	Medical Clinic	Surgical Clinic	Family Practice	Prev. Med. Clinic	Ob.-Gyn. Clinic
1:30- 2:20	Medicine Outpatient Department	Medicine Outpatient Department	Medicine Outpatient Department	Medicine Outpatient Department	Medicine Outpatient Department	
2:30- 4:30						

SURGICAL (SECOND) TRIMESTER (*)***

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
8:30- 9:20	Surgery	Surgery	Surgery	Surgery	Neuro-Surgery(†)	Fundamental Sciences Clinic**
9:30-10:20					Surgery	Surgery
11:30-12:20	Pediatric Clinic	Medical Clinic	Surgical Clinic	Family Practice	Prev. Med. Clinic	Ob.-Gyn. Clinic
1:30- 2:20	Surgery Outpatient Department	Surgery Outpatient Department	Surgery Outpatient Department	Surgery Outpatient Department	Surgery Outpatient Department	
2:30- 4:30						

(Footnotes will be found on Page 52)

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FOURTH YEAR SCHEDULE (*Continued*)

SPECIALTIES (THIRD) TRIMESTER (*)
OBSTETRICS AND GYNECOLOGY (5½ weeks)

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
8:30- 9:20	Ob.-Gyn.	Ob.-Gyn.	Ob.-Gyn.	Ob.-Gyn.	Neurology(†)	Fundamental Sciences Clinic**
9:30-10:20					Ob.-Gyn.	Ob.-Gyn.
11:30-12:20	Pediatric Clinic	Medical Clinic	Surgical Clinic	Family Practice	Prev. Med. Clinic	Ob.-Gyn. Clinic
1:30- 2:20	Ob.-Gyn. Outpatient Department	Ob.-Gyn. Outpatient Department	Ob.-Gyn. Outpatient Department	Ob.-Gyn. Outpatient Department	Ob.-Gyn. Outpatient Department	
2:30- 4:30						

PEDIATRICS (5½ weeks)

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
8:30- 9:20	Pediatrics	Pediatrics	Pediatrics	Pediatrics	Neurology(†)	Fundamental Sciences Clinic**
9:30-10:20					Pediatrics	Pediatrics
11:30-12:20	Pediatric Clinic	Medical Clinic	Surgical Clinic	Family Practice	Prev. Med. Clinic	Ob.-Gyn. Clinic
1:30- 2:20	Pediatrics Outpatient Department	Pediatrics Outpatient Department	Pediatrics Outpatient Department	Pediatrics Outpatient Department	Pediatrics Outpatient Department	
2:30- 4:30						

(*) The class is divided into three rotating groups, which are designated medical section (MS), surgical section (SS), and specialties section (SpS). The trimesters are also listed as (first), (second), and (third), in order to indicate what period during the college year a particular course is presented.

* Tropical medicine during autumn trimester. Entire class.

** Fundamental Sciences Clinic. First trimester, chemistry; second trimester, physiology; third trimester, pathology. Entire class.

(†) Neurology during first and third trimester; neurosurgery during second trimester. Entire class.

*** Students assigned to Surgery rotate through general surgery, neurosurgery, orthopedics, and urology.

M.D. DEGREES CONFERRED

Abernethy, Joseph Whitener—June, 1945 ..... North Carolina
Abernethy, Paul McBee—December, 1943 ..... North Carolina
Aikawa, Jerry Kazuo—[redacted] ..... [redacted]
Alderman, Allison Montlouville, Jr.—December, 1946 ..... North Carolina
Alexander, Joseph Black—December, 1947 ..... North Carolina
Allen, LeRoy, Jr.—December, 1946 ..... North Carolina
Alsobrook, William Lewis—September, 1944 ..... Tennessee
Anderson, George Arthur—December, 1947 ..... Nebraska
Arrington, Thomas Marshall—September, 1944 ..... Florida
Ashley, Grant Dale—June, 1945 ..... North Carolina
Atkins, Junius Ernest, Jr.—September, 1944 ..... North Carolina
Ausband, John Rufus—December, 1943 ..... North Carolina
Austin, James Addison—December, 1946 ..... North Carolina
Avera, John William, Jr.—March, 1944 ..... North Carolina
Aycock, James Bernice—June, 1944 ..... North Carolina
Bailey, Jean Elizabeth—September, 1944 ..... North Carolina
Batten, Woodrow—December, 1944 ..... North Carolina
Beale, Jefferson Davis, Jr.—September, 1944 ..... North Carolina
Bean, Elmer Oscar—September, 1945 ..... North Dakota
Beckmann, Albert Jules—June, 1945 ..... New York
Bellamy, William Edward, Jr.—December, 1947 ..... North Carolina
Berger, Phil R.—September, 1945 ..... North Dakota
Berry, James William—September, 1944 ..... North Carolina
Best, James Ernest—June, 1945 ..... North Carolina
Bingham, William Louis—March, 1946 ..... North Carolina
Bivens, Edward Shirley—December, 1946 ..... North Carolina
Blackshear, Joe Randall—December, 1947 ..... Alabama
Boyer, George Norman—March, 1946 ..... North Carolina
Bradsher, James Donald—June, 1945 ..... North Carolina
Bridger, Clarence Edgerton—March, 1946 ..... North Carolina
Britt, Tilman Carlisle, Jr.—December, 1947 ..... North Carolina
Brooks, Thomas Joseph, Jr.—September, 1945 ..... Florida
Brooks, William Henry—December, 1947 ..... Georgia
Browdy, Sol—March, 1946 ..... New Jersey
Brown, Dwight Joseph, Jr.—December, 1946 ..... North Carolina
Bruton, Charles Wilson—June, 1945 ..... North Carolina
Buie, Roderick Mark, Jr.—September, 1944 ..... North Carolina
Bullard, Alton Lane—June, 1945 ..... North Carolina
Burnett, Thomas Jesse McCormick—December, 1946 ..... District of Columbia
Burns, Robert Alexander—December, 1947 ..... North Carolina
Caccamo, Leonard Paul—December, 1947 ..... Ohio
Caldwell, Eston Robert—June, 1945 ..... North Carolina
Calvert, Samuel James—September, 1947 ..... North Carolina
Campbell, Lindsey Drayton—September, 1947 ..... North Carolina
Carpenter, Kenneth Carrington—December, 1947 ..... North Carolina
Chastain, Loren Lee—September, 1944 ..... North Carolina
Cheek, John Merritt—June, 1945 ..... North Carolina
Cheek, Kenneth Maurice—December, 1943 ..... North Carolina
Clarke, James Sabrit—March, 1946 ..... North Carolina
Clayton, Eugene Cook—June, 1945 ..... North Carolina
Cline, Wayne Allen—December, 1946 ..... South Carolina
Coker, Walter George, Jr.—December, 1946 ..... Florida
Colom, George Andrew—December, 1947 ..... North Carolina
Coppridge, Thomas Oliver, Jr.—March, 1947 ..... North Carolina
Craig, William Kenneth—December, 1946 ..... North Carolina

Crescenzo, Victor—December, 1943 ..... New York
Crumpler, Warren Harding—December, 1943 ..... North Carolina
Cushman, Robert Gale—December, 1946 ..... Florida
Dahlen, Gregory Amund, Jr.—December, 1944 ..... North Dakota
Daly, Roswald Bernard—December, 1946 ..... North Carolina
Dameron, Joseph Thomas—June, 1945 ..... North Carolina
Daniel, Thomas Brantley—December, 1943 ..... North Carolina
Darden, James Lee, Jr.—December, 1947 ..... North Carolina
Davis, Aaron Heide, Jr.—December, 1946 ..... North Carolina
Davis, Oscar Theodore—December, 1943 ..... Kentucky
Dimmette, Robert Marvin—September, 1944 ..... North Carolina
DuBose, Bolling Stovall, Jr.—March, 1946 ..... Georgia
Eisenberg, Seymour—September, 1944 ..... North Carolina
Fagan, Harry Jr.—December, 1947 ..... Florida
Fisher, George Walton, Jr.—December, 1943 ..... North Carolina
*Fisher, Walter Clark—March, 1946 ..... North Carolina
Fleetwood, Joseph Anderton, Jr.—December, 1947 ..... North Carolina
Foushee, John Caldwell—September, 1944 ..... North Carolina
Fowler, Henry Jackson—December, 1946 ..... North Carolina
Fowler, John Alvis—March, 1946 ..... North Carolina
Fowlkes, William M., Jr.—September, 1944 ..... North Carolina
Freeman, William Harrison—September, 1944 ..... North Carolina
Froke, Leo Burton—September, 1945 ..... North Dakota
Gabbert, William Ries—March, 1946 ..... Kentucky
Gaddy, Clifford Garland—September, 1947 ..... South Carolina
Garrison, Robert Lee—September, 1944 ..... North Carolina
Geiser, Peter Michael—December, 1944 ..... North Dakota
Gibbs, Stuart Wynn—September, 1944 ..... North Carolina
Gibson, George Clive, Jr.—June, 1945 ..... Georgia
Gillikin, Charles Monroe—March, 1946 ..... North Carolina
Givens, George Howard, Jr.—December, 1947 ..... Virginia
Glenn, Richard Reece—December, 1946 ..... North Carolina
Glod, Albert Paul—December, 1943 ..... North Carolina
Gobble, Fleetus Lee, Jr.—September, 1944 ..... North Carolina
Griffin, Thomas Ray—December, 1947 ..... North Carolina
Griggs, Boyce Powell—December, 1943 ..... North Carolina
Griggs, James Young—September, 1944 ..... North Carolina
Gross, Frank Blackburn, Jr.—June, 1945 ..... North Dakota
Gryte, Clifford Folson—December, 1943 ..... North Carolina
Hadley, Herbert Wood—December, 1943 ..... Ohio
Hadlow, Walter Richard, Jr.—December, 1946 ..... North Carolina
Hallman, Bernard Lingo—March, 1946 ..... Georgia
Hammett, James Frank, Jr.—December, 1947 ..... North Carolina
Hamrick, Ladd Watts, Jr.—March, 1946 ..... Florida
Hankins, Joseph Banks—December, 1943 ..... North Carolina
Hardin, Richard Henry—March, 1946 ..... North Carolina
Hare, Roy Allen—June, 1945 ..... Georgia
Harris, Carlton McKenzie—December, 1947 ..... Alabama
Harris, Ruth—September, 1945 ..... Virginia
Hart, Lillard Franklin—June, 1944 ..... Pennsylvania
Hatfield, Charles Ross—December, 1947 ..... North Carolina
Hayes, William Clayton—December, 1947 ..... North Carolina
Hedgepeth, Albert William—September, 1947 ..... South Carolina
Hendricks, Paul Eugene—December, 1946 ..... North Carolina
Herndon, Euclid Garland, Jr.—March, 1946 ..... North Carolina
Hester, Joseph McMurray—March, 1944 ..... North Carolina

*Deceased

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Highsmith, George Perry—March, 1946 ..... North Carolina
Hill, Samuel Richardson, Jr.—December, 1946 ..... North Carolina
Hill, William Henry—September, 1944 ..... North Carolina
*Hobbs, Homer Lafayette—September, 1944 ..... North Carolina
Hobbs, Ralph Jordan Waldo—December, 1943 ..... North Carolina
Hoggard, William Alden—September, 1944 ..... North Carolina
Holbrook, William Douglas—December, 1946 ..... North Carolina
Holt, Lawrence Byerly—June, 1945 ..... North Carolina
Horan, Robert Vincent—September, 1944 ..... Arizona
Horn, Paul Lafleur, Jr.—September, 1947 ..... North Carolina
Hudson, Miles Hildebrand—September, 1944 ..... North Carolina
Jacobs, Erwin Melvin—March 1948 ..... New Jersey
Jarvis, James Luther—March, 1946 ..... North Carolina
Jarvis, Thomas Ralph, Jr.—September, 1944 ..... South Carolina
Jennings, Royal Green, Jr.—September, 1945 ..... North Carolina
Johnson, Elbert Neil, Jr.—December, 1947 ..... North Carolina
Johnston, Harold Wilkes—December, 1943 ..... North Carolina
Jones, William Robert—December, 1947 ..... North Carolina
Joyce, Charles Weldon—September, 1947 ..... North Carolina
Kahn, Alvin Jerome—December, 1946 ..... New York
Kearns, Paul Rutherford—March, 1946 ..... North Carolina
Kiger, Roger Sylvester, Jr.—June 1945 ..... North Carolina
Kinchelor, Franklin Stith, Jr.—March, 1946 ..... Kentucky
King, Robert Rogers, Jr.—September, 1944 ..... North Carolina
Kistler, Clark Clemmons—September, 1947 ..... Colorado
Kornegay, Raymond DeWitt—June, 1945 ..... North Carolina
Labser, Charles Irving—March, 1946 ..... North Carolina
Lamm, LeRoy Barden—March, 1946 ..... North Carolina
Lampley, Charles Gordon—March, 1946 ..... North Carolina
Lane, Edgar Winslow—September, 1944 ..... New Jersey
Lazenby, Marguerite Elizabeth—December, 1946 ..... North Carolina
Lockhart, Walter Samuel, Jr.—September, 1944 ..... North Carolina
Long, Rowland Veach—June, 1946 ..... North Carolina
Lovegren, Lloyd August—March, 1946 ..... Alabama
Lyda, Edgar Witherby—September, 1944 ..... North Carolina
Mankin, James Wallace—December, 1946 ..... Virginia
Margoshes, Stanley—June, 1945 ..... Pennsylvania
Marks, Edgar Seymour—June, 1945 ..... North Carolina
Marshburn, Elisha Thomas, Jr.—December, 1947 ..... North Carolina
May, William Joseph—September, 1944 ..... North Carolina
Means, Robert Lee—December, 1947 ..... North Carolina
Miller, Cameron Eugene—December, 1946 ..... North Carolina
Miller, Ira Ben—March, 1946 ..... North Carolina
Miller, Roland Elmer—December, 1946 ..... Pennsylvania
Mock, David Carlton—March, 1946 ..... North Carolina
Morgan, Benjamin Edward—December, 1947 ..... North Carolina
Morris, Leslie Morgan—December, 1943 ..... North Carolina
Morris, Marshall Glenn, Jr.—December, 1946 ..... North Carolina
Mundorf, Percy George, Jr.—December, 1946 ..... Pennsylvania
MacKay, James Calvin—December, 1947 ..... District of Columbia
McMillan, James Fulford—December, 1947 ..... North Carolina
McMurray, Clarence McCain—December, 1946 ..... North Carolina
McNeill, Claude Ackle, Jr.—December, 1943 ..... North Carolina
McNiel, Thomas Lee—December, 1947 ..... North Carolina
McRae, James Thomas—June, 1945 ..... Mississippi
Nabors, Grover Cooley—March, 1946 ..... South Carolina

*Deceased

Nelson, Irving Robert—December, 1943 ..... New York
Nicholson, Nell Graham, Jr.—March, 1946 ..... North Carolina
Northup, Edwin Charles—June, 1946 ..... New York
Nowlan, Fagg Bernard—March, 1946 ..... North Carolina
Padgett, Joe Carl—March, 1946 ..... North Carolina
Pate, Marion Butler—June, 1945 ..... North Carolina
Patterson, Harold Calvin—June, 1945 ..... North Carolina
Perkinson, Neil Gramling—March, 1946 ..... Georgia
Perry, David Russell, Jr.—December, 1946 ..... North Carolina
Phillips, David Lawrence—June, 1945 ..... North Carolina
Phillips, DeWitt Dewey, Jr.—December, 1946 ..... North Carolina
Phipps, Dorothea Rights—December, 1946 ..... Florida
Pierce, LeRoy Courtney—December, 1947 ..... North Carolina
Pittman, Dorn Carl—June, 1945 ..... North Carolina
Pittman, Hal Watson—June, 1945 ..... North Carolina
Pittman, James Graham—December, 1946 ..... North Carolina
Poe, William Dunlap—December, 1943 ..... Virginia
Pope, Robert Clyde—June, 1945 ..... North Carolina
Powers, Joel Eugene—December, 1947 ..... North Carolina
Pressman, Maurie David—March, 1946 ..... Pennsylvania
Prevette, William Carter—September, 1944 ..... Michigan
Proctor, Richard Culpepper—September, 1945 ..... North Carolina
Pugh, Alice De Shong—December, 1947 ..... North Carolina
Rankin, Pressley Robinson, Jr.—December, 1947 ..... North Carolina
Rayle, Wiley Wallace—December, 1947 ..... North Carolina
Reinhart, John Belvin—December, 1943 ..... Wisconsin
Reynolds, William Ward—December, 1947 ..... Ohio
Rhodes, James Kent—December, 1947 ..... North Carolina
Rice, Moses Edward—December, 1943 ..... North Carolina
Richards, Paul De—September, 1944 ..... South Dakota
Richardson, Clarence Dixon—March, 1946 ..... North Carolina
Rights, Clyde Siewers—December, 1947 ..... Florida
Robertson, Leon Whitfield—June, 1945 ..... North Carolina
Rogers, Henry Moore, Jr.—December, 1947 ..... North Carolina
Rothfeld, Benjamin—June, 1945 ..... New Jersey
Sapp, Oscar LeMay, III—December, 1947 ..... North Carolina
Satterwhite, James Pumphrey—March, 1946 ..... Florida
Sawyer, Charles Glenn—September, 1944 ..... North Carolina
Schrum, David Irving—December, 1944 ..... North Carolina
Seife, Marvin—December, 1946 ..... New York
Shackelford, Robert Hilliard—December, 1947 ..... North Carolina
Sherrill, John Franklin, Jr.—December, 1946 ..... North Carolina
Shields, William Ernest—September, 1944 ..... North Carolina
Shingleton, William Warner—December, 1943 ..... North Carolina
Sluder, Harold Miles—June, 1945 ..... North Carolina
Smith, David Clark—December, 1943 ..... North Carolina
Smith, Joseph Pinkney—June, 1945 ..... North Carolina
Spurling, Carrol Lattimore—December, 1947 ..... North Carolina
Stallings, Stephen Durwood, Jr.—December, 1946 ..... North Carolina
Stringfield, Preston Calvin, Jr.—December, 1943 ..... North Carolina
Sweel, Alexander—March, 1946 ..... New Jersey
Taylor, John David—June, 1945 ..... Kansas
Thomas, James Valentine—June, 1945 ..... South Carolina
Thompson, Jamie Campbell, Jr.—March, 1946 ..... Kentucky
Thompson, John Junior—March, 1944 ..... Minnesota
Tiller, Wendell Howard—March, 1945 ..... South Carolina
Trivette, Parks DeWitt—March, 1946 ..... North Carolina
Truslow, Roy Earl—June, 1945 ..... North Carolina

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Tyner, Hugh Edward—March, 1946 ..... North Carolina
Upchurch, Kent Paschal—March, 1946 ..... North Carolina
Vann, Robert Lee—June, 1945 ..... North Carolina
Wallace, Stanley Lawrence—December, 1946 ..... New York
Ward, Doctor Ernest, Jr.—June, 1945 ..... North Carolina
Warr, Charles Monroe, Jr.—December, 1947 ..... North Carolina
Webb, Melvin Walter—June, 1945 ..... North Carolina
Wells, Helen Lewis—December, 1946 ..... North Carolina
Whelchel, Merritt Cofer—March, 1946 ..... Georgia
Wheless, Thomas Omega—December, 1943 ..... North Carolina
White, William Elliott—December, 1946 ..... North Carolina
Wilkerson, Joseph Louis—December, 1943 ..... North Carolina
Williams, Jerome Otis—December, 1946 ..... Tennessee
Williford, John Kenneth—March, 1946 ..... North Carolina
Wood, William Lupton—June, 1945 ..... Alabama
Woolbert, Edwin Smith—December, 1943 ..... New Jersey
Yount, Harold Alexander—[redacted] ..... [redacted]
Yow, Ellard Melton—March, 1944 ..... North Carolina

ROSTER OF STUDENTS

THIRD YEAR CLASS

Barnes, M. Russell, Jr. ..... Wilmington
B. S., Wake Forest College, 1943

Biggs, Dennis Walter, Jr. ..... Lumberton

Bjork, Ray Ormenzo ..... Helena, Montana
B.S., Moorhead State Teachers College, 1927
M.A., University of Minnesota, 1936

Bland, William Herbert ..... New Bern
B.S., Wake Forest College, 1945

Brenton, Harold La Verne ..... Charles City, Iowa

Brunt, Manly Yates, Jr. ..... Winston-Salem

Clark, Clarence Ford, Jr. ..... Nashville, Tennessee
B.S., Carson-Newman College, 1947

Clarke, Len Gordon ..... Draper

Collier, William Jewell ..... Albany, Missouri
B.S., Tulane University, 1947

Creel, Frank Lamar ..... Pensacola, Florida

Crow, John Buren ..... Shelby
B.S., Wake Forest College, 1946

Dickerson, Andrew Jackson ..... Monroe

Fernandez, Frank Louis ..... High Point
B.S. High Point College, 1942

Fisher, Joseph Franklin ..... Clinton

Flanagan, Brian Patrick ..... Grosse Point, Michigan

Glenn, Leland Kirk ..... Hickory

Hayward, John Charles ..... Battle Creek, Michigan
B.S., University of Chicago, 1945

Hedberg, Louis Allen ..... Patchogue, New York

Heller, Edgar Elwood ..... Ringtown, Pennsylvania
A.B., Ursinus College, 1943

Henry, Ozmer Lucas, Jr. ..... Lumberton
B.S., Wake Forest College, 1946

Hood, Richard Thornton, Jr. ..... Kinston
A.B., Duke University, 1945

Isley, Joseph Keener, Jr. ..... Greensboro

Jaehning, David Grover ..... Fargo, North Dakota
B.S., University of North Dakota, 1947

Leeds, Robert Melvin.....Brooklyn, New York
Lipton, Edgar Louis.....Los Angeles, California
Maher, Robert William.....Chicago, Illinois
Martinat, Edwin Henry.....Lenoir
Moorman, Lemuel Talbott.....Florence, South Carolina
McDaniel, Grover Cleveland, Jr.....Forest City
Nance, John Wesley.....Graham
B.S., Wake Forest College, 1941
Palmer, Etna Little.....Thomasville
A.B., Catawba College, 1936
Pate, James Lloyd.....Fayetteville
Sharp, James Vance.....Reidsville
Smith, Loy Connell.....Fuquay Springs
Smith, Thelma Ruth.....Fort Mill, South Carolina
B.S., Winthrop College, 1945
Spangler, Harold Benjamin.....Shelby
Thompson, Diana.....Reidsville
A.B., Duke University, 1940
Thompson, Dolores MacGillis.....Lexington, Kentucky
A.B., University of Kentucky, 1943
Tuttle, James Gray.....Raleigh
A.B., Duke University, 1945
Will, Thomas Augustine.....New Baltimore, Pennsylvania

SECOND YEAR CLASS

Anderson, Henry Shaw.....Mocksville
Bethea, William Thaddeus, Jr.....Dillon, South Carolina
B.S., The Citadel, 1942
Brown, James Luther.....High Point
B.S., High Point College, 1946
Bumgarner, James Irwin.....Wilkesboro
B.S., Wake Forest College, 1939
Burack, Richard.....Brookline, Massachusetts
Butler, Radford Norman.....Clinton
B.S., Wake Forest College, 1946
Byrd, William Carey, Jr.....Angier
B.S., Wake Forest College, 1947
Carter, Numa Richardson, Jr.....Winstom-Salem
B.S., Davidson College, 1947
Cochran, John Leach, Jr.....Star
B.S., Wake Forest College, 1941
Coleman, Lester Livingston, Jr.....Columbus, Georgia
B.S., Presbyterian College, 1943
Coston, Harold Prestwood.....Winston-Salem
B.S., Wake Forest College, 1946
Couturier, Maurice George.....Mebane
Curlee, Lewis Elton.....Marshville
Daugherty, Charles Hines.....Tulsa, Oklahoma
B.S., University of Tulsa, 1946
Davis, James Matheson, Jr.....Wadesboro
B.S., Wake Forest College, 1947
Early, Ira Gordon.....Thomasville
Folk, Edgar Estes, III.....Wake Forest
B.S., Wake Forest College, 1947
Garrison, Paul Leslie.....Winston Salem
B.S., Wake Forest College, 1947
Glass, Frederick William.....Kannapolis
B.S., Wake Forest College, 1946
Hand, LeRoy Corbett, Jr.....Gatesville
B.S., Wake Forest College, 1947
Hays, Glenn Bare.....Etters Postoffice, Pennsylvania
B.S., Georgia School of Technology, 1940

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Hayslip, Gordon Woodrow.....Columbus, Ohio
B.A., Ohio State University, 1946
Henderson, Andrew McKnitt, Jr.....Mooresville
B.S., Appalachian State Teachers College, 1942
Highsmith, William Jesse, Jr.....Plymouth
B.S., Wake Forest College, 1935
Holzworth, Robert Haviland.....Syracuse, New York
A.B., Syracuse University, 1940
A.M., Duke University, 1942
Ichelson, David Leon.....Palo Alto, California
A.B., Stanford University, 1943
Jang, Gloria.....Berkeley, California
Jones, Warren Hunter.....Lakeport, New Hampshire
B.S., University of New Hampshire, 1941
Kay, Charlotte Rita.....Charlotte
B.A., Queens College, 1946
Mabe, Henderson David, Jr.....Kinston
B.S., Wake Forest College, 1946
Maxey, Edward Stanton.....Miami, Florida
B.S., Wake Forest College, 1947
McClure, Claude, Jr.....Spruce Pine
B.S., Wake Forest College, 1947
Nowell, David Maclyn.....Wake Forest
B.S., Wake Forest College, 1946
Padgett, Martin Jehu.....Elizabeth City
B.S., Wake Forest College, 1932
Pope, James Kenneth.....Mt. Mourne
B.S., Davidson College, 1940
Register, Samuel Tilden.....Tallahassee, Florida
B.S., University of Florida, 1942
Sakai, Henry Katsumi.....San Francisco, California
B.A., Washington University, 1944
Schwartze, Erich Wilhelm.....Washington, D. C.
B.S., Baylor University, 1947
Stafford, Florence Eleanor.....Kernersville
B.S., Salem College, 1938
Tyson, George Stackley.....Florence, South Carolina
B.S., Davidson College, 1943
Weininger, Herbert Luis.....New York, N. Y.
B.S., Wake Forest College, 1945

FIRST YEAR CLASS

Allen, Charles Insley, Jr.....Wadesboro
Allen, John O. Henry.....Marion
B.A., Furman University, 1943
B.S., Furman University, 1947
Blackmon, Bruce Bernard.....Buies Creek
B.S., N. C. State College, 1943
M.S. N. C. State College, 1945
Boone, John Woodie, Jr.....Seaboard
Boyette, Ben Robert, Jr.....Goldsboro
Bunch, Mary Elizabeth.....Asheboro
B.S.N., Duke University, 1941
Christian, Bernie Joseph.....Rocky Mount
B.S., Wake Forest College, 1947
Council, Albert Barbee, Jr.....Mount Airy
Courts, Sara Anne.....Reidsville
A.B., Duke University, 1946
Crawley, Sam Jones, Jr.....Lattimore
Donald, William Blanton, Jr.....Greensboro
Fesperman, Joseph Claude.....Granite Quarry
A.B., Duke University, 1947
Freeman, David Franklin.....Raleigh

Futrell, John Marion ..... Greensboro
Garrett, John Bostian ..... Rockingham
Gulley, Marcus Marcellus ..... Alexandria, Virginia
B.S., Wake Forest College, 1947
Gwynn, Thomas Lee ..... Yanceyville
Hanes, Gideon Isaac, Jr. ..... Winston-Salem
B.S., Wake Forest College, 1947
Harper, Robert Norment ..... Raleigh
Herman, John David ..... Fayetteville
Hiott, Greer Fleetwood, Jr. ..... Charlotte
Hollandsworth, Luther Clarence ..... Welch, West Virginia
Hudson, William Rucker ..... Cramerton
Huntley, Robert Ross ..... Wadesboro
B.S., Davidson College, 1947
Jemison, Howard Allan, Jr. ..... Winston-Salem
Johnson, Livingston ..... Winston-Salem
A.B., Wake Forest College, 1947
Johnson, William Robert ..... Sonora, Texas
Jones, Joseph Reid, Jr. ..... King
B.S., Wake Forest College, 1947
Jordan, Riley Moore ..... Raeford
B.S., Wake Forest College, 1947
Klein, Robert Edward ..... Huntington, West Virginia
B.S., Marshall College, 1947
Knight, Ruth Maxine ..... Stokesdale
B.S., Wake Forest College, 1947
Lancaster, James Monroe ..... Goldsboro
Lomax, Donald Henry ..... Linwood
McLean, William Thaddeus, Jr. ..... Clinton
Miller, Horace William, Jr. ..... Asheville
B.S., Wake Forest College, 1947
Mills, Randolph Dennis ..... Henderson
Moore, Robert Alexander, Jr. ..... Winston-Salem
A.B., University of North Carolina, 1946
Norton, James Robert ..... Spruce Pine
B.S., Wake Forest College, 1947
Peak, Latham Conrad ..... High Point
Pena, Joe A. ..... Brownsville, Texas
Prevette, John Edgar ..... Pontiac, Michigan
Seife, Irwin ..... Brooklyn, New York
Sherrill, Frank Howard, Jr. ..... Asheville
B.S., Wake Forest College, 1947
Sherrill, Glenn David ..... Spartanburg, South Carolina
B.S., Duke University, 1946
A.B., Wofford College, 1947
Silverthorne, Ray Guilford ..... Washington
A.B., Atlantic Christian College, 1941
B.D., College of the Bible, 1944
Smith, Albert Heyward, Jr. ..... Sumter, South Carolina
Tolson, James Monroe ..... Henderson
Turpin, William Richmond ..... Greenville, South Carolina
B.S., Furman University, 1947
Tysinger, Donald Shuford, Jr. ..... Salisbury
Wadsworth, Walter Arnold ..... Ridgewood, New Jersey
Woodward, Betty Mabel ..... Phenix City, Alabama
B.S., Wake Forest College, 1947
Yount, Arthur White ..... Statesville

Separate bulletins are issued by each School. Requests for bulletins of The College, The School of Law, and the Summer Session should be made to Registrar Grady S. Patterson, Wake Forest, N. C. Application for a bulletin of the Medical School should be made to The Dean, Bowman Gray School of Medicine, Winston-Salem 7, N. C.

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WAKE FOREST COLLEGE

WAKE FOREST, N. C.

An institution of high scholastic standing fostering Christian and Cultural leadership

Wake Forest College is the oldest Baptist school in the United States and for more than a century has been training students [illegible] denomination, in community building, and in the professional life of the nation.

The student body is non-sectarian, but the institution is distinctly Christian, and in a day when true culture and religious freedom are threatened throughout the world, Wake Forest recognizes its obligation to the ideals of its founders. Students are encouraged to search for the truth, express the truth, and live in the freedom of truth.

Men and women are admitted to all classes, graduate work, professional schools, and the Summer School.

The college holds membership in the American Association of Colleges, the Southern Athletic Conference, and has a chapter of Phi Beta Kappa. It is accredited by the North Carolina Department of Public Instruction, the Southern Association of Colleges and Secondary Schools, the American Association of Universities. Its professional schools of law and Medicine are accredited by their respective national agencies.

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

RESEARCH CONTRACT

CONTRACT NO.: AT-(40-1)-288

CONTRACTOR: THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

ADDRESS: Winston-Salem 7, North Carolina

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

1112119

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

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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.

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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 such 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.

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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.

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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)

BY: C. Carpenter

TITLE: Dean

WITNESSES:

Mary O. Parker

Katherine Davis

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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 anione - 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. Mount	$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) Expendable Supplies

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.

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 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.

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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 [signature]
Project Leader

DATE: 7/6/49

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APPENDIX "A"

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

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

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phosphorus as a tracer for the phosphate part of the molecule. By labeling the methyl group of choline with C^{14}, 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. Cornatzer~~
Dr. M. A. Swanson
Marietta Crowder, Graduate Student

(2) Overhead allocable to the contract work.

Appendix "A" (Cont'd) TITLE II Contract No. AT-(40-1)-288
(The Bowman Gray School of Medicine
of Wake Forest College)

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)

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 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: T. Carroll Poston
Project Leader

DATE: 7/6/49

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APPENDIX "A"

Contract No. AT-(40-1)-238
(The Bowman Gray School of Medicine
of the 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

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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 P^{32} 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. C. Artom, 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

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: Roger T. Howell
Project Leader

E. Camille Artom
Associate Project Leader

David Cuyk
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.

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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.

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

RESEARCH CONTRACT

CONTRACT NO.: AT-(40-1)- 28

CONTRACTOR: THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

ADDRESS: Winston-Salem, North Carolina

AMOUNT OF CONTRACT: ~~$25,875.00~~ $25000

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

1112139

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

THIS CONTRACT, entered into this _____ day of _____, 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 $ ~~[illegible]~~ 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

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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.

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ARTICLE IV - [illegible] THE 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 such 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 at periods provided 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.

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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 six (6) copies of all reports and papers. Three (3) 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.

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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: _____

WITNESSES:

THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE
(Contractor)

_____

BY: _____

_____

TITLE: _____

1112144

APPENDIX "A" 6

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 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:

1. 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.

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

3. 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.

1112145

Appendix "A" (Cont'd) TITLE I Contract No. AT-(40-1)-288

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) Expendable Supplies		
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.

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Appendix "A" (Cont'd) TITLE I CONTRACT NO. AT-(40-1)- 288
(The Bowman Gray School of Medicine
Of Wake Forest College)

e. 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 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.

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: _____

1112147

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

DEPARTMENT OF
BIOCHEMISTRY

Outline of the Research Project on:

HORMONAL AND PHARMACOLOGICAL ACTIONS ON THE FORMATION OF TISSUE PHOSPHOLIPIDES

Project Leader: Camillo Artom, M.D.
Research Contract No. AT -(40-1)-
Title II

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 C^{14}, 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.

1112148

[redacted]

Contract No. AT-(40-1)- 288
(The [redacted] of Medicine
of Wake Forest College)

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. Camille Artom as Project Leader.
ARTOM

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

(Secure a copy of last years proposal for complete description of project. Current proposal incomplete in that it refers to last years proposal.)

1112149

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. Camille Artom as Project Leader
Dr. W. E. Cornatzer
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)...	[illegible]	
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.....	850.00	
Geiger-Muller counter.....	450.00	
Shielded manual sample changer with amplifier.....	800.00	
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..... ..... [illegible] 150.00	
~~500.00~~	500.00
~~Rodent drawings reproduction.....~~	~~[illegible]~~
TOTAL.....	$11,000.00

1-1-2-1-50

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.

e. 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 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: _____
Project Leader

DATE: _____

APPENDIX "A"

Contract No. AT-[illegible]-266
(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. Gayer.

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 [illegible]

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 [illegible] 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 P^{32} 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. [illegible]

1112152

Appendix "A" (Cont'd) TITLE III Contract No. AT-(40-1)-288

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. C. Arton, C. T. Harrell and D. Sayer.

(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 hemogenizer 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

It is understood and agreed by and between the parties hereto, that the Contractor in expending the funds provided by the Government shallbe 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: _____
Project Leader

_____
Associate Project Leader

_____
Associate Project Leader

DATE: _____

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.

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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 (1½) 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.

1112157

Appendix "A" (Cont'd) **TITLE I** Contract No. AT-(40-1)-288
(The Bowman Gray School of Medicine of Wake Forest College)

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 $9875.00 to be spent roughly as follows:

(1) Personnel

Parttime salary ~~[illegible] permit release of Dr. E. Yount to work on project~~	$1800.00	
Technician	2400.00	
Electronic engineer, part-time	~~500.00~~	
		$4,700.00

(2) Permanent Equipment

Shielded sample changer	~~290.00~~	
Scaling circuit	450.00	775.00
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	
		$2,025.00

(3) Expendible Supplies

Glassware	750.00	400.00
Chemicals	500.00	
Animals	1500.00	
		$2,750.00

(4) Travel 200.00 $ 200.00

(5) Miscellaneous 200.00

TOTAL $9,875.00

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.

1112158

Appendix "A" (Cont'd) TITLE I Contract No. AT-(40-1)-288

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	180.00	
Metabolism cages	350.00	
Vacuum pump	75.00	
		$2,750.00
(3) Expendible Supplies		
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.

1112159

Appendix "A" (Cont'd) TITLE I Contract No. AT-(40-1)-288

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	250.00	
Deep Freeze Unit	160.00	
Metabolism cages	350.00	
Vacuum pump	75.00	
		$2,750.00
(3) Expendible Supplies		
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.

1112160

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

RESEARCH CONTRACT

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

CONTRACTOR: BOWMAN-GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

ADDRESS:

WINSTON-SALEM 7, NORTH CAROLINA

AMOUNT OF CONTRACT:

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

1112161

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

THIS CONTRACT, entered into this _____ day of _____, 1949, by the UNITED STATES OF AMERICA (hereinafter called the "Government"), acting through the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission") and 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 $_____ _____ 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

1112162

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.

1112163

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 such 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 ~~quarterly~~ progress reports 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.

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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)~~ six copies of all reports and papers. ~~Two (2)~~ three 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.

1112165

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: _____

WITNESSES:

_____

_____

_____
(Contractor)

BY: _____

TITLE: _____

1112166

DAVID FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO : C. Vanlen Bulck, Assistant to the Manager DATE: June 5, 1950

FROM : Harry Stoeckle, M.D., Medical Advisor, Office of Research and Medicine

SUBJECT: RECORD OF EXPENDITURES OF UNCLASSIFIED UNIVERSITY MEDICAL CONTRACTS

SYMBOL: RMM:HS

In accordance with your recent suggestion, the "Record of Expenditures" of the following universities have been reviewed and are concurred in by this office:

✓ Rice Institute
University of Virginia
Baylor University
University of Tennessee
✓ Texas A&M

When differences appear in the estimate of expenditures for the months of May and June, as compared to the rest of the year, these differences usually amount to several hundred dollars. Such amounts seem reasonable to this office.

I believe that the estimates for Title II of Bowman Gray contract should be revised in light of the letters from Parker and Artom, dated May 18. According to Parker's letter, expenditures for Title II for the first 10 months should be:

$ 4,763.27	As of April 30
1,100.00 ✓	Expenditures for April
1,350.00 ✓	Spectrophotometer
$ 7,213.27	

This leaves a balance of:

$11,000.00	
7,213.27	
$ 3,786.73	As of April 30.

Estimated expenditures for May and June (Dr. Artom's letter):

$ 365.00	Salaries
175.00	Glassware
100.00	Pipettes
50.00	Animals
44.00	Incidentals
$ 734.00	

111267

This itemized [illegible] differs from Dr. Artom's letter of May 18, in that the purchase of these items would be duplication budgeted for (and to be funded) in next year's budget. For example:

	1950 Proposal	May & ~~April~~ Estimated Expenditure	1951 Proposals
Glassware	$ 600.00	$ 350.00	$ 600.00
Chemicals & Solvents	800.00	300.00	900.00
C^{14} Compounds	1,250.00	1,135.00 — 1955	1,250.00

Total expenditures (expended and estimated) as of June 30, 1950, are $7,947.27. This then leaves an estimated balance unexpended as of June 30, 1950, of $3,057.73, say $3,000.00.

Harry Stoeckle

Harry Stoeckle, M.D.

Stoeckle:ec

1112168

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

RECORD OF EXPENDITURES

PROJECT	CONTRACT AMOUNT	EXPENDITURES TO 4-30-1950	BALANCE UNEXPENDED AS OF 4-30-1950	ESTIMATED EXPENDITURES PERIOD 5/1 - 6/30/1950	ESTIMATED BALANCE UNEXPENDED 6-30-1950
TITLE I	$11,000.00	$8,386.08	$2,613.92	$2,613.92	
TITLE II	11,000.00	~~4,763.27~~ 7213.27	~~6,236.73~~ 3788.73	~~4,500.00~~ 734.00	~~$1,736.73~~ —
TITLE III	3,000.00	2,322.46	677.54	677.54 + 54.73 = 786.73	3,000.00
TITLE IV					
TITLE V					
TOTAL	$25,000.00	$15,471.81	$9,528.19	$7,791.46	~~$1,736.73~~ 3,000.00

delete - audit - per term; not allowable under contract.

See Dr Stubbs' memo dated 6/5. OK

HES May 22, 1950 See Carson's & Parker's letters of May 19, 1950

RECORD OF PAYMENTS RECEIVED BY CONTRACTOR

--------- PROJECT ----------

	TITLE I	TITLE II	TITLE III	TITLE IV	TITLE V	TOTAL
INITIAL VOUCHER (ADVANCE OF FUNDS)	$6,150.00	$6,260.00	$1,550.00			$13,960.00
REIMBURSEMENTS (Subsequent Vouchers)	$4,850.00	$4,539.94	$1,450.00			$10,839.94
TOTAL	$11,000.00	$10,799.94	$3,000.00			$24,799.94

REPORT SUBMITTED BY:

Bowman Gray School of Medicine of Wake Forest College
(Contractor)

BY: Stanley R. Parker
Controller

DATE: May 11, 1950

1112169

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

RECORD OF EXPENDITURES

PROJECT	CONTRACT AMOUNT	EXPENDITURES TO 4-30-1950	BALANCE UNEXPENDED AS OF 4-30-1950	ESTIMATED EXPENDITURES PERIOD 5/1 - 6/30/1950	ESTIMATED BALANCE UNEXPENDED 6-30-1950
TITLE I	$11,000.00	$8,386.08	$2,613.92	$2,613.92	
TITLE II	11,000.00	4,763.27	6,236.73	4,500.00	$1,736.73
TITLE III	3,000.00	2,322.46	677.54	677.54	
TITLE IV					
TITLE V					
TOTAL	$25,000.00	$15,471.81	$9,528.19	$7,791.46	$1,736.73

RECORD OF PAYMENTS RECEIVED BY CONTRACTOR

--------- PROJECT ---------

	TITLE I	TITLE II	TITLE III	TITLE IV	TITLE V	TOTAL
INITIAL VOUCHER (ADVANCE OF FUNDS)	$6,150.00	$6,260.00	$1,550.00			$13,960.00
REIMBURSEMENTS (Subsequent Vouchers)	$4,850.00	$4,539.94	$1,450.00			$10,839.94
TOTAL	$11,000.00	$10,799.94	$3,000.00			$24,799.94

REPORT SUBMITTED BY:

Bowman Gray School of Medicine of Wake Forest College
(Contractor)

BY: Harry O. Porter
Controller

DATE: May 11, 1950

1112170

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

OFFICE OF THE CONTROLLER

May 11, 1950

U. S. Atomic Energy Commission
Oak Ridge Operations
Oak Ridge, Tennessee

Reference: CO:RGH
Contract No. AT-(40-1) 288

Gentlemen:

Reference is made to your letter of May 8/1950 in which you enclosed forms on which to show the status of expenditures of the subject grant incident to the extension of our contract for the year beginning July 1, 1950. These forms, filled out according to instructions thereon, are enclosed herewith.

If there is any further information which you desire in connection therewith, please let us know.

Yours very truly,

Harry O. Parker

Harry O. Parker
Controller

HOP:nh

Enclosure

Mr. Harry Stoble called Harrell and Parker on 5/16/50 for an explanation of the high rate of expenditures in May & June. Figures were furnished by Atom was out. Parker will get [illegible]

CONTRACTS

1112171

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

OFFICE OF THE CONTROLLER

May 18, 1950

Dr. Harry Stoeckle, Medical Advisor
Office of Research and Medicine
U. S. Atomic Energy Commission
Oak Ridge Operations
Oak Ridge, Tennessee

Dear Dr. Stoeckle:

Reference is made to your telephone conversation with me day before yesterday relative to the estimated expenditures in the amount of $4,500 for May and June 1950, Title II, Appendix A under Contract No. AT (40-1) 288.

As I told you over the telephone, this estimate was obtained from Dr. Artom, the principal investigator, and I would confer with him relative to your questions. The delay in writing you was due to the fact that Dr. Artom was out at the time I talked to you due to the death of his father-in-law.

I am enclosing herewith a rather comprehensive letter addressed to you by Dr. Artom which we hope sufficiently justifies this large estimated expenditures as compared to the expenditures for the past ten months. According to the statement which we sent you, expenditures through April 30, 1950 for Title II of the contract amounted to $4,763.27, with a resulting unexpended balance of $6,236.73. The estimated expenditures for the months of May and June, 1950 were shown as $4,500 with an estimated unexpended balance at June 30, 1950 of $1,736.73. As indicated in Dr. Artom's letter, expenditures in May, 1950, for April and prior invoices have amounted to approximately $1,100.00. Among other items, there is now on order a Spectrophotometer with attachment which will amount to $1,350.00.

We hope that the above information together with Dr. Artom's letter will furnish you the information which you desire in connection with this estimated expenditures for Title II under this contract.

Yours very truly,

Harry O. Parker

Harry O. Parker
Controller

HOP:nh

MAY 22 1950

1112172

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

DEPARTMENT OF
BIOCHEMISTRY

May 18, 1950

Dr. Harry Stoeckle
Medical Advisor
Office of Research and Medicine
Oak Ridge, Tennessee

Dear Dr. Stoeckle:

I am referring to the questions raised by you in your telephone conversation with Dr. G. T. Harrell and Mr. Harry Parker, concerning the expenditures on Title II, appendix A, Contract No. AT-(40-1)-288. As I have indicated in my progress reports of last March, while our work with P^{32} has progressed satisfactory, the experiments with C^{14} labeled compounds have suffered a considerable delay.

First, our fully trained technician, Miss M. L. Haigler, left in October and since then we have been able to secure only occasional help from partially trained persons. This accounts for most of the balance which we estimate will remain unexpended on June 30, 1950. Second, considerable difficulties have been encountered in the synthesis of isotopic choline. This compound, which Dr. Roe of the University of North Carolina had undertaken to synthesize for us, has not been ready until last month. Third, the teaching of Biochemistry to Medical Students in our school was concentrated in the trimester January through March 1950. In this period, very little time could be given by my collaborators and myself to investigative work. For these reasons we thought it advisable to delay the purchase of equipment, glassware and chemicals needed for the work with C^{14} until we were sure that we actually would be able to start these experiments before the end of the current fiscal year.

In addition, from various data which have appeared lately in the literature, as well as from observations in the course of our experiments, we became aware of the difficulties in identifying compounds related to choline (such as dimethyl- and monomethylethanolamine, betaine, dimethylglycine) in the presence of choline itself. It appears that the spectrophotometric examination in the ultraviolet region of derivatives of these compounds might offer considerable aid toward their identification. We therefore, attempted to do without several pieces of equipment which were listed in our original application (such as a new scaling unit, a direct reading balance for animals and various accessories for radioactivity and Warburg apparatus) in order to be able to purchase instead of these items, a Beckman Spectrophotometer with ultraviolet attachment. Our old Geiger Counter has worked reasonably well until recently, so we ordered the spectrophotometer which is now in our laboratory, ready to be used.

The above explanations account for the limited amount of expenditures up to April 30, 1950. At this date, according to Mr. Parker's figures, $4,763.27 had been actually spent. However, to this figure should be added the sums of

1112173

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

DEPARTMENT OF
BIOCHEMISTRY

$893.80 for supplies and travel, and of $123.04 for an electrical recorder which has long been in use but which was paid for subsequent to April 30th. Items ordered and received but which have not been actually paid (including the spectrophotometer and ultraviolet attachment) amount to approximately $1,528.00.

These expenditures plus the estimated unexpended balance on June 30, 1950 would leave a sum of approximately $2,544.00 which, according to my estimation, would be used as follows:

Salaries	$365.00
Glassware and accessories for C^{14} work only	350.00
Equipment (Pipette Washer and safety pipettes)	100.00
Chemicals and organic solvents	300.00
Animals	50.00
1 millicurie C^{14} labeled methionine (U. S. Testing Co., Hoboken, N. J.)	600.00
1 millicurie C^{14} labeled methyl iodide (Tracerlab, Inc., Boston, Mass.- to be used in the synthesis of betaine)	285.00
1 millicurie C^{14} labeled formaldehyde (to be used in the synthesis of dimethylglycine)	250.00
Incidentals	244.00
	$2,544.00

While it is realized that some of the C^{14} labeled compounds will not be ready for use before some time, it seems that it would be wise not to risk to delay further the synthesis of these substances because of the unavailability of the labeled materials. Likewise most of the items purchased or to be purchased before June 30 will also be used for our experiments after this date.

Finally, it is, of course, our understanding that any item which will not be actually in our hands before June 30, 1950 will not be charged against the present Title II and that at that date the unexpended balance will be correspondingly increased.

Sincerely yours,

Camillo Arton

Camillo Arton, M. D.
Professor and Head of the Department of Biochemistry

CA/c

1112174

MEMO ROUTE SLIP
Form AEC-98 (Rev. May 14, 1947)

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

TO (Name and unit)	INITIALS / DATE	REMARKS		
Mr. Voibles Off. asst. Gen. Counsel.		Brown-Gray AT-(40-1)-288		
		Title I	Title II	Title III
TO (Name and unit)	INITIALS (1st year) (2nd year) DATE	REMARKS		
Expenditures Appr. Budget		11,000.00	8000.00	3000.00
Contract Amounts (2 years)		13,858.00	11,437.00	6,453.00
		24,858.00	19,437.00	9,453.00
TO (Name and unit)	INITIALS / DATE	REMARKS		
Paid to 6/1/50		-11,000.00	10,799.94	3000.00
Bal. to be paid		$13,858.00	8,637.06	$6,453.00
FROM (Name and unit)		REMARKS		
R. B. Humphries		NOTE: attached papers reflect former NAVY property, title to which is to be vested in Brown-Gray by this modification. Return property records to me when you are finished.		
PHONE NO.	DATE 6/18/50			

USE OTHER SIDE FOR ADDITIONAL REMARKS

16—86067-1 U. S. GOVERNMENT PRINTING OFFICE

1112175

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO : C. Vanden Bulck, Assistant to the Manager DATE: May 3, 1950

FROM : Albert H. Holland, Jr., M.D., Director of Research and Medicine

SUBJECT: RENEWAL OF CONTRACT NO. AT-(40-1)-288 - THE BOWMAN GRAY SCHOOL OF MEDICINE

SYMBOL: RM:AMC

We are enclosing a memorandum from L. W. Tuttle, Asst. Chief, Medical Branch, Division of Biology and Medicine, Washington, requesting the renewal of Contract No. AT-(40-1)-288 with The Bowman Gray School of Medicine for a period of one year from July 1, 1950 to June 30, 1951, at a level of $29,396, plus 8%, totalling $2,352. We are enclosing the proposal for renewal of the contract.

Dr. Harry Stoeckle, Medical Advisor, is the technical representative to contact for making arrangements for renewal of the contract. It is requested that provision be made in this modification to transfer title of property acquired under Navy Contract Nos. N8-ONR-63701 and N8-ONR-63702 in the amount of $16,300.02 from the AEC to Bowman Gray School of Medicine.

for John H Roberson
Albert H. Holland, Jr., M.D.

Encl.:
Memo dtd 4/19/50 w/proposal

CC: Dr. Stoeckle

Corley:tw

0-1745

1112176

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO : Dr. A. H. Holland, Jr.
Chief, Medicine & Research Division, OCRO

DATE: April 19, 1950

FROM : L. W. Tuttle, Asst. Chief, Medical Branch
Division of Biology and Medicine, Washington, D.C.

SUBJECT: REQUEST TO RENEW CONTRACT AT(40-1)-288 THE BOWMAN GRAY SCHOOL OF MEDICINE WINSTON-SALEM, NORTH CAROLINA UNDER DR. GEORGE T. HARRELL

REFER TO SYMBOL: BMM:LWT

It is requested that the subject contract be renewed at a level of $29,396 for the research to be performed under titles I, II, and III combined, plus 8% overhead, totalling $2,352. Funds in the amount of $31,748 will be suballotted to the Office of Oak Ridge Operations for the above purpose.

Attachment
Cpy of Title I, II, and III for
Renewal of Contract
Cpy ltr. to Commission from Harrell, 4/15/50

1112177

COPY

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, N. CAROLINA
ZONE 7

APRIL 15, 1950

ATOMIC ENERGY COMMISSION
Division of Biology and Medicine
1901 Constitution Avenue, N.W.
Washington 25, D.C.

Gentlemen:

We are enclosing two copies of the proposal for renewal of our contract no. AT-(40-1)-. Titles I, II, and III are discussed separately; a single recapitulation sheet summarizing the individual budgets is also attached. We regret that these proposals have been delayed several days due to the press of teaching with the end of the Winter Quarter and the beginning of the Spring teaching quarter. We sincerely hope that you have not been seriously inconvenienced by this short delay.

We should like to reserve the right to submit within the next two months an additional title covering another study on a different type of functional damage produced by irradiation. These additional experiments were discussed with Dr. L. W. Tuttle, of the Medical Branch, Division of Biology and Medicine, here in October, 1949 and have been more recently discussed by Dr. Eugene Cornatzer, of our staff, with Dr. Tuttle in Oak Ridge during the Symposium on Nucleopriteins.

Please let me express to you the deepest appreciation of all of the members of our staff working on these projects and of the administration for your most generous help in our research program. It would have been completely impossible to have undertaken any of these studies without your support. We would like particularly to emphasize the pleasure it has been to work administratively with you on these projects.

We have added to the combined total in the recapitulation, at the suggestion of the Controller, an amount of overhead comparable to that which the administration of the school received under the ONR contracts and which they currently receive under other federally supported research contracts such as those with the United States Public Health Service. We trust the handling of this detail is satisfactory.

If there is any additional information we can give, or any clarification of points which are not clear that we can offer, please command us. We should be most happy to meet with you here, in Washington, or in Oak Ridge, at your convenience to negotiate further the details of the contract if you would so desire.

Respectfully yours,

George T. Harrell, M.D.

1112178

COPY

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, N. CAROLINA
ZONE 7

APRIL 15, 1950

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If there is any additional information we can give, or any clarification of points which are not clear that we can offer, please command us. We should be most happy to meet with you here, in Washington, or in Oak Ridge, at your convenience to negotiate further the details of the contract if you would so desire.

Respectfully yours,

George T. Harrell, M.D.

1112179

April, 1950
Contract No. AT-(40-1)-
Bowman Gray School of Medicine
of Wake Forest College

TITLE I

1. a. Project Leader: Dr. George T. Harrell

b. Term: July 1, 1950 to June 30, 1951

c. Program: Distribution and turnover of sodium and potassium in acute infections.

ORIENTATION

Patients recovering from infectious diseases or from serum sickness have a diuresis during recovery in which water and chlorides are lost. In the acute phase of certain human infections, such as Rocky Mountain spotted fever and trichinosis, edema develops and the blood chlorides and proteins drop. No data are available on changes in the blood or urinary sodium and potassium. With the alterations in distribution of fluid, peripheral circulatory collapse often develops and leads to the death of the patient.

It is not known from blood volume and thiocyanate tissue space studies whether the extravasated fluid is found between cells or within them. The increase in permeability of capillary and cell wall membranes can be visualized as a graded series of pores. In mild instances of disease, only crystalloids leave the blood stream; in more severe instances small protein molecules such as albumin, or larger ones such as globulin, will leak out. A small defect should be detectable by the extent to which radioactive ions such as Na^{24} and potassium are diluted following injection; a larger defect should be detectable by the diffusion from the blood stream of protein molecules of various sizes tagged with I^{131}. In Rocky Mountain spotted fever the time at which the edema and circulatory collapse are maximal suggests that an antigen-antibody reaction may be responsible for the alteration in permeability of membranes.

If the mechanism can be established by which increased amounts of electrolytes are passed across capillary and cell membranes, it may be possible to devise means to correct the physiologic abnormality in infections or in pure antigen-antibody systems such as serum sickness. Eventually, it may be possible to induce an increase in permeability so that radioisotopes could be encouraged to enter certain tissues and there exert an intracellular radiation effect.

Some tumors may be caused by filterable viruses; others can concentrate viruses such as vaccinia. If a virus could be introduced into a cancer and immune serum were administered, an antigen-antibody reaction should take place only on parasitized cells; the local alteration in permeability would allow any circulating radioisotope to be concentrated in the cancerous tissue. If - through application of the auto-antibody technique - an antiserum against cancerous cells could be made, a similar reaction would take place only on malignant cells and should locally alter permeability so that an isotope administered therapeutically could be concentrated in the tumor.

1112180

PROGRESS TO DATE

A progress report on the experiments conducted July 1, 1949 to March 15, 1950 has already gone forward.

Techniques for determination of plasma volume, thiocyanate space, and Na^{24} space have been standardized for use in rabbits and human beings. Techniques for tissue analysis for total sodium and potassium and for Na^{24} content of tissues have been developed and standardized and control data accumulated for comparison with experimental data.

Pure antigen-antibody reactions without infection have been studied by inducing serum sickness in rabbits by 1) the injection of fractions of human plasma; and 2) by passive transfer techniques utilizing anti-human immune serum previously prepared in other rabbits. Measurements of the plasma volume, thiocyanate space, Na^{24} space, and of the tissue changes have been made. A preliminary draft of a paper with the passive transfer technique is attached; this paper is being submitted to the JOURNAL OF IMMUNOLOGY. A preliminary draft of the control data in normal animals is attached; this paper is being submitted to the AMERICAN JOURNAL OF PHYSIOLOGY, and the raw data will be deposited with the American Documentation Institute. Manuscripts on the serum sickness experiments have not yet been completed.

A technique is being developed, through preliminary experiments, studying a pneumococcal skin infection ("dermal pneumonia") in rabbits for determination of alterations in blood volume, thiocyanate and Na^{24} spaces.

PROPOSED PLAN OF EXPERIMENTS FOR 1950-51.

Physiology of Immune Reactions

The experiments completed, but not yet reported, utilized human plasma fractions in an attempt to simulate as closely as possible immunological problems in human disease. The experiments failed to produce consistent changes with the regularity desired. Other investigators, utilizing horse serum which contains antigen not present in human serum, have produced more consistent histologic lesions resembling those of rheumatic fever and periarteritis nodosa in rabbits. No physiologic studies have been done utilizing the techniques discussed above. The experiments in rabbits should be continued using horse instead of human plasma fractions as antigen. It is hoped that changes of sufficient magnitude will be obtained so that tissue analyses will be statistically significant in localizing in various organs or tissues the shift in radiosodium distribution.

I^{131} tagged rabbit serum protein fraction will be prepared by Dr. Donalee L. Tabern, Abbott Laboratories, North Chicago, Illinois; authorization (no. 5675) for the use of I^{131} has already been obtained. The location of tissues into which proteins leak should be detectable by this technique. The physiologic studies will be cross-checked for specific cellular localization of antigen and antibody by radioautographic techniques.

Identical experiments can be done by the passive transfer technique utilizing a much shorter time interval than in the preliminary experiments. In this fashion as pure a humoral antigen-antibody reaction as possible will be obtained with a minimal cellular component.

In the course of these investigations the role of the heterophile antigen-antibody reaction in the production of these changes will be investigated and contrasted with the isophile reaction.

Autoantibody Studies

Previous investigators have reported the production of auto-antibody to rabbit heart by sensitization of animals to a mixture of group A hemolytic streptococci and normal rabbit heart. Repeated infection of rabbits with different types of group A hemolytic streptococci causes histologic lesions in tissue resembling rheumatic fever. Some common antigenic factor contained in the different types of streptococci may be the sensitizing agent partially responsible for production of the cellular lesion.

An attempt will be made to produce auto-antibody to rabbit heart using as antigen a mixture of streptococcus somatic group specific fractions which have been combined with normal rabbit heart. If the attempt is successful, the immunologic and physiologic methods previously described will be applied to this study. The antibody 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.

The effect of repeated sensitization of rabbits with the group specific fractions alone would be studied by the same techniques for contrast with the results obtained by the auto-antibody technique.

Extracellular Infection

In the preliminary pneumococcal experiments, satisfactory local edema has been produced. An attempt is now being made to design an experiment which would permit longer survival of the animals by delaying invasion of the blood stream by the organism; in this fashion more marked edema and greater alteration in permeability should develop. These experiments will be pursued utilizing the techniques described above.

Intracellular Infections

We had originally intended to study the immunophysiology of Rocky Mountain spotted fever - an acute rickettsial infection in which the pathogenic organisms are located intranuclearly - in human patients. The development of potent antibiotics - aureomycin and chloramphenicol - has greatly reduced the number of clinical instances of rickettsial spotted fever admitted to the hospital; those cases which are appearing for study are arrested by the antibiotics so quickly that the physiologic changes do not develop to the

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extent seen in previous years, if at all. It will, therefore, be necessary to study intracellular infections - for contrast with extracellular infections and pure antigen-antibody systems - in experimental animals.

The laboratory is not now set up for the culture of rickettsiae which grow only in embryonated chick eggs. The personnel are familiar with the techniques, and the equipment required is not extensive. An attempt will be made to tag rickettsiae with P^{32} in order to study more accurately their localization when injected into normal or into previously immunized rabbits. Serial physiologic and immunologic studies utilizing the techniques described above will be made to study the shifts in body fluids and electrolytes.

Tissue analyses will be done.

Autoradiography is planned in order to localize both the etiologic agent and the extravasated fluid and protein, as described above.

If time permits, the results of the above studies will be contrasted with those obtained in other groups of animals injected with killed rather than living rickettsiae.

It probably will not be possible to do virus studies in addition to rickettsial infections this year, but the techniques will have been largely developed and equipment and personnel will be available to continue such studies the following year.

CLINICAL STUDIES

As clinical cases are available, studies with Na^{24} - for which approval (no 5393) has already been obtained - will be done on individuals with various infectious diseases, allergic manifestations, and rheumatic fever. As controls, selected cases of myxedema, congestive heart failure, and other clinical conditions will be studied.

FACILITIES AVAILABLE

Construction of the isotope laboratory on the fifth floor of the medical school has been completed and the major items of the equipment have been installed. A fume hood designed for radioactive work is in place. A flame photometer, spectrophotometer, shielding equipment and monitoring equipment are available. A floor plan of the laboratory showing the site of installation of equipment has already been furnished (November 10, 1949). Animal space is available for observing infected and radioactive animals.

PERSONNEL AVAILABLE

Dr. Jerry K. Aikawa completes the second year of his AEC Fellowship October, 1950 and is trained in the necessary techniques.

Miss Eloise Rhoades, a technician, has been trained.

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A negro animal technician, Claude Taylor, is being trained. He will be responsible for the breeding of rabbits as well as some technical procedures.

Dr. Ernest Yount will begin a Markle Scholarship in Medicine at this School in July, 1950. He will be available for clinical work on all patients studied.

NEEDS FOR 1950-51

Personnel

It has been found impossible this year to conduct all the experiments with a single technician; additional technical help will be required. During the remainder of this year an attempt will be made to carry on with the two technicians now working - Rhoades and Taylor.

The AEC Fellowship for Dr. Aikawa ends October, 1950. We have been able to obtain some financial support for him from the American Heart Association, but it will be necessary to supplement these funds in order to retain him full time on the project.

The amount of time Dr. Yount will be available on the project will depend upon the amount of continuing financial support for release from other duties.

Equipment

No item of permanent equipment requiring a major outlay of funds is requested. The relatively minor items requested in the attached budget are necessary to set up chick egg technique. A research microscope can be borrowed from another project. A few more cages will be necessary.

Supplies

Some expendable supplies will be required for chick egg work and for replacement of Geiger-Muller tubes.

The requirement for isotopes will be about the same as last year.

The variability in the response of rabbits obtained this year as compared with those utilized in the preceding years has already been discussed in the progress report. Other investigators have encountered the same problem and have arrived at the same ultimate solution. Apparently we must plan to raise our own animals from an inbred strain under controlled conditions of diet so that we can obtain groups of the same sex, age, and weight for the experiments. The negro animal technician has been hired with this end in view; it may be a year before the full benefit to the animal breeding program can be achieved, but it should be initiated now.

1112184

BUDGET

The total amount of the budget is increased very slightly from last year. With the completion of the laboratory the requirements for major items of equipment have been reduced, but the requirement for salaries of personnel has increased. The detailed budget is appended.

1112185

Title I

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

2. PROPOSED BUDGET - JULY 1, 1950 to JUNE 30, 1951

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

(1) Salary of Project Leader
Major portion of salary of Dr. Jerry K. Aikawa
Major portion of salary of Dr. Ernest H. Yount

(2) Laboratory space, secretarial help and other services.

b. The Commission is requested to furnish :

(1) Personnel

Part time salary of Dr. Yount to permit release to work on project	$ 1800.00	
Part time salary of Dr. Jerry K. Aikawa	1800.00	
Technician	2400.00	
Technician	2100.00	
Electronic engineer, part time	300.00	
		$8,400.00

(2) Permanent Equipment

Dipping tube horizontal shield housing	200.00	
Bacteriologic incubator	120.00	
Water bath	100.00	
Microscope lamp	49.00	
Sterling hand pipette	42.00	
Animal cages	120.00	
Internal sample counter	300.00	
Microscope attachments	200.00	
		1,131.00

(3) Expendible Supplies

Geiger-Muller tubes	300.00	
Supplies for Egg Work: Iris scissors, cutting tools, oxygen torch, etc.	100.00	
Bottled gas and chemicals	200.00	
Isotopes - Cost and shipping charges	300.00	
Glassware	500.00	
Animals	1800.00	
		2,900.00

(4) Travel	200.00	
		200.00
(5) Miscellaneous	200.00	
		200.00
TOTAL		$12,831.00

O/H @ 8% 1,027.00

TOTAL - 13,858.00

111218b

April, 1950
Contract No. AT-(40-1)-288
Bowman Gray School of Medicine
of Wake Forest College

TITLE II

PROJECT LEADER: Dr. Camillo Artom

TERM: July 1, 1950 to June 30, 1951

PROGRAM: Formation of tissue phospholipides.

ORIENTATION:

Phospholipides are constant and universal constituents of living bodies. Recent data (including those of the present investigations), have shown that certain cell structures, the mitochondria which are probably responsible for most chemical operations of the cells, are composed chiefly of phospholipides and proteins. Because of the association of a high content of phospholipides with the most important enzyme system, it would seem that changes in the composition of the cell phospholipides or in the ability of the tissues to build up these essential components will lead to very serious disturbances in the functioning of the body. In the present investigations an attempt has been made to determine, if and to what extent the composition and the rate of formation of phospholipides in the tissues in the liver is affected by changes in the composition of the diet or by the administration of various drugs, poisons, or hormones.

PROGRESS TO DATE:

The formation of phospholipides has been studied with the aid of radioactive phosphorus both in the liver of intact animals and in *in vitro* experiments with surviving liver slices. As indicated in our previous reports (the last of which covered the work done from July 1, 1949 to March 15, 1950) these experiments on the formation of liver phospholipides have progressed satisfactorily. The results obtained thus far suggest that the liver which is the main organ for the synthesis of phospholipides, retains, to a considerable degree, its ability to build up adequate amounts of phospholipides even under very adverse conditions, such as marked dietary restrictions or administration of substances which probably act as cell poisons. In other words, as far as the formation of phospholipides is concerned, the liver seems to have a

1112181

remarkable capacity of compensating the destruction or the damage of part of its cells by stepping up the activity of the remaining tissue. Furthermore, this capacity seems to indicate that in the general economy of the organism, the formation of phospholipides is given a very high degree of priority.

Some phases of these investigations have been completed. Others have been or will be reported in preliminary papers, but it is felt that more experimental work should be done before definite conclusions can be reached. On the basis of the work done under the present title, the following completed or preliminary reports have been published in 1949:

C. Artom, W. E. Cornatzer, and M. Crowdert The Action of An Analogue of Ethanolamine (Diethanolamine) on the Formation of Liver Phospholipides. Journal of Biological Chemistry, Vol. 180, No. 2, p. 495, September 1949 (complete report).

C. Artom, and W. E. Cornatzer: Lipide Phosphorylation in the Liver as Related to the Dietary Supply of Methyl Donors and Methyl Acceptors. Abstracts of the First International Congress of Biochemistry, Cambridge, England, August 1949, p. 22; Journal of the Elisha Mitchell Scientific Society, Vol. 65, No. 2, December 1949 (preliminary reports).

W. E. Cornatzer and C. Artom: Lipide Phosphorylation in the Liver of Rats Fed Thiourea and Related Compounds. Journal of the Elisha Mitchell Scientific Society, Vol. 65, No. 2, December 1949 (preliminary report).

In 1950 the following reports were placed on the program of scientific meetings:

M. A. Swanson and C. Artom: The Lipide Composition of the Mitochondria from Rat Liver, Society of Experimental Biology and Medicine, Southeastern Section, Durham, N. C., January 1950.

C. Artom, and M. A. Swanson: Lipide Phosphorylation by Surviving Slices of the Liver of Rats on Various Diets, Federation of the American Biological Societies, Atlantic City, N. J., April 1950.

Complete manuscripts on the last two subjects are being prepared for publication.

1112188

PROGRAM OF THE EXPERIMENTS PROPOSED FOR 1950 AND 1951:

A. Formation of phospholipides in the liver of intact animals.

These experiments will be essentially a continuation and extension of the similar previous experiments. Rats under various experimental conditions (especially hormone deficiencies and administration of hormones) will be injected with radioactive phosphate and, after a definite time interval, isotopic and analytical determinations will be made on the phospholipides extracted from the liver.

B. Formation of phospholipides in surviving slices or in the mitochondria of the liver.

As in previous experiments, the formation of phospholipides will be studied using liver slices maintained in a medium containing radioactive phosphate. In addition, some experiments are planned in which suspension of mitochondria will be used; such a material may offer some important advantage for symplifying the interpretation of the isotopic determinations and perhaps clarifying certain factors involved in phospholipide synthesis. In the future experiments the effect of the addition *in vitro* of a number of substances which may possibly interfere with some phases of the phospholipides synthesis will be studied further. Special attention in this direction will be given to specific metabolic antagonist, such as diethanolamine or triethylcholine.

C. Incorporation of choline into phospholipides and other experiments on the synthesis and degradation of choline by liver slices.

In the past months we have had considerable difficulties in elaborating a method for choline synthesis. With the aid of Dr. Arthur Roe at the University of North Carolina, such difficulties have now been overcome. We believe that we are finally ready to start the experiments in which C^{14} labeled choline will be added *in vitro* to surviving slices of the liver and its incorporation studied by isotopic determinations in the phospholipides.

The availability of methyl labeled choline seems to offer also an excellent opportunity for studying certain problems of the metabolism of choline (either free or as a phospholipide moiety). Some of the possible reactions which might be

1112189

investigated are here mentioned: (a) Demethylation of choline to dimethylethanolamine; (b) Oxidation of the alcohol group of choline to betaine, followed by demethylation of the latter to dimethylglycine; and (c) Oxidation of the methyl groups to formaldehyde or formate with the possibility that these are involved in biological transmethylations (including the synthesis of choline or choline-containing phospholipides). Such type of experiments may substantially contribute to the clarification of problems which are of considerable importance for both normal nutrition and clinical conditions.

We have on hand C^{14} labeled formaldehyde and formate. On the basis of our experiments in the synthesis of choline, we believe that we will be able to elaborate relatively simple methods for labeling some of the compounds related to choline which we mentioned, and which we are planning to use in our future experiments.

PROPOSED BUDGET:

The budget proposed for 1950 and 1951 is approximately the same as the one allowed for the investigations presently underway. With the following exceptions, the expenses for permanent equipment has been cut in half. However, a sealing unit and timer are included, since it is presumed that their purchase will be made necessary by the increased number of C^{14} determinations.

The item consumable supplies has been increased by the additional expense which will be required for synthesizing several compounds related to choline.

1112190

April, 1950
Contract No. AT-(40-1)-288
Bowman Gray School of Medicine
of Wake Forest College

TITLE II

PROJECT LEADER: Dr. Camillo Artom

TERM: July 1, 1950 to June 30, 1951

PROGRAM: Formation of tissue phospholipides.

BUDGET FOR PROPOSED PROJECT: Period July 1, 1950 to June 30, 1951

Personnel:		
Dr. Camillo Artom as Project Leader, Professor	None	Salary from Bowman Gray
Dr. M. A. Swanson, Assistant Professor	None	" " " "
Marietta Crowder, Graduate Student	None	" " " "
Full-time technician (Not selected)	$2160.00	
2 Part-time technicians (Not selected)	2160.00	
		$4,320.00
Permanent Equipment:		
Sealing Unit, Model 165	600.00	
Timer, T-10250	120.00	
Freezing cabinet for the high speed centrifuge	500.00	
Van Slyke's manometric carbon apparatus	300.00	
		$1,320.00
Consumable Supplies:		
Radioactive Phosphorus	250.00	
Radioactive Compounds C^{14} labeled	1250.00	
Expenses for synthesizing new C^{14} labeled compounds	600.00	
Animals	500.00	
Chemicals	600.00	
Glassware	600.00	
Organic Solvents	500.00	
		$4,100.00
Travel:		
Scientific Conferences and Meetings in this country		$250.00
Other Expenses:		
Maintenance, repairs and replacements of radioactivity apparatus	350.00	
Incidentals	250.00	
		$600.00
	Total	$10,590.00

0/H 3 8%

847.00

11 437.00

1112191

April, 1950
Contract No. AT-(40-1)-
Bowman Gray School of Medicine
of Wake Forest College

TITLE III

1. a. PROJECT LEADER: Dr. George T. Harrell associated with Doctors Camille Artom and David Cayer

b. TERM: July 1, 1950 to June 30, 1951.

c. PROGRAM: Toxicity of radiation as related to previous damage and the functional capacity of an organ; the effect of P_{32} and x-rays on liver and marrow.

ORIENTATION

Radiation in sufficient amounts can exert a lethal toxic effect on cells. Sub-lethal doses cause damage which can be most easily detected clinically by changes in the blood - anemia and leukopenia. The two organs chiefly concerned in the formation of red blood cells are the liver and the bone marrow. The effect on the extent of the damage produced of underlying sub-clinical damage preceding irradiation is not known. The simple process of aging, degenerative diseases - such as arteriosclerosis which may interfere with oxygenation - intercurrent infections, exposure to industrial poisons, or deficiency states may all produce subclinical damage to organs.

It is known that vitamins in the diet are incorporated in many instances into intracellular enzyme systems. Radioisotopes can enter cells and be incorporated into protoplasmic constituents, there exerting a radiation effect in immediate proximity to the intracellular enzyme systems. The effects of internal radiation may not necessarily, therefore, duplicate the effect of external radiation as produced by x-rays.

The additive effect of sub-lethal doses of internal radiation within cells on organs previously damaged by any process which might be expected to occur in an average sample of the population is unknown. The additive effect of radiation from even tracer doses of isotopes introduced into the body may possibly harm cells already partially damaged, thus reducing their functional capacity below a level required to maintain life. Since the liver is especially susceptible to damage by some dietary deficiencies and by industrial poisons, and since P_{32} is synthesized very actively into organic compounds such as phospholipides in the liver, this tissue offers many advantages for study.

Protection against or correction of radiation damage in the liver or bone could be studied by the administration of substances which are known to affect the metabolism of hematopoietic tissue in these areas or to facilitate the removal of an isotope.

Any corrective effect could then be applied to prevention of radiation damage from accidental exposure to an external source or to an internal source resulting from ingestion or inhalation of an isotope.

1112192

Cells altered by malignant change are known to be more susceptible to radiation than are normal cells. If radioactive isotopes are applied to the therapy of human cancer, any positive results might give some protection to normal cells against the undesirable harmful effects of radiation directed at malignant cells.

PROGRESS TO DATE

A progress report on the work done from July 1, 1949 to March 15, 1950 has already been submitted. Normal mice were placed on experimental diets containing various amounts of protein, fat, minerals, and vitamins. After five days on the diet, P_{32} was injected.

The LD_{50} dose was determined to lie between 4 and 6 microcuries per gram of body weight.

In acute experiments partial damage by carbon tetrachloride - an industrial poison, and dietary fatty infiltration of the liver plus radiation with P_{32} did not reveal any protection by choline.

Variations in the level of dietary fat and protein showed that susceptibility to P32 rose as the content of protein in the diet increased, suggesting that the elevation in the rate of metabolism from the specific dynamic action of the dietary component may partially explain the mechanism of damage.

Increase in the phosphate content of the diet prolonged life by apparently improving the mobilization and excretion of P32 initially deposited in bone.

In acute experiments, large doses of folic acid added to the diet did not protect the mice.

Since the bacterial flora in the intestine elaborate several vitamins of the B complex - including folic acid -, preliminary experiments are now being conducted in an attempt to inhibit by chemotherapy this source of vitamins and control better the amount actually available to the animal.

PROPOSED PLAN OF EXPERIMENTS FOR 1950-51.

All the experiments done thus far have been acute and of short duration (21 days); the dose of P32 has been large with a resulting high mortality. In such experiments, the factor of tissue damage is far greater than the factor of repair, so that substances used will most likely either enhance or decrease the inherent toxic effect of the isotope and its radiations.

In future experiments, smaller doses of P32 should be used in chronic experiments and the animals observed over longer periods of time (6 weeks and longer). Single or multiple injections may be used. Thus it will be possible to study factors which might affect directly or indirectly the recovery and repair of damaged tissues.

1112193

In future experiments of a more chronic nature simple observation of the mortality rates and times of death would be inadequate to detect a possible beneficial effect of any substance administered. Morphologic changes in the blood and bone marrow should be followed. Serial functional studies could be done if they are feasible on small animals; and morphologic studies at autopsy should be done.

The action of vitamins, especially those which may be important for the regeneration of hematopoietic tissue, should be studied. Various groups of mice should receive folic acid, B_{12}, ascorbic acid, and the effect or recovery from internal radiation observed.

Because of the suspected effect of radiation on enzyme systems containing sulf-hydryl groups, the effect of BAL on the toxic effects of intracellular radiation should be studied.

The effect of chemicals known to concentrate in the liver and to affect intracellular metabolism - as do the antimalarials, or to lower cellular metabolism - as do the anti-thyroid compounds, or to block cellular division or repair - as do cinconhen and the folic acid antagonists - should be investigated.

The action of several steroids, especially cortical hormone - on which preliminary data seem encouraging -, should be studied.

The same types of experiments outlined above could be duplicated substituting for internal radiation external radiation in an amount sufficient for LD_{90}.

FACILITIES AVAILABLE

Monitoring and counting equipment is already available in the Isotope Laboratory and in the Department of Biochemistry. Animal rooms suitable for P_{32} work are available.

PERSONNEL AVAILABLE

Dr. Camillo Artom is already well known to the Commission as project leader in Title II of this contract.

Dr. David Cayer served as associate investigator in this project last year, and has also conducted clinical experiments in human beings on the synthesis of P_{32} into phospholipides.

Dr. Harrell is known to the Commission as project leader in Title I of this contract.

NEED FOR 1950-51.

Personnel

One trained technician will be available part time only. Additional technical help will be required because of the increased number of animals it is anticipated will be studied this year.

1112194

Equipment

Because of the increased number of animals, some additional cages, a scale for weighing diets, and a refrigerator for storing some dietary components are needed. Some blocks for shielding and additional minemeters for health protection of personnel have been recommended by a health physicist who recently reviewed the project and should be obtained.

Supplies

The larger number of animals will moderately increase the amount of each item in the supply category.

BUDGET

The total amount of the budget is increased over last year. Conversations in October, 1949 with Dr. L. W. Tuttle of the Medical Branch, Division of Biology and Medicine, Washington indicated that the Commission was interested in pursuing such experiments as rapidly as possible. It has been impossible until completion of the present teaching schedule to release supervisory personnel from other duties sufficient time to justify an increase in the budget before this summer. A detailed budget is attached.

1112195

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

2. BUDGET - PERIOD JULY 1, 1950 - JUNE 30, 1951

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

(1) Salaries of the three principal investigators, Drs. Artom, Cayer, and Harrell.

(2) Space, use of ordinary laboratory equipment, animal care.

b. The Commission is requested to furnish the following:

(1) Salaries

Technician.....	$2100	
Technician (part-time).....	1500	
		$3600

(2) Permanent Equipment

Metabolism cages.....	250	
Refrigerator for diets.....	300	
Scales for diets.....	200	
Shielding - bricks.....	100	
minometers.....	100	
		950

(3) Expendable Supplies

Radioactive phosphorus.....	400	
Dietary components.....	300	
Animals.....	400	
Glassware.....	200	
		1300

(4) Miscellaneous.....	125	
		125

TOTAL.....	$5975

e/4 @ 8% — 478.

$6453.00

1112196

April, 1950

PROPOSAL FOR RENEWAL

RESEARCH CONTRACT

Contract No. AT-(40-1)-

CONTRACTOR: The Bowman Gray School of Medicine of Wake Forest College

ADDRESS: Winston-Salem 7, North Carolina

AMOUNT OF CONTRACT:

	Title I	Title II	Title III
Personnel	8400	4320	3600
Permanent equipment	1131	1320	950
Consumable supplies	2900	4100	1300
Travel	200	250	
Misc., reparis and replacements	200	600	125
Sub Totals	12831	10590	5975

I, II, and III combined	$29,396.00
Overhead at 8%	2,351.68
TOTAL	$31,747.68

1112197

April, 1950

PROPOSAL FOR RENEWAL

RESEARCH CONTRACT

Contract No. AT-(40-1)-

CONTRACTOR: The Bowman Gray School of Medicine of Wake Forest College

ADDRESS: Winston-Salem 7, North Carolina

AMOUNT OF CONTRACT:

	Title I	Title II	Title III
Personnel	8400	4320	3600
Permanent equipment	1131	1320	950
Consumable supplies	2900	4100	1300
Travel	200	250	
Misc., repairs and replacements	200	600	125
Sub Totals	12831	10590	5975

I, II, and III combined	$29,396.00
Overhead at 8%	2,351.68
TOTAL	$31,747.68

1112198

Office Memorandum • UNITED STATES GOVERNMENT

TO : D. C. Bogart, Chief, General Accounts Branch DATE: March 6, 1950

FROM : Albert H. Holland, Jr., M.D., Director of Research and Medicine

SUBJECT: ACCOUNTABILITY OF PROPERTY AT BOWMAN GRAY

SYMBOL: RM:AMC

We are attaching Copy No. 5 of Nav. S. and A. Form 127 covering the transfer of accountability of property at The Bowman Gray School of Medicine from the Navy Department to the AEC. This property was acquired by Bowman Gray through Contract Numbers N8-ONR-63701 and N8-ONR-63702. This transfer has been effected without reimbursement as the material was purchased with the AEC funds.

Since the nature of the property is such that the Commission will have no continuing interest in it upon completion of the scientific program now being conducted with the support of AEC funds, we do not contemplate that it will be returned to the Commission. Arrangements will be made to transfer this property to the college at the time a modification to Contract No. AT-(40-1)-288 is negotiated.

for John H Roberson
Albert H. Holland, Jr., M.D.

Encl.:
Copy No. 5

CC: C. Vanden Bulck

Corley:tw

Doug— In lieu of the usual Contract action as complete. Then add reference and abstract of contract and file without entry

1112799

RECEIPT/EXPENDITURE INVOICE

[redacted] INVOICE NO. [redacted]

FROM: [redacted]

DATE: [redacted] RECORD NO. [redacted]

TO: [redacted]

TITLE FROM WHICH EXPENDED

AUTHORITY [redacted]

TITLE AND ACCOUNT TO WHICH EXPENDED

DELIVERY DESIRED BY

APPROPRIATION CHARGEABLE

DELIVER TO [redacted]

PACKAGES TO BE MARKED

BILL OF LADING NO.

DATE OF SHIPMENT

SHIPPED VIA: [redacted]

ITEM NO.	STANDARD STOCK CATALOG NO. OR CLASS NO.	DESCRIPTION OF ARTICLE	QUANTITY DELIVERED	UNIT OF QUANTITY	UNIT PRICE	EXTENSION
		[redacted]				
		CAPITAL NON-EXPENDABLE ARTICLES				
1.	[redacted]	Developing Tray (Walgreen Drug)	1			[redacted]
2.	"	Buckets (Sears, Roebuck & Co.)	2			[redacted]
3.	"	Triple Beam Stainless Bal. Balance	1			[redacted]
4.	"	Clinical Shaker (Fisher Scientific Co.)	1			[redacted]
5.	"	Biochemical Prep.	Vol.I			[redacted]
6.	"	Subscription to: Nucleonics	1 yr			[redacted]
7.	"	" Pharmacological Reviews	yr of 1949			[redacted]
8.	"	1/2 Cylinder of Oxygen Plus CO2				[redacted]
9.	"	Boring Blender with 2 jars	1			[redacted]
10.	"	Bain Marie Heat (Fisher Scientific Co.)	1			[redacted]
11.	"	Potter Homogenizers	2			[redacted]
12.	"	White Ink. Scale (Ambrose Bros.)	2			[redacted]
13.	"	Subscription for Jnl. of Biol. Chem.	1 yr			[redacted]
14.	"	Top-Light Stock Jelish	1			[redacted]
15.	"	Aneurous Heater (Fisher scientific Co.)	1			[redacted]
16.	"	Mixture & Profiles of Stainless Sil.(Fortinbacher)	2			[redacted]
17.	"	Intermediate Centrifuge (A.H.Alex Co.)	1			[redacted]
18.	"	Stand for above	1			[redacted]
19.	"	Drying Oven (E.H.Sargent Co.)	2			[redacted]
20.	"	Auto Shaver with Impeller shaft	1			[redacted]
21.	"	Carbon & Hydrogen Anal. app.	1			[redacted]
22.	"	Higher Flow Meter (Fisher Scientific Co.)	1			[redacted]
23.	"	Magnetic Stirring App.	1			[redacted]
24.	"	Animal Balance Ohaus Triple Beam(A.H.Thomas Co)	1			[redacted]
25.	"	Hand G-Glass for Centrifuge	1			[redacted]
26.	"	Hand G-glass for Centrifuge	1			[redacted]
27.	"	Trunnion Rings for Centrifuge	16			[redacted]
28.	"	Metal Shields for Centrifuge	16			[redacted]
		(continued)				

1112200

NAV. S. AND A. FORM 127
REVISED SEPTEMBER 1943

[redacted] Atlanta, Ga. TRANSFER INVOICE NO [redacted] (sheet 2)

FROM:

DATE: 11-30-46

RECORD NO. [redacted]

TO:

TITLE FROM WHICH EXPENDED: [redacted]

AUTHORITY

TITLE AND ACCOUNT TO WHICH EXPENDED

DELIVERY DESIRED BY

APPROPRIATION CHARGEABLE

DELIVER TO

PACKAGES TO BE MARKED

BILL OF LADING NO.

DATE OF SHIPMENT

SHIPPED VIA

ITEM NO.	STANDARD STOCK CATALOG NO. OR CLASS NO.	DESCRIPTION OF ARTICLE	QUANTITY DELIVERED	UNIT OF QUANTITY	UNIT PRICE	EXTENSION
	[redacted]					
[redacted]	[redacted]	Reducing Aluminum Caps for Centrifuge	8			[redacted]
[redacted]	"	Trunion Caps for Centrifuge	4			[redacted]
[redacted]	"	Rubber Gaskets for Centrifuge	[redacted]			[redacted]
[redacted]	"	Bunsenrollgerm (Sen. Scientific Co.)	2			[redacted]
[redacted]	"	Servall Angle Centrifuge with accessories	1			[redacted]
[redacted]	"	Constant Temp. Bath with thermometer	1			[redacted]
35.	"	Warburg-Barkenstein Manometers with clamps, with accessories (A.H.Thomas Co.)	7			[redacted]
36.	"	G.E. Deep Freeze	1		235	66
37.	"	Supports with channel and rod extending from channel and clamps	7		54	80
38.	"	Vacuum slotted base accessories for Warburg apparatus	1		7	50
39.	[redacted]	SO-3 Washer and Mount	1		[redacted]	[redacted]
40.	"	SO-1 Ashcrusher	1		[redacted]	[redacted]
41.	"	SO-1 90 Sample Holder and tube mount	1		[redacted]	[redacted]
42.	"	Micrometer compl. with cam 0.2	1		160	[redacted]
43.	"	V-2 Victerem pocket dosage meter	3		37	50
44.	"	2-5 capped pinchcock	100		2	08
45.	"	Remote pipetting device	1		[redacted]	[redacted]
46.	"	Rectangular Lead container	1		[redacted]	[redacted]
47.	"	Remote handling tongs	2		[redacted]	[redacted]
48.	"	Coulfield pipettors	2		12	[redacted]
49.	"	Clamps, flask, Fisher-stainless stl. H3T5	2		7	[redacted]
50.	"	Stainless stl. drawing carriage	1		[redacted]	[redacted]
51.	"	Servall Angle Centrifuge type SF/X	1		210	[redacted]
[redacted]	"	Ringer Adapters, [redacted]	[redacted]		[redacted]	[redacted]
[redacted]	"	2-1/2 Gal. craftsman paint tank	1		[redacted]	[redacted]
[redacted]	"	Furnace-Muffle portable with rheostat	1		[redacted]	[redacted]
[redacted]	"	Craftsman jigger	1		[redacted]	[redacted]
[redacted]	"	Auto tonometer electric	1		[redacted]	[redacted]
[redacted]	"	Steel brick, [redacted] 2-1/[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	"	[redacted]	[redacted]			[redacted]

1112201

RECEIPT EXPENDITURE INVOICE

NAV. S. AND A. FORM 12
REVISED SEPTEMBER 1941

FROM: DMC Atlanta TRANSFER

INVOICE NO 000876 (sheet 3)

DATE: 11-10-49

RECORD NO QM (Atomic Energy Comm)

TO

TITLE FROM WHICH EXPENDED

AUTHORITY

TITLE AND ACCOUNT TO WHICH EXPENDED

DELIVERY DIRECTED BY

APPROPRIATION CHARGEABLE

DELIVER TO

PACKAGES TO BE MARKED

BILL OF LADING NO

DATE OF SHIPMENT

SHIPPED VIA

ITEM NO.	STANDARD STOCK CATALOG NO OR CLASS NO	DESCRIPTION OF ARTICLE	QUANTITY DELIVERED	UNIT OF QUANTITY	UNIT PRICE	EXTENSION
59.	N8onr-63702	Home freezer, G.E.	1			153 78
60.	"	Refrigerator, G. E.	1			183 23
61.	"	2-shelf steel book truck 4-5 sw. casters	1			54 00
62.	"	Gray metal filing cabinet, letter-size	1			65 45
63.	"	Waste paper basket	1			1 35
64.	"	Desk	1			119 43
65.	"	Chair	1			63 75
66.	"	File	1			65 45
67.		25x72" Acme stainless stl. double bowl sink top with 4" back, double sink faucet, Duo strainers, twin waste & sink trap	1			170 00
68.	"	72" stainless stl. top for cabinets	1			107 00
69.	"	48" stainless stl. top for cabinets	1			75 13
70.	"	36" stainless stl. top for cabinets	1			11[illegible] [illegible]
71.	"	G.E. Kitchen Cabinet #KBC 1-36";1-24"	2		59.99	[illegible]
72.	"	G.E. Kitchen Cabinet [illegible]	4			13[illegible] 52
73.	"	BCL Mark I Model 80 Thin Wall Dipping Counter	1			30 98
74.	"	[illegible]-13 Sturtevant Rexvane Ventilator	1			57 [illegible]
75.		[illegible]-16 Sturtevant Rexvane Ventilator	1			110 [illegible]
76.	"	Boiler plate	1			18 20
77.	"	Micro Balance Torsion Type with 2 tare weights	1			166 55
78.	"	Battery charger and hydrometer	1			14 83
79.	"	Fume Hood	1			1,754 20
		[illegible]				
80.	N8onr-63701	Pyrex Flasks ground neck 25cc(Scientific Glass)	12			21 32
81.	"	Filter Paper (Schleicher Co.)	50 sheets			4 33
82.	"	Centrifuge Tubes (Scientific Glass Co.)	6			15 [illegible]
83.	"	1/2 ml.Pipettes (Sou. Scientific Co.)	12			8 16
84.	"	Guanido Acetic Acid (Genesee Research Corp)	250g.			5 16
85.	"	Hemocyctine, dl.(Bias Lab.,Inc.)	2 gms.			8 00
86.	"	18/32" Sausage casing (Viking Corp.)	100 ft.			1 75
87.		25/32 Sausage Casing (Viking Corp.)	100 ft.			[illegible] 20

1112202

REVISED SEPTEMBER 1947

FROM

TO

AUTHORITY

DELIVERY REQUIRED BY

DELIVER TO

PACKAGES TO BE MARKED

Los Alamos, TRANSFER INVOICE NO 000076 (Sheet 4)

DATE 11-10-49

RECORD NO (Atomic Energy Com.)

TITLE FROM WHICH EXPENDED

TITLE AND ACCOUNT TO WHICH EXPENDED

APPROPRIATION CHARGEABLE

BILL OF LADING NO

DATE OF SHIPMENT

SHIPPED VIA

ITEM NO.	STANDARD STOCK CATALOG NO. OR CLASS NO. Contract No.	DESCRIPTION OF ARTICLE	QUANTITY DELIVERED	UNIT OF QUANTITY	UNIT PRICE	EXTENSION
88.	W6ont-63701	Nutritional Biochem.Corp. Betaine	25	gms.	1	75
89.	"	" DL Methionine	50	gms.	2	25
90.	"	" Dopa	1	gm.	6	25
91.	"	" Adenylic acid	1	gm.	4	50
92.	"	" Cholesterol	50	gms.	4	00
93.	"	" Cytochrome C	50	mg.	2	75
94.	"	" Coenzyme	50	mg.	4	25
95.	"	Ethyl Ether	25	lb.	25	00
96.	"	Chloroform (Fisher Scientific Co.)	25	lb.	15	75
97.	"	Pipettes (Sou. Scientific Co.)	15	doz.	107	64
98.	"	Centrifuge Tubes (Sou. Scientific Co.)	1	case	41	04
99.	"	Pyrex Receiving Tubes (Sou. Scientific Co.)	1	case	30	64
100.	"	Cylinders 10 ml. (Sou. Scientific Co.)	12		17	28
101	"	Cartridges for demineralizer (Sou. Scientific)	6		54	00
102	"	Butyl Alcohol	1		1	05
103	"	Iso-Butyl Alcohol	1			85
104	"	Salicylaldehyde	100	gm.	1	75
105	"	Cylinder glass (Fisher Scientific Co.)	1		6	50
106	"	Pipettes, 5 ml.	1	ea.	13	93
107	"	" 10 ml.	2	doz.	23	28
108	"	Cylinders, 10 cc.	1	doz.	10	80
109	"	" 25 cc.	2	doz.	23	28
110	"	Test Tubes 150 x 16	1	gross	3	30
111	"	Burettes, 25 ml.	6		20	[illegible]
112	"	" 50 ml.	6		21	84
113	"	Funnels, 65 ml.	2	doz	8	64
114	"	Flasks, 250 ml.	4	doz	15	36
115	"	Crucibles, size 1	12		5	64
116	W6ont-63702	Geiger tubes, TGC-1	2		100	00
117	"	Ammonium sulfate	1			59
118	"	100 Gm.Bottles Baste-Riboflavin Assay Medium	5		15	33
119	"	Cesium Chloride	2	gm	3	27

(continued)

1112203

NAV S AND A FORM 127
REVISED SEPTEMBER 1947

DW Atlanta

TRANSFER

INVOICE NO 000076 (sheet 5)

FROM

DATE 11-10-49

RECORD NO CM(Atomic Energy)

TO

TITLE FROM WHICH EXPENDED

AUTHORITY

TITLE AND ACCOUNT TO WHICH EXPENDED

DELIVERY DESIRED BY

APPROPRIATION CHARGEABLE

DELIVER TO

PACKAGES TO BE MARKED

BILL OF LADING NO

DATE OF SHIPMENT

SHIPPED VIA

ITEM NO	STANDARD STOCK CATALOG NO OR CLASS NO	DESCRIPTION OF ARTICLE	QUANTITY DELIVERED	UNIT OF QUANTITY	UNIT PRICE	EXTENSION
	contract no.					
120	W8onr-63702	Lithium chloride reagent	1/4#		1	85
121	"	Rubidium chloride	1 Gm		1	75
122	"	Silver Nitrate, ACS cryst.	1/4#		3	70
123	"	Barbital	1/4#		1	66
124	"	Special Indicating Drierite, Anhydrous $CaSO_4$	1#		2	20
125	"	Atomizer assby for Beckman flame spectrophotometer(1)			15	16
126	"	4-gal. water coolers	2		6	20
127	"	Corks	1 bag		2	90
128	"	10 ml. centrifuge tubes - lusteroid	25		1	50
129	"	50 ml. centrifuge tubes - lusteroid	100		9	60
130	"	No. 0 corks	2 bags of 500		4	00
131	"	No. 10 corks	1 bag of 100		2	10
132	"	Test tubes - 75mm X 10 mm	1 case		20	47
133	"	5 ml. beakers for Beckman PH meter	3 doz		4	50
134	"	10 ml. beakers	2			60
135	"	30 ml. beakers	2			50
136	"	Brush - centrifuge tube	2			30
137	"	15 ml. centrifuge tube - undraduated pyrex	6		1	44
138	"	12 ml. centrifuge tube - heavy duty pyrex	6		1	[illegible]
139	"	40 ml. centrifuge tube-round bottom hvy pyrex	4		1	89
140	"	50 ml. lusteroid centrifuge tube	12		1	44
141	"	Ring supports outside dia. 4"	2		1	94
142		Flasks (10cc. with stoppers) volumetric	6		4	5[illegible]
143	"	#1 crucibles	10			47
144	"	#00 crucibles	10			[illegible]
145	"	Covers for #1 crucibles	10			24
146	"	Covers for #00 crucibles	10			20
147	"	50 ml. beakers	1 doz		1	50
148	"	100 ml. beakers	1 doz		3	24
149	"	7-1/2 surgical gloves	1/2 doz		1	80
150	"	Charts(6) "Nuclear Physicis Charts" with bk	1 set		1	00
151	"	of information (32 pages)				

1112204

NAV. S. AND A. FORM 127
REVISED SEPTEMBER 1943

[redacted] INVOICE NO. [redacted] (sheet 6)

FROM:

DATE 11-30-49

RECORD NO. [redacted]

TO:

TITLE FROM WHICH EXPENDED

AL JRITY

TITLE AND ACCOUNT TO WHICH EXPENDED

DELIVERY DESIRED BY

APPROPRIATION CHARGEABLE

DELIVER TO

PACKAGES TO BE MARKED

BILL OF LADING NO.

DATE OF SHIPMENT

SHIPPED VIA

ITEM NO.	STANDARD STOCK CATALOG NO. OR CLASS NO.	DESCRIPTION OF ARTICLE	QUANTITY DELIVERED	UNIT OF QUANTITY	UNIT PRICE	EXTENSION	
	Contract No.						
[redacted]	[redacted]	Book of the Atom	[redacted]			[redacted]	[redacted]
[redacted]	"	Book of electro-magnetic radiations	[redacted]			[redacted]	[redacted]
[redacted]	"	APPLIED NUCLEAR PHYSICS by R.E.Fellows and W.L.Davidson	[redacted]			[redacted]	[redacted]
[redacted]	"	ASPECTS OF RADIATIONS ON LIVING CELLS by R.H.Ross	[redacted]			[redacted]	[redacted]
[redacted]	"	SYMPOSIUM ON ISOTOPES	[redacted]			[redacted]	[redacted]
[redacted]	"	RADIOACTIVE TRACERS IN BIOLOGY, M.D.Kamen	[redacted]			[redacted]	[redacted]
[redacted]	"	"Atomic Energy" film	[redacted]			[redacted]	[redacted]
[redacted]	"	Glassware cabinets	[redacted]			[redacted]	[redacted]
[redacted]	"	Desiccator, 200 mm.	[redacted]			[redacted]	[redacted]
[redacted]	"	Automatic Pipette washer	[redacted]			[redacted]	[redacted]
[redacted]	"	Flasks, 250 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 500 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 1000 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	Cylinders, 50 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 100 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 250 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 500 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 25 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 50 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 100 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 250 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	Desiccator 200 mm.	[redacted]			[redacted]	[redacted]
[redacted]	"	Flask, Filtering, 125 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 250 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 500 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	" 1000 ml.	[redacted]			[redacted]	[redacted]
[redacted]	"	Funnel, size 0	[redacted]			[redacted]	[redacted]
[redacted]	"	" size 2	[redacted]			[redacted]	[redacted]
[redacted]	"	" size 24	[redacted]			[redacted]	[redacted]

1112205

REVISED SEPTEMBER 1943 [redacted] INVOICE No. [redacted]

FROM:

DATE [redacted] PROJECT NO. [redacted]

TO:

TITLE FROM WHICH EXPENSED

AL RITY

TITLE AND ACCOUNT TO WHICH EXPENDED

DELIVERY DESIRED BY

APPROPRIATION CHARGEABLE

DELIVER TO

PACKAGES TO BE MARKED

BILL OF LADING NO.

DATE OF SHIPMENT

SHIPPED VIA

ITEM NO.	STANDARD STOCK CATALOG NO. OR CLASS NO.	DESCRIPTION OF ARTICLE	QUANTITY DELIVERED	UNIT OF QUANTITY	UNIT PRICE	EXTENSION	
	[redacted]						
180.	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
181.	"	[redacted]	[redacted]			[redacted]	[redacted]
182.	"	3 [redacted] tubes, [redacted] 20 ml.	[redacted]			[redacted]	[redacted]
183.	"	Test tubes 16 x 150 mm.	[redacted]			[redacted]	[redacted]
184.	"	Thermometer -20 to 150 deg. C	[redacted]			[redacted]	[redacted]
185.	"	Hot plate electric [redacted]	[redacted]			[redacted]	[redacted]
186.	"	Forceps	[redacted]				[redacted]
187.	"	Dissecting forceps size 115 mm.	[redacted]			[redacted]	[redacted]
188.	"	Scissors, dissecting medium straight blades	[redacted]			[redacted]	[redacted]
189.	"	Scissors	[redacted]			[redacted]	[redacted]
190.	"	Watch glasses 25 mm.	1	doz.			[redacted]
191.	"	" " 50 mm.	1	doz.			[redacted]
192.	"	" " 75 mm.	1	doz.			[redacted]
193.	"	Corks, [redacted]	1	X 100		[redacted]	[redacted]
194.	"	Corks, assorted	[redacted]	bags		[redacted]	[redacted]
195.	"	Beakers, 50 ml.	1	doz.		[redacted]	[redacted]
196.	"	" [redacted] ml.	1	doz.		[redacted]	[redacted]
197.	"	" 250 ml.	1	doz.		[redacted]	[redacted]
198.	"	" [redacted] ml.	1	doz.		[redacted]	[redacted]
199.	"	" 600 ml.	1	doz.		[redacted]	[redacted]
200.	"	Flasks, 50 ml.	[redacted]	doz.		[redacted]	[redacted]
201.	"	" 250 ml.	[redacted]	doz.		[redacted]	[redacted]
202.	"	" 1000 ml.	6			[redacted]	[redacted]
203.	"	" [redacted] ml.	[redacted]			[redacted]	[redacted]
204.	"	" 125 ml.	[redacted]			[redacted]	[redacted]
205.	"	" [redacted] ml.	[redacted]			[redacted]	[redacted]
206.	"	" 500 ml.	[redacted]			[redacted]	[redacted]
207.	"	Syringes size 2 cc.	6			[redacted]	[redacted]
208.	"	" 20 cc.	6			[redacted]	[redacted]
209.	"	Bunsen burner	2				[redacted]
210.	"	"	[redacted]			[redacted]	[redacted]

1112206

REVISED SEPTEMBER 1948

[redacted] INVOICE NO. [redacted] (sheet 4)

FROM: [redacted]

DATE: 11-30-49

RECORD NO.: [redacted]

TO:

TITLE FROM WHICH EXPENDED:

AUTHORITY:

TITLE AND ACCOUNT TO WHICH EXPENDED:

DELIVERY DESIRED BY:

APPROPRIATION CHARGEABLE:

DELIVER TO:

PACKAGES TO BE MARKED:

BILL OF LADING NO.:

DATE OF SHIPMENT:

SHIPPED VIA: No physical transfer

ITEM NO.	STANDARD STOCK CATALOG NO. OR CLASS NO.	DESCRIPTION OF ARTICLE	QUANTITY DELIVERED	UNIT OF QUANTITY	UNIT PRICE	EXTENSION
	Contract No.					
211.	Nbsr-43702	Burner block M L T type	1			6 [illegible]
212.	"	Rubber stoppers size 4	[illegible]			[illegible]
213.	"	" " size 2	[illegible]			[illegible]
214.	"	" " size 0	[illegible]			[illegible]
215.	"	" " size 4	[illegible]			[illegible]
216.	"	" " size 2	[illegible]			[illegible]
217.	"	" " size 0	[illegible]			[illegible]
		ALTERATION/CONSTRUCTION WORK DONE				
218.	Nbsr-43702	Partitionings and construction work for the Isotope Laboratory, 9th Floor				4,250 00
219.	Nbsr-43702	Carpenter work and plumbing on fume hood, 9th Floor, Isotope Lab.				350 00
220.	"	Construction and installation of stand for stainless steel sink and gas and air outlets, Isotope Lab., 9th Floor				89 76
221.	"	Balance installation, 9th Flr., Isotope Lab.				19 75
222.	"	Piping, 9th Floor, Isotope Laboratory				15 80
				TOTAL		16,300. 02

CHECKED BY | PACKED BY | POSTED AND PRICED | RECEIVED THE ABOVE MENTIONED ARTICLES ACCOMPANIED BY PRICED INVOICES [redacted]

RE CKED BY | EXTENDED | VERIFIED | DATE

SUED BY

Bowman Gray School of Medicine of Wake Forest College

2/1/50 John H. Roberson By Harry E. [illegible]

JOHN H. ROBERSON
ASSISTANT DIRECTOR
[redacted]

5

1112207

Oak Ridge, Tennessee
October 17, 1951

The Bowman Gray School of Medicine
of Wake Forest College
Winston-Salem, North Carolina

Attention: Mr. Harry O. Parker, Controller

Subject: MODIFICATION NO. 2, CONTRACT NO. AT-(40-1)-[illegible]

Gentlemen:

This is in reply to your letters dated September 7, 1951, and July 5, 1951, in which you request an adjustment of the contract amount payable to you for your services under subject contract during Fiscal Year 1952, beginning July 1, 1951. Your letter of September 7, 1951, included a report of your actual expenditures through June 30, 1951, as distinguished from your June 1951 report which was based partly on estimated expenditures.

You are correct in your statement that we should have taken into consideration the actual unexpended balances for the contract period ending June 30, 1950, as shown in your June 1951 report, in calculating the balance to be applied in partially funding the Fiscal Year 1952 program. Actually, we used only the estimated balances for the one year ending June 30, 1951, instead of the combined figures for both years.

In reply to your question I would like to state that with two exceptions it is our policy to adjust the previous estimates to actual experience in connection with negotiations for an extension of the contract term. We do not adjust for actual expenditures which exceed the amount of the approved budget for any Title for the year involved, nor do we adjust the contract amount for the terminal year of the contract. It is noted in your record of actual expenditures as set forth in your September 7th letter that your expenditures on Title I exceed the amount of the approved budget for Title I for Fiscal Year 1951. Accordingly, this amount cannot be recognized in any adjustment of the contract amount. Title I for Fiscal Year 1951 will be treated as zero balance instead of the estimated balance of $21,[illegible] reported in June 1951.

Enclosed is a schedule which shows the adjustments as actually made to date, the adjustments which should have been made in Modification No. 2 to adjust

1112208

Fiscal Year 1950 to actual, and the adjustment as it would appear as of this date when both Fiscal Year 1950 and Fiscal Year 1951 are adjusted to actual, in accordance with our policy as expressed above.

You will note that you would be entitled to an additional payment of $785.14 as of this date to completely fund the Fiscal Year 1952 approved budgets for the three titles. Although we recognize that you are entitled to this additional sum we would greatly prefer not to modify the contract amount at this time since your experience during the past two years has shown that it is very likely you will have a balance at the end of Fiscal Year 1952 greater than the present underpayment. If this proposal is satisfactory to you I can assure you that the sum of $785.14 will be credited to you in June 1952, in computing the estimated balances at the end of Fiscal Year 1952 for application to Fiscal Year 1953 operations.

I wish to thank you for calling this matter to our attention and I hope the proposal for delaying the adjustment will meet with your approval.

Very truly yours,

Fred W. Ford
Acting Assistant Manager
Oak Ridge Operations

Enclosure:
Schedule of Adjustments

Humphries:hl

CC: Dr. N. H. Woodruff
Mr. J. W. Ould, Jr., w/back up letters
Mr. L. D. MacKay
Mr. S. W. Crosby
Mr. Ed. Ziegler

1112209

SUMMARY OF ADJUSTMENTS

	Approved Budgets	Adjustments As Actually Made in Computing Contract Amount	Adjustment Which Should Have Been Made Based on June'51 Est.	As Adjustment Would Appear Based on Actual Thru 6-30-51, Per Sept. 7 Letter
TITLE I				
Fiscal Year 1950	$11,000.00	—	$ 37.43 (actual)	$ 37.43 (Actual)
Fiscal Year 1951	14,858.00	21.01	21.01 (Est.)	— (Actual)
Fiscal Year 1952	15,951.60	—	—	—
	$41,809.60	$ 21.01	$ 58.44	$ 37.43
TITLE II				
Fiscal Year 1950	$11,000.00	$3,000.00	$1,868.74 (actual)	$1,868.74 (Actual)
Fiscal Year 1951	11,437.00	2,169.86	2,169.86 (Est.)	2,397.15 (Actual)
Fiscal Year 1952	11,113.20	—	—	—
	$33,550.20	$5,169.86	$4,038.60	$4,265.89
TITLE III				
Fiscal Year 1950	$ 3,000.00	—	$ 6.96 (Actual)	$ 6.96 (Actual)
Fiscal Year 1951	6,453.00	$ 345.97	345.97 (Est.)	441.42 (Actual)
Fiscal Year 1952	6,264.00	—	—	—
	$15,717.00	$ 345.97	$ 352.93	$ 448.38
	$91,076.80	$5,536.84	$4,449.97	$4,751.70
Total Approved Budgets - All Titles for 3 years		$91,076.80	$91,076.80	$91,076.80
Less Adjustment for Available Balances at Year end.		5,536.84	4,449.97	4,751.70
Amount of Payment to Contractor		$85,539.96	$86,626.83	$86,325.10
			$85,539.96	$85,539.96
Additional adjustment due		$ 6.00	$ 1,086.87	$ 785.14

1112210

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

OFFICE OF THE CONTROLLER

September 7, 1951

United States Atomic Energy Commission
Oak Ridge Operations
Oak Ridge, Tennessee

Subject: Modification No. 2
Contract No. AT(40-1)288

Attention: Mr. C. V. Bulck, Contracting Officer

Gentlemen:

You will recall that, upon receipt of the supplemental agreement, modification No. 2 to the subject contract, we called you relative to the stipulation on page 2 that $30,791.96 would be paid to us for the fiscal year ending June 30, 1952. It was suggested that we execute the contracts as submitted and return them, accompanied by a letter setting forth our position in regard to the stipulated payment of $30,791.96. Such a letter was written to you on July 5, 1951; however, we have had no word from you relative thereto.

The $30,791.96 payment stipulated is $2,536.84 less than the approved budgets under supplement No. 2 to appendix "A" for Titles I, II and III for the year ending June 30, 1952. This $2,536.84 represents the estimated unexpended balances for the second period of the contract, i.e. year ended June 30, 1951. In view of the fact that this is a lump sum contract, it would appear that the balances for the period of the contract would have to be taken into consideration in determining the amount to be paid as compared to the budget. Certainly it would seem that estimated expenditures and balances would not govern the amount to be deducted from approved budgets as was done in this case.

The budget, receipts and expenditures under the subject contract from July 1, 1949 to June 30, 1951 are as follows:

	Title I	Title II	Title III	Total
Approved budgets and receipts	$25,858.00	$19,437.00	$9,453.00	$54,748.00
Expenditures	25,958.85	18,171.11	9,004.63	53,134.58
Excess receipts over expenditures from July 1, 1949 to June 30, 1951	(100.85)	1,265.89	448.38	1,613.42

1112211

It would therefore appear that the amount to be paid us under the contract for the year ending June 30, 1952 would be the total of the approved budgets of $33,328.80 less the excess receipts as of June 30, 1951 or $1,613.42, or a total of $31,715.38, instead of $30,791.96 as stipulated.

If our position as set forth above is not concurred in by you, it would seem that you should recognize the statement of actual expenditures for the year ended June 30, 1951 as submitted by us in determining the amount to be deducted from the approved budgets instead of an estimated statement of expenditures as was used.

It will be greatly appreciated if we can have an answer from you to this and/or our letter of July 5, 1951, in order that we may know what our budget status is for the current year.

Yours very truly,

Harry Parker

Harry O. Parker
Controller

HOP:ahc

1112212

WAKE FOREST COLLEGE
THE BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NORTH CAROLINA
ZONE 7

OFFICE OF THE CONTROLLER

July 5, 1951

U. S. Atomic Energy Commission
Oak Ridge Operations
Oak Ridge, Tennessee

Subject: Modification No. 2, Contract No. AT(40-1)288

Attention: Mr. C. Vanden Bulch, Contracting Officer

Gentlemen:

Reference is made to our telephone conversation relative to the provision set forth in paragraph 3 b., page 2 of modification No. 2 of the subject contract; and in accordance with your suggestion this letter is written to accompany the executed modification and to point out what appears to be an error in the amount to be paid thereunder.

The approved budgets under Supplement No. 2 to appendix "A" for the fiscal year ending June 30, 1952, total $33,328.80 for Titles I, II, and III. However, paragraph 3 b., page 2 of modification No. 2, states that "...the Government will pay to the contractor the total sum of thirty thousand seven hundred ninety-one and 96/100 dollars ($30,791.96)..." This $2,536.84 difference represents the estimated unexpended balances for the second period of the contract as shown on the Report of Expenditures as of April 30, 1951 which was submitted to you (after giving consideration to the receipt of the $1,000.00 adjustment provided in paragraph 1. modification No. 2).

In arriving at the unexpended balances you failed to consider the balances as of June 30, 1950 which were likewise shown at your request on the Report of Expenditures. For this period it will be noted that Title II was overexpended in the amount of $1,131.26, which was the result of the $3,000.00 adjustment in modification No. 1 dated in June, 1950; consequently the expenditures were made prior to our knowledge of the retroactive adjustment. However, the estimated unexpended balance for Title II as of June 30, 1951 is in excess of the over-expenditure at June 30, 1950.

It therefore appears that the balances as of June 30, 1950 should also be taken into consideration in determining the amount to be paid for the fiscal year ending June 30, 1952; and the payment should be $31,878.83 instead of the specified amount of $30,791.96. In this connection, and in justification of our position, reference is made to a letter dated April 30, 1951 from Mr. Edward McGrady, Chief, Biology Division, Office of Research and Medicine, in answer to our letter of April 9, 1951, relative to receipts and expenditures for the two years ending June 30, 1951. Mr. McGrady stated "you are correct that the

1112213

total expenditures for FY 1950 and 1951 would be applied to the total receipts for this period". Consequently, in accordance with this understanding, it would appear that the difference of $1,449.97 between total receipts for the two years ending June 30, 1951 amounting to $54,748.00 (including the $1,000.00 supplement) and total expenditures, shown on the Report of Expenditures referred to above, for the same period amounting to $53,298.03, should be deducted from the total budgets for 1951-52 in determing the amount to be paid us.

Your consideration of this request for an adjustment of $1,086.87 in the amount to be paid under modification No. 2 of contract No. AT(40-1)288 will be greatly appreciated; and we await your advice pertaining thereto.

Yours very truly,

Harry Parker

Harry O. Parker
Controller

1112214

Office Memorandum • UNITED STATES GOVERNMENT

TO J. Wallace Ould, Jr., Assistant General Counsel DATE June 15, 1951

FROM R. G. Humphries, Contract Coordinator

SUBJECT: RENEWAL OF CONTRACT AT-(40-1)-288 - BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

SYMBOL: CO:RGH

At the present time the Commission is supporting research under subject contract which is covered by three separate titles with three separate project leaders involved under the one contract. The present term of this contract is due to expire June 30, 1951.

There is forwarded herewith an approved proposal for extending the work under the three titles for another year.

It will be noted that the Contractor had proposed a new Title for the new period. By separate correspondence the Commission has advised the Contractor that approval will not be granted for the proposed new title during the coming year.

Accordingly, it is requested that you prepare an appropriate modification to this contract to continue the work under the present three titles for another year on a lump sum basis.

There is enclosed a report of expenditures and estimated balances of funds unexpended as of June 30, 1951. There is also enclosed a memorandum dated June 14, 1951, from Dr. Woodruff advising that Washington has approved an increase of $1,000 under the item "Supplies and Shop" under Title I of the contract for the present period beginning July 1, 1950, and ending June 30, 1951. This additional $1,000 will result in the contract amount for fiscal year 1951 under Title I of the contract being shown as $14,858 and the "Supplies and Shop" item being shown as $4,100.

It is requested that you make the necessary revision in the current year's budget in the same modification extending the work under the three titles for the new year.

In making adjustments for the balances of funds expected to be available as of June 30, 1951, I have taken into account the additional $1,000 for Title I during the current year which then shows a balance as of June 30, 1951, in the amount of $21.01 instead of a deficit of $978.99 as originally reported by the Contractor on the enclosed report.

1112215

The description of the work for the new period and separate budgets for the three titles are included in the Contractor's extension proposal which is furnished herewith.

You will note that certain red pencil corrections have been made on the budget to give effect to the elimination made by the Washington office in approving these extensions and also to reflect the effect of the cash balances available under the present contract period as of June 30, 1951.

Dr. Edward McCrady will serve as technical advisor on this contract action.

R. G. Humphries

Enclosures:
Rec. of Expenditures
Cy ltr to Bowman Gray 5-29-51
Cy. ltr fm Tuttle to Harrell 5-24-51
Memo fm Woodruff 5-25-51
Memo fm Woodruff 6-14-51
Memo fo Tuttle 5-18-51
Contractor's proposal

CC: Dr. Edward McCrady
Mr. Ed. Ziegler
Mrs. J. Nicholson

Humphries:lm

1112216

Office Memorandum • UNITED STATES GOVERNMENT

TO R. G. Humphries, Contract Coordinator DATE June 14, 1951

FROM Nathan H. Woodruff, Director of Research and Medicine

SUBJECT: CONTRACT NO. AT-(40-1)-288 - BOWMAN GRAY SCHOOL OF MEDICINE

SYMBOL: RM:AMC

By Procurement Directive No. BM-51-185 dated April 23, 1951, (which is in the Finance Division) an increase of $1,000 was authorized for the 1951 budget of the subject contract. This was a supplement to the present contract to provide funds for the purchase of isotopes.

It is desired that arrangements be made to include provision for this increase in the above contract.

Nathan H. Woodruff

Nathan H. Woodruff

Corley:oc

1112217

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO : R. G. Humphries, Contract Coordinator DATE: May 25, 1951

FROM : Nathan H. Woodruff, Director of Research and Medicine

SUBJECT: RENEWAL OF CONTRACT NO. AT-(40-1)-288 - BOWMAN GRAY SCHOOL OF MEDICINE

SYMBOL: RM:EC

Enclosed is a memorandum from the Division of Biology and Medicine, Washington, authorizing renewal of the subject contract for a period of one year.

Dr. Edward McCrady will act as technical advisor for this office.

for Kenneth Cassidy
Nathan H. Woodruff

Encl.:
File

Cressman:ec

Issued by PD-BM-51-198
$33,328.80
5/18/51

1112218

Contractor: Bowman Gray School of Medicine of Wake Forest College

REPORT OF EXPENDITURES

TITLE I

Period	Contract Amount	Actual Expenditures to 6-30-50	Balance Unexpended as of 6-30-50
7/1/49-6/30/50	$11,000.00	$10,962.57	$ 37.43

7/1/50-6/30/51	Contract Amount	Actual Expenditures to 4/30/51	Balance Unexpended as of 4/30/51	Estimated Expenditures 5/1/51-6/30/51	Estimated Balance Unexpended 6/30/51
Capitol Equip.	$ 1,131.00	$ 771.68	$ 359.32	-	$ 359.32
Salaries	8,400.00	6,802.50	1,597.50	$ 1,430.00	167.50
Supplies & Sh	3,100.00	3,501.12	~~(401.12)~~ 548.88	1,000.00	(401.12)
Travel	200.00	304.69	(104.69)	-	(104.69)
Overhead	1,027.00	1,027.00	-	-	-
TOTALS...	$13,858.00	$12,406.99	~~$1,451.01~~ >451.01	$ 2,430.00	~~($ 978.99)~~ BAL. $ 21.01

4,100.

14,858.00 as changed by this mod.

TITLE II

Period	Contract Amount	Actual Expenditures to 6-30-50	Balance Unexpended as of 6-30-50
7/1/49-6/30/50	$ 8,000.00	$ 9,131.26	$(1,131.26)

7/1/50-6/30/51	Contract Amount	Actual Expenditures to 4/30/51	Balance Unexpended as of 4/30/51	Estimated Expenditures 5/1/51-6/30/51	Estimated Balance Unexpended 6/30/51
Capitol Equip.	$ 1,320.00	$ 2,104.26	($ 784.26)	$ 140.00	($ 924.26)
Salaries	4,320.00	1,940.00	2,380.00	415.00	1,965.00
Supplies & Shop	4,700.00	2,651.05	2,048.95	900.00	1,148.95
Travel	250.00	160.24	89.76	109.59	(19.83)
Overhead	847.00	847.00	-	-	-
TOTALS...	$11,437.00	$ 7,702.55	$ 3,734.45	$ 1,564.59	$ 2,169.86

TITLE III

Period	Contract Amount	Actual Expenditures to 6-30-50	Balance Unexpended as of 6-30-50
7/1/49-6/30/50	$ 3,000.00	$ 2,993.04	$ 6.96

7/1/50-6/30/51	Contract Amount	Actual Expenditures to 4/30/51	Balance Unexpended as of 4/30/51	Estimated Expenditures 5/1/51-6/30/51	Estimated Balance Unexpended 6/30/51
Capitol Equip.	$ 950.00	$ 686.53	$ 263.47	$ 263.47	$ -
Salaries	3,600.00	2,028.90	1,571.10	520.00	1,051.10
Supplies & Shop	1,425.00	1,680.13	(255.13)	450.00	(705.13)
Travel	-	-	-	-	-
Overhead	478.00	478.00	-	-	-
TOTALS...	$ 6,453.00	$ 4,873.56	$ 1,579.44	$ 1,233.47	$ 345.97

This amount to be reimbursed to $1,000 See memo from Woodruff dated 6/14/51

$ 2,536.84 Total

1112219

Oak Ridge, Tennessee
May 29, 1951

Mr. Harry G. Parker, Controller
The Bowman Gray School of Medicine of
Wake Forest College
Winston-Salem 7, North Carolina

Subject: CONTRACT NO. AT-(40-1)-[illegible]

Dear Mr. Parker:

Your application for renewal of support of Titles I, II and III covering the research of Drs. Harrell, Arton and Gerstner has been approved by the Commission's Division of Biology and Medicine, in Washington, D. C.

Your renewal proposal also included the proposal of a new Title IV "The Influence of Physical Factors in the Permeability of Membranes Concerned in the Formation of Ascitic Fluid". Approval of this new project has not been received at this time from the Washington office since it is understood that it is still being considered by the Research Committee. If approval of this project is received at a later date it is planned to cover the work by a separate contract with you.

In approving the renewal of Titles I, II and III the Washington office took the following action:

a. Eliminated the miscellaneous item of $200 for Title I.

b. Eliminated the item for incidentals, set forth under Other Expenses in the amount of $200 under Title II.

c. Eliminated the miscellaneous item of $175 in Title III.

The elimination of the above items from the budget came based on the Research Committee's feeling that all funds requested should be identified within a definite category in the budget and that no funds should be allowed for items classed as "miscellaneous", "other" or "contingent".

Otherwise your renewal proposal was approved as submitted.

Z-1986 - Dr. N. H. Woodward

1112220

It is noted that you have not included in your renewal proposal any information concerning your expenditures during the past period as well as an estimate of your expenditures for the remaining period of the current term, all as contemplated by Section 3 of Article III of the contract.

Accordingly, it is desired at this time that you furnish a report of your expenditures under the several titles of the contract, together with an estimate of your expenditures during the remaining period of the current year. In preparing this report it would be helpful if you would furnish an explanation on any item where the estimated monthly rate of expenditures in the last period of this year exceeds the monthly rate of expenditures experienced by you in the preceding period. There is enclosed a form with a suggested arrangement of the data to be furnished under each title of the contract.

In view of the short remaining time before the present term of the contract will expire it would be appreciated if you could furnish the requested report at your earliest convenience.

You may be assured that we will process the extension modification to your contract immediately upon receipt and evaluation of the above requested information.

Future requests for renewal of the work under this contract should, of course, include a report of your expenditures as mentioned above.

Your cooperation in furnishing this additional information will be appreciated.

Very truly yours,

Nathan K. Woodruff
Director of Research & Medicine

Enclosure:
Suggested form of
Record of Expenditures

Humphries:lm

CC: Dr. Edward McCrady
Mr. Ed. Ziegler

1112221

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON 25, D. C.

IN [redacted]ER TO:

May 24, 1961

Dr. George T. Harrell
Department of Internal Medicine
Wake Forest College
The Bowman Gray School of Medicine
Winston-Salem, North Carolina

Dear Dr. Harrell:

This is to advise you that our Research Committee in considering your new proposal IV. "The Influence of Physical Factors in the Permeability of Membranes Concerned in the Formation of Ascitic Fluid" felt that while the work was unquestionably sound scientifically, it was somewhat outside of our main field of interest, and that with our somewhat restricted budgetary situation, its support at this time could not be recommended.

I am sorry that we will not be able to participate in this particular phase of your research program and hope that you will be able to obtain support elsewhere.

Sincerely yours,

L. W. Tuttle
Asst. Chief, Medical Branch
Division of Biology & Medicine

cc Woodruff - CRD

[redacted]N 1 '95

A-3725

1112222

Following file

Oak Ridge, Tennessee
May 29, 1951

Mr. Harry G. Parker, Controller
The Bowman Gray School of Medicine of
Wake Forest College
Winston-Salem 7, North Carolina

Subject: CONTRACT NO. AT-(40-1)-288

Dear Mr. Parker:

Your application for renewal of support of Titles I, II and III covering the research of Drs. Harrell, Artom and Gorastner has been approved by the Commission's Division of Biology and Medicine in Washington, D. C.

Your renewal proposal also included the proposal of a new Title IV "The Influence of Physical Factors in the Permeability of Membranes Concerned in the Formation of Ascitic Fluid". Approval of this new project has not been received at this time from the Washington office since it is understood that it is still being considered by the Research Committee. If approval of this project is received at a later date it is planned to cover the work by a separate contract with you.

In approving the renewal of Titles I, II and III the Washington office took the following action:

a. Eliminated the miscellaneous item of $200 for Title I.

b. Eliminated the item for incidentals, set forth under Other Expenses in the amount of $200 under Title II.

c. Eliminated the miscellaneous item of $175 in Title III.

The elimination of the above items from the budget was based on the Research Committee's feeling that all funds requested should be identified within a definite category in the budget and that no funds should be allowed for items classed as "miscellaneous", "other" or "contingent".

Otherwise your renewal proposal was approved as submitted.

1112223

It is noted that you have not included in your renewal proposal any information concerning your expenditures during the past period as well as an estimate of your expenditures for the remaining period of the current term, all as contemplated by Section 3 of Article XIV of the contract.

Accordingly, it is desired at this time that you furnish a report of your expenditures under the several titles of the contract, together with an estimate of your expenditures during the remaining period of the current year. In preparing this report it would be helpful if you would furnish an explanation on any item where the estimated monthly rate of expenditures in the last period of this year exceeds the monthly rate of expenditures experienced by you in the preceding period. There is enclosed a form with a suggested arrangement of the data to be furnished under each title of the contract.

In view of the short remaining time before the present term of the contract will expire it would be appreciated if you could furnish the requested report at your earliest convenience.

You may be assured that we will process the extension modification to your contract immediately upon receipt and evaluation of the above requested information.

Future requests for renewal of the work under this contract should, of course, include a report of your expenditures as mentioned above.

Your cooperation in furnishing this additional information will be appreciated.

Very truly yours,

Nathan H. Woodruff
Director of Research & Medicine

Enclosure:
Suggested form of
Record of Expenditures

Humphries:lm

CC: Dr. Edward McCrady
Mr. Ed. Ziegler

1112224

UNITED STATES ATOMIC ENERGY COMMISSION
DIVISION OF BIOLOGY AND MEDICINE
WASHINGTON, D. C.

DATE: MAY 1 8 1951

TO : Dr. ~~John Roberson~~ Nathan Woodruff, Dir. Research and Medicine, Oak Ridge Operations Office

FROM : L. W. Tuttle, Asst. Chief, Medical Branch

SUBJECT: TRANSMITTAL OF RESEARCH PROPOSAL FOR CONTRACT NEGOTIATION

SYMBOL : BMM:LWT

This letter with enclosures, in triplicate, is sent in accordance with the procedure described in a letter from the General Manager to all Managers of Operations dated January 27, 1949.

1. **Institution:** Wake Forest College - Bowman Gray Sch. of Med.

2. **Investigator (s):** See comments

3. **Title:** See comments

4. ( ) New Contract or (x) Renewal of Contract No. AT(40-1)-288

5. **Duration - From:** 7-1-51 **To:** 6-30-52

6. **AEC Technical Supervision:** Medical Branch

7. **Recommended Support:** $33,328.80

   Authorized by Procurement Directive No. BM-51-198

   Issued MAY 1 8 1951 $ 33,328.80

   Activity No. 6300

8. **Other Comments:** The total amount is allocated as follows:

Title I - Investigator: Dr. George T. Harrell
Amount: $15,951.60
Title: "Distribution and Turnover of Sodium and Potassium in Acute Infections"

Title II - Investigator: Dr. Camillo Artom
Amount: $11,113.20 11,221.20
Title: "Formation of Phospholipides in Tissues"

Title III - Investigator: Drs. C. Artom, W.E. Cornatzer and G. T. Harrell
Amount: $6,264.
Title: "Toxicity of P^{32} as related to the Diet and to the Chemical nature of the Compound"

It is recommended that the miscellaneous items of $200. for Title I, $200. for Title II, and $175. for Title III be deleted. Our

A-3517

1112225

8. **Comments** (Continued)

Research Committee feels that all money requested should be identified within a definite category in the budget and that no funds should be allowed under such headings as "miscellaneous", "other" or "contingent".

Title IV "The Influence of Physical Factors in the Permeability of Membranes concerned in the Formation of Ascitic Fluid" is a new part to the proposal, it is still being considered by our Research Committee. It is suggested that negotiations for renewal not be held up pending final action on Title IV.

9. **Security Requirements:**

In accordance with the provisions of GM-93 (Revised March, 1950), and the requirements of the Declassification Guide, the Division of Biology and Medicine has determined that the following security precautions should be taken in connection with the proposed research contract.

The research program proposed involves essentially zero chance that restricted data will be required or developed during the course of investigation. It is recommended that the program be established without security requirements.

10. **Reports:** (x) Reports are to be required as provided for by Memorandum Instruction of November 9, 1949, on subject "Direct Research Contract Reports".

( ) Special Reports Instructions are as follows:

Enclosures:

(x) "A" - Proposal, dated _____

( ) "B" - Notification letter, dated MAY 1 9 1951

(x) "C" - Other correspondence, _____ letters

(x) "D" - Procurement Directive BL-51-198

Distribution:

Addressee:	Original (w encl.)	**Division File:**	Yellow Copy (w encl.)
	1st Copy (" ")		Pink Copy (w/o encl.)
	2nd Copy (" ")		Green Copy (" ")
Program Analysis Branch:	White Copy (w/o encl.)	**Branch File:**	White Copy (w ")

1112226

PROPOSAL FOR RENEWAL
Research Contract AT-(40-1)-288

CONTRACTOR: The Bowman Gray School of Medicine of Wake Forest College

ADDRESS: Winston-Salem, 7, North Carolina

AMOUNT OF CONTRACT

	Title I	Title II	Title III	Title IV (TOTAL)
Personnel	$ 7,750.00	$ 5,280.00	$ 3,300.00	$ 2,650.00
Permanent Equipment	870.00	1,460.00	700.00	500.00
Consumable Supplies	5,850.00	3,000.00	1,600.00	2,100.00
Travel	300.00	300.00	200.00	200.00
Miscellaneous	See previous page. ~~200.00~~	~~350.00~~ 350.00	~~175.00~~	100.00
Sub Totals	~~$14,970.00~~ 14,770.00	~~$10,390.00~~ 10,390.00	~~$5,975.00~~ 5,800.00	30,460.00
Plus 8% O/H	1,181.60	831.20	464.00	2,476.80
Total appl. budget FY 52	15,951.60	11,221.20	6,264.00	33,436.80
TOTALS TITLES I, II, III, IV				$ 37,135.00
Overhead at 8%	21.01	169.86	345.97	536.84
				2,970.00
Bal. funds 6/30/51. (See continuation report)	$15,930.59	$9,051.34	$5,918.03	$ 40,105.80
				$30,899.84

- This item contains repairs and replacements which in the other titles are divided between salaries and consumable supplies.

Request for FY '52

1112227

April 6, 1951
Contract No. AT-(40-1)-288
Bowman Gray School of Medicine
of Wake Forest College

TITLE I

1. a. Project Leader: Dr. George T. Harrell

b. Term: July 1, 1951 to June 30, 1952

c. Program: Distribution and turnover of sodium and potassium in acute infections.

ORIENTATION

Patients recovering from infectious diseases or from serum sickness have a diuresis during recovery in which water and chlorides are lost. In the acute phase of certain human infections, such as Rocky Mountain spotted fever and trichinosis, edema develops and the blood chlorides and proteins drop. No data are available on changes in the blood or urinary sodium and potassium. With the alterations in distribution of fluid, peripheral circulatory collapse often develops and leads to the death of the patient.

It is not known from blood volume and thiocyanate tissue space studies whether the fluid lost from the blood is found between cells or within them. The increase in permeability of capillary and cell wall membranes can be visualized as a graded series of pores. In mild instances of disease, only crystalloids leave the blood stream; in more severe instances small protein molecules such as albumin, or larger ones such as globulin, will leak out. A small defect should be detectable by the extent to which radioactive ions such as Na^{24} and K^{42} are diluted following injection; a larger defect should be detectable by the diffusion from the blood stream of protein molecules of various sizes tagged with I^{131}. In Rocky Mountain spotted fever the time at which the edema and circulatory collapse are maximal suggests that an antigen-antibody reaction may be at least partly responsible for the alteration in permeability of membranes.

If the mechanism can be established by which increased amounts of electrolytes are passed across capillary and cell membranes, it may be possible to devise means to correct the physiologic abnormality in infections or in pure antigen-antibody systems such as serum sickness. Eventually, it may be possible to induce an increase in permeability so that radioisotopes could be encouraged to enter certain tissues and there exert an intracellular radiation effect.

Some tumors may be caused by filterable viruses; others can concentrate viruses such as vaccinia. If a virus could be introduced into a cancer and immune serum were administered, an antigen-antibody reaction should take place only on parasitized cells; the local alteration in permeability would allow any circulating radioisotope to be concentrated in the cancerous tissue. If - through application of the auto-antibody technique - an antiserum against cancerous cells could be made, a similar reaction would take place only on malignant cells and should locally alter permeability so that an isotope administered therapeutically could be concentrated in the tumor.

1112228

PROGRESS TO DATE

The detailed progress report on the experiments conducted July 1, 1950 to March 1, 1951 has already gone forward.

Methods: Techniques for determination in rabbits of plasma volume, thiocyanate space, and Na^{24} space have been developed and standardized. ~~The data have been published in the AMERICAN JOURNAL OF PHYSIOLOGY and the raw data have been deposited with the American Documentation Institute.~~

Techniques for tissue analysis of total sodium and Na^{24} content in rabbits have been developed and standardized and control data accumulated for comparison with experimental data.

Similar techniques have been developed and are being standardized for K^{42} space in normal rabbits and for tissue analysis for total potassium and K^{42} content in rabbits.

In human beings methods for the comparison of thiocyanate space, sodium-24 space, and potassium-42 space have been standardized. Control data and data in various states are being collected.

The Evans blue and iodinated serum methods for the determination of plasma volume are being compared in normal rabbits using labeled rabbit albumin and in normal and diseased human beings using labeled human albumin.

So far the technique for interstitial pneumococcal infection ("dermal pneumonia") in rabbits has been difficult to standardize.

Experiments in Progress: Pure antigen-antibody reactions without infection have been studied in rabbits by inducing serum sickness with the injection of 1) whole human plasma; and 2) albumin or globulin fractions of human plasma.

Experiments on fluid changes in immune reactions induced in rabbits 1) by passive transfer techniques, utilizing anti-human immune serum previously prepared in other rabbits; and 2) by active induction of immunity through injection of horse serum have been done. The data are as yet too variable to be suitable for publication; additional refinements in technique and improvements in design of experiment are necessary before satisfactory definitive experiments are done.

Experiments on an extracellular infection in rabbits, trichinosis, have been completed and accepted for publication.

Studies on the fluid changes in normal human beings following therapeutic doses of digitoxin and in normal rabbits following therapeutic or toxic doses of digitoxin have been completed.

Experiments in normal rabbits, utilizing intravenous injections of hyaluronidase or histamine, have not resulted in alterations in the plasma volume or thiocyanate space.

1112229

Experiments with pneumococcal extracellular infections in rabbits have not given clear cut results.

PROPOSED PLAN OF EXPERIMENTS FOR 1951-52

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 ~~[illegible]~~ 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 should 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. ~~The first shipments of I^{131} tagged rabbit serum have not yet been received; but arrangements have been made for their preparation and authorization received from the Isotopes Division, AEC.~~

"Depending upon the relative alteration of Na^{24}, K^{42} and I^{131} values as determined in the above experiment, autoradiography of the organs

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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 leached 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 K^{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 ~~(T-1824)~~ techniques, should be done. ~~Approval for use of I^{131} in human beings has just been received from the Isotopes Division and our first experiments in human beings performed. These studies would standardize the technique for use in later experiments in infections.~~

"~~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. ~~Dr. Hirve is familiar with the technique for culture of rickettsiae in embryonated chick eggs. The laboratory is not now set up for this technique, but the equipment required is not expensive and is readily available.~~ It will be necessary to standardize 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}, K^{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 immunized 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 ~~our~~ 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 Na^{24}, K^{42} and I^{131} 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 auto-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.

"~~Clinical studies~~: ~~We are still applying~~ The techniques developed and standardized in human beings to the study of infectious diseases in human patients. The development ~~[illegible]~~ of ~~[illegible]~~ 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 ~~just~~ 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 cummulative 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 preceeding 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 ~~just~~ been received from the Isotopes Division to enable ~~them~~ repeat 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) ~~should~~ 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.

end

FACILITIES AVAILABLE

The Isotope Laboratory on the fifth floor is essentially unchanged from that previously described to the Commission.

A fume hood suitable for tracer work at low levels of activity has been obtained from other funds and installed in the third floor laboratory. This piece of equipment can be made available during periods of optimum research activity.

PERSONNEL AVAILABLE

Dr. Jerry K. Aikawa has completed his AEC Fellowship. We have been able to obtain partial financial support from other funds through October 1952. Long-range planning must consider the possibility of increasing the contribution of the Commission to his financial support after that time if we are to retain him.

Miss Eloise Rhoades, technician, continues in her present position and is doing excellent work.

A negro animal technician, Claude Taylor, continues in his present position and is doing good work. He is responsible for the breeding of rabbits as well as some technical procedures.

Dr. George T. Harrell is still available for a limited amount of time. More time could be made available, if financial arrangements could be made to release him from other duties in the School.

Dr. Ernest Yount will be available for limited consultations on clinical problems, particularly those involving the use of I^{131} and those patients with renal disease. Because of the increased need for funds for isotopes, the partial financial support given him in the past has been withdrawn this year, but the time available for this project unfortunately has had to be correspondingly reduced.

NEEDS FOR 1951-52

Personnel: In order not to increase the budget request for this project, an attempt is being made to obtain financial support for additional technical help through other funds. The work is progressing at an entirely satisfactory rate but could move faster were additional technical help available.

Equipment: A new and improved flame photometer attachment is required. The basic spectrophotometer instrument is quite satisfactory and is performing well, so that only the flame attachment is needed. Relatively

minor additional shielding is required.

Supplies: The requirements for isotopes will be considerably greater than in past years. It has been found possible to continue experiments steadily by utilizing whatever clinical material is available on the wards. Isotopes have been received during the latter part of 1950-51 at weekly intervals instead of the more widely scattered interval previously used. Because of the short life of the Na^{24} and K^{42}, each shipment is usable for only two to three days. The difficulties in transportation have already been described in the progress report. The occasional necessity for shipment via Washington or Tri-City has increased the air freight cost appreciably. We have been able this year to share part of the cost of Na^{24} with another grant and the amount requested for next year takes that fact into account.

The cost of animals has increased somewhat so that this item is slightly larger than last year.

The considerable increase in the amount of work done after weekly shipments of isotopes were arranged has increased over previous years the amounts of chemicals used, particularly the bottled gas for the flame photometer.

George T. Harrell

1112235

2. PROPOSED BUDGET - July 1, 1951 to June 30, 1952

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

(1) Salary of Project Leader
Major portion of salary of Dr. Jerry K. Aikawa

(2) Laboratory space, secretarial help and other services.

b. The Commission is requested to furnish:

(1) Personnel

Part time salary of Dr. Jerry K. Aikawa	$ 2400.00	
Technician, Miss Elbise Rhoades	2400.00	
Technician, Claude Taylor	2250.00	
House officer for clinical studies, part time	400.00	
Electronic engineer, part time	300.00	
		$7,750.00

(2) Permanent Equipment

Clock-timer	90.00	
Flame photometer attachment	400.00	
Bricks - lead on steel	180.00	
Vertical tube shield	200.00	
		870.00

(3) Expendable Supplies

Isotopes - 25 shipments, Na at $50.00	1250.00	
25 shipments, K at 50.00	1250.00	
25 shipments, I at 10.00	250.00	
	2750.00	
Animals	1800.00	
Glassware	500.00	
Chemicals and Gas	500.00	
Egg work	100.00	
Geiger-Muller tubes	200.00	
		5,850.00
(4) Travel	300.00	
		300.00
~~(5) Miscellaneous .....~~	~~200.00~~	
		~~200.00~~
TOTAL		~~$14,970.00~~
		14,770.00
(5) Overhead @ 8%		1,151.60
		15,954.60
Less Cash balance		24.01
New payment requested		$15,930.59

See contractor's report

1112236

Proposal for renewal of research project contract No. AT-(40-1)-288, Title II

Principal Investigator: Dr. Camille Artom

Term: July 1, 1951 to June 30, 1952

Subject: Formation of Phospholipides in Tissues

A. Statement of the problem and progress to date.

here Title II

"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). ~~We have~~ 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, ~~our~~ investigations have progressed ~~mainly~~ along the following lines: 1) Lipide 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.

The results obtained have been summarized in my recent progress report. It appears that several of these results represent interesting contributions to the problems of the synthesis of phospholipides in tissues as well as of the mechanism of action of choline in the prevention and treatment of the fatty infiltration of the liver.

Several of the findings have been reported at scientific meetings (Feder. Amer. Soc. Biol.; N. C. Academy Science; XVIII Intern. Congress of Physiology; S. E. Section of the Soc. of Biol. and Med.; R. Gould Symposium on Lipides, Rochester, N. Y.) or published in scientific periodicals (J. Biol. Chem., 167:281 (1950); Arch. Biochem. 29:237 (1950)). Other manuscripts have been either submitted to editorial boards, or are being prepared for publication.

B. Program of the investigations for 1951-52.

"During this period the Contractor will ~~It is planned to~~ continue and extend the above mentioned groups of investigations. The following seem ~~at the present as~~ the most promising, and the ~~during the coming year, we are planning to devote to these points most of our activities~~ 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

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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 synthesize 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. Our 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 CO_2; 2) Formation of trimethylamine and trimethylamine oxide; 3) Formation of compounds highly resistant to hydrolysis.

The Contractor in the operation postulated that the last mentioned compounds are the Contractor inorganic esters of choline (such as choline phosphate) but it is planned to obtain a more convincing evidence of their identity. At the same time we will try to identify other likely metabolic products of choline 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 our attempts will be successful, a balance sheet of choline

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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 our 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.

end

C. Facilities and needs.

The general facilities, space and equipment are considered sufficient for the continuation of the present program. However, an additional Warburg apparatus, preferably of the rotary type, would be required in order to speed up the work which in the future will consist almost exclusively of experiments on isolated tissue preparations. The purchase of a line noise monitor is also contemplated in order to exclude possible causes of error during the radioactive measurements. It is hoped that the sum requested for maintenance and repair of radioactivity apparatus will allow to carry on our measurements with the existing equipment without the need of buying additional radioactivity apparatus. The sum requested last year for technical help will probably be sufficient for the coming year.

It is the feeling of the writer that the main limiting factor in extending and speeding up investigations of the type which we are doing is the amount of work, time and thought actually given to the project by the more mature professional investigators and that a simple increase in technical help will not be sufficient to overcome such a limitation. One of the investigators, Miss Marietta Crowder, who last year received the M. S. degree, has contributed a large share to this project. Because of financial difficulties it does not seem possible to the administration of this School to raise Miss Crowder's salary to a figure adequate to the increased cost of living and to the degree of maturity which she has attained. Accordingly, in an attempt to insure the continuation of her collaboration to this project, I would like to include in the category of salaries a small sum to be used as a supplement to her salary. It seems feasible to compensate the increased expense in the salaries item with a corresponding decrease in the amounts requested for other items, especially for the expendable supplies. Thus the grand total requested for the coming year will be exactly the same as the one requested last year.

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Proposed budget:

a. **Salaries:**

Full time technician (Charlotte Terhune)	$2160.00	
2 Part time technicians	2160.00	
Supplement to the salary of Marietta Crowder, M. S.	960.00	
		$5280.00

b. **Permanent equipment:**

Warburg apparatus (rotary)	$ 850.00	
Accessories for above	250.00	
Line noise monitor	150.00	
Other minor items	200.00	
		$1450.00

c. **Consumable supplies:**

Radioactive compounds C^{14} labeled	$1250.00	
Expenses for the synthesis of new C^{14} labeled compounds	450.00	
Animals	200.00	
Chemicals and organic solvents	500.00	
Glassware	600.00	
		$3000.00

d. **Travel:** $ 300.00

e. **Other expenses:**

Maintenance for repairs and replacement of radioactivity apparatus	$350.00	
~~Incidentals~~	~~200.00~~	
		~~$550.00~~ 350.00
Total		~~$10500.00~~ 10390.00
f. Overhead: @ 8%		~~$847.00~~ 831.20
Grand total		~~$11487.00~~ 11221.20 11,113

Less Cash before 4/30/57 2 16986

add. payment Sept. Camillo Artom $ 9051.34

Camillo Artom, M. D.
Professor and Head of the Biochemistry Laboratory

10290
3320
13610

10290
3320
11113.20

$ 9,051.34
108
8,943

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Proposal for renewal of research contract No. AT-(40-1)-288, Title III

Principal Investigators: Dr. Camille Artom, Dr. W.E. Cornatzer, and Dr. George T.Harrell,

Term: July 1, 1951 to June 1952

Program: Toxicity of P^{32} as Related to the Diet and to the Chemical Nature of the Compound

A. Statement of the problem and progress to date.

The toxicity of P^{32} represents an interesting problem, theoretically, because P^{32} is a pure emitter of beta rays with a medium range of penetration, and, practically, because of its extended use as a research tool and as a therapeutic agent. When it is introduced in the body as inorganic phosphate, P^{32} exchanges rapidly with the inorganic components of the skeleton. In this respect, the toxic action of P^{32} should consist primarily in a damage to the bone marrow; however, because of the anionic nature of P^{32}, the mechanisms by which treatment or protection against its toxicity might be obtained would probably be different from those effective against other bone-seeking elements (such as Ra, Pu, Pb, etc.).

~~As mentioned in our progress reports,~~ 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 LD_{50} 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. 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 B_{12} and folic acid could be demonstrated in animals receiving sulfaguanidine (in order to reduce the synthesis of the vitamins in the gastro intestinal tract).

The results have been discussed at several scientific meetings and reported in two complete papers, one published and one presently in press.

B. Proposed plan of the investigation for 1951-52.

~~It is planned to continue~~ 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 P^{32}.

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 counteracted by the administration of vitamin analogues. Accordingly, ~~we are planning to~~ compare the toxicity of P^{32} in animals receiving either antibiotics, or vitamin analogues (e.g., desoxypyridoxin) with the toxicity of the isotope in animals generously supplied with the natural vitamins (e.g., pyridoxin).

the Laboratory will

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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. Alkalosic and acidosic diets.

"Preliminary ~~data~~ indicate that acid-producing substances tend to decrease the survival of mice injected with P^{32}. 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^{32} from the skeleton.

"Among the various experimental dispositions ~~which we have~~ 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, ~~we feel that~~ additional experiments are needed before definite statements on this point can be made.

"In addition, the Contractor will ~~we are planning to~~ test the effects of the administration of other "chelating" agents (such as "varsenes"), 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 ~~proposed~~ 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.

end

C. Principal investigators.

Because of the pressure of other work, Dr. Cayer finds it difficult to continue in the future his direct participation to this investigation. However, he has assured the other investigators of his continued interest in this project. Dr. Cornatzer, who in the past has collaborated to these investigations, will have completed in June his work for a Medical Degree. He will be directly associated with Dr. Artom and Dr. Harrell in the development and supervision of the work.

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D. **Facilities available and needs.**

Thanks to the generous support of the AEC during the preceding years, adequate space and equipment are now available for the housing or the animals, preparation of the diets, and safety of the personnel. The only non-expendable items which will be needed are an additional homogenizer for the diets, cages for mice and rats (chiefly to replace those worn out) and new larger cages for housing rabbits. For the chemical and isotopic analyses on blood and urine, apparatus and equipment available in the Biochemistry laboratory for other purposes will be used, and only the purchase of one additional Klett-Summerson colorimeter is contemplated. On the other hand, the use of larger size animals will increase the cost for animals, chemicals and radioactive phosphorus.

As for technical personnel, one technician working half day will be permanently in charge of the experiments. In addition, it is hoped that, as in the past, considerable contribution will be obtained from students and other qualified individuals, devoting some of their free time to the care of the animals, preparation of the diets, recording of the data, etc. This would make the total sum for technical help equivalent to the salary of one full-time and one part-time technician.

Except for the inclusion of a moderate sum for travel of the principal investigators in connection with the present work, and for minor shifts from one category to another, the proposed budget is essentially similar to that of the current year with exactly the same grand total.

E. Budget

a) Salaries of personnel:

One half-time technician	$1200.00	
Other technicians working part-time	2100.00	
		$3300.00

b) Permanent equipment:

Metabolism cages for small animals (chiefly replacements)	$150.00	
Metabolism cages for larger animals	250.00	
Klett-Summerson colorimeter and accessories	240.00	
Homogenizer for diets	60.00	
		$ 700.00

c) Expendable supplies:

Radioactive phosphorus	$500.00	
Chemicals and dietary components	400.00	
Glassware	200.00	
Animals	500.00	
		$1600.00

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d) Travel $200.00

~~e) Miscellaneous~~

Total ~~$150.00~~ ~~$5085.00~~ 5,800.00

(e) Overhead @ 8% ~~$450.00~~ 464.00

Grand total ~~$6480.00~~ 6264.00

Less Cash balance 6/30/51 345.97

Adj. payment required by Gov - $ 5,918.03

Carillo Artom, M. D.

W. E. Cornatzer, Ph. D.

George T. Harrell, Jr., M. D.

April, 1951
Contract No. AT-(40-1)-288
Bowman Gray School of Medicine
of Wake Forest College

TITLE IV

1. a. PROJECT LEADERS: Dr. David Cayer, Dr. W. Eugene Cornatzer

b. TERM: July 1, 1951 to June 30, 1952

c. PROGRAM: The Influence of Physical Factors in the Permeability of Membranes concerned in the Formation of Ascitic Fluid.

ORIENTATION

In infections, immune processes, chemical intoxications, and following irradiation, permeability of membranes is altered. It is difficult to interpret data in such complex systems since little is known concerning the individual factors in stable systems, particularly those influencing the shift of fluid across intact membranes in human beings. Patients with effusions into the various body cavities, offer an excellent opportunity for the study of such factors, since the diseases most frequently producing such changes, for example portal cirrosis or congestive failure, progress slowly and can be stabilized for weeks thereby allowing the individual factors - protein-salt - sodium and potassium, and lipides to be varied. By isotopic techniques the volume of fluid in circulation, in the peritoneal cavity as ascites or pleural space as an effusion, the total body stores, and the amount in the fluid spaces can be determined and the rate of turnover in ascitic fluid as measured by passage across the peritoneal membrane compared with the rate in the body as a whole.

Some idea of re-absorptive power in the peritoneum or its lymphatics could be obtained by reversing the experiment, placing labeled materials in the ascitic fluid and tracing their appearance in the blood, urine, and feces, etc. The only factor which cannot be readily controlled or measured is the hydrostatic venous portal pressure which would probably remain fairly constant over a period of weeks and be affected little by alterations in ion or protein content of the blood.

Such an approach will complement studies on the permeability of membranes in infection (Title I), the importance of phospholipide turnover in the liver (Title II), the toxicity of P^{32} as related to diet (Title III), reflected in the ion exchange in the skeleton and rate of absorption from the intestine with alkalosic and acidosic diets.

PROGRESS TO DATE

During the past three years the proposed investigators have been carrying out a research program on the influence of lipotropic materials in the treatment of liver diseases. This study has correlated clinical findings, tests of liver function, the histologic appearance of the liver as determined by needle biopsy and the rate of phospholipide turnover using P^{32} as an indicator.

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The results to date have been fruitful and have demonstrated a distinct and accurate correlation of the findings with the histologic picture of the liver and indicate in which instances the administration of lipotropic factors are of value. These findings have been of use as an immediate guide to therapy and for an estimate of the ultimate prognosis.

The presence of ascites has been found to be of distinct prognostic importance. If, and when, the factors influencing the development of ascites in such patients can be determined a more definitive general plan of treatment should be available.

PROPOSED PLAN OF THE EXPERIMENT

The degree of the pathologic process and extent of anatomic change will be determined by physical examination by at least two competent observers, and liver aspiration biopsies. The extent of physiologic defect will be determined by liver function tests such as bromsulfalein retention, hippuric acid excretion, prothrombin time, estimation of total serum proteins, albumin and globulin fractions, cephalin flocculation, thymol turbidity and alkaline phosphatase. In addition, routine study of the blood including determination of hemoglobin content, red and white cell counts, differential counts, and urinalysis will be performed.

Volume and turnover of sodium-24 and potassium-42 will be studied by the injection of not more than two microcuries of Na^{24} per kilogram of body weight (not to be repeated within three weeks) and determination of radioactivity and total sodium content. The radiosodium dilution and "radiosodium space" will be calculated from blood, ascitic, and pleural fluid as well as excretion by urine samples. Membrane permeability and protein studies will be done utilizing the turnover of iodine (I^{131}) labeled human serum albumin (Abbott), by the intravenous injection of human serum containing 20 to 30 microcuries of I^{131}, and the results used to calculate the role of protein in the origin of altered membrane permeability and fluid extravasation. This is to be done approximately one week after radiosodium studies. Samples of blood serum and fluid will be taken at 15 and 30 minute, one hour, 3, 5, 8, 12, and 24 hour intervals to establish a curve for the turnover studies. Radioactivity and total protein content as well as albumin and globulin will be determined. From this it may be possible to determine the value of proteins in altering osmotic pressure and the rate of diffusion and metabolism. Plasma volume and ascitic fluid may also be calculated.

FACILITIES AVAILABLE

Monitoring and counting equipment is already available in the present laboratories. Certain equipment for chemical procedures is available.

Hospitalization of patients will be made available by the Bowman Gray School of Medicine and the North Carolina Baptist Hospital.

111224b

PERSONNEL AVAILABLE:

Dr. David Cayer and Dr. W. Eugene Cornatzer as project leaders are known to the Commission.

A house officer can be made available part time.

NEEDS FOR 1951-1952

1. Personnel: A full time technician who has not yet been selected will be needed.

2. Equipment: Because of the nature of the study a Coleman Spectrophotometer will be necessary.

3. Supplies: Glassware, chemicals, radioactive sodium, potassium, and I^{131} albumin and globulin. It is intended wherever possible to share the shipments of K^{42} and I^{131} with the work being carried out under Title I. However, the volume of patients may exceed the present estimates and increase requirements in this category, especially for Na^{24} which Title I is already sharing for other studies.

David Cayer

David Cayer, M.D.

W. E. Cornatzer

W. E. Cornatzer, Ph.D.

2. PROPOSED BUDGET - July 1, 1951 to June 30, 1952

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

(1) Salaries of Project Leaders.
Part time salary for house officer

(2) Laboratory space, secretarial help and other services.

b. The Commission is requested to furnish:

(1) Personnel

Full time technical help	$2400.00	
Electronic engineer, part time, maintenance of equipment	250.00	
		$2,650.00

(2) Equipment

Coleman Junior Spectrophotometer	500.00	
		500.00

(3) Supplies

Geiger tubes and parts.....	200.00	
Radio Na and K, air transportation, 12 shipments at $50.00	600.00	
I^{131} albumin and globulin, 30 shipments at $10.00	300.00	
Glassware	500.00	
Chemicals and solvents	500.00	
		2,100.00

(4) Photography, illustrations, slides 100.00

(5) Travel 250.00

TOTAL ..... $ 5,600.00

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