649 R+W file

OPTIONAL FORM NO. 10
5010-104

UNITED STATES GOVERNMENT

Memorandum

707845

TO : R. G. Humphries, Director
Contract Division

DATE: AUG 17 1965

FROM : Herman M. Roth, Director
Research and Development Division

SUBJECT: REQUEST FOR CONTRACT ACTION

ORS:JDB

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

1. Nature of Action Requested:

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

☒ Modification of Contract
Number: **AT-(40-1)-2459**
Contractor: **Medical College of Virginia**
Richmond, Virginia

2. Nature of Services to be Covered by Contract: Research

Title: **"The Effect of Radiation on Transplantation Immunity"**

3. Type of Contract: ☒ Lump Sum ☐ Cost-Type ☐ Other

4. Amount to be Obligated by this Contract Action: **$45,391.00**

5. Description of Other Changes to be Covered by Contract Action:

Modify contract to provide for the performance of additional research to be completed during the period October 1, 1965 through September 30, 1966. The AEC will contribute $45,391 in new funds to the project. ORB

6. Authority:

Form AEC-481 (Contract Authorization) from G. L. Dunham to S. R. Sapirie dated August 16, 1965.

Herman M. Roth

Herman M. Roth

REPOSITORY Oak Ridge Operations Records Holding Area
COLLECTION Documents 1943-1994
BOX No. H-75-4 Bldg. 2714-H
No. 2 Cont. 2459
FOLDER Med. College of Virginia

ORS Burham 8/17/65

U 5370

CONTRACTS-2459(VA)

1039009

APPENDIX "A"

For the Period October 1, 1965 through September 30, 1966.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue to conduct research on the effect of radiation on transplantation immunity utilizing long term irradiation of circulating blood cells, lymph nodes, bone marrow, and other organs, by means of implants, or shunts, containing Yttrium 90 or Strontium 90. These studies will be extended to include combinations of internal blood irradiation and other immunosuppressent agents. Cross circulation studies will be carried out between two animals receiving continuous internal irradiation. Pending the working out of dosage and general effects in dogs, blood irradiation using an external, portable, continuous, radioactive shunt will be employed in man during periods of threatened rejection of renal homografts and for treatment of lymphatic leukemia. Internal irradiation with or without concomitant external irradiation will be used in animals which are rejecting renal homografts in an effort to determine whether threatened rejection can be reversed once it is established.

A-II APPROXIMATE LEVEL OF RESEARCH EFFORT

(a) Contractor Personnel:

	Approx. % of time
Dr. D. M. Hume, Principal Investigator	25%
3 Research Associates	21%
Research Assistant	60%
Laboratory Specialist	100%
4 Laboratory Technicians	71%
Laboratory Aide	75%
Animal Caretaker	50%

(b) Premises, Facilities, and Materials to be Furnished by the Contractor:

Surgical operating rooms for humans and animals are available in addition to Tissue Culture, Hematology and Chemical Laboratories. All the necessary facilities and equipment are available to conduct research on the effect of radiation on transplantation immunity. Available facilities include X-ray equipment and 1000 KVP machine.

A-III ITEMS OF EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR COSTING $500 OR MORE — Estimated Cost

None

Form AEC-481
(1-64)

AECPR 9-4.51

U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE: AUG 13 1965

2. AUTHORIZATION NO. BM-65-74

3.A. TO S. R. Sapirie, Manager
Oak Ridge Operations Office

3.B. FROM C. L. Dunham, M.D., Director
Division of Biology and Medicine

4.A. CONTRACTOR (*Name, Address, Department, etc.*)
MEDICAL COLLEGE OF VIRGINIA
Richmond, Virginia

4.B. PRINCIPAL INVESTIGATOR (S)
DAVID M. HUME, M.D.

5. ☐ NEW CONTRACT ☒ RENEWAL ☐ OTHER

6. TERM OF CONTRACT: 10-1-65 thru 9-30-66

7. CONTRACT NUMBER: AT(40-1)2459

8. RECOMMENDED TYPE OF CONTRACT:
☒ FIXED PRICE
☐ COST REIMBURSEMENT
☐

9. PROPERTY TITLE TO VEST IN:
☐ AEC ☒ CONTRACTOR
☐ CONTRACTOR UNDER AUTHORITY OF PUBLIC LAW 85-934. *This has been determined to be in furtherance of the objectives of the Atomic Energy Commission.*

10. SECURITY CLASSIFICATION:
Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE: THE EFFECT OF RADIATION ON TRANSPLANTATION IMMUNITY

12. HEADQUARTERS TECHNICAL CONTACT
William R. Bibb

13. FINANCING (*New AEC Funds, Not To Exceed Amounts Indicated*):

A. OPERATING EXPENSES ..... $ 45,391
Budget and Reporting Classification: 06 03
Allotment Transfer: 06-61-91(24)

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

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

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

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

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

15. SCOPE OF WORK

Studies on the immunology of whole organ transplants and the effect of irradiation on these grafts.

F-7991
CONTRACTS-2459(VA)

1039011

AUG 13 1965

David M. Hume, M.D.
Department of Surgery
Medical College of Virginia
1200 East Broad Street
Richmond 19, Virginia

Dear Dr. Hume:

I am pleased to inform you that Atomic Energy Commission contribution toward support of your project, "The Effect of Radiation on Transplantation Immunity," has been approved.

The negotiation of the contract, including financial detail, will be handled by our Oak Ridge Operations Office, and you may expect to hear from a representative of that office shortly. Responsibility for the technical and scientific administration will, of course, remain with the Division of Biology and Medicine in Washington.

We wish you every success in your work.

Sincerely yours,

William R. Bibb
Medical Research Branch
Division of Biology and Medicine

cc: Oak Ridge Operations Office ✓

1039012

II EXPENDITURE STATEMENT

A. Cost of project to date.

1. Expenditures on A.E.C. Grant thus far 10/1/64 to 6/30/65

Personnel

G. Robertshaw	$ 1,380.60	
L. Venable	1,384.73	
F. Winckler	505.06	
M. Greene	2,484.00	
E. Borum	3,760.00	
E. Brown	497.82	
J. Dwyer	4,000.00	
P. Fens	1,502.56	
C. Beneke	512.72	
S. Aikens	948.42	
V. Cornett	1,666.64	
L. Garnett	628.81	
M. Gazayerli	500.00	
	$ 19,771.36	$ 19,771.36
Social Security 3.625%		716.71
Overhead - 22%		4,349.70
		$ 24,837.77
Supplies and Equipment		2,340.71
Reprints and Publications		10.00
Animals and Care		8,563.98
Travel		000.00
TOTAL EXPENSES A.E.C.		$ 35,752.46
Renewal of Grant 10/1/64		43,884.38
		35,752.46
BALANCE 6/30/65		$ 8,131.92

2. Institutional Contribution, expenses

Salaries

Dr. Hume, 35%	$ 8,250.00	
Dr. Kauffman, 50%	4,875.00	
Dr. Lee, 50%	6,563.00	
Dr. Cleveland, 50%	3,300.00	
Dr. Wolf, 75%	4,781.00	
Dr. Dalton, 40%	2,520.00	
Dr. Slapak, 25%	1,500.00	
Dr. Graham, 25%	600.00	
R. Davis, 50%	1,476.00	
R. Tinsley, 75%	2,025.00	
P. Sadler, 10%	353.00	
P. Fens, 100%*	2,114.00	
	$ 38,357.00	$ 38,357.00
Social Security 3.625%		1,391.00
		$ 39,748.00
Overhead - 22%		8,745.00
		$ 48,493.00

* $1,502.56--this portion of yearly salary paid by A.E.C.

1039013

2. Institutional Contribution, expenses (continued)

Maintenance of Research Facilities	$ 9,000.00
TOTAL EXPENDITURES, INSTITUTION	$ 57,493.00
TOTAL EXPENSES, A.E.C. 6/30/65	35,752.46
GRAND TOTAL - A.E.C. AND INSTITUTION	$ 93,245.46

B. List of Anticipated Expenses--Estimate of the Costs for the remainder of the contract period.

1. Anticipated expenses on A.E.C. Grant 7/1/65 to 9/30/65

Personnel

E. Borum	$ 1,470.00	
J. Dwyer	1,500.00	
M. Greene	828.00	
G. Robertshaw	666.00	
F. Winckler	155.93	
	$ 4,619.93	$ 4,619.93
Social Security 3.625%		167.47
Overhead - 22%		1,016.39
		$ 5,803.79
Supplies and Equipment		$ 000.00
Reprints and Publications		140.00
Animals and Care		1,388.13
Travel		800.00
TOTAL ANTICIPATED EXPENSES A.E.C.		$ 8,131.92

2. Anticipated expenses of Institution Contribution 7/1/65 to 9/30/65

Salaries

Dr. Hume	$ 2,750.00	
Dr. Kauffman	1,625.00	
Dr. Lee	2,182.00	
Dr. Cleveland	1,100.00	
Dr. Wolf	1,594.00	
Dr. Dalton	880.00	
Dr. Slapak	500.00	
R. Davis	492.00	
R. Tinsley	450.00	
P. Sadler	117.00	
P. Fens	704.00	
	$ 12,394.00	$ 12,394.00
Social Security 3.625%		449.00
		$ 12,843.00
Overhead - 22%		2,825.00
		$ 15,668.00
Maintenance of Research Facilities		3,000.00
TOTAL ANTICIPATED EXPENSES INSTITUTIONAL		$ 18,668.00
TOTAL ANTICIPATED EXPENSES A.E.C.		8,131.92
GRAND TOTAL - A.E.C. AND INSTITUTION		$ 26,799.92

C. Estimate of funds available during remaining period of project.

1. A.E.C. = $ 8,131.92

2. Institution = $ 18,668.00

III RENEWAL PROPOSAL

Contract AT-(40-1)-2459

Atomic Energy Commission Renewal Request July 1, 1965

1. Title of Project: EFFECT OF RADIATION ON TRANSPLANTATION IMMUNITY.

2. Institution: Department of Surgery, Medical College of Virginia Richmond, Virginia.

3. Project abstract.

   A. Blood or local irradiation and canine renal homografts.

      1. Strontium^{90}.

      2. Yttrium^{90} plus Imuran.

      3. Yttrium^{90} plus Actinomycin C.

      4. 100 r Local Graft Radiation plus Actinomycin C or D.

      5. Neck and Pelvis Transplants--local graft radiation to 1 of 2 transplants.

   B. Delayed irradiation in treatment of rejecting renal homografts.

      1. Yttrium^{90} Implantation on Day 3 or 4.

      2. 1500 r on Day 3 plus Serial Biopsies of Renal Transplants.

      3. 100 r Local Graft Radiation plus 1500 r on Day 3.

   C. Second set transplants after treatment of first transplant.

      1. Radiation to carotid artery vs. Yttrium^{90}.

      2. Azathioprine treatment.

   D. Prevention and treatment of secondary disease with rabbit anti-rat lymphocyte antiserum.

   E. Strontium^{90} radiation of blood circulating in teflon-silastic arterial-venous shunts in the human.

      1. Renal transplant rejection in the human.

      2. Acute lymphatic leukemia.

1039016

4 & 5. Scientific background and scope of project. (See also Progress Report).

A. Blood irradiation and concomitant canine renal homografts.

1. Strontium^{90} treatment of renal homografts. As is outlined in the progress report, significant prolongation of renal homograft survival has been achieved with the beta emittor Yttrium^{90} which has a physical half-life of 64 hours. Yttrium^{90} induces a profound lymphopenia but because of its short physical half-life the lymphopenia is temporary. Strontium^{90}, with a long half-life, will be used instead of Yttrium^{90} in an attempt to produce a sustained lymphopenia and to test the effect of this state on renal homograft survival.

2. Yttrium^{90} plus Imuran. Because Imuran is the most useful drug in clinical transplantation today and because of its proven success in canine renal transplantation, it is planned to perform a series of canine renal homotransplants in which small doses (2-3 mgms/kgm.) of Imuran are used in combination with Yttrium^{90} implantation. Imuran use in this dose range will not consistently prolong renal homograft survival. When Imuran is used in sufficient dosage to prolong homograft survival, adverse side effects are frequently seen. It is hoped to achieve additive effects in immunosuppression without having additive adverse effects.

3. Yttrium^{90} plus Actinomycin C. Intermittent doses of Actinomycin C will be used in conjunction with Yttrium^{90} implants because it has been demonstrated that Actinomycin C is one of two drugs which can reverse renal homograft rejection. Furthermore, Actinomycin has been shown to be a readiation sensitizer. Dogs with Yttrium^{90} implants will be given Actinomycin C in a dose of 15 micrograms/kgm. on alternate days. These results will be compared with the results of Actinomycin C alone and with Yttrium^{90} alone.

1039017

4. 100 r local graft radiation plus Actionmycin C or D.

This experiment is to be performed for 4 reasons:

1.) Since it has been demonstrated that 100 r X 6 local graft radiation does not significantly prolong renal homograft survival, while 150 r X 6 does, 100 r X 6 local graft radiation is an appealing experimental model for demonstrating additive effects of combination therapy. Since 100 r X 6 has no adverse hematological or generalized immunosuppresive effects, it can be used with other modalities of therapy without fear of encountering hematological or other side effects.

2.) The actinomycins have been described as radiation potentiators and this experiment should determine whether or not Actinomycin C or D can potentiate the effect of local graft radiation in prolonging graft survival.

3.) Most transplant work to date has involved the use of Actinomycin C rather than Actinomycin D. The literature has many reports on the radiation potentiating effects of Actinomycin D as compared with Actinomycin C on tumor cells. These experiments should allow a direct comparison of C vs. D in regard to radiation potentiating effects as applied to prolongation of homograft survival.

4.) Actinomycin C has been described as one of two drugs which can reverse established renal homograft rejection. This has not been described for Actinomycin D and therefore under these circumstances the effects of the drugs in preventing and/or reversing rejection can be evaluated.

5. Neck and pelvis transplants. The experiments in which local graft radiation is administered to 1 of 2 transplants from the same donor will be continued. These experiments are currently under way, and it is anticipated that definitive data will be obtained during the remainder of the current year. However if the experiments are not completed during

1039018

this period of time the work will be continued into the next grant year.

B. Delayed irradiation in treatment of rejecting renal homografts.

1. Yttrium^{90} implantation on day 3. It has been previously shown that when the first dose of 150 r local graft radiation is administered on days 2, 3 or 4 there is no significant prolongation of functional survival of renal homografts. However Zukowski has shown that significant prolongation of renal homografts can be achieved by starting the administration of either 6-mercaptopurine, azathioprine, or 6-methylmercaptopurine on days 1, 2 or 3 post-transplantation. This demonstrates at least one definite difference in the mechanism of action of 6-MP and its derivatives as compared to local graft radiation in prolonging kidney homograft survival. In an attempt to get further information on the mechanism by which Yttrium^{90} prolongs homograft survival, it is planned to implant Yttrium^{90} on post-transplant day 3 or 4 while the homograft is rejecting. If Yttrium^{90} is able to prolong graft survival when implanted on day 3 or 4 it is logical to combine Yttrium^{90} with local graft radiation to see whether the combination of these two modalities of radiation would have an additive effect on homograft survival. Histological and functional data indicate by the 3rd or 4th post-transplant day the rejection process is usually well established, and therefore any treatment which is instituted at this period of time must have an effect either on the central immune mechanism or on the efferent arc of the immune response.

2. 1500 r on day 3 plus serial biopsies of renal transplants. Technical difficulties encountered with this experiment have been enumerated in the progress report. However it is planned in spite of somewhat discouraging results at present to continue this experiment until a definitive number of animals can be achieved in an attempt to see if a single dose of 1500 r can be significantly reverse rejection in

1039019

animals who are receiving no other treatment. This experiment is, as previuosly mentioned, being performed in an attempt to ascertain if local graft radiation has any effect on the efferent arc of the immune response to canine homografts. Two consecutive 1000 r doses will also be tried.

3. 100 r local graft radiation plus 1500 r on day 3. If the experiments listed above of 100 r X 6 plus Actinomycin C and/or D prove to be a useful experimental model for demonstrating additive effects of treatment, it is planned to perform a series of transplants in which animals will receive 100 r every other day x 6 doses plus 1500 r on day 3. This will be done to demonstrate whether or not a large dose of radiation can reverse rejection after it has been established, and whether or not local graft radiation has an effect on the efferent arc of the immune mechanism.

C. Second set transplant after treatment of first transplant.

It is planned to perform a series of second-set renal homographs in animals receiving either radiation to the carotid artery neck pedicle or Yttrium^{90} implants with the first-set kidney. These experiments will be performed in an attempt to ascertain whether radiation of the arterial inflow to the renal homograft or intra-arterial radiation effects the afferent arc of the immune response. Since the animal will receive no treatment with second-set graft, any prolongation of survival must be presumed to be due to inhibition of the afferent arc of the immune response as a consequence of the treatment given during the primary graft.

2. Azathioprine treatment of second-set kidneys. In an attempt to ascertain whether or not azathioprine can abolish established homograft immunity first-set renal homografts will be placed and will receive no treatment. Following removal of the first-set graft the appropriate rest period will be allowed. Second-set grafts will be placed and animals will be given high doses of azathioprine in an attempt to overcome the established transplant immunity.

1039020

D. Prevention and treatment of secondary disease with rabbit anti-rat lymphocyte antiserum.

This represents work that currently is in progress as outlined in the Progress Report. From the data acquired thus far, it is apparent that a large number of experiments will have to be performed in order to establish the presence or absence of a beneficial effect of RARL treated bone marrow on the incidence of secondary disease. We are currently performing such experiments using 850 r total body radiation plus cell doses in the range of 50×10^6 cells. Because of the high 30 day mortality previously observed in animals receiving RARL treated bone marrow grafts, it may be necessary to alter other variables of the experiment in the future. Such variables include the number of doses of RARL administered before using the marrow for grafting, the number of cells transplanted, the dose of radiation, and whether the bone marrow cells are used alone or in combination with spleen cell grafts. As spleen cell transplants generally result in a higher incidence of secondary disease, it may be desirable to repeat the experiments using spleen cell grafts in place of or in combination with the bone marrow transplants.

E. $Strontium^{90}$ radiation of blood circulating in teflon-silastic arterio-venous shunts in the human.

Next month we plan to begin cautious clinical trails of $Strontium^{90}$ sources placed in arterio-venous shunts in 2 clinical situations. The first of these is during threatened renal homograft rejection, the second is for acute lymphatic leukemia.

1. Renal transplant rejection in the human. Most of our human kidney transplant patients have functioning teflon-silastic arterio-venous shunts for purposes of hemodialysis prior to the time of transplantation. These shunts will be left in place. At times of threatened graft rejection $Strontium^{90}$ will be added to the shunts for purposes of radiating circula-

1039021

ting blood. The remainder of the patients' immunosuppressive therapy will not be altered, and it will be ascertained whether this modality of therapy will reverse threatened rejection. We have been working with Dr. O'Foghludha in the Department of Radiation Physics in the construction of the Strontium^{90} shunts and on ways of shielding the patients from the beta emissions. Dr. O'Foghluda will continue to work with us in this project on technical details, calculation of dose, and in radiation protection of both the patient and of the nursing personnel on the transplant unit.

2. Acute lymphatic leukemia. Using the same technic of Strontium^{90} arterio-venous shunt radiation, treatment of selected cases of acute lymphatic leukemia will be performed in collaboration with members of the Department of Hematology and Pediatrics. Treatment will at first only be used for cases which are refractory to other more standard means of therapy. Routine hematological evaluation and patient care will be performed by the Division of Pediatric Hematology, and calibration of dose and radiation protection will be under the supervision of Dr. O'Foghludha.

1039022

6. Scientific personnel.

Principal Investigator: David M. Hume, M.D., Professor of Surgery and Chairmand of the Department. Publications given with original application and subsequent progress reports. Time 25%.

Co-Principal Investigator: H. Myron Kauffman, Jr., M.D., Assistant Professor of Surgery. Time 30%.

Other Staff Investigators: H. M. Lee, M.D., Assistant Professor of Surgery, 30%; Richard J. Cleveland, M.D., Instructor of Surgery, 30%; James S. Wolf, M.D., Research Fellow in Surgery, 90%; Dr. F. O'Foghludha, Radiation Physicist, 3%.

Newly Appointed Personnel: G. Melville, Williams, M.D., Assistant Professor of Surgery, 50%. Dr. Williams has been in Australia the past year working on transplantation antigens with Drs. Nossal and Burnett. J. Dickinson McGavic, M.D., Research Fellow in Surgery, 50%; Humphrey J.O. White, M.D., Research Fellow in Surgery, 90%., M. Gazayerli, Research Fellow in Surgery, 90%.

7. Other Personnel.

Research Associate-		J. Dwyer	-- 60%
Lab Spec. B.	--	E. Borum	--100%
Lab. Tech. A.	--	L. Venable	--100%
Lab. Tech. B.	--	M. Green	-- 100%
Lab. Tech. B.	--	G. Robertshaw	- 65%
		(undergraduate student)	
Radiation Assistant	--		20%

1039023

8. Other Finicial Assitance.

No other financial assistance is received for any of the personnel proposed to be paid from A.E.C. funds except J. Dwyer, who will receive $4,000 per year from other sources (The N.I.H. Institutional Grant). The professional personnel are all paid completely from Institutional sources or as instructors or trainees on a departmental Training Grant in Transplantation.

9. Premises, facilities, equipment, and materials to be furnished by the contractor.

Fully equipped animal operating rooms, laboratories, isotope counting equipment, machine shop, animal x-ray (diagnostic and treatment) and animal care facilities covering approximately 40,000 square feet are available for the study. A Clinical Transplant Center is in operation in the hospital. No major items of equipment are needed to carry out the study.

1039024

10. Proposed budget for 10-1-65 to 9-30-66

A.E.C. Contribution

Personnel	% Time		
Research Assistant, J. Dwyer	60%	$ 6,000.00	
Lab. Spec. B, E. Borum	100%	5,880.00	
Lab. Tech. B, G. Robertshaw	65%	2,400.00	
Lab. Tech. A, L. Venable	100%	3,456.00	
Lab. Tech. B, M. Green	100%	3,456.00	
Lab. Tech. A, (Radiation Asst.)	20%	720.00	
		$21,912.00	$ 21,912.00
Social Security 3.625%			794.00
			$ 22,706.00
Overhead - 22%			4,995.00
			$ 27,701.00

Supplies and Equipment

Glassware, etc.	$ 750.00	
Reagents, Drugs	1,200.00	
Yttrium Activation (20)	2,000.00	
Shunt Material for Sr^{90} (20)	1,800.00	
Maintenance and Repair	200.00	
Office Supplies and Photography	200.00	
Telephone and Telegraph	50.00	
Pathology (150 slikes @ $1/slide)	150.00	
	$ 6,350.00	$ 6,350.00

Reprints and Publications	$ 200.00

Animals and Care

Operating Expense	$ 4,260.00	
Dog Purchase 200 @ $10/dog	2,000.00	
Dog Care 200 @ .60/dog x 30 days	3,600.00	
Rats 250 @ 1.20 ea.	300.00	
Rats @ .03/day x 30 days	180.00	
	$ 10,340.00	$ 10,340.00

Travel	$ 800.00
TOTAL A.E.C. REQUEST	45,391.00

11. Amount Requested

A. Institutional Contribution *

Salaries

Dr. Hume, 25%	$ 8,000.00	
Dr. Kauffman, 30%	4,785.00	
Dr. Lee, 30%	5,700.00	
Dr. O'Foghludha, 3%	630.00	
R. Davis - Animal caretaker, 50%	1,968.00	
R. Tinsley - Lab aide, 75%	2,475.00	
	$ 23,558.00	
Social Security 3.625%	854.00	
Overhead - 22%	5,183.00	
	$ 29,595.00	$ 29,595.00
Maintenance of research facilities	$ 12,000.00	$ 12,000.00
Animal procurement, care, and Processing	$ 10,000.00	$ 10,000.00
		$ 51,595.00

B. Other non-Univeristy sponsors *

Salaries

Dr. Williams, 50%	$ 7,150.00 (NIH)	
Dr. McGavic, 50%	3,500.00 (NIH)	
Dr. White, 90%	7,650.00 (NIH)	
Dr. Cleveland, 30%	3,345.00 (NIH)	
Dr. Wolf, 90%	7,650.00 (NIH)	
Dr. Gazayerli, 90%	7,650.00 (NIH)	
	$ 36,945.00	$ 36,945.00

C. TOTAL INSTITUTIONAL AND NON-AEC CONTRIBUTION	$ 88,540.00
TOTAL AEC REQUEST	$ 45,391.00
GRAND TOTAL AEC PLUS OTHER	$133,931.00

* Cost of clinical transplant unit not included. This amounts to about $300,000 per year.

12. Authentication.

Signed for the Medical College of Virginia:

Principal Investigator: _____

David M. Hume, M. D.

Comptroller: L. Daniel Crooks

Mr. L. Daniel Crooks

IV SIE Summaries

1039028

R. & D. Files

OPTIONAL FORM NO. 10
5010-104

UNITED STATES GOVERNMENT

Memorandum

TO : C. L. Dunham, Director
Division of Biology & Medicine, HQ

DATE: June 30, 1965

FROM : Herman M. Roth, Director
Research and Development Division, OR

SUBJECT: RENEWAL OF CONTRACT NO. AT-(40-1)- 2459 - MEDICAL COLLEGE OF VIRGINIA (DR. DAVID M. HUME)

ORS:JDB

We are submitting for your review and appropriate action the following information concerning the contract which will expire on September 30, 1965.

1. Renewal Proposal (4) 1, 2, and 3 incorporated
2. Progress Report (4) into one document
3. Financial Statement (4)
4. 200-Word Summary (3) - 2 each
5. Reprints & Preprints - Listed Below (4)

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

Herman M Roth
Herman M. Roth

Enclosure:
As Listed Above

Preprints

1. "Comparison of Antibody Response to Sheep Erythrocytes and Response to Skin Homografts in Rats Receiving Appropriate Antiserum".
2. "The Variation of Glomerular Filtration Rate After Renal Homotransplantation in the Human and the Dog as Measured by the Blood Clearance of Co^{57} Vit. B_{12}".
3. "Studies of Transplant Immunity in Animals with Lymphocytopenia Induced by Indwelling Beta Irradiation".
4. "Prolongation of Renal Homograft Survival by Inhibition of the Afferent Arc of the Immune Response".

Reprints

1. "Serum and Urinary Lactic Dehydrogenase in Patients with Renal Homotransplants".
2. "Prolongation of Renal Homograft Function by Local Graft Radiation".
3. "Preservation of the Cadaver Kidney for Renal Homotransplantation in Man".
4. "A New Method of Estimating Glomerular-Filtration Rate".
5. "Significance of Lymphocyturia in Renal Homograft Rejection".

DRS Bussey 6-30-65

U 4295

(See Attachment)

CONTRACTS-2459 (VA)

1039029

CONTRACT NO. AT-(40-1)-2459
MEDICAL COLLEGE OF VIRGINIA

ATTACHMENT

Reprints (Cont'd)

6. "Studies of Renal Homotransplantation in Man".

7. "Selective Immunosuppression by Local Radiation of Renal Homografts".

bc: C. S. Shoup w/encl.
D. S. Zachry w/progress report
Alice Brown

MEDICAL COLLEGE OF VIRGINIA
1200 EAST BROAD STREET
RICHMOND 19, VIRGINIA

DAVID M. HUME, M.D.
STUART MCGUIRE PROFESSOR
AND CHAIRMAN, DEPARTMENT OF SURGERY

June 25, 1965

United States Atomic Energy Commission
Research and Development Division
Post Office Box E
Oak Ridge, Tennessee 37831

Gentlemen:

Enclosed are a progress report, expenditure statement, renewal proposal, SIE summary and 10% voucher for A.E.C. Grant AT-(40-1)-2459.

There are no reportable incidents during the past nine months.

We would like to take this opportunity to thank you for the contract support during this past year, and to express the hope that the support will continue during the coming year.

Very sincerely yours,

David M. Hume

David M. Hume, M. D.

DMH:nm

ok nk Enclosures

1039031

JUN 28 1965

CONTRACTS- 2459(VA)

NOTICE OF RESEARCH PROJECT
SCIENCE INFORMATION EXCHANGE
SMITHSONIAN INSTITUTION

PUBLICATION BY AEC HEREBY AUTHORIZED

PROJECT NO. (Do not use this space)

Division of Biology and Medicine

SUPPORTING AGENCY: UNITED STATES ATOMIC ENERGY COMMISSION

NAME AND ADDRESS OF INSTITUTION: Please state also the Division, Department, or Professional School (medical, graduate, or other) with which this project should be identified:

Department of Surgery, Medical College of Virginia, Richmond, Virginia.

TITLE OF PROJECT

Effect of radiation on transplantation immunity.

Give names, department, and official titles of PRINCIPAL INVESTIGATORS and OTHER PROFESSIONAL SCIENTIFIC PERSONNEL (not including graduate students) engaged on the project, and fraction of man-year devoted to the project by each person.

David M. Hume, M.D., Professor of Surgery, and Chairman of Department, H. Myron Kauffman, Jr., M.D., Asst. Prof. Surgery, H.M. Lee, M.D., Asst. Prof. Surg., Richard J. Cleveland, M.D., Inst. Surg., G. Melville Williams, M.D., Asst. Prof. Surg., J. Dickinson McGavic, M.D., H.J.O. White, M.D., M. Gazayerli, M.D., James S. Wolf, M.D., Research Fellows in Surgery.

How many graduate students on project? 3 How many graduate student man-years?

SUMMARY OF PROPOSED WORK - (200 - 300 words. Omit confidential data.) Summaries are exchanged with government and private agencies supporting research, are supplied to investigators upon request, and may be published in AEC documents. Please make your summary SUBSTANTIVE, giving initially and for each annual revision the following: OBJECTIVE; scientific BACKGROUND or REASON for study; proposed PROCEDURE; TEST OBJECTS and AGENTS; and RESULTS TO DATE if any.

Internal irradiation of circulating blood.

The objective of this study is to determine the effect upon circulating blood cells, lymph nodes, bone marrow, and other organs, of continuous long-term internal irradiation of circulating blood with implants or shunts containing Yttrium^{90} or Strontium^{90}. It has already been demonstrated that profound lymphopenia can be produced by this technic and that prolongation of renal homografts can be achieved in the animal rendered lymphopenic by internal blood radiation. These studies will be extended in combinations of internal blood irradiation and other immunosuppressent agents will be tested. Cross circulation will be carried out between two animals receiving continuous internal irradiation. When the dosage and general effects have been well worked out in the dog, blood irradiation using an external, portable, continuous, radioactive shunt will be employed in man during periods of threatened rejection of renal homografts and for the treatmetn of lymphatic leukemia. Internal irradiation with or without comcomitant external irradiation will be given to animals who are rejecting renal homografts in an effort to see whether threatened rejection can be reversed once it is established.

For Period:

	Program Category Number
Budget	
Primary	
Secondary	

Signature of Principal Investigator _____ Date _____

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1039032

NOTICE OF RESEARCH PROJECT
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How many graduate students on project? 3 How many graduate student man-years? 3

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The prevention and treatment of secondary disease in irradiated rats given bone marrow and lymphatic homografts.

After total body irradiation and the administration of homologous bone marrow of lymphocytes secondary disease develops in a high percentage of animals and leads to their death. This is presumed to be due to the immunological capabilities and activities of the grafted cells. Control irradiated grafted animals will be compared with: 1) irradiated animals grafted from animals previously treated with heterologous antilymphocyte serum, or 2) animals who following the graft are themselves treated with antilymphocyte serum. If the antilymphocyte serum is capable of preventing secondary disease this will stimulate renewed interest in a study of bone marrow and lymphatic grafts after total body irradiation and in the induction of tolerance by lymphocytes in newborn animals.

For Period:

	Program Category Number
Budget	
Primary	
Secondary	

Signature of Principal Investigator: David M. Hume Date: 6/24/65

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1039033

NOTICE OF RESEARCH PROJECT

SCIENCE INFORMATION EXCHANGE
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PROJECT NO. (Do not use this space)

SUPPORTING AGENCY: Division of Biology and Medicine
UNITED STATES ATOMIC ENERGY COMMISSION

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How many graduate students on project? 3 How many graduate student man-years?

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Second-set transplants after radiation treatment during the first-set transplant.

Kidney homografts will be performed in dogs. The animal will be treated with intermittent or continuous radiation of the blood and the primary transplant will be left in until rejected or will be removed after a period of two weeks. Second set renal homotransplants from the original donor will then be put into the recipients. The function and histological changes in the second-set grafts will then be followed to determine whether the animal has been immunized by the first graft or not. If the treatment of the first-set graft prevents immunization, then it must have done so by interference in some way with the afferent arc involving the pick-up or transport of antigen. If these effects are significant, subsequent experiments will be designed to investigate the mechanism in more detail.

For Period:

	Program Category Number
Budget	
Primary	
Secondary	

Signature of Principal Investigator: David M. Hume Date: 6/24/6

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1039034