

Office Memorandum • UNITED STATES GOVERNMENT

TO : C. L. Dunham, Director
Division of Biology and Medicine, Headquarters

DATE: December 12, 1962

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

SUBJECT: RENEWAL OF CONTRACT NO. AT-(40-1)-1001 - UNIVERSITY OF MISSISSIPPI
MEDICAL CENTER (DR. MORRIS T. HARVIN)*

OK: JJA

We are submitting for your review and appropriate action the following information concerning the contract which will expire on **January 31, 1963**:

1. Renewal Proposal (4)
2. Progress Report (4) / 1 ONE DOCUMENT
3. Financial Statement (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

*Dr. Harvin will be on sabbatical leave from February 1, 1963 through December 1963. Dr. T. M. Gable has been selected by the Medical Center to direct the project during the absence of Dr. Harvin. A curriculum vitae for Dr. Gable is contained in the Medical Center's proposal dated November 30, 1960. Please advise whether you concur in the appointment of Dr. Gable as Acting Senior Investigator under contract no. AT-(40-1)-2681.

ECs: C. S. Shoup, w/encl.
D. E. Zachry, w/ progress report
Alice Brown ✓

UNITED STATES GOVERNMENT

Memorandum

TO : Herman M. Roth, Director
Research and Development Division, CRO

DATE: February 11, 1963

FROM : C. L. Dunham, M.D., Director
Division of Biology and Medicine, Headquarters

S. Allan Foy
Acting Director

SUBJECT: CONTRACT AT(49-2)-2681 TO DR. H. MARVIN, UNIVERSITY OF
ARKANSAS, LITTLE ROCK, ARKANSAS

BMD:FWL

In view of the fact that the above mentioned contract has been funded for what is to be its terminal year, consideration must be made of the title to the Whole Body Counting Facility that was constructed during the first year of this contract.

It is the position of the Division of Biology and Medicine that the contractor's contribution has been of sufficient magnitude to justify the transfer of title of this equipment from the Atomic Energy Commission to the University of Arkansas. The Oak Ridge Operations Office is hereby instructed to implement this transfer.

ATTACHMENT "A"

Modify contract to provide for the performance of additional research to be completed during the period February 1, 1963 through January 31, 1964. The AEC will support the project in the amount of \$13,853 in new funds. Designate Dr. T. H. Oddie as Co-Senior Investigator. Transfer title to the Government-owned whole body scintillation counter and associated equipment under Contract No. AT (40-1) 2691 to the Contractor. The equipment consisting of the following items is presently in the possession of the Contractor:

- Steel Room
- RCLiac 128 Channel Analyzer
- Power Supply
- Detector Crystal Assembly
- Visual and Auditory Control
- Control Panel
- Crystal Assembly Support
- Air Conditioning Unit
- Oscilloscope
- Pulse Generator
- Chair
- Specialized Replacement Parts and Tubes
- Small Liquid Scintillator

APPENDIX "A"

For the Contract Period February 1, 1963 through January 31, 1964.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue to conduct research on whole body determinations of radioisotope burdens in humans and animals. This work will include utilization of whole-body counting techniques to (1) survey the isotope burden of normal children and adults and of pregnant women before and after delivery, (2) study turnover of Iodine-131 in human patients under various conditions, (3) study of the Iodine-131 level in the thyroid tissue of the general population, (4) determine erythrocyte survival of Chromium-51 labeled red blood cells, (5) study calcium turnover in normal humans and in patients with osseous disease using Calcium-47, (6) study of the effect of various hormones on the Ca-47 turnover in mice, and (7) study of manganese homeostasis in parakeets using Manganese-54.

A-II APPROXIMATE LEVEL OF RESEARCH EFFORT

	<u>Approx. % of time</u>
(a) <u>Contractor Personnel:</u>	
Dr. H. N. Marvin - Co-Principal Investigator	25%
Dr. T. H. Oddie - Co-Principal Investigator	25%
Research Technician	50%
Secretary-Technician	100%
(b) <u>Premises, Facilities, and Materials to be Furnished by the Contractor:</u>	

Adequate laboratory space and facilities necessary to conduct research on whole body determinations of radioisotope burdens in humans and in animals will be available to the project. Equipment available includes scintillation counters to accommodate (1) the entire human being and (2) small animals. The scintillation facility consists of a steel room, 128 channel analyzer, power supply, detector crystal assembly, visual and auditory control, oscilloscope, pulse generator, small liquid scintillator and other items including the ones listed in A-III below.

<u>A-III EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR</u>	<u>Estimated Cost</u>
1. Typewriter, Power Supply and Conversion	\$2,200.00
2. Scintillation Crystal, Shield, Collimator and Conversion	4,000.00

RESEARCH PROPOSAL FOR 1963

A. Work on human beings with large crystal

1. A survey of the isotope burden of people

(Staff)

This survey on normal children and adults, pregnant women before and after delivery, and on their new-born children will be continued and expanded. This survey has been retarded because of a lack of proper facilities and personnel. Request is being made herein for a new scaler-analyzer and print-out mechanism so that data can be processed directly by an electronic computer. This computer center has been under development here for some time and is now coming to fruition. Computer service is now available under direction of a professional in this field at the Medical Center. Preliminary tests of the utility of this service have shown that with proper data format, this service will greatly expedite the calculations which have been prohibitively time consuming to date.

2. Studies on turn-over of I-131 in patients under various conditions

(Dr. Oddie)

To eliminate some of the difficulties we have found, we propose to install a smaller, say 3" diameter X 3" thick crystal, shielded at the sides with lead and collimated at the front with a short conical collimator. This shield would eliminate much of the radiation from I-131 in other parts of the patient. A flat field conical collimator gives satisfactory results for I-131 uptakes and is not subject to the large positioning errors characteristic of other crystal arrangements. The Argonne chair would be abandoned for these particular studies in favor of a low couch with the patient lying supine and the crystal pointing vertically downwards at the thyroid

PURPOSE BUDGET

For Contract Period 1 February 1963 through 31 January 1964

I. Approximate Level of Research Effort

A.

<u>Personnel</u>	<u>% of Time (in Project)</u>	<u>U. of A.M.C. Contribution</u>	<u>A.M.C. Funds Requested</u>
1. Dr. H. N. Marvin Principal Investigator	25%	\$ 4,500	
2. Dr. T. H. Oddie Coinvestigator	25%	\$ 3,786	
3. To be named Research Associate	100%		\$ 8,000
4. Charles Rogers Research Technician	50%		\$ 2,400
5. Mrs. Sylvia Holder Secretary-Technician	100%		\$ 3,600
	TOTALS - - - -	\$ 8,286	\$ 14,000
B. Consumable Supplies			\$ 1,000
C. Travel			\$ 700
D. Equipment			
1. For continuation program			
400 Channel Analyzer			\$ 9,650
IBM Typewriter Printout			\$ 900
Driver-Coupling Power for above			\$ 750
2. For proposed I-131 neckscanning			
3 x 3" crystal, shield, and collimator			
Part of Research Associate's (vide supra)			
time diverted to this purpose if approved			\$ 4,000
E. Other Items			
Electronic Maintenance			\$ 400
F. Indirect Costs		\$ 1,483	\$ 2,506
	TOTALS - - - -	\$ 9,769	\$ 33,906

II. Institutional Facilities Available
Described in detail in previous proposals

Horace N. Marvin

gland. A focussing or distance measuring device would be needed to place the crystal at an exact and reproducible distance from the skin.

It is proposed to investigate first the necessary corrections for precise measurements in patients of various sizes and then to carry out a pilot series of I-131 uptakes to prove that the method agrees with the standard methods for I-131 uptakes. Serial counting will also be used for thyroid discharge experiments.

3. Levels of I-131 in thyroids of general population

(Dr. Oddie and Dr. Marvin)

Of particular note is the use of this smaller crystal for determining the I-131 content of the thyroids of children and adults on a continuing basis. This application, which has been discussed with interested parties, will serve as a constant check on accumulation of this isotope arising from fall-out after nuclear testing. This would make this medical center one check point in a system monitoring this particular aspect of radiological health.

4. Erythrocyte survival determinations with the whole body counter

(Dr. Marvin)

Efforts will be made to continue and extend the study of red cell survival by the whole body counter. The preliminary results summarized in the progress report are encouraging and merit extending the procedure to autologous Cr-51 tagging of infants and adults. Injecting tagged cells back into the individual from whom they are obtained avoids the danger of transfusion reactions which are not predictable by serological cross-matching techniques. There is ample experimental evidence to support the reality of this factor

as a potential hazard.

The procedure will be carried as before, namely withdrawal of 10 ml of blood, tagging the cells with Cr-51 according to customary procedures, and reinjecting the tagged cells into the donor. A whole body count will be made before the test to establish the individual person's background count, a count immediately after reinjecting the tagged cells, then counts made at intervals thereafter. Blood counts of 50,000 will be made concurrently.

The time at which the blood is zero will be correlated with the sharp change in slope of a semilog plot of whole body counts which is known to occur.

A procedure which avoids the use of high levels of isotopes, and does not necessitate repeated blood samples is mandatory for use in infants. It is felt that perfection of this technique would result in such a method.

5. Calcium turnover in normal persons and patients with osseous disease

(Dr. Sanders and Dr. Marvin)

The availability of gamma emitting Ca-47 makes possible a study of calcium metabolism in patients with demineralization of the osseous system of unknown etiology. Preliminary data on excretion rate of Ca-47 in the normal and prednisolone-treated adult justifies a study of this in others.

Normals and patients with selected osteolytic disease will be given 10 μ c Ca-47 intravenously and the biological decay curve followed with the whole body counter. Departures from normal values will be determined, as well as changes in turnover related to treatment prescribed for each patient. These results will in turn be related to studies carried out on experimental animals as described under that division.

6. Continuation of study on iron absorption in anemic infants

(Dr. Hughes and Dr. Porter)

The results obtained using a 5 μ c dose have been summarized in the progress report. Further efforts will be directed toward determining the minimal amount of radioactivity which can be successfully used for a valid study of absorption. In addition, attempts will be made to study the rate of loss of absorbed iron, and relate this to the clinical status of the patient.

B. Animal work with liquid scintillating counter

1. Studies of the effect of various hormones on the Ca-47 turnover in mice

(Dr. Suzuki and Dr. Marvin)

Mice are unusually adapted to studies of calcium metabolism of bone formation because of their capacity for medullary bone formation under estrogen influence. Male and female mice, both estrogen-pretreated and controls, will be given Ca-47 intravenously and the estrogen treatment continued. The biologic decay of the calcium will be followed by whole body counting until turnover is complete, or physical decay terminates the experiment.

By selecting appropriate timing of estrogen administration and discontinuance, the effects of bone formation and resorption, respectively, on the calcium decay curve can be determined.

Doctor Suzuki is well known for his work in this area, and has developed a method of tibial transplantation. Using this technique it will be possible to remove the transplanted tibia and determine its Ca-47 content after it has been subjected to selected hormonal treatment in the presence of Ca-47. Hormones such as thyroxine, androgen, and of course estrogen have been shown to affect mouse bone growth.

2. Studies on manganese homeostasis in parakeets

(Dr. Hughes)

In contrast to rats, parakeets seem to have no homeostatic mechanism as far as manganese is concerned. This unusual physiologic mechanism will be studied by administering Mn-54 with carrier in the diet. Once an equilibrium is established, stable manganese will be given at various levels to determine if Mn-54 loss is accelerated and if there is a relation between intake of manganese and the rate of loss of Mn-54.

Signed

Horace N. Marvin
Horace N. Marvin, Ph.D.
Principal Investigator

Date - November 15, 1962

PROGRESS REPORT

This report covers the period from November 1, 1961 to October 31, 1962 and is divided into two parts:

A. Work on human beings with large crystal

1. Potassium-40 and cesium-137 contents of prenatal women and of mother and child immediately post-natally

(Dr. Marvin and Dr. Panos)

Some data have been collected for this project, but too little for analysis and summary. The feasibility of the project, however, has been established and the study will be continued.

2. Alimentary absorption of iron-59 by anemia infants

(Dr. Hughes and Dr. Porter)

The patients selected were: seven with sickle cell disease, one with sickle-C disease, and one with acute acquired hemolytic anemia. All patients were studied first by the following procedures: routine blood work, serum iron determinations, latent serum iron binding capacities, bone marrow aspirations, and liver biopsies. The patients were given a total of 5 μ c Fe-59 and 1 mg carrier iron per kilogram body weight orally in orange juice on an empty stomach. An immediate whole body count was made, daily counts for 8 days, and semiweekly counts for 3 weeks. All counts were corrected for intrinsic pretreatment counts in the selected channels. Each post-treatment count was calculated as per cent of initial count, the latter corrected for physical decay.

The Fe-59 declined rapidly for the first 2-4 days and then the body counts stabilized. The level at which stabilization occurred was considered to

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be due to the iron absorbed. This value ranged from 1.8% to 44.0%, and could not be correlated with: hemoglobin concentration, reticulocyte percentage, serum iron concentration, latent serum binding capacity, or stainable liver iron.

Two conclusions can be drawn from the data, although the data are yet too meager for publication. One is that 0.5 μ c or less of Fe-59 can be used for such absorption tests. The other is that the post-absorption iron loss can be determined effectively.

3. Whole body counting of patients receiving I-131

(Dr. Oddie)

Preliminary trials have been run to test the feasibility of counting patients who have received I-131 in the whole-body counter. Interesting results should be obtained with repeated counts to find the release rate from the thyroid gland. This rate may change following I-131 therapy or during medication with thyroid-affecting drugs.

Experiments made to date have been done with the patients sitting in the Argonne chair using the large 8" unshielded crystal with the thyroid unshielded, and then covered by a lead plate 3/4" thick.

Difficulties have been encountered with this method of measurement for the following reasons:

- (1) Counting rates are too high with the large crystal when studying patients soon after relatively large doses of I-131.
- (2) It is difficult to be sure that all of the thyroid gland is shielded under the lead plate, because the chair geometry varies with patient size in an irregular manner.
- (3) With the present arrangement, radiation from the thyroid gland enters the crystal more or less diagonally.

In spite of these difficulties, it is considered that suitable methods can be developed for low level counting of I-131 in patients of varying sizes.

4. Influence of prednisolone on release of Ca-47 from the body

Studies have been carried out on the effect of an adrenal steroid, prednisolone on calcium excretion. Ten adult volunteers each received 10 μ c of Ca-47 Cl_2 intravenously and a count was made immediately. Subsequent counts were made on alternate days for twenty days. On the seventh day, five of the subjects received 20 mg of the steroid three times a day for six consecutive days.

Each count was corrected for the pretreatment counts of the subject, and then calculated as per cent of the initial count. The initial count was in turn corrected for physical decay.

Beginning on the third day of steroid treatment, the treated group lost calcium at a slightly greater rate than the controls. The difference in calcium content established during the period of treatment was maintained after the cessation of treatment. On day twenty, the treated group had 34.8% and the controls 37.3% of the initial calcium. On day 43 both groups had less than 6% of the initial levels.

5. Use of whole body counter in determining erythrocyte survival time

(Dr. Marvin, Dr. Zapata, and Dr. Panos)

For this study twelve infants were available as donors, and these donors had been on a variety of home diets which were suspected of inducing anemia. Blood was drawn from each, tagged with Cr-51 and given intravenously to hematologically compatible, adult recipients. The Cr-51 levels were determined both by whole body counts, and by well type scintillator with blood sample. Determinations with whole body counter were carried out for 3 weeks after the blood levels were zero. Levels in both methods were referred

to the initial value as 100%. When whole body counts were plotted on semi-log paper, a sharp change in the slope of the curve occurred at the same time the blood sample counts reached zero levels.

It would seem that this technique may be used for red cell survivals, and would be particularly useful in infants. In such individuals it is difficult to obtain repeated blood samples for the usual technique, and the low levels of isotope activity possible with the whole body counter would be desirable.

B. Work on animals with the small liquid scintillator

1. Erythrocyte survival and sequestration in normal and splenectomized rats and in normal pigeons

(Dr. Marvin)

This project has been completed and the data is being processed for publication. Briefly, Cr-51 tagged blood was reinjected autologously into the animals mentioned in the title. Cr-51 reduced prior to use for tagging was also used to determine the fate of untagged chromium. Survival curves determined on 0.1 ml samples of blood, and whole body counts were made. Animals in groups of 5 were sacrificed at intervals during the course of the experiment, and the activities of spleen, kidney, liver, thymus and bone marrow were determined in a well type scintillator. The data show the time-related shift of tagged and untagged chromium from the blood to the various reticulo-endothelial organs.

2. Effect of thyroidal function on erythrocyte survival in rats

This study is complete and being prepared for publication. Neither surgical nor chemical thyroidectomy changed the survival time of erythrocytes

as determined on blood samples, nor altered whole body counts.

On the other hand, thyroxine injections inducing a hypermetabolic state, significantly shortened the maximal survival time, and increased the rate of loss of Cr-51 from the body. It is important to note that values at $T_{0.5}$ (a criterion used clinically) appeared to indicate a lengthening of survival time in thyroxine-treated animals. Yet when the curves were followed to extinction, the survival times of the thyroxine-treated rats were definitely shortened.

3. Biological turnover of Mn-54 in bird and mammal

(Dr. Hughes)

The administration of Mn-54 to parakeets results in tagging of liver microsomes as well as retention of the nuclide by other tissues. Transplantation of pituitary tumors into tagged parakeets results in an increased rate of whole body turnover of Mn-54, and loss of the isotope from liver microsomes.

Signed

Horace N. Marvin
Horace N. Marvin, Ph.D.
Principal Investigator

Date - November 15, 1962

INCIDENT REPORT

No incident of isotope contamination, loss or breakage occurred during the period from original application to present date.

Signed

Horace W. Marvin
Horace W. Marvin, Ph.D.
Principal Investigator

Date - November 1, 1962

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