

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

58-57

NYO-149

1. Project Title: Medical Research		717676	2. Date: April 1957	
3. Budget Activity No: 6120, 6310, 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, M.D.		11. Starting Date: Continuing		

SUMMARY

The considered long range plan of effort by the Medical Department is an integrated program of laboratory and experimental medical science and of therapeutic and diagnostic clinical application. In any given year the emphasis will be in those portions of the program for which unusual capabilities exist in the staff at that time or for which most promising leads have been developed. Explanatory studies and minor testing 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 ultimate manpower requirements will be those authorized and planned for by the orderly expansion of the Medical Department to its final size now expected to be reached about fiscal 1960.

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.

- 6120 I. Laboratory and experimental medical science - The biological effects of radiation of cellular and microsomal dimensions.
- 6120-1 A. 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.
- 6120-2 B. 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

COLLECTION

BOX No.

FOLDER

Brookhaven National
Lab
M109 Med. Dept. 106

(See continuation sheet)

4002070

Project Title: Medical Research - Summary

17. Operating Costs	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
Total Cost	\$1,685,000	\$2,142,000	\$2,078,000	\$2,375,000

18. Cost of Plant & Equipment Directly Required (shown here for information only)				
	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
(A) Construction	---	---	---	---
(B) Equipment	\$ 85,000	\$ 175,000	\$ 165,000	\$ 190,000

19. Direct Man Power	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
<u>No. of Man Years</u>				
Scientists & Engineers	37.0	39.5	35.5	43.5
Technical	89.0	95.0	92.0	102.0
Administration & Service	16.5	19.0	19.0	19.0
Total	142.5(2.5)	153.5(2.5)	146.5(2.5)	164.5(2.5)

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

20. Comments	REPOSITORY
	<i>Brookhaven Natl Lab</i>
	<i>JM 189 Med. Dept. 1950-61</i>
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- 6120-3 C. Effects of radiation. Page 6000- 11
1. Effects on viability.
 2. Effects on specific chemical and enzyme systems.
 3. Effects compared with regional penetrating radiation.

II. Therapeutic and Diagnostic Clinical Application.

- 6310 A. Therapeusis of Cancer. Page 6000- 13
1. Glioblastoma multiforme.
 2. Hepatoma and hepatic metastases.
 3. Other metastatic cancers.

- 6320 B. Diagnostic Implications.

1. Cardiovascular system.
2. Renal system.
3. Neurological systems.
4. Muscular and skeletal systems.
5. Gastro-intestinal systems.
6. Integument.
7. Endocrine system.

REPOSITORY

COLLECTION

BOX No.

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Brookhaven Med. Dept.
M 189 Med. Dept. 1956

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 four scientists on the Senior Staff. By June 30, 1956, the Senior Staff had increased to 13 and during fiscal 1957, to 15. In 1952 the total staff was 19, at end of fiscal year 1956 it was 32 and by the end of fiscal year 1957 it is expected to be 33. The increase in staff to final size should be as rapid as possible that the potentialities of the new medical center may be promptly realized. The additional facilities provided by the new building lend significant energy to the provisions of technical assistance and equipment required to maintain the momentum achieved in the research program. By dint of constant scrutiny it is possible now to make realistic estimates of capital equipment considered most useful in the program.

The participation in work at the laboratory by scientists from universities and teaching hospitals continues as a most promising aspect of the Brookhaven program in medicine. In 1952, eleven medical scientists participated for varying lengths of time in the collaborative program. By March of fiscal 1957 this program included 42 research collaborators, guests, consultants and students and will probably reach 48 by the end of fiscal 1957. This program will be more effective with the new building since more scientists can be accommodated for longer periods of time. The increasing requests for appointment to this medical department both as regular staff members and as research collaborators indicates strongly that the Brookhaven 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.

The Medical Department has now developed its program in outline. During 1958 there should logically be an increase in intensity of work on most of the basic divisions of investigation particularly the following: 1) Neutron capture therapy and RBE studies of heavy particles; 2) the study of kinetics of distribution of metals as pioneered by work in Mn⁵⁶; 3) the application of mathematics to description of kinetics of distribution for further development of tracer theory with its manifold immediate applications such as capacity to alter fixation or to remove fixed isotopes; 4) the usefulness of short lived isotopes in cancer therapy; 5) the effects of radiation as a carcinogenic and mutagenic agent with development of better methods of determining whole body burdens and their relation to fallout; 6) the effects of radiation on hematopoietic tissue and methods for prevention or amelioration; 7) intensive study of specific metabolic reactions both for placement of radioactive isotopes and for understanding and control of mechanisms involved therein; 8) the effects of radiation on production of antibodies and allergies.

This list could be extended usefully but it may be more desirable to summarize the effort to two main areas: 1) The biological effects and medical implication of radiation exposure; 2) the effect of development of reactors on medical concepts of their use and hazards. The originally requested increase in staff was to augment and intensify the effort in these two areas. The importance of the first is currently exemplified by the present controversy on the effects of fallout. One or two suitable whole body counters and additional animal facilities would have

(See continuation sheet)

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Project Title: Medical Research

enabled the increased staff productively to work on this problem. The importance of the second problem regarding reactors is pointed up by the number of reactors built, building or planned for the United States and the world. Some additional instrumentation and operating personnel again could profitably build on the present solid foundation. The cost increment while significant in terms of present budget is very small in terms of expenditures making these studies of importance. FY 1959 as presented in the A + B Budget would normally see further intensification of these areas of primary effort rather than extension.

REPOSITORY

COLLECTION

BOX No.

FOLDER

Rockhaven Natl Lab
7M189 Med Dept. 170-61

4002073

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: The Biological Effects of Radiation of Cellular and Microsomal Dimensions			2. Date: April 1957	
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

<u>Sub-Activity No.</u>	<u>Project Title</u>	<u>Page No.</u>
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 - 11

REPOSITORY *Brookhaven Natl Lab*
 COLLECTION *M189 Med. Dept. 1957-61*
 BOX NO. _____
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400207

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Production of Radiation of Desired Character			2. Date: April 1957		
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, M.D. Drs. Bond, Robertson, Stickley, Maxfield			11. Starting Date: Continuing		
12. Background:					
<p>1. Neutron capture reaction to produce heavy particle radiation, i.e. utilization of Li^6, B^{10}, U^{235}.</p> <p>Studies are being continuously engaged in to determine the range of particle distribution from source atom within mammalian tissue. These studies 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.</p> <p>2. Neutron capture reactions to produce beta particle radiation.</p> <p>At proper stage of development of the heavy particle radiation study it is planned to embark on studies 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 effectiveness of radiation produced will be compared with a standard gamma ray exposure.</p> <p>3. Selection and production in usable state of other suitable radioactive isotopes.</p> <p>Production of short lived isotopes preferably with alpha or beta emission suitably purified for biological use is being carried out. Effects of radiation in localized sites is being compared when differing transport mechanisms are used. Resulting radiation effects are being compared with <i>in situ</i> heavy particle and beta particle production and same will be compared with standard gamma ray exposure to determine relative biological effectiveness.</p>					
13. Related Projects:					
See general statement of integrated Medical Department program.					
14. Status as of April 1957:					
<p>Use of the nuclear reactor for neutron capture therapy of cancer Farr, L.E., Robertson, J.S. and Stickley, E. Intl. Conf. on Peaceful Uses of Atomic Energy, Geneva, July 1955</p> <p>The effects of sickling on ion transport. I. Effect of sickling on potassium transport. Tosteson, D.C., Carlsen, E. and Dunham, E.T. J. Gen. Physiol. <u>39</u>, 31-53 (Sept 20, 1955)</p> <p>The effects of sickling on ion transport. II. Effect of sickling on sodium and cesium transport. Tosteson, D.C. J. Gen. Physiol. <u>39</u>, 55-67 (Sept 20, 1955)</p> <p>The proposed Brookhaven medical research reactor No. _____ Robertson, J.S., Stickley, E., Bond, V.P. and Farr, L.E. Nucleonics <u>13</u>:12, 64-68 (December 1955) FOLDER _____ (see continuation sheet)</p>					

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Brookhaven Natl Lab
11189 Med Dept ASD-61

14. Status as of April 1957: (continued)

Radioisotope Development: Europium-155
Robertson, J.S. and Straub, R.

Calibration of Irradiation Sources
Stickley, E.E.

Isotope Standards Comparator
Weller, R.I.

15. Program for FY 1958 and FY 1959:

1. While the major effort will remain on B^{10} , as manpower and equipment permit brief investigations will be carried out on Li^6 and U^{235} particularly with collaborative participation.

2. It is not anticipated that this will be a significant part of the effort of the department in fiscal 1958.

3. Efforts to continue development of useful radioactive isotopes among those not now in medical use will continue. Manganese⁵⁶ studies will progress at present rate together with other manganese isotopes as Manganese⁵⁴ and several short lived isotopes of Zinc. Utilization will depend on capacity of other BNL units to furnish material in requisite purity. The many possibilities of activation analysis are being explored and will continue to be with particular reference to suitability of this procedure to trace metal study. Both reactor and particle accelerator activation are being used and efforts are under way to determine the most efficient procedures to follow in order that one or several components of a complex mixture can be activated while other components of larger concentration but not of immediate interest are subjected to procedures suppressing their activation.

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REPOSITORY *Brockhaven Natl Lab*
COLLECTION *JAN 189 Med. Dept. 1950-61*
BOX No _____
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PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Control of Radiation Distribution in Mammalian Organism			2. Date: April 1957	
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, M.D. Drs. Cotzias, Dahl, Hughes, Sinex, Hankes, Van Slyke, LeFevre, Shreeve, Stoner, Robertson, Stickley, Maxfield		11. Starting Date: Continuing		
12. Background:				
1. Transport mechanisms, specific				
a. Chemical				
<p>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.</p> <p>Continuing work is being carried on in 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 -- those elements whose distribution is determined solely by the element itself, i.e. sodium; elements whose distribution follows body water, i.e. boron; elements whose distribution may be conditioned by accompanying ion of opposite charge, i.e. manganese.</p>				
b. Enzymological				
<p>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.</p> <p>Monoamine oxidases, acetylcholinesterase, lipases, and proteases are enzyme systems which have received especial attention.</p>				
c. Physical				
<p>The utilization of colloidal size and change for physiological placement is receiving only attention at this time in a collaborative program, though fundamental theoretical considerations now being developed will lead to experimental testing of hypotheses at an appropriate time.</p>				
d. Immunological				
<p>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.</p>				
REPOSITORY COLLECTION SHEET (See continuation sheet) BOX No _____ FOLDER _____				

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71189 Med. Dept. 1950-51

12. Background: (Continued)

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 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 suitable elements for study will be sought in cooperation with BNL Hot Laboratory, Reactor and Accelerator operating units. 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 parallel, substantiate and supplant biological dosimetry will be under constant development with appropriate collaborators as well as within the department.

13. Related Projects:

See general statement of integrated Medical Department program.

REPOSITORY

COLLECTION

(See continuation sheet)

BOX No

FOLDER

Brookhaven Nat'l Lab
11189 Med. Dept. 193-61

14. Status as of April 1957:

Metabolism of Cobalt-60-Labeled Vitamin B₁₂

Meyer, L. M.; Cronkite, E. P. and Willigan, D.
(See also Quarterly Progress Reports in press)

Tagging Gelatin with I¹³¹ Utilizing P-iodo-phenyl Sulfonyl Chloride
Terres, G. and Wolins, W.

Incorporation of C¹⁴-Labeled Amino Acids by "Trichinella spiralis" Larvae
Stoner, R. D. and Hanks, L. V.

Mechanism of Immune Reaction
Stoner, R. D.

The Nature of the Protein Associated with the Urinary Acid Mucopolysaccharide
DiFerrante, N. and Popenoe, E. A.

A Study of Metabolic Pathways of Pentose Formation by Mammalian Species
Shreeve, W. W.

Metabolism of Quinolinic Acid Ring Labeled with Tritium
Hanks, L. V.

The Metabolism of DL-Tryptophan-3a, 7a, 7-C¹⁴ and DL-Tryptophan-a-C¹⁴ in the Rat
Henderson, L. M. and Hanks, L. V.

Beta Applicator Calibration
Weller, R. I.

Neutron Dosimetry by Photographic Film
Stickley, E. E.

Calibration of Irradiation Sources
Stickley, E. E.

Tritiated Thymidine
Hughes, W. L.

The Effect of Starvation on the Disappearance Rate of Tagged (I¹³¹) Bovine Serum Albumin has been Investigated in Mice
Terres, G. and Wolins, W.

Incorporation of Glycerol-1, 3-C¹⁴ into the Triglycerides and Phosphatides of Human Serum and Serum Lipoproteins
Gidez, L. I. and Eder, H. A.

Urinary Excretion of Acid Mucopolysaccharides in Patients with Rheumatoid Arthritis
Di Ferrante, N.

Action of Clostridium Perfringens on Orosomucoid
Popenoe, E. A. and Drew, R. M.

Biological Activity of Thyroxine Analogues
Shellabarger, C. J.

A Study of Metabolic Pathways of Carbohydrate Formation in Diabetes by Means of Carbon-14-Labeled Ethyl Alcohol
Shreeve, W. W. and Conovitz, M.

Synthesis and Metabolism of Tritium-Labeled Quinolinic Acid
Hanks, L. V. and Segel, I. H.

Lipid Metabolism in Experimental Lipemia
Gidez, L. I. and James, J. A.

The Determination of Acid Aminopolysaccharide in Urine
Rich, C. and DiFerrante, N.

REPOSITORY
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Brothman Nat'l Lab
77009 Med. Dept. 1958-61

BOX No. _____
(See Continuation Sheet)
FOLDER _____

14. Status as of April 1957: (Continued)

Basic Physiology of Manganese

Borg, D. C. and Cotzias, G. C.

(See also Quarterly Progress Reports in press)

Role of Carbohydrate and Mineral Metabolism in Control of the Cerebral Excitatory State

LeFevre, P. G.

I. Active Transfer of Metabolites Through Cell Membranes

II. Evaluation of the Glucose Transport System in the Red Cell as a Hematopathologic Index

LeFevre, P. G.

Radiosensitivity of Choline Chloride

Serlin, I.

State of Tissue Acetylcholinesterase as Determined by Cobalt-60 Gamma Irradiation

Serlin, I.

Neutron Dosimetry

Stickley, E. E.

Dosimetry of x- and Gamma-Rays

Stickley, E. E.

Isotope Standards Comparator

Weller, R. I.

Beta Applicator Calibration

Weller, R. I.

(See also Quarterly Progress Reports in press)

Halide Metabolism

Robertson, J. S., Sohn, D. and Durbin, P.

Studies of Light Scattering

Maxfield, M.

Precursors of Desoxyribose in Rat Liver Studies with C¹⁴-Labeled Glycine

Shreeve, W. W. and Grossman, A.

The Role of Hydroxylysine in the Synthesis of Collagen

Sinex, P. M. and Van Slyke, D. D.

15. Program for F. Y. 1958 and F. Y. 1959:

Since the effective therapeutic value of isotopes is to place them on target and have them remain there for their effective half lives, we must know the specific and non-specific transport mechanisms and their relation to radiological control. Studies with regard to boron in neutron capture, manganese in metastatic cancer and utilization of labeled compounds will continue at a somewhat accelerated rate when additional personnel is available.

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COLLECTION

BOX No

FOLDER

Brookhaven Natl Lab
TRC9 Med. Dept. 1958-61

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Effects of Radiation			2. Date: April 1957		
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, M.D. Drs. V. P. Bond, R. A. Conard, E. P. Cronkite, J. S. Robertson, R. M. Drew			11. Starting Date: Continuing.		
12. Background:					
1. Effects of viability.					
<p>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 continues to be systematically investigated. In particular, the relationship between lethal dose and organizational complexity is sought. 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.</p>					
2. Effects on specific chemical and enzyme systems.					
<p>Radiation effects on specific enzyme systems such as acetylcholinesterase is 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 is 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.</p>					
3. Effects compared with regional penetrating radiation.					
<p>Equivalent dosage of localized radiation is compared in biological effects to regional penetrating radiation from gamma sources and x-rays. Effects of dose rates are 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.</p>					
13. Related Projects:					
See general statement of integrated Medical Department program.					
REPOSITORY <i>Brookhaven Natl. Lab</i>					
COLLECTION <i>TM 189 Med. Dept. 1950-61</i>					
14. Status as of April 1957:					
BOX No. _____					
Gamma irradiation of pneumococcus deoxyribonucleic acid Drew, R. M. Radiation Research <u>3</u> , 116-120 (October 1955)					
Response of human beings accidentally exposed to significant fall-out radiation Cronkite, E. P.; Bond, V. P.; Conard, R. A.; Shulman, N. R.; Farr, R. S.; Cohn, S. H.; Dunham, D. L. and Browning, L. E. JAMA <u>159</u> , 430-434 (October 1955)					
Medical survey of Marshallese two years after exposure to fallout radiation Conard, R. A.; Huggins, C. E.; Cannon, B.; Richards, J. B. and Lowery, A. BNL Report 412 (T-80), March 1956					
(See continuation sheet)					

400208j

14, Status as of April 1957: (Continued)

Function and fate of labeled platelets

Cronkite, E. P. and Paglia, D. E.

(See also Quarterly Progress Report in press)

Cancerogenic Action of Graded Doses of Whole-Body Irradiation

Cronkite, E. P.; Shellabarger, C. J.; Bond, V. P. and Lippincott, S. W.

(See also Quarterly Progress Report in press)

Radiosensitivity of Choline Chloride

Serlin, I.

Biological effects of the radiation from the neutron capture reaction

Bond, V. P. and Gilmartin, J.

(See also Quarterly Progress Report in press)

Combined Effects of Beta Irradiation of the Skin and Whole Body X-irradiation on Carcinogenesis in the Skin

Conard, R. A.; Cronkite, E. P. and Bond, V. P.

Studies on the Toxicity of Irradiated Intestine

Conard, R. A. and Quastler, H.

Long Term I¹³¹ Studies of Rats

Shellabarger, C. J. and Godwin, J. T.

Beta Applicator Calibration

Weller, R. I.

15. Program for F. Y. 1958 and F. Y. 1959:

Present studies are planned to continue during Fiscal 1958 and 1959 and break-throughs in knowledge will be exploited with determination. Development and procurement of whole body and multiple foci counting equipment to be ready for use on occupying the new building is being stressed.

REPOSITORY

COLLECTION

BOX No.

FOLDER

*Brookhaven Natl Lab
M189 Med Dept. 9006*

4002082

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Beneficial Applications of Atomic Energy- Therapeutic and Diagnostic Clinical Application - Therapeusis of Cancer			2. Date: April 1957		
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, M.D. Drs. Cotzias, Lippincott, Wolins, Bagnall, Borg, Easterday, Robertson, Stickley		11. Starting Date: Continuing			
12. Background:					
1. Glioblastoma Multiforme					
Neutron capture therapy is continuing. Clinical studies on a third series of patients have begun. Comprehensive pathological studies on autopsy specimens have been initiated incorporating new procedural patterns aimed at lessening toxicity and complications.					
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. Status as of April 1957:					
Use of the nuclear reactor for neutron capture therapy of cancer Farr, L.E., Robertson, J.S. and Stickley, E. Intl. Conf. on Peaceful Uses of Atomic Energy, Geneva, July 1955					
Tolerance of large doses of sodium borate intravenously by patients receiving neutron capture therapy Locksley, H.B. and Farr, L.E. J. Pharm. & Exp. Therap. <u>114</u> , 484-489 (August 1955)					
Effect of large intravenous doses of sodium borate on the human myocardium as reflected in the electrocardiogram Conn, H.L., Antal, B.B. and Farr, L.E. Circulation <u>12</u> , 1043-1046 (December 1955)					
The experimental application of neutron capture therapy to glioblastoma multiforme Farr, L.E. Contra Cancrum ACTA <u>11</u> , 500-504 (1955)					
Perfusion studies on the isolated heart Carey, R.W. and Easterday, O.D.					
Biological Effects of the Radiation from the Neutron capture reaction Bond, V.P., Easterday, O.D. and Cronkite, E.P. (see continuation sheet)					

REPOSITOR

COLLECTION

BOX No.

Brookhaven Natl. Lab.
JM 189 Med. Dept. 1956

4002083

17. Operating Costs	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
Total Cost	\$ 390,000	\$ 532,000	\$ 518,000	\$ 590,000

18. Cost of Plant & Equipment Directly Required (shown here for information only)				
	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
(A) Construction	---	---	---	---
(B) Equipment	(See Medical Research Summary)			

19. Direct Man Power	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
<u>No. of Man Years</u>				
Scientists & Engineers	8.5	9.5	8.5	11.0
Technical	20.5	23.5	23.0	25.5
Administration & Service	3.5	4.5	4.5	4.5
Total	32.5(0.5)	37.5(0.5)	36.0(0.5)	41.0(0.5)

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

20. Comments
REPOSITORY <u>Brookhaven Natl Lab</u> COLLECTION <u>M189 Med. Dept. 1950-61</u> BOX No. _____ FOLDER _____

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Project Title: Beneficial Applications of Atomic Energy Therapeutic and Diagnostic Clinical Application - Therapeusis of Cancer (continued)

14. Status as of April 1957: (continued)

Study of the plasma proteins in neoplastic diseases
Lippincott, S.W., Fong, C. and Wolins, W.

Further studies with transplantable mouse brain tumors
Farr, L.E., Antal, B.B., Konikowski, T. and Easterday, O.D.

Basic Physiology of manganese
Borg, D.C. and Cotzias, G. C.

Studies of viability of mouse brain tumor following B¹⁰ neutron capture irradiation
Farr, L.E., Konikowski, T. and Easterday, O.D.

Computer Program for probit analysis
Easterday, O.D., Mumford, P. and Rideout, S.

Remotely controlled variable flow injection apparatus
Easterday, O.D., Richards, P. and Banslaben, A.J.

Neutron capture therapy
Farr, L.E., Bagnall, H.J., Easterday, O.D., Antal, B. and Konikowski, T.

15. Program for FY 1958 and FY 1959:

During the coming fiscal year, neutron capture therapy in glioblastoma multiforme will continue at the most rapid pace consonant with alteration of procedures suggested or indicated by other experimental results becoming available. With occupancy of the new medical center there will begin at least six months of intensive testing of the new reactor, which it is hoped will permit initiation of new series of studies utilizing the medical reactor during FY 1959.

Exploration of usefulness of radioactive manganese in palliation of hepatic and metastatic cancer will be accelerated in coming year following leads developed in the laboratory and experimental procedures during fiscal 1957. Patients with other metastatic cancers and primary malignancies will be studied with particular reference to abnormalities in protein metabolism to determine if metabolic abnormalities are present in neoplastic diseases and if present, how exploited.

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4002085

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Beneficial Applications of Atomic Energy - Therapeutic and Diagnostic Clinical Applications			2. Date: April 1957	
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, M. D. Drs. Cotzias, Dahl, Cronkite, Shreeve, Wolins, Borg		11. Starting Date: Continuing		

12. Background:

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.)

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 with suitably labeled tracers. Work will depend upon availability of proper subjects.

6. Integument.

Effects of radiation on the skin particularly associated with neutron capture therapy will continue to be carried out. 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

(See continuation sheet)

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17. Operating Costs	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
Total Cost	\$ 295,000	\$ 380,000	\$ 370,000	\$ 425,000

18. Cost of Plant & Equipment Directly Required (shown here for information only)				
	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
(A) Construction	---	---	---	---
(B) Equipment	(See Medical Research Summary)			

19. Direct Man Power	Estimated 1957	Estimated 1958	Estimated 1959-A	Estimated 1959-A+B
<u>No. of Man Years</u>				
Scientists & Engineers	6.5	7.0	6.5	7.5
Technical	15.5	17.0	16.5	18.0
Administration & Service	3.0	3.5	3.5	3.5
Total	25.0(0.5)	27.5(0.5)	26.5(0.5)	29.0(0.5)

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

20. Comments
<p>REPOSITORY <u>Brookhaven Natl Lab</u></p> <p>COLLECTION <u>JM 189 Med Dept 1960-61</u></p> <p>BOX No. _____</p> <p>FOLDER _____</p>

normally functioning endocrine systems as well as specific observations in disease states. At this time particular attention is being given to C¹⁴ studies in diabetes mellitus patients to determine the rate of conversion of fats to carbohydrates. Adrenal effects in this system are also observed. 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. Status as of April 1957:

Study of certain phases of cell dynamic states with short-lived isotopes exemplified by Mn⁵⁶ partition studies in organs and intracellular organelles.

Cotzias, G. C. and Maynard, L. S.
Intl. Conf. on Peaceful Uses of Atomic Energy, Geneva, July 1955.

Use of radioactively labeled compounds in study of metabolic interrelationships of host and parasitic helminths.

Stoner, R. D. and Hankes, L. V.
Intl. Conf. on Peaceful Uses of Atomic Energy, Geneva, July 1955.

The effects of sickling on ion transport. I. Effect of sickling on potassium transport.

Tosteson, D. C., Carlsen, E. and Dunham, E. T.
J. Gen. Physiol. 39, 31-53 (Sept. 20, 1955)

The effects of sickling on ion transport. II. Effect of sickling on sodium and cesium transport.

Tosteson, D. C.
J. Gen. Physiol. 39, 55-67 (Sept. 20, 1955)

Aspiration Biopsy: Technique and application.

Godwin, J. T.
Annals New York Acad. Sci 63, 1348-1373 (March 1956)

In vitro metabolism of DL-Alanine-2-C-14 and Glycine-2-C-14 by trichinella spiralis larvae.

Hankes, L. V. and Stoner, R. D.
Proc. Soc. Exp. Biol. & Med. 91, 443-446 (March 1956)

Treatment of Radiation Injuries.

Conkrite, E. P.
Mil. Med. 118, 328-334 (April 1956)

Basic physiology of manganese.

Borg, D. C. and Cotzias, G. C.
(See also Quarterly Reports in progress)

A study of metabolic pathways of carbohydrate formation in diabetes by means of carbon-14-labeled ethyl alcohol.

Shreeve, W. W. and Conovitz, M.

Clinical observations on antiparkinson drugs.

Cotzias, G. C. and Borg D. C.

Effect of adrenal steroid hormones on the fate of C¹⁴-labeled metabolic intermediates in human subjects.

Shreeve, W. W. and Hennes, A. R.

Urinary excretion of acid mucopolysaccharides in patients with rheumatoid arthritis.

DiFerrante, N.

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(See continuation sheet)

*Goodman Natl. Lab
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4002088

15. Program for F. Y. 1958 and F. Y. 1959:

The continuing aspects of this program are included in the discussion under Item 12, Background.

For a 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: Civil Effects Test Program - Nevada Studies			2. Date: August 1957		
3. Budget Activity No: 6600	4. Budget Item No:	5. Contractor's No:	6. Method and Time of Reporting Progress: Quarterly and Special Reports		
7. Contractor: Associated Universities, Inc. Brookhaven National Laboratory		8. Working Location: Upton, New York & Mercury, Nevada	9. Contract No: AT-30-2-GEN-16		
10. Person in Charge: Dr. V. P. Bond			11. Starting Date: F. Y. 1957		
12. Background: It is well known from previous laboratory and field data that the degree of biological response in the mammal is highly dependent on the distribution of absorbed dose throughout the organs and tissues. Thus, for the same monitored air dose, the degree of response can vary greatly depending on the absorption characteristics of the radiation in tissue. The objectives of the present experiments were to determine, in tissue-equivalent phantoms approximating the size of man (1) the ratio of monitored "air" dose bomb gamma radiation to the absorbed dose of gamma radiation through the tissue equivalent material. Studies of this nature at Operation Greenhouse yielded no information because of dosimetric difficulties; preliminary data were obtained at Operation Upshot/Knothole.					
13. Related Projects: Other Civil Effects Programs See General Statement of Integrated Medical Department Program, Brookhaven National Laboratory					
14. Status as of August 1957: The initial shot (spring 1957) was considerably below expected yield, and no data were obtained. A second shot yielded results with all dosimeters used, which have been analyzed and reduced to graphical form. An outline report has been prepared in rough form. The gamma curves are consistent and different from those obtained with usual laboratory radiation. The neutron yield was higher than expected, and the effect of neutrons on the gamma curves obtained is being evaluated. The preliminary neutron curves revealed patterns again different from laboratory radiations or the field gamma radiation.					
15. Program for F. Y. 1958: It is important that the preliminary neutron depth dose data be verified and extended. It is proposed that if adequate neutron dosimetry can be provided by the ORNL group, that additional data be obtained during September 1958. This can be accomplished with minimal additional procurement and with the same personnel used previously. Future participation will depend on the results obtained. Personnel to be affiliated with the 1958 program will be: BNL: Dr. Bond, Dr. Cronkite, Dr. Stickley, Mr. Gilman, Mr. Buzzelli (temp) Mr. Adamik, NMRI: Mr. Imiric, Mr. Manley.					
			REPOSITORY: <i>Brookhaven Natl Lab</i>		
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4002090

PROPOSAL AND AUTHORIZATION
FOR RESEARCH OR DEVELOPMENT

NYO-149

1. Project Title: Civil Effects Test Program - Marshallese Survey F. Y. 1958			2. Date: August 1957	
3. Budget Activity No: 6600	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, N. Y. & Marshall Islands	9. Contract No: AT-30-2-GEII-16	
10. Person in Charge: R. A. Conard, M. D.			11. Starting Date: September 1, 1957	
12. Background: In March 1954, following detonation of a nuclear device, 239 Marshallese people were accidentally irradiated with fallout. These people have been taken care of and studied initially and annually by AEC-Naval medical teams under the auspices of the Division of Biology and Medicine of the AEC. Dr. C. L. Dunham of that Division has requested Dr. Robert A. Conard of the Medical Department, Brookhaven National Laboratory to take charge of the continuing annual medical surveys of the exposed Marshallese and accordingly since 1956 these surveys have been sponsored by BNL. Much valuable information has been and is being obtained on the effects of fallout radiation on human beings and is being made available to the medical profession through publications. These studies are greatly facilitated by the fact that a large group of unexposed Marshallese living under the same environmental conditions, are available for comparative studies.				
13. Related Projects: See General Statement of Integrated Medical Department Program, Brookhaven National Laboratory.				
14. Status as of August 1957: A report is being written on the three year post exposure medical survey which was completed in the Marshall Islands in April 1957. This report will contain results of extensive clinical and laboratory examinations on these people.				
15. Program for F. Y. 1958 and F. Y. 1959: Plans are underway for the next annual medical survey to take place in March 1958 at four years post exposure. The scope of the examinations will be enlarged. Extensive studies will again be carried out, similar to those of the last survey, with considerable emphasis on hematological investigations and on growth and development studies in the children as well as studies on long term effects of radiation. An X-ray machine will be needed at Rongelap in order to carry out the growth and development studies as well as for use in diagnosis. In addition, special studies on whole body gamma spectroscopy and radiochemical analyses of the urine to determine body burdens of radioisotopes in the people will necessitate the acquisition of a whole body gamma counting facility to take to the Islands. It is anticipated that this device will be used repeatedly on the Marshallese in future annual surveys. Personnel to be affiliated with the 1958 program will be: BNL Regular: Dr. Conard, Dr. Robertson, Dr. Wolins (3/4)*, Mr. Greenough BNL Temporary: Dr. Meyer, Dr. Wolins (1/4)*, Physician to be attached, Mr. Sipe, Mr. Jones NMRI: Col. Lowrey, Mr. Eicher, Mr. Clutter, Mr. Heston NRDL: Mr. Hamby, Mr. Murray NIH: Dr. Rall Navy: Dr. Roth, Dr. Nolan, Dr. King It is anticipated that similar annual medical surveys will take place in 1959 and indefinitely.				

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*Regular Laboratory appointment for Dr. Wolins is 3/4 time only.

400209

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17. Operating Costs	Estimated 1957	Estimated 1958	Estimated 1959
Labor	\$ 2,665	\$ 4,900 ⁽²⁾	To be
M/S	4,389	6,300	Detailed
Travel	6,363	9,000	After
Purchased Services	166	11,300 ⁽³⁾	Completion
Special Procurement and Contingency against loss	(1)	48,500 ⁽⁴⁾	Of
Technical Services (BNL)	215	1,000	F. Y. 1958
General & Administrative.	7,087	6,000 ⁽⁵⁾	Program
Total:	\$20,884	\$87,000	

- (1) Miscellaneous items furnished from Laboratory Capital Equipment.
- (2) Salaries and wages of temporary personnel hired by BNL. Does not include labor costs for permanent BNL employees or personnel from military establishments.

(3) Allotments to other agencies:

NMRI	\$6,200
MRDL	\$2,000
N. Y. Navy Yard	\$3,100

- (4) Equipment and other special procurement - not to be capitalized.

X-ray for use at Rongelap	\$ 8,500
Shielded facility for use on LST	16,000
One 100 channel analyzer (spare required because of remote use)	9,000
Sub Total -	\$33,500
Contingency to cover BNL supplied whole body counter if damaged or lost	15,000
Total -	\$48,500

- (5) Based on Labor, Materials and Supplies Procurement, and Technical Services.

18. Cost of Plant and Equipment Directly Required:

Basic equipment items required for whole body counter, which will have continued use at BNL, will be supplied from regular Laboratory equipment funds. Equipment destined for this study only is not to be capitalized as noted above.

19. Direct Man Power	Estimated 1957	Estimated 1958	Estimated 1959
<u>No. of Man Years</u>			
Scientists & Engineers	1.5	1.6	
Technical	1.0	.6	
Administration & Service			
Total:	2.5	2.2	

Note: These are total man years contributed by all organizations supplying personnel for this work.

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4002092

Project Title: Civil Effects Test Program - Nevada Studies

17. Operating Costs	Estimated 1957	Estimated 1958	Estimated 1959
Labor	\$ --	\$ 1,000 ⁽¹⁾	
M/S	2,104	1,000	
Travel	4,257	7,000	
Purchased Services	--	500 ⁽²⁾	
Technical Services (B.N.L)	46	500	
General & Administrative (B.N.L)	3,175	-- ⁽³⁾	
	\$ 9,582	\$10,000 ⁽⁴⁾	

(1) Temporary labor only engaged for this work.

(2) Allotment to NMRI for trucking and special transportation.

(3) No G&A assigned in view of spot nature work and its relatively small size.

(4) Includes contingency of \$2,500 to cover postponements in field (\$500 in labor, \$1,500 in travel).

18. Cost of Plant and Equipment Directly Required:

Small items of miscellaneous equipment not now available will be procured from regular Laboratory equipment funds.

19. Direct Man Power	Estimated 1957	Estimated 1958	Estimated 1959
<u>No. of Man Years</u>			
Scientists & Engineers	0.7	0.15 - 0.3	
Technical	0.9	0.15 - 0.3	
Administration & Service			
Total:	1.6	0.3 - 0.6 ⁽¹⁾	

(1) Depends upon delays in shot time.

Note: These are total man years contributed by all organizations supplying personnel for this work.

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