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HARVARD UNIVERSITY
Dr. B. Hastings
Medical Research in Nuclear Physics
to June 30, 1949
NR 171 105

\$126,661.20

0013618

REQUEST BY THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE
TO THE OFFICE OF NAVAL RESEARCH FOR FUNDS IN SUPPORT OF MEDICAL RESEARCH
FOR THE PERIOD JUNE 1, 1948 TO MAY 31, 1950

Submitted for the Committee on Medical Research in Biophysics

by

Joseph C. Aub
Seymour J. Gray
A. Baird Hastings
A. K. Solomon
DeWitt Stetten, Jr.
Shields Warren

Present Navy Contract
N5ori-76, Task No. 7

December 19, 1947

0013619

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REQUEST BY THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE
TO THE OFFICE OF NAVAL RESEARCH FOR FUNDS IN SUPPORT OF MEDICAL RESEARCH

1. Introduction

On June 1, 1946, with the joint support of the Office of Naval Research and Harvard University, the Biophysical Laboratory was established. Since then, within the laboratory, and in the Departments of Biological Chemistry, the Tumor Diagnosis Clinic, and the Collis P. Huntington Memorial Hospital, there has developed an increasing amount of research on medical problems, studied by the utilization of isotopes. This present request for an extension of the grant from the Office of Naval Research for two additional years is supported by a review and summary of the work already accomplished. A report has already been submitted covering progress to July 1, 1947, which provides a complete list of projects underway and completed. This list extended and brought up to date is submitted as a separate status report. As this second year of the initial contract proceeds, it is reasonable to expect that many of the projects in that list will be completed, and new ones will be undertaken.

In general terms, the proposal for an extension can be summarized by quoting an extract from the present contract (N5ori-76, Project 7), as follows:

- (a) Research with isotopes on medical problems, development of techniques for the measurement of isotopic concentrations on

- biological material, training as required of other research groups and fellows or students in isotopic techniques, and advice and assistance of research groups with their problems;
- (b) research on enzyme action, quantitative histochemistry, and use of isotopes to study the metabolism of organic substances of mammalian tissues;
 - (c) investigations of radioactive isotopes for potential use as therapeutic and diagnostic agents, including applications to the treatment of malignancies of various types; and
 - (d) study, by means of suitable isotopes, of the metabolic activities of living systems, both as tissue cultures and in the intact animal.

It must be emphasized that the work already completed has provided the organization with considerable experience in training new personnel in the handling and use of isotopes. In addition to the normal training program at the University, a limited number of qualified Navy personnel could be accepted, should this be desirable, as students in the special research techniques developed. Acceptance of such students would be subject to their meeting the requirements of the Harvard Medical School and the faculty head of the project.

One aspect of training deserves special mention: advice and assistance is being rendered to other research groups who are anxious to become acquainted with these techniques. Problems involving the active cooperation

of the Biophysical Laboratory, for example, are now being pursued with:

Department of Chemistry
Harvard University

Department of Biology
Harvard University

Department of Surgery
Massachusetts General Hospital

Department of Neurosurgery
Massachusetts General Hospital

School of Dental Medicine
Harvard University

Department of Nutrition
School of Public Health
Harvard University

Department of Industrial Hygiene
School of Public Health
Harvard University

Furthermore, informal advice and assistance have been rendered to many of the hospitals in the Boston area, including other departments in the Massachusetts General Hospital, the Beth Israel Hospital, The Boston Lying-In Hospital, and the Boston City Hospital. Such cooperation is considered to be an integral part of the program and will continue to the extent that the facilities of the Biophysical Laboratory can provide.

Balance from Page 4

2.1.3 Overhead at provisional rate of 3.25%

Additional overhead of 6.75% now being determined

Grand total

2.2 The contract, in force from June 1, 1946 to May 31, 1948, was for a sum of \$173,160, distributed among the several cooperating projects as follows:

	1946 - 1947	1947 - 1948
Biophysical Laboratory		
A. Baird Hastings		
Shields Warren		
Joseph C. Aub		

2.3 The increase of \$53,610 in the amount requested for the two-year period (\$26,805 per year) is accounted for by the following items evaluated on a one-year basis:

(a) Increase in salary to non-senior personnel

- Biophysical Laboratory
- Assistants to A. Baird Hastings
- Assistants to Shields Warren
- Assistants to Joseph C. Aub

(b) University overhead increase

6,792

(c) Inclusion of salary items to reimburse the University for time spent by senior personnel

(d) During the tenure of the existing two-year contract, it was found necessary to increase the funds allocated to salaries of technical personnel. This transfer was made from funds originally allocated to supplies and not used during the first year of the contract. Specifically in the case of the Biophysical Laboratory, this reallocation of funds was approved by the Office of Naval Research and amounted to an increase in the allotment for salary for non-senior personnel of \$15,956 per year. This increase in funds for technical assistance over that projected in the original estimate has proved essential for the adequate prosecution of the work.

In the present request for renewal of contract, it is requested that this existing allocation of funds for technical personnel be continued. The present scale of work can thereby be maintained.

It should be noted that this does not constitute an expansion of the existing program of work, but only its maintenance at its present level. For example, again in the specific case of the Biophysical Laboratory, the budget attached as Exhibit A to the Progress Report for 1946-1947, shows a proposed expenditure of \$54,139.42 in 1947-1948 without overhead. This figure is to be compared with the present request in 2.1.1 for \$53,898 without overhead, for 1948-1949.

For these reasons, an increase in funds over the previous average for 1946-1948 in the following amount is requested:

Biophysical Laboratory	\$8,548	
Project of A. Baird Hastings	---	
Project of Shields Warren	3,282	
Project of Joseph C. Aub	<u>1,333</u>	
		\$13,163
Items (a), (b), (c) from Page 5		<u>13,642</u>
Total		\$26,805

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2.4 It is anticipated that a surplus will exist in the funds of the present contract at its expiration on May 30, 1943. An approximate estimate of the amount of this surplus can be provided a few months in advance of this date, should the Office of Naval Research so desire.

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3. Specific Proposal from Biophysical Laboratory, Harvard Medical School, Seymour J. Gray, DeWitt Stetten, Jr., A. K. Solomon

3.1 General

3.1.1 Field of research

Conduct research with isotopes on medical problems, develop techniques for the measurement of isotope concentrations on biological material, be available for training other research groups and fellows or students in isotopic techniques and advise and assist other research groups with their problems.

3.1.2 Previous work in the field of research

See Status Report.

3.1.3 Other research programs in laboratory

Studies on the mechanism of the formation of gastric hydrochloric acid; studies on the uptake of phosphorus by normal brain and by brain tumors.

3.2 Outline of Project

3.2.1 Object of research

Continuation of problems described in Status Report.

3.2.2 Procedure

Continuation of the development of techniques for the measurement of radioactive and stable isotopes, and the use of these techniques in the study of intermediary metabolism and other biological problems.

3.2.3 Expected duration

Request for two-year period. It is our hope to continue research in these and related subjects for at least ten years.

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3.2.4 Contractor's present facilities

A well-equipped laboratory for the separation and measurement of radioactive isotopes and the measurement of stable isotopes. Biological and chemical laboratories for the synthesis of tracer marked precursors and for their application to biochemical problems.

3.2.5 Additional facilities needed

None except as indicated in the budget below which covers the routine operation of the facilities at present available.

3.3 Personnel

3 Ph.D. assistants (one not named)	\$10,500
Senior technician	3,350
Secretary	2,200
4 Junior technicians	7,600
(Casual employees)	
Laboratory helper	700
Student assistants and summer help	3,600
Outside consultants	<u>1,000</u>
	\$28,950

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3.4 Budget Per Year

3.4.1 Salaries		\$28,950
3.4.2 Pensions (4% of total salaries)		1,158
3.4.3 Material expendable		
Isotopes	3,500	
Glassware and chemicals (general)	4,000	
Maintenance of electronic equipment	2,000	
Construction of electronic equipment	1,800	
Animals	1,000	
Tools	<u>300</u>	12,600
3.4.4 Capital equipment		
Counters and equipment for radio- autographs, etc.	3,000	
Capital equipment for chemical work as, for example: platinum ware, cen- trifuge, still, polarimeter, pH meter, absorption spectrophotometer, etc.	2,500	
Health protection equipment	<u>500</u>	6,000
3.4.5 Other expenses		
Animal care	1,000	
Health protection service	500	
Supplies, stationery, etc.	1,200	
Long distance telephone	300	
Postage and express	300	
Travel	1,000	
Insurance	390	
Repairs and alterations	<u>500</u>	5,190
3.4.6 Total proposed cost		\$53,898

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4. Specific Proposal from A. Baird Hastings, Department of Biological Chemistry, Harvard Medical School

4.1 General

4.1.1 Field of research

Conduct research on enzyme action, quantitative histo-chemistry, and use of isotopes to study the metabolism of organic substances in mammalian tissues.

4.1.2 Previous work by institution in field of research

See Status Report.

4.1.3 Other research programs in the department

Numerous research problems are being carried out in the Department of Biological Chemistry in the fields of (1) enzyme chemistry, (2) intermediary metabolism, and (3) quantitative histo-chemistry.

4.2 Outline of Project

4.2.1 Object of research

Continuation of problems in Status Report.

4.2.2 Procedure

Continuation of the use of biochemical and radiochemical methods in the study of intermediary metabolism.

4.2.3 Expected duration

Request funds for two-year period. It is our hope to continue research on these and related subjects for at least ten years.

4.2.4 Contractor's present facilities

Well-equipped biochemistry laboratory. Biophysical Laboratory's facilities at our disposal.

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4.2.5 Additional facilities needed

None beyond the usual facilities required to carry out research as detailed above.

4.3 Personnel

Organic chemist, Ph.D.	\$3,600
Research assistant	<u>3,000</u>
	<u>\$6,600</u>

4.4 Budget Per Year

4.4.1 Salaries	\$6,600
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4.4.2 Pensions (4% of total salaries)	264
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4.4.3 Material expendable

Glassware and chemicals	\$1,600	
Animals and care	<u>750</u>	
		2,350

4.4.4 Capital equipment

Special equipment for C 14 counting		500
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4.4.5 Other expenses

Travel	250	
Insurance	66	
Repairs and alterations	<u>250</u>	
		<u>566</u>

4.4.6 Total proposed cost		\$10,280
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5. Specific Proposal from Shields Warren, Laboratory of Pathology of the Harvard Cancer Commission, Harvard Medical School and N. E. Deaconess Hospital, Boston 15, Mass.

5.1 General

5.1.1 Field of research

Investigate radioactive isotopes for potential use as therapeutic and diagnostic agents.

5.1.2 Previous work in field of research

See Status Report.

5.1.3 Other research programs in the department

Numerous research problems are being carried out in the field of pathology with special reference to malignancies.

5.2 Outline of Project

5.2.1 Object of research

Continuation of problems in Status Report.

5.2.2 Procedure

Continuation of the uses of radiochemical and histological methods of study of the action of radioactive isotopes as therapeutic and diagnostic agents.

5.2.3 Expected duration

Request funds for two-year period. It is our hope to continue research on these and related subjects for at least ten years.

5.2.4 Contractor's present facilities

Well-equipped pathological laboratory.

5.2.5 Additional facilities needed

None beyond the usual facilities required to carry out research as detailed above.

5.3 Personnel

Research associate	\$4,000	
Research associate	2,400	
Technician	2,400	
Technician	<u>2,100</u>	
		<u>\$10,900</u>

5.4 Budget Per Year

5.4.1 Salaries		\$10,900
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5.4.2 Pensions (4% of total salaries)		436
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5.4.3 Material expendable

Chemical supplies	\$1,000	
Animals and animal supplies	<u>2,000</u>	
		3,000

5.4.4 Capital equipment

Counting equipment		500
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5.4.5 Other expense

Insurance	\$126	
Travel	400	
Office supplies, postage and express	<u>600</u>	
		<u>1,126</u>

5.4.6 Total proposed cost		\$15,962
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6. Specific Proposal from Joseph C. Aub, Medical Laboratories of the Collis P. Huntington Memorial Hospital, located at Massachusetts General Hospital, Boston 14, Mass.

6.1 General

6.1.1 Field of research

Study by means of suitable isotopes the metabolic activities of living systems, both as tissue cultures and slices and in the intact animal.

6.1.2 Previous work in field of research

See Status Report.

6.1.3 Other research programs in the department

Several projects are directed towards factors involved in growth of both normal and cancer tissue.

1. Endocrine effects on growth of normal tissues such as regenerating liver, and the antlers of deer. Their effects on tumor growth and metabolism particularly on breast and prostatic tumors.

2. Intracellular enzymes determined biochemically and cytochemically. Their changes as observed in the above tissues.

3. The influence of age, cirrhosis, irritation and other deviations on the regeneration of depleted liver.

6.2 Outline of Project

6.2.1 Object of research

Continuation of problems in Status Report.

6.2.2 Procedure

Continuation of the uses of biochemical and radiochemical

methods of the study of metabolic activities of living systems, both as tissue cultures and slices and in the intact animal.

6.2.3 Expected duration

Request funds for two-year period. It is our hope to continue research on these and related subjects for at least ten years.

6.2.4 Contractor's present facilities

Well-equipped laboratories for animal experimentation and for all the investigations now in progress.

6.3 Personnel

One assistant	\$4,500	
One assistant	4,000	
Two technicians	<u>4,000</u>	
		<u>\$12,500</u>

6.4 Budget Per Year

6.4.1 Salaries		\$12,500
6.4.2 Pensions (4% of total salaries)		500
6.4.3 Material expendable		
Chemical supplies, glassware, animals		700
6.4.4 Other expense		
Insurance		133
Travel		<u>200</u>
6.4.5 Total proposed cost		\$14,033

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7. Bibliography7.1 Project 7(a)

Solomon, A. K., "Protection Memorandum" distributed by Isotopes Branch, Atomic Energy Commission, AEC's circular B-2.

Solomon, A. K., "Determination of Soft Radiation Including Preparation of Samples," Symposium, American Chemical Society New York meeting, September, 1947; in press, to be published by the Office of Naval Research.

Solomon, A. K., Gould, R. G., and Anfinsen, C. B., "Energy of Beta Radiation from S^{35} and Cl^{34} ," Phys. Rev. 72, 1097, 1947.

Solomon, A. K. and Estes, H. D., "The Measurement of Radioactivity in Solution," Rev. Sci. Inst., in press for January, 1948.

7.2 Project 7(b)

Hastings, A. B., Anfinsen, C. B., Gould, R. G., Rosenberg, I. S., and Solomon, A. K., "In Vitro Observations on $C^{14}O_2$ Incorporation in Liver Glycogen," Federation of American Societies for Experimental Biology, Chicago, 1947.

Anfinsen, C. B., Beloff, A., Hastings, A. B., and Solomon, A. K., "The In Vitro Turnover of Dicarboxylic Amino Acids in Liver Slice Proteins," J. Biol. Chem., 168, 771, 1947.

Villee, C. A., Sinex, F. M., and Solomon, A. K., "In Vitro Utilization of Glucose by Rat Diaphragm Muscle;" to be presented at the Federation of American Societies for Experimental Biology, Atlantic City, 1948.

7.3 Project 7(c)

Warren, S., "Treatment of Leukemia and Allied Diseases with Radioactive Isotopes," presented at International Postgraduate Medical Assembly of S. W. Texas, San Antonio, January 28, 1947.

Warren, S., "Effects of Irradiation on Neoplastic Tissue with Emphasis on Tumor Sensitivity" presented at Philadelphia Roentgen Ray Society, Philadelphia, March 31, 1947.

Warren, S., "Radio Sensitivity of Tumors," presented at Rocky Mountain Cancer Conference, Denver, July 9, 1947.

Warren, S., "Health Physics," Symposium at Edgewood Arsenal, Maryland, August 14, 1947.

Cowing, R. F., "Photographic Effects of Various Radiations" presented at International Cancer Congress, St. Louis, September 6, 1947.

Warren, S., "Atomic Energy in Japan and in America," presented at the Medical and Dental Societies, St. Louis, November 24, 1947.

Dixon, F. J., "Distribution of P-32 in Incubated Eggs," submitted to Proceedings of the Society for Experimental Biology and Medicine for publication.

7.4 Project 7(d)

Frantz, I., Jr., Loftfield, R. B., and Miller, W. W., "Incorporation of C^{14} from Carboxyl-Labeled dl-alanine into the Proteins of Liver Slices," Science, 106, 544, 1947.

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