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

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

Enclosed for your review and consideration is a letter from Dr. David M. Hume, dated December 10, 1971, concerning additional financial assistance under the above contract relative to the development of the extracorporeal irradiation bracelet under the project.

Please advise us in this matter at an early date.

ORIGINAL SIGNED BY
JAMES W. NEHLS

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

OLE:JDB

Enclosure: NFF
Ltr frm DMH dtd 12/10/71 (4)

REPOSITORY Oak Ridge Operations Records Holding area
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BOX No. H-75-4 Bldg. 2714-H No. 2 Cont 2459
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CONTRACTS-2459 (Va.)

OFFICE ▶	Adm. Ser. Br.	L&U Division				
SURNAME ▶	Burleson:oo	Nehls				
DATE ▶	12-10-71	12/15				

Form AEC-318 (Rev. 9-53)

U.S. GOVERNMENT PRINTING OFFICE : 1969— O-364-598

Virginia Commonwealth University

December 10, 1971

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

Dear Dr. Shoup:

I am writing you to thank you for having renewed our AEC contract for the upcoming year, and to ask for your suggestions about how we might finance the extracorporeal irradiation bracelet which we are extremely anxious to complete and test. I am enclosing copies of that part of our proposal which dealt with the bracelet, and the one proposed budget for this work.

As you remember, the company that had originally proposed to make the bracelets for us went out of business, and we were finally able to get the Atomchem Corportation to agree to carry out the isotope testing, the development of a prototype, and the modification of the prototype--including the supplying of three completed devices. The cost for this project, as you will notice, is $32,800.

Since we pioneered in this work in transplantation, we are most anxious to bring it to a state of clinical fruition. Another group in Sweden has followed our lead in this matter, and has published a paper recently which is very enthusiastic about the use of extracorporeal radiation in renal homotransplantation in patients. They used a device which, unlike ours, is not portable and can only be used when the patient is in the hospital, over a relatively short time span. With a portable model we should be able to use it for many weeks and accomplish a much greater degree of immunosuppression.

We would appreciate any suggestions you might have as how we could accomplish the financing of this venture, since we feel that it needs to be done, and we are the most logical group to do it.

Very sincerely yours,

David M. Hume

David M. Hume, M.D.

cc: Mr. Gene Pierce
Dr. Jim Wolf

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Medical College of Virginia • Health Sciences Center • Richmond, Virginia 23219

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E. Extra-Corporeal Blood Irradiation.

Further studies of beta irradiation of circulating blood will involve three areas: 1) development of a portable, disposable beta-emitting shunt, 2) pre-transplant blood irradiation of patients while on dialysis, and 3) continuous blood irradiation in patients with renal homografts.

A major aspect of the proposed project will involve a resumption of studies of blood irradiation using a disposable lightweight blood irradiation bracelet. These studies have been interrupted by the financial failure of the company which was to develop the prototype of the shunt on which we had finally settled after experimentation with many other types. The great advantage of this shunt is that the radioactivity would have a short half life, it would be from a beta source and easily shielded, it would be incorporated into the actual wall of the tubing to which the blood circulates and would thus not excape from the shunt if it were cut or broken, and it is lightweight and could be worn for many days without difficulty. With a transfer of the patents that regulate the process of incorporating the radioactive material in the wall of the tubing to a new and viable company and the receipt from this company of a proposal to make working madels of the shunt, we are now in a position to carry out the physical and biological testing of such a device.

The biological testing will be carried out both on pre-transplant and post-transplant patients. In the first instance we could study the effect of the shunt on immunological mechanisms and the absence of

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other immunosuppressive agents and in the absence of the graft antigens. Following the transplant, we could examine the body's response to the transplanted organ, and the combined effect of the blood irradiation and other immunosuppressive agents on immunological reactivity.

The studies which we contemplate doing on the patients involve the effect of blood irradiation on the bone marrow, the lymph nodes, the peripheral blood, and on the general immunological reactivity of the patient.

1. Bone Marrow Studies.

Bone marrow biopsies would be taken at weekly intervals while the patient was on blood irradiation. These would be examined for the effect of the irradiation on the percentage of the various cell types and the general histological appearance of the marrow.

2. Lymph Nodes.

Three types of studies would be done on the lymph nodes. The first of these would be to examine the general changes in the architecture of the lymph nodes brought about by blood irradiation, and specifically to determine whether the thymus derived lymphocyte population was reduced disproportionately in comparison to the bone marrow derived lymphocytes. The second study would be to determine the lymph node kinetics in response to a standard antigenic stimulus. The antigen would be injected into the patient's leg, and at the appropriate time interval, the patient would be given 50 microcuries per kilogram of 32P and the lymph node excised two hours later. The specific activities of the acid soluable precursor pool of phosphorus and DNA phosphorus in the lymph node would be determined. From these

data the hourly turnover fraction of DNA could be calculated, and one could assess the degree of responsiveness of the local lymph node to the peripheral antigen and compare it with the response of the non-irradiated patient. A third series of tests would involve placing the lymphocytes from the lymph nodes in mixed lymphocyte culture (MLC), with mitomycin treated lymphocytes with known HL-A antigens, from the prospective donor to see if the reactivity of the lymph node lymphocytes had been altered by the blood irradiation.

Peripheral blood studies would involve a measurement of lymphocytes, reticulocytes, platelets, and other blood elements to the blood irradiation itself, and a determination of the reactivity of the peripheral lymphocytes by the MLC techniques listed above for the lymph node.

The final series of studies of the blood irradiated patients would involve studies of the immunological response to standard antigens including tuberculin, dinitrochlorobezene (DNC), diphtheria toxoid, and typhoid-paratyphoid. The reactivity of non-irradiated recipients will be compared with that of irradiated recipients.

When these patients receive transplants, the blood irradiation will continue and all of the tests that were done in the pre-transplant period will then be repeated. It is planned to continue the blood irradiation for a period of a month after the transplant, and if the patient is doing well, it will be discontinued at this time. The disposable blood irradiation bracelets are essential to the study, since they are the only means by which the patient can be continuously radiated for a period of many weeks under ambulatory conditions, and

by means of which many patients can be studied since the multiple disposable bracelets will provide many radiation sources that can be used simultaneously in contrast to a single cobalt source where only one patient can be treated at a time.

F. Renin-Angiotensin Studies.

We are still committed to the ideas presented in the previous progress report. Of special benefit is the delineation of patients with end stage renal disease whose hypertension would be ameliorated by nephrectomy. Patients with high renin activity would be in this category. Several reports now have appeared concerning renal artery stenosis in transplant patients; relevant work-up of this problem includes studies of the renin-angiotensin system. Also, an extension of the concept of monitoring transplant rejection by plasma renin determinations would be that of erythropoeitin assay. Collaboration with other laboratories appears possible in this area. During the past year nothing has appeared in the literature to de-emphasize the importance and pertinence of our proposed studies. The advantages of isotopic usage in the context of radioimmunoassay are becoming more evident each year in an ever-widening range of applications. We are encouraged by our most recent progress to believe our radioimmunoassays will soon be fully operational and applicable to our particular studies.

G. Local Radiation Effects With Microbeam Technique.

As presented in the progress report, the techniques of local radiation with microbeam will be used to extend studies of local tissue effect to radiation as it applies specifically to kidney structures. The advantages of this approach have been outlined. Because of the

ATOMCHEM CORPORATION

516-433-5100 Nuclear Laboratory
Plainsboro, New Jersey

SEVEN FAIRCHILD COURT
PLAINVIEW, NEW YORK 11803

July 8, 1971

Outline of Projected Development Program
for ECI Bracelet for Medical College of Virginia

Phase I. Selection of Optimum Isotope

A brief period will be spent evaluating the characteristics of several isotopes available to determine the optimum source. The isotopes to be considered are probably limited to three, namely: P^{32}, Tm^{170}, and Kr^{85}.

Phase II. Development of Prototype Source

This phase will comprise a major part of the effort. Included will be development of isotope loading techniques, source matrix selection, source configuration optimization, and engineering design and fabrication of the external bracelet housing.

An inactive model of the prototype will be submitted for inspection followed by at least one active source for testing purposes.

Phase III. Modified Prototype

Based upon the recommendations of the customer, the ECI will be modified, if necessary, to better accomplish its purpose.

Modified devices will be fabricated and submitted for evaluation and testing until an optimum design is agreed upon.

At least three devices based upon the final design will be supplied for clinical use.

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Plainsboro, New Jersey

SEVEN FAIRCHILD COURT
PLAINVIEW, NEW YORK 11803

July 9, 1971

Cost Estimate for Medical College of Virginia ECI Bracelet Development.

Direct Labor	Man Hours	Approx. Hourly Rate	Total
Project Director	300	$9.00	$2700
Engineer	500	$7.00	$3500
(2) Technician @ 500 each	1000	$4.60	$4600
Secreterial Support			300
	Total Direct Labor		$11,100
	Overhead @ 65%		7,200
	Material		5,000
	Travel		500
			$23,800
	G & A @ 20%		4,750
			$28,550
	Profit @ 15%		4,250
	Total Cost		$32,800

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