PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

F 57-58

NYO-149

1. Project Title: Medical Research 717668			2. Date: APRIL, 1956
3. Budget Activity No: 6120 - 6220 - 6310 - 6320	4. Budget Item No: Summary	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly & Special Reports
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York	9. Contract No: AT-30-2-GEN-16
10. Persons in Charge: L. E. Farr		11. Starting Date: Continuing	

SUMMARY

The integrated program of basic science and applied science of the Medical Department is given below in outline schema. This is a considered long range plan of effort. In any given year the emphasis will be in those portions of the program for which unusual capability exists in the staff at that time or for which most promising leads have been developed. Minor testing and exploratory studies not specifically mentioned are planned for all years to validate theoretical hypotheses or exploit instrumentation developments. Significant accomplishments will be shown in listed publications. Total manpower requirements will be those budgeted and planned for in the orderly expansion of the Medical Department to its final size now expected to be reached about fiscal 1959.

General Program

The application of short-lived radioactive isotopes to diagnosis, therapy and the study of biological effects of radiation of cellular and microsomal dimensions.

I. (6120) Basic Science - The biological effects of radiation of cellular and microsomal dimensions.

A. (6120 - 1) The production of radiation of desired character (Page 6000 - 5).

1. Neutron capture reaction to produce heavy particle radiation, i.e. Li^6, B^{10}, U^{235}.

2. Neutron capture reaction to produce beta particle radiation.

3. Selection and production of other suitable radioactive isotopes.

B. (6120 - 2) Control of radiation distribution in mammalian organisms (Page 6000 - 7).

1. Transport mechanisms, specific.

a. Chemical - protein, fat, carbohydrate, mineral, hormone.
b. Enzymological.
c. Physical - colloid: size and charge.
d. Immunological.
e. Other as regional application with local physiological control, i.e. ascites.

2. Transport mechanisms, non-specific.

a. Body compartment water.
b. Differential solubility - as lipid.

3. Radiological control, Dosimetry.

a. Half-life.
b. Decay scheme.
c. Energy of radiation and components.

REPOSITORY Brookhaven Nat'l Lab
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FOLDER

(See continuation sheet)

4001727

Project Title: Medical Research - Summary

17. Operating Costs	Estimated 1956	Estimated 1957	Estimated 1958
Total Cost	$1,535,000	$1,825,000	$2,210,000

18. Cost of Plant & Equipment Directly Required
(Shown here for information only)

	Estimated 1956	Estimated 1957	Estimated 1958
(A) Construction	---	---	---
(B) Equipment	35,000	85,000	220,000

19. Direct Man Power	Estimated 1956	Estimated 1957	Estimated 1958
No. of Man Years			
Scientists & Engineers	30.5	40.5	51.5
Technical	85.5	100.0	115.0
Administration & Service	15.0	17.0	20.0
Total	131.0 (2.0)	157.5 (2.0)	186.5 (2.0)

(Figures in parentheses represent additional scientific man-years contributed by unpaid guests)

20. Comments

REPOSITORY Brookhaven Nat'l Lab
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Summary: (continued)

C. (6120 - 3) Effects of radiation (Page 6000 - 13).

1. Effects on viability.

2. Effects on specific chemical and enzyme systems.

3. Effects compared with regional penetrating radiation.

II. Applied Science - Use in diagnosis and therapy.

A. (6310) Therapeusis of cancer (Page 6000 - 16).

1. Glioblastoma multiforme.

2. Hepatoma and hepatic metastases.

3. Other metastatic cancers.

B. (6320) Diagnostic implications (Page 6000 - 18).

1. Cardiovascular system.

2. Renal system.

3. Neurological systems.

4. Muscular and skeletal systems.

5. Gastro-intestinal systems.

6. Integument.

7. Endocrine system.

REPOSITORY Brookhaven Nat'l Lab
COLLECTION 74189 Med Dept. 1950-61
BOX No.
FOLDER

In 1952 the definitive plan for the ultimate staffing of the Medical Department was presented and approved in principle. Since that time additions to the staff have been made in fulfillment of that plan. In 1952 there were only four scientists on the Senior Staff. In 1955 by June 30 the Senior Staff had increased to 10 members. In 1956 this had increased further to 13. Planned additions during 1957 will raise the total Senior Staff to 17 and in 1958 it will reach the maximum number of 24. In 1952 the total staff was 19 men, in 1956 it was 30 men, in 1957 it will be 36 men increasing to the final number of 48 in 1958. The marked increase in the Senior Staff has resulted in development of the scientific program at a rapid rate. Unless additional facilities, equipment and technical assistance can now be provided the momentum achieved in the research program cannot be maintained. The new building expected to become available in 1958 will provide space adequate for the program but acquisition of instrumentation, devices and technical assistance cannot be delayed to that time without resulting in a serious loss of productive effort. The medical program as a whole has now stabilized to a degree that permits realistic estimates for capital equipment. Items previously delayed in purchase are now obviously and urgently required. Serious and careful consideration of each item and its usefulness in the program is required before requests are initiated.

One of the most promising aspects of the Brookhaven program in medicine is the participation in work at the Laboratory by scientists from universities and teaching hospitals. In 1952 eleven such medical scientists were in our collaborative program. In 1956 this figure had tripled to 31 and further rapid expansion of this program is anticipated. The increasing requests for appointment to this medical department both as regular staff members and as research collaborators indicates strongly that our program is filling a need of universities and teaching hospitals both for fully qualified individuals and for opportunities for research experience in the field of atomic medicine.

During the interim period from now until the new medical reactor is placed in operation, intensive researches are planned both on a clinical and experimental level using present reactor facilities. Since at least six months of intensive testing of the new reactor will be required when it comes into operation in 1958,

(See continuation sheet)

Summary: (continued)

it is necessary that all presently planned work be pushed at maximum speed that full advantage can be taken of the new device.

Likewise in 1958 during and immediately after the move of the Department from present quarters to the new building there will be a loss of productive research effort. It is our estimate that about January 1959 the ultimate stable program should be taking final form insofar as numbers of participants are concerned. It should be pointed out that no new program ventures are anticipated. All expansion is the result of growth of programs begun at the time the Medical Department commenced operations in 1949.

REPOSITORY Brookhaven Natl Lab
COLLECTION FM189 Med Dept 1950-61
BOX No.
FOLDER

4001730

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Radiation Effects on Biological Systems - Medical Research			2. Date: APRIL, 1956
3. Budget Activity No: 6120	4. Budget Item No: Summary	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly & Special Reports
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York	9. Contract No: AT-30-2-GEN-16
10. Persons in Charge: L. E. Farr		11. Starting Date: Continuing	

SUMMARY

Sub-Activity No.	Project Title	Page No.
6120 - 1	Production of Radiation of Desired Character	6000- 5
6120 - 2	Control of Radiation Distribution in Mammalian Organism	6000- 7
6120 - 3	Effects of Radiation	6000- 13

REPOSITORY Brookhaven Nat'l Lab
COLLECTION FM189 Med. Dept. 1950-61
BOX No.
FOLDER

Project Title: Medical Research 6120

17. Operating Costs	Estimated 1956	Estimated 1957	Estimated 1958
Total Cost	$ 175,000	$1,070,000 (1)	$1,305,000

(1) New distribution of Medical Research costs. It is believed that this more realistically reflects the current effort.

18. Cost of Plant & Equipment Directly Required
(Shown here for information only)

	Estimated 1956	Estimated 1957	Estimated 1958
(A) Construction	---	---	---
(B) Equipment	(See Medical Research Summary Sheet)		

19. Direct Man Power	Estimated 1956	Estimated 1957	Estimated 1958
No. of Man Years			
Scientists & Engineers	2.5	26.5	34.0
Technical	14.0	50.5	58.5
Administration & Service	2.5	8.5	10.5
Total	19.0 (2.0)	85.5 (2.0)	103.0(2.0)

(Figures in parentheses represent additional scientific man-years contributed by unpaid guests)

20. Comments

REPOSITORY Brookhaven Natl Lab
COLLECTION FM 189 Med. Dept. 1950-61
BOX No.
FOLDER

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Production of Radiation of Desired Character			2. Date: APRIL, 1956
3. Budget Activity No: 6120 - 1	4. Budget Item No:	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly & Special Reports
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York	9. Contract No: AT-30-2-GEN-16
10. Persons in Charge: L. E. Farr		11. Starting Date: Continuing	

12. Purpose and Need:

1. Neutron capture reaction to produce heavy particle radiation, i.e. utilization of Li^6, B^{10}, U^{235}.

Studies will be continuously engaged in to determine the range of particle distribution from source atom within mammalian tissue. These studies will include attenuation of thermal neutron flux with depth, utilization of epithermal neutrons to provide tissue thermalization and determination of relative biological effectiveness of particle radiation produced in comparison with a standard gamma ray exposure.

2. Neutron capture reaction to produce beta particle radiation.

Studies will be begun to determine effectiveness of neutron capture procedure for localized beta irradiation when suitable target elements are used. Selection will encompass the production of beta particles of varying energies to determine accuracy of range prediction in mammalian tissue. Criticality of cross section capture properties in relation to biological specificity will be investigated. Relative biological affectiveness of radiation produced will be compared with a standard gamma ray exposure.

3. Selection and production in usable state of other suitable radioactive isotopes.

Production of short lived radioactive isotopes preferably with alpha or beta emissions suitably purified for biological use will be carried out. Effects of radiation in localized sites will be compared when differing transport mechanisms are used. Resulting radiation effects will be compared with in situ heavy particle and beta particle radiation and same will be compared with standard gamma ray exposure to determine relative biological effectiveness.

REPRODUCTION COLLECTION
BOX No.
FOLDER

13. Related Projects:

See general statement of integrated Medical Department program.

14. Accomplishments - FY 1955:

Evidence for relationship between sodium (chloride) intake and human essential hypertension. Dahl, L. K. and Love, R. A., A.M.A. Arch. Int. Med. 94, 525-531 (Oct. 1954).

Metabolic effects of marked sodium restriction in hypertensive patients: changes in total exchangeable sodium and potassium. Dahl, L. K., Stall, B. G. and Cotzias, G. C. J. Clin. Invest. 33, 1397-1406 (Oct. 1954).

Renal tubular failure of shock and nephritis. Van Slyke, D. D., John Phillips Memorial Lecture, Amer. Coll. Physicians, Chicago, Apr. 7, 1954. Ann. Int. Med. 41, 709-738 (Oct. 1954).

Accuracy of a radiopotassium dilution (Stewart principle) method for the measurement of cardiac output. Conn, H. L., J. Appl. Physiol. 7, 542-548 (Mar. 1955).

(See continuation sheet)

4001133

14. Accomplishments - FY 1955: (continued)

Metabolic effects of marked sodium restriction in hypertensive patients. Skin electrolyte losses. Dahl, L. K., Stall, B. G. and Cotzias, G. C., J. Clin. Invest. 34, 462-470 (Mar. 1955).

15. Expected Results - FY 1956:

See Quarterly Progress Report - BNL 367 (S-27).

Dynamics of Production and Destruction of Formed Elements of the Blood Under Normal and Abnormal Conditions. (E. P. Cronkite and V. P. Bond with G. J. Jacobs, Naval Medical Research Institute, Bethesda, Md.) (Page 41).

THE USE OF RADIOACTIVELY LABELED COMPOUNDS IN STUDY OF METABOLIC INTER-RELATIONSHIPS OF HOST AND PARASITIC HELMINTHS. R. D. Stoner and L. V. Hankes. (Page 43).

THE ACCURACY OF A RADIOPOTASSIUM (STEWART PRINCIPLE) METHOD FOR THE MEASUREMENT OF CARDIAC OUTPUT. H. L. Conn, Jr. (Page 49).

See Quarterly Progress Report - BNL 375 (S-28).

"In Vitro" Incorporation of C^{14}-labeled Amino Acids by "Trichinella Spiralis" Larvae. (R. D. Stoner and L. V. Hankes) (Page 47-48).

CHARACTERIZATION OF A GLYCOPROTEIN IN THE URINE OF PATIENTS WITH PROTEINURIA. E. A. Popenoe. (Page 51).

THE EFFECTS OF SICKLING ON ION TRANSPORT. I. EFFECT OF SICKLING ON POTASSIUM TRANSPORT. D. C. Tosteson, E. Carlsen, and E. T. Dunham. (Page 55-56).

THE EFFECTS OF SICKLING ON ION TRANSPORT. II. THE EFFECT OF SICKLING ON SODIUM AND CESIUM TRANSPORT. D. C. Tosteson. (Page 56).

See Quarterly Progress Report - (In Press).

Calibration of the Slow Neutron Beam by Biological Means. (V. P. Bond, O. D. Easterday, E. E. Stickley, J. S. Robertson).

Medical Research Reactor Mock-up. (H. J. C. Kouts, [illegible]*, and G. A. Price*)

REPOSITORY Brookhaven Nat'l Lab
COLLECTION BNL Med. Dept. Rec'd
BOX No.
FOLDER

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* Reactor Physics Group, Nuclear Engineering Department, BNL

Isotopic Sources as X-ray Substitute. (J. S. Robertson).

THE EFFECTS OF TOTAL-BODY FAST NEUTRON IRRADIATION IN DOGS. V. P. Bond, R. E. Carter*, J. S. Robertson, P. H. Seymour*, and H. H. Hechter*.

Preliminary Uranium Toxicity in Mice. (O. D. Easterday and V. P. Bond)

Toxicological Investigation of Several Organometallic Dyes. (O. D. Easterday).

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* U. S. Naval Radiological Defense Laboratory, San Francisco, Calif.

16. Anticipated Problems - FY 1957 and FY 1958:

General activities in these fields will continue.

For discussion of overall trends, see Summary Statement for Medical Research Program.

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Control of Radiation Distribution in Mammalian Organism			2. Date: APRIL, 1956
3. Budget Activity No: 6120 - 2	4. Budget Item No:	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly & Special Reports
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York	9. Contract No: AT-30-2-GEN-16
10. Persons in Charge: L. E. Farr		11. Starting Date: Continuing	

12. Purpose and Need:

1. Transport mechanisms, specific

a. Chemical

To utilize specific chemical reactions or series of reactions to place radioactive isotopes in body systems such as malignancies it is necessary to know the various metabolic pathways, the primary sources and final end products of metabolism. This involves studies of chemical structure of proteins, lipids, and carbohydrates as well as all reactions in which these substances or their products participate and their relation to mineral metabolism. Further hormonal influences must be specifically understood. The effects or non-effects of radioactive materials entering these metabolic pathways must clearly be demonstrated.

Work is presently underway on protein structure, lipo-protein complexing, fat metabolism and carbohydrate metabolism using classical methods as well as suitable tracer procedures. Distribution of mineral elements is being studied and results suggest three main factors at this time—those elements whose distribution is determined solely by the element itself, i.e. sodium; elements whose distribution follows body water, i.e. [illegible] distribution may be conditioned by accompanying ion of opposite charge, i.e. manganese.

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BOX No.
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b. Enzymological

Control of rates of energy release in mammalian physiology is largely controlled by a complex system of enzymes. Disturbance in their function leads to varying degrees of disability. The full extent of enzyme control must be elucidated, the effects of radiation upon enzymes themselves as well as utilization of enzyme substrates for specific placing of radioactive materials within specific physiological systems.

Monoamine oxidases, acetylcholinesterase, lipases, and proteases are enzyme systems which have received especial attention.

c. Physical

The utilization of colloidal size and charge for physiological placement is receiving only secondary attention at this time in our program though fundamental theoretical considerations now being developed may lead to experimental testing of hypotheses in the future at an appropriate time.

d. Immunological

The effects of radiation on immune mechanisms have been intensively studied since 1949. The capacity of radiation to alter the immune response is of great physiological significance. The ultimate utilization of immune processes to localize radiation is a goal and work particularly with At^{211} is underway with this in mind.

e. Regional application with local physiological control

The rates of distribution out of a local region vary with different tissues. With suitable short lived radioactive elements of different half lives the events can accurately be assessed and in some instances make

(See continuation sheet)

12. Purpose and Need: (continued)

possible therapeutic applications as control of hydrothorax from malignancy with chlorine 38 wherein the radiological half life is less than the elements physiological half time in the local area. Various pilot studies are engaged in from time to time and any of promise are given more extensive study.

2. Transport mechanisms, non-specific

a. Body compartment water

Factors which govern distribution of body water between cellular and extracellular spaces are under study. The attempts made are to characterize the system so that for each organ the predominant phenomenon can be ascertained. In some instances water changes are accompanied by actual shift of water across cell membranes, in others compensation is effected by solute transfer. Specific transfer mechanisms are under study for both organic and inorganic substances. Hormonal factors must also be given attention. Radiation in large amounts disturbs normal water distribution.

b. Differential solubility

Localization of radiation by differential solubility has potential diagnostic and treatment significance. Best example to date is our study of labeled anesthetic agents as xenon and chloroform which are liposoluble. Rates of accumulation and differential distribution may give insight into mechanisms of action.

3. Radiological control, Dosimetry

a. Half-life

The exploration of radioactive isotopes of the same element but with differing half lives provides a means of single system study not now generally employed. This appears to have fruitful possibilities and cooperation of Hot Laboratory Operation and Reactor Operations will be sought together with Accelerator Department in obtaining suitable elements for study. One of the primary tests will be substantiation of dosimetric calculations in biological systems.

b. Decay Scheme

The exploration of usefulness of complex decay schemes for utilizing specialized physiological placement is under careful study. Proper experimental models have not yet been evolved but as these are developed experimental activity will increase.

c. Energy of radiation and its components

Precise knowledge of the energy of each component of radiation is necessary for proper dosimetry. Instrumentation to analyze, measure and supplant biological dosimetry will be under constant development with appropriate collaborators as well as within the Department.

REPOSITORY
COLLECTION
BOX No.
FOLDER

13. Related Projects:

See general statement of integrated Medical Department program.

14. Accomplishments - FY 1955:

Effects of cortisone on thyroid function in white leghorn cockerels. Shellabarger, C. J. Endocrinol. 55, 100-104 (July 1954).

Mammalian conversion of C^{14} carboxy-labeled 3-hydroxyanthranilic acid into N^1-methylnicotinamide. Hankes, L. V. and Urivetsky, M. Arch. Biochem. and Biophys. 52, 484-485 (Oct. 1954).

Effect of ionizing radiation on immunity. Hale, W. M. and Stoner, R. D. Rad. Resch. 1, 459-469 (Oct. 1954).

(See continuation sheet)

14. Accomplishments - FY 1955: (continued)

Pulmonary vascular effects of moderate and severe hypoxia in the dog. Stroud, R. C. and Conn, H. L. Am. J. Physiol. 179, 119-122 (Oct. 1954).

Studies on the thyroidal uptake of astatine in the rat. Shellabarger, C. J. and Godwin, J. T. J. Clin. Endo. and Metab. 14, 1149-1160 (Oct. 1954).

The effects of adrenocorticotrophic hormone and cortisone upon acquired immunity to trichinosis in mice. Stoner, R. D. and Godwin, J. T. Am. J. Path. 30, 913-918 (Sept.-Oct. 1954).

Physics and physiology of neutron capture therapy. Farr, L. E., Robertson, J. S. and Stickley, E. Proc. Nat. Acad. Sci. 40, 1087-1093 (Nov. 1954).

The wet carbon combustion and some of its applications. Van Slyke, D. D., Fisher Award Lecture, Am. Chem. Soc., Los Angeles, Calif., Mar. 18, 1953. Anal. Chem. 26, 1706-1712 (Nov. 1954).

Effects of thyroxine and KSCN on capacity of rat thyroid gland to accumulate astatine-211. Shellabarger, C. J., Durbin, P. W., Parrott, M. W. and Hamilton, J. G. Proc. Soc. Exp. Biol. Med. 87, 626-629 (Dec. 1954).

Chemistry of the proteins, peptides, and amino acids. Hughes, W. L. and Sinex, F. M. Ann. Rev. Biochem. 23, 177-214 (1954).

An electric heater for the Van Slyke-Folch carbon combustion apparatus. Hankes, L. V. Anal. Chem. 27, 166-167 (Jan. 1955)

Determination of total carbon and its radioactivity. II. Reduction of required voltage and other modifications. Sinex, F. M., Plazin, J., Clareus, D., Bernstein, W., Van Slyke, D. D. and Chase, R. J. Biol. Chem. 213, 673-680 (April 1955).

— The kinetics of potassium transfer in the left ventricle of the intact dog. Conn, H. L. and Robertson, J. S. Am. J. Physiol. 181, 319-324 (May 1955).

The partition of manganese among organs and intracellular organelles of the rat. Maynard, L. S. and Cotzias, G. C. J. Biol. Chem. 214, 489-495 (May 1955).

Influence of chelates on the metabolism of radioyttrium (Y-90). Dudley, H. C. J. Lab. Clin. Med. 45, 792-799 (May 1955).

REPOSITORY Brookhaven Nat'l Lab
COLLECTION Med Dept. 952-6

15. Expected Results - FY 1956:

See Quarterly Progress Report - BNL 367 (S-27).

The effects of 2-amino, 5-nitrothiazole on thyroid function in the rat. C. J. Shellabarger and F. C. Schatzlein. (Page 42).

The biological activity of triiodothyronine, triiodothyroacetic acid, and thyroxine. C. J. Shellabarger. (Page 42).

"In vitro" incorporation of C^{14}-labeled amino acids by "Trichinella spiralis" larvae. R. D. Stoner and L. V. Hankes. (Page 43).

A mechanism for the fixation of carbon dioxide into the number-6 carbon atom of uric acid. D. Shemin, guest from the College of Physicians and Surgeons, Columbia University, New York, N. Y. (Page 44).

The metabolism of C^{14}-labeled tryptophan. L. M. Henderson, guest from the University of Illinois, Urbana, Ill. and L. V. Hankes. (Page 45).

A study of metabolic pathways of carbohydrate formation in diabetes by means of carbon-14. W. W. Shreeve and M. Conovitz, student from Harvard Medical School, Boston, Mass. (Page 45).

Observations on nephrotic hyperlipemia in children. J. James, G. A. Smith, student from Mount Holyoke College, South Hadley, Mass. and L. I. Gidez. (Page 45).

(See continuation sheet)

15. Expected Results - FY 1956: (continued)

Observations on nephrotic hyperlipemia in rats. L. I. Gidez, G. A. Smith and J. James. (Page 45-46).

The source and state of the hydroxylysine of collagen. F. M. Sinex and D. D. Van Slyke. J. Biol. Chem. 216, 245 (1955) (Page 46).

"In Vitro" Degradation of iodoalbumin. H. Sandberg and C. G. Lewallen. (Page 47).

Synthesis of several morpholinium derivatives. O. D. Easterday and D. H. Ives, student from Cornell College, Mt. Vernon, Iowa. (Page 47-48).

Cation transport by human red cells "in vitro". E. T. Dunham (Page 48).

Microdiffusion of acetic acid as an assay for acetylcholinesterase. I. Serlin and G. C. Cotzias. J. Biol. Chem. 215, 263-268 (1955) (Page 48).

Medical Research Reactor. L. E. Farr, J. S. Robertson, V. P. Bond, E. E. Stickley. (Page 50).

Calibration of the slow neutron beam by biological means. V. P. Bond, O. D. Easterday, E. E. Stickley and J. S. Robertson. (Page 50-51).

Gut permeability studies. J. S. Robertson, V. P. Bond and E. P. Cronkite. (Page 51).

Borate chemistry. R. F. Straub. (Page 52).

Tissue equivalent ionization chamber. R. I. Weller and E. E. Stickley. (Page 52).

Isotope standards comparator. R. I. Weller and E. E. Stickley. (Page 52).

See Quarterly Report - BNL 375 (S-28).

Dynamics of production and destruction of formed elements of the blood and relation to blood coagulation and hemostasis under normal and abnormal conditions. E. P. Cronkite, G. J. Jacobs*, and D. E. Paglia. (Page 46).

The biological effects of astatine on the rat thyroid gland. J. K. Basson**, C. J. Shellabarger and S. W. Lippincott. (Page 46-47).

The thyroidal metabolism of astatine in the rat. C. J. Shellabarger. (Page 47).

REPOSITORY Brookhaven Nat'l Lab
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BOX No.
FOLDER

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* Naval Medical Research Institute, Bethesda, Md.

** Guest of the Medical Department from the National Physical Laboratory, Pretoria, South Africa.

Antithyroid properties of 2-amino, 5-nitrothiazole in rats. C. J. Shellabarger and F. C. Shatzlein. Proc. Soc. Exptl. Biol. Med. 90, 470 (1955). (Page 47).

Incorporation of C^{14}-labeled amino acids by "Trichinella spiralis" larvae. R. D. Stoner and L. V. Hankes. Explt.Parasitol. 4, 435 (1955) (Page 48).

Antibody production by thymus and Peyer's Patches intraocular transplants. R. D. Stoner and W. M. Hale*. J. Immunol. 75, 203 (1955) (Page 48).

Observations on nephrotic hyperlipemia in rats. L. I. Gidez. (Page 48-49).

The reaction of the α_1-acid glycoprotein with nitrous acid. E. A. Popenoe. (Page 49-50).

The reaction of the α_1-acid glycoprotein with carboxypeptidase. E. A. Popenoe. (Page 50).

(See continuation sheet)

15. Expected Results - FY 1956 (continued)

The state of hydroxylysine in collagen. F. M. Sinex. (Page 50-51).

Assay of noradrenaline deamination by monoamine oxidase. G. C. Cotzias and I. Serlin. (Page 51).

Physiology of radiomanganese. G. C. Cotzias and D. C. Borg. (Page 51).

Extracerebral factors in the uptake of sugars by the cerebral cortex. P. G. LeFevre. (Page 52).

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* Present address: Institute of Pathology, University of Tennessee, Memphis, Tenn.

I. Active transfer of metabolites through cell membranes. II. Evaluation of the glucose transport system in the red cell as an hematopatholgic index. P. G. LeFevre. (Page 52).

Use of P^{32} to measure the severity of beta-ray skin lesions. C. M. Neil. (Page 54-55).

Acute toxicity of β-mercaptoethylamine hydrochloride. O. D. Easterday and V. P. Bond. (Page 55).

Low energy beta counting. J. S. Robertson, F. M. Sinex and W. Bernstein, Instrumentation and Health Physics Department. (Page 57).

Total body water. J. James and J. S. Robertson. (Page 57).

Calibration of the slow neutron beam by biological means. V. P. Bond, O. D. Easterday, E. E. Stickley and J. S. Robertson. (Page 57-58).

Tissue equivalent triple chamber for thermal neutron depth dose measurements. R. I. Weller and E. E. Stickley. (Page 58).

Lithium-6. R. F. Straub. (Page 58).

Boron uptake in mouse brain neoplasm. P. G. Kruger, (Reactor Department). Radiation Research 3, 1 (1955) (Page 58).

The proposed Brookhaven medical research reactor. J. S. Robertson, E. E. Stickley, V. P. Bond, and L. E. Farr. Nucleonics 13, [illegible] (Page 58-59).

See Quarterly Progress Report (In Press).

In vitro radioactivity survey equipment. J. S. Robertson, E. E. Stickley and W. Higginbotham (Electronics Dept, BNL).

Medical reactor facility gamma component. E. Stickley.

Medical research reactor. E. Stickley, J. S. Robertson, and R. Powell (Reactor Operations Group).

Triple neutron chamber. R. I. Weller.

Production of skin lesions in swine by the B^{10} (n,α) Li^7 reaction. J. S. Robertson, V. P. Bond, E. P. Cronkite and O. D. Easterday. Fed. Proc. 16, 154 (1956).

Efficacy of hematopoietic protective procedures in rats x-irradiated with intestine shielded. M. N. Swift, S. T. Taketa of U. S. Naval Radiological Defense Laboratory, San Francisco, Calif., and V. P. Bond. Radiation Research 4, 186-192 (1956).

(See continuation sheet)

REPOSITORY
COLLECTION M09 Med. Dept. 1950-61
BOX No.
FOLDER

15. Expected Results - FY 1956: (continued)

Neutron capture therapy - slow neutron depth distribution measurements in tissue. E. E. Stickley. Am. J. Roentgenology, Radium Therapy and Nuclear Med. 75, 609-618 (Mar. 1956).

The state of hydroxylysine in collagen. F. M. Sinex and D. D. Van Slyke.

Immunochemistry of the α_1-acid glycoprotein. E. A. Popenoe and R. D. Stoner.

Glucogenesis from 1-C^{14}-acetate in non-diabetic and diabetic man. W. W. Shreeve, Fed. Proc. 15, 354-355 (1956).

The metabolism of C^{14}-carboxyl-labeled 3-hydroxyanthranilic acid in the rat. L. V. Hankes and L. M. Henderson, University of Illinois, Urbana, Ill., Fed. Proc. 15, 267-268 (1956).

The metabolism of C^{14}-tryptophan in the rat. L. M. Henderson, University of Illinois, Urbana, Ill., and L. V. Hankes. Fed. Proc. 15, 271 (1956).

Studies on the physiology of manganese. G. C. Cotzias and D. C. Borg.

Study of submolecular acetylcholinesterase organization using ionizing radiation. I. Serlin and D. J. Fluke, Dept. of Biology, BNL.

Trace metal metabolism. D. C. Borg and G. C. Cotzias.

Rheumatoid arthritis program. W. Wolins.

Extracerebral factors in the uptake of sugars by the cerebral cortex. P. G. LeFevre.

Studies on the metabolism of plasma proteins in the nephrotic syndrome. I. Albumin, γ-globulin and iron-binding globulin. D. Gitlin, Harvard Medical School, Children's Medical Center, Boston, Mass., C. A. Janeway, Harvard Medical School, Boston, Mass. and L. E. Farr. J. Clin. Invest. 25, 44-56 (1956).

The effect of N-methyl-phenyl-ethyl barbituric acid on thyroid function in the rat. C. J. Shellabarger. Endocrinol. 58, 347-351 (1956).

A comparison of triiodothyronine and thyroxine in the chick goiter prevention test. C. J. Shellabarger. Poultry Sci. 34, 1437-1440 (1955).

Anti-inflammatory activity of thyroid hormone compounds. C. J. Shellabarger and V. P. Bond.

Studies on the thyroidal accumulation of rhenium in the rat. C. J. Shellabarger. Endocrin. 58, 13-22 (1956).

The effects of various agents on rat thyroid function. C. J. Shellabarger.

16. Anticipated Problems - FY 1957 and FY 1958:

General activities in these fields will continue.

For discussion of overall trends, see Summary Statement for Medical Research Program.

REPOSITORY Brookhaven Natl Lab
COLLECTION TM 189 Med. Dept. 1950-61
BOX No.
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PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Effects of Radiation			2. Date: APRIL, 1956
3. Budget Activity No: 6120 - 3	4. Budget Item No:	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly & Special Reports
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York	9. Contract No: AT-30-2-GEN-16
10. Persons in Charge: L. E. Farr		11. Starting Date: Continuing	

12. Purpose and Need:

1. Effects on viability

The effects of radiation of varying dosage on the viability of intact organisms ranging from viruses, bacterial and unicellular organisms to mammals of the size of goats and pigs will be systematically investigated. In particular, there will be sought the relationship between lethal dose and organizational complexity. Radiation both external and internal will be used. Particle radiation, gamma radiation and x-radiation will be investigated. Studies will be correlated with other parts of the medical department program.

2. Effects on specific chemical and enzyme systems

Radiation effects on specific enzyme systems such as acetylcholinesterase will be continuously studied with efforts made to observe the effects on the enzyme system within the intact animal. The usefulness of radiation as a tool to explore distribution and state of aggregation of enzymes will be explored. Specific chemical systems such as coenzyme B under different types of radiation will be studied as well as components of specialized cells such as those found in the hematopoietic system.

3. Effects compared with regional penetrating radiation

Equivalent dosage of localized radiation will be compared in biological effects to regional penetrating radiation from gamma sources and x-rays. Effects of dose rates will be observed. Regional penetrating radiation studies will be used to bridge differences in experimental procedures between many used in this laboratory and others more generally available in university centers.

13. Related Projects:

See general statement of integrated Medical Department program.

14. Accomplishments - FY 1955:

Data accumulated, see item 15 for progress reports.

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15. Expected Results - FY 1956:

See Quarterly Progress Report - BNL 367 (S-27).

Cancerogenic action of local and graded doses of whole-body irradiation. E. P. Cronkite, V. P. Bond and C. J. Shellabarger in collaboration with R. A. Conard, Naval Medical Research Institute. (Page 41).

Radiosensitivity of Tissues. R. D. Stoner (Page 43).

State of Tissue Acetylcholinesterase as studied by Co^{60} -radiation. G. C. Cotzias and I. Serlin. (Page 46-47).

(See continuation sheet)

15. Expected Results - FY 1956: (continued)

Use of P^{32} to measure the severity of γ-ray skin lesions. C. M. Neil. (Page 47).

The effects on skin or radiation from the reactor. J. S. Robertson, E. P. Cronkite, V. P. Bond, E. E. Stickley. (Page 50).

See Quarterly Progress Report - BNL 375 (S-28).

Cancerogenic action of local beta and graded doses of whole-body irradiation. E. P. Cronkite, V. P. Bond, C. J. Shellabarger, S. W. Lippincott, and R. A. Conard. (Page 46).

Heavy Particle irradiation of "E. coli" Strain B. B. Seife**, R. M. Drew, and V. P. Bond. (Page 47).

Gamma irradiation of pneumococcus desoxyribonucleic acid. R. M. Drew. Radiation Research 3, 116 (1955) (Page 48).

Effect of temperature on acetylcholinesterase inactivation by gamma irradiation. I. Serlin and G. C. Cotzias. (Page 51).

Preliminary studies of viability of mouse brain tumor following B^{10}-borax neutron capture irradiation. L. E. Farr, B. B. Antal, and O. D. Easterday. (Page 54).

See Quarterly Progress Report (In Press).

Effect of heavy particles from the B^{10} (n,α) Li^7 reaction on acute mortality in the mouse. V. P. Bond and O. D. Easterday. Fed. Proc. 15, 21 (1956).

The effects of total-body fast neutron irradiation in dogs. V. P. Bond, R. E. Carter*, J. S. Robertson, P. H. Seymour*, and H. H. Hechter*. Radiation Research 4, 139-153 (1956). (abstract).

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* U. S. Naval Radiological Defense Laboratory, San Francisco, Calif.

** Student guest of the Medical Department from the University of Rochester School of Medicine, Rochester, N. Y.

Studies of viability of mouse brain tumor following B^{10}-borax neutron capture irradiation. L. E. Farr, B. B. Antal and O. D. Easterday.

16. Anticipated Problems - FY 1957 and FY 1958:

General activities in these fields will continue.

For discussion of overall trends, see Summary Statement for Medical Research Program.

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PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Combating Radiation Detrimental Effects - Medical Research			2. Date: APRIL, 1956
3. Budget Activity No: 6220	4. Budget Item No:	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly & Special Reports
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York	9. Contract No: AT-30-2-GEN-16
10. Persons in Charge: L. E. Farr		11. Starting Date: Continuing	

It is now believed that the effort originally budgeted under this category for F. Y. 1957 is more appropriately reported under other activities of the Medical Research Program.

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Project Title: Medical Research 6220

17. Operating Costs	Estimated 1956	Estimated 1957	Estimated 1958
Total Cost	$ 120,000	$ ---	$ ---

18. Cost of Plant & Equipment Directly Required
(Shown here for information only)

	Estimated 1956	Estimated 1957	Estimated 1958
(A) Construction	---	---	---
(B) Equipment	---	---	---

19. Direct Man Power	Estimated 1956	Estimated 1957	Estimated 1958
No. of Man Years			
Scientists & Engineers	3.5	-	-
Technical	4.5	-	-
Administration & Service	1.0	-	-
Total	9.0	-	-

20. Comments

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4001744 OFFICIAL USE ONLY

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Beneficial Application of Atomic Energy - Medical Research - Applied Science - Use of short lived radioactive isotopes in therapeusis of cancer.			2. Date: April 1956
3. Budget Activity No: 6310	4. Budget Item No:	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly & Special Reports
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York	9. Contract No: AT-30-2-GEN-16
10. Persons in Charge: L. E. Farr		11. Starting Date: Continuing	

12. Purpose and Need:

1. Glioblastoma multiforme

Neutron capture therapy is continuing. During fiscal 1956 the final clinical studies were done on a second series of 9 patients. Pathological studies on autopsy specimens will be greatly extended in coming year and new procedural patterns aimed at lessening toxicity and complications will be instituted with start of treatment of third series of patients in fiscal 1957.

2. Hepatoma and hepatic metastases

The observation that radioactive manganese localizes in liver regions and metastases is being further exploited. Various manganese salts of differing characteristic distributions are being studied in patients with metastatic malignancies to determine those compounds best suited for more intensive therapeutic assay.

3. Other metastatic cancers

Patients with widespread metastases will be studied with a variety of radioactive isotopes internally administered in an endeavor to determine factors favoring localization and therefore therapeutic effectiveness, limits of tolerance for various isotopes and means of combatting radiation induced complications. Studies will be largely dependent on specific patients becoming available from time to time. It is planned to carry on much of this work through temporary addition of collaborators from other institutions on a visiting basis.

13. Related Projects:

See general statement of integrated Medical Department program.

14. Accomplishments - FY 1955:

Neutron capture therapy of gliomas using boron10. Farr, L. E., Sweet, W. H., Locksley, H. B., and Robertson, J. S. Trans. Am. Neurol. Assn. 1954, 110-113.

Pathological study of eight patients with glioblastoma multiforme treated by neutron capture therapy using boron-10. Godwin, J. T., Farr, L. E., Sweet, W. H., and Robertson, J. S. Cancer 8, 601-615 (May-June 1955)

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15. Expected Results - FY 1956:

See Quarterly Progress Report - BNL 367 (S-27)

Some Pharmacological studies with boron. O. D. Easterday and R. W. Carey. (Pages 48-49)

The tolerance of large doses of sodium borate intravenously by patients receiving neutron capture therapy. H. B. Locksley and L. E. Farr (Page 49)

(See Continuation Sheet)

15. Expected Results - FY 1956 (Continued)

The effects on skin of radiations from the reactor. J. S. Robertson, E. P. Cronkite, V. P. Bond, E. E. Stickley (Page 50)

Mouse Gliomas. N. Bauman, student from New York University College of Medicine, New York, N. Y. and J. S. Robertson (Page 51)

See Quarterly Progress Report - BNL 375 (S-28)

Mn^{56} as a possible palliative agent in liver cancer. G. C. Cotzias and D. C. Borg. (Page 51-52)

The effect of large intravenous doses of sodium borate on the human myocardium as reflected in the electrocardiogram. H. L. Conn, Jr., B. B. Antal, and L. E. Farr. Circulation 12, 1043 (1955). (Page 56)

16. Anticipated Problems - FY 1957 & FY 1958

General activities in these fields will continue.

For discussion of overall trends, see Summary Statement for Medical Research Program.

REPOSITORY Brookhaven Nat'l Lab
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4001746

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Beneficial Application of Atomic Energy Medical Research - Applied Science Diagnostic Implications			2. Date: APRIL, 1956
3. Budget Activity No: 6320	4. Budget Item No:	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly & Special Reports
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York	9. Contract No: AT-30-2-GEN-16
10. Persons in Charge: L. E. Farr		11. Starting Date: Continuing	

12. Purpose and Need:

1. Cardiovascular system.

Radioactive isotopes are being used systematically to explore the possibility of abnormal patterns of distribution or body content of electrolytes in essential hypertension. In particular, studies are underway to determine the significance of sodium in the pathogenesis of the condition. Exploration of circulation times and local vascular competence is also carried out. Blood volume studies using isotopes are correlated with disease states. The general program utilizing inorganic salts is a long range one.

2. Renal system.

It is planned to institute a long range series of studies of renal physiology using multiple radioactive isotopes simultaneously to get a more complete picture of complex tubular functions without exceeding normal physiological concentrations of ions studied. (To be initiated with appointment of proper Senior Staff member planned for 1957).

3. Neurological systems.

During the past, isotopic study of the neurological system has been limited largely to isotopic studies on formation and circulation of the cerebrospinal fluid with particular reference to effects of neutron capture therapy. Present interest in the physiological usefulness of manganese and the production of a Parkinsonian syndrome by manganese has led to investigation of the role of manganese in patients with Parkinson's Disease.

4. Muscular and skeletal systems.

Studies are being carried out with inorganic radioactive tracers on patients with arthritis. Regional studies of fluid formation and effects of present therapy are planned. Later, labeled organic compounds protein, glyco-protein and muco-protein will be studied.

5. Gastro-intestinal system.

In patients developing radiation illness it is planned to study some aspects of gastro-intestinal function without [illegible] will depend upon availability of proper subjects.

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6. Integument.

Effects of radiation on the skin particularly associated with neutron capture therapy will continue to be studied. ~~Observations of skin responses~~ to all types of radiation will be made as opportunities occur.

7. Endocrine system.

Continuing but not necessarily continuous studies are made on the use of radioactive isotopes to gain better information regarding normally functioning endocrine systems as well as specific observations in disease states. At this time particular attention is being given to C^{14} studies in diabetes mellitus patients to determine the rate of conversion of fats to carbohy-

(See continuing sheet)

12. Purpose and Need: (continued)

drates. Adrenal effects in this system are also observed. Radioactive iodine I^{132} is being explored for diagnostic use in thyroid disorders and is being compared with I^{131} for this purpose. Treatment of hyperthyroidism while not strictly diagnostic is included under this category since studies carry radiation effect results to larger magnitudes than encountered in purely diagnostic tests.

13. Related Projects:

See general statement of integrated Medical Department program.

14. Accomplishments - FY 1955:

Evidence for relationship between sodium (chloride) intake and human essential hypertension. Dahl, L. K. and Love, R. A., A.M.A. Arch. Int. Med. 94, 525-531 (Oct. 1954).

Metabolic effects of marked sodium restriction in hypertensive patients: changes in total exchangeable sodium and potassium. J. Clin. Invest. 33, 1397-1406 (Oct. 1954) Dahl, L. K., Stall, B. G., and Cotzias, G. C.

Renal tubular failure of shock and nephritis. Van Slyke, D. D., John Phillips Memorial Lecture, Amer. Coll. Physicians, Chicago, April 7, 1954. Ann. Int. Med. 41, 709-738 (Oct. 1954).

Accuracy of a radiopotassium dilution (Stewart principle) method for the measurement of cardiac output. Conn, H. L., J. Appl. Physiol. 7, 542-548 (Mar. 1955).

Metabolic effects of marked sodium restriction in hypertensive patients. Skin electrolyte losses. Dahl, L. K., Stall, B. G. and Cotzias, G. C. J. Clin. Invest. 34, 462-470 (Mar. 1955).

15. Expected Results - FY 1956:

See Quarterly Progress Report - BNL 367 (S-27).

Dynamics of production and destruction of formed elements of the blood under normal and abnormal conditions. E. P. Cronkite and V. P. Bond with G. J. Jacobs, Naval Medical Research Institute, Bethesda, Md. (Page 41).

The use of radioactively labeled compounds in study of metabolic interrelationships of host and parasitic helminths. R. D. Stoner and L. V. Hankes. International Conference on Peaceful Uses of Atomic Energy, Geneva, Switzerland, August 8-20, 1955. (Page 43).

The accuracy of a radiopotassium (Stewart Principle) method for the measurement of cardiac output. H. L. Conn, Jr. J. Appl. Physiol. 7, 542-548 (1955) (Page 49).

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See Quarterly Progress Report - BNL 375 (S-28).

"In Vitro" incorporation of C^{14}-labeled amino acids by "Trichinella Spiralis" larvae. R. D. Stoner and L. V. Hankes (Page 47-48).

Characterization of a glycoprotein in the urine of patients with proteinuria. E. A. Popenoe. J. Biol. Chem. 217, 61 (1955) (Page 51).

The effects of sickling on ion transport. I. Effect of sickling on potassium transport. D. C. Tosteson, E. Carlsen and E. T. Dunham. J. Gen. Physiol. 39, 31 (1955) (Page 55).

The effects of sickling on ion transport. II. The effect of sickling on sodium and cesium transport. D. C. Tosteson, J. Genl. Physiol. 39, 55 (1955) (Page 56).

(See continuation sheet)

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15. Expected Results - FY 1956: (continued)

See Quarterly Progress Report (In Press).

In vitro incorporation of C^{14}-labeled amino acids by "Trichinella spiralis" larvae. R. D. Stoner and L. V. Hankes.

A study of metabolic pathways of pentose formation in mammalian species. W. W. Shreeve.

Use of P^{32} to measure the severity of β-ray skin lesions. C. M. Neil.

16. Anticipated Problems - FY 1957 and FY 1958:

General activities in these fields will continue.

For discussion of overall trends, see Summary Statement for Medical Research Program.

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