AEC-189

1. Medical Research.

February 9, 1953

The medical research program is increasingly using the special facilities of Brookhaven in its work. On the assumption that the future medical center may be constructed during the next few years, the present facilities are reasonably adequate although improvement in some of the animal quarters are necessary which it is hoped may be obtained during Fiscal 1954. The Medical Department is composed of Divisions of Bacteriology, Biochemistry, Pathology, Physiology, the Research Hospital and Industrial Medicine, the latter being budgeted elsewhere as a general expense of the Laboratory. In the investigations carried out in the Medical Department all of the divisions are engaged to a greater or lesser degree in all the major problems of study. It has proved impractical to continue segregation of projects devoted exclusively to cancer since many of these also are of fundamental importance in radiation work and vice versa. To our best estimate about 22 percent of the total effort should be charged against cancer per se and 78 percent against general medical research. It is expected that each year will be increasingly productive of results, now that a "core" staff has been assembled with one or two exceptions. Some greater depth in staff is required for the basic group and this in turn will permit greater use of visiting and rotating scientists. The percentage figures in brackets indicate the relative fractional scientific effort of the entire BNL medical program devoted to that aspect of the work.

(30) A. Utilization of thermal neutrons from the reactor to determine their biological effects, their application to medical therapy and their effects on biological, biochemical, cytological and physiological systems.

(15) B. The distribution of body water and its solutes in body compartments and factors affecting the movement of these constituents.

(30) C. The effects of isotopic radiation on physiology and histology of body systems and the exploration of the use for medical purposes of short-lived radioactive isotopes.

(17) D. The mechanisms of protein synthesis and degradation in the intact animal body as elucidated by radioactive labelled proteins, precursors and products.

(8) E. The use of radioactive isotopes to evaluate disease states and the therapy thereof.

F. Collaborative studies and developments. Projects with collaborating institutions in which Brookhaven facilities will be utilized for special segments of studies agreed upon.

MEDICAL RESEARCH

BROOKHAVEN NATIONAL LABORATORY

M E M O R A N D U M

Date: August 6, 1954

To:

From: Leland J. Haworth

Subject: Expenditures & Commitments as of 6/30/54

	Budget	Expense	Commitments	Balance Available
Materials, Supplies & Services, Travel, Development Subcontracts:	146,000.00	151,789.80	7,797.73	(13,587.53)
Capital Equipment:				

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F. Collaborative studies and developments.

12. Collaboration by the Brookhaven medical staff on segments of problems with investigators in other institutions utilizing the special facilities at Brookhaven are desirable both for the staff and the program. These make relatively small demands on staff efforts. A few representative collaborations are detailed below.

1. A study of the effects of tissue implantation of germanium oxide needles containing Au^{198}, P^{32} and other radioactive isotopes.
H. C. Dudley, CDR (MC) USN, and staff. St. Albans Naval Hospital, St. Albans, N. Y.

Germanium oxide appears to be slowly dissolved by tissues and the germanium quantitatively excreted. The use of needles of germanium oxide as carriers for radioactive isotopes is being explored and the radiation effects studied at Brookhaven National Laboratory.

2. The distribution of radioactive xenon in nervous structures and other body tissues.
Dr. R. M. Featherstone et al, State Univ. of Iowa.

In FY 1952 it was learned that radioactive xenon administered by breathing and acting as an anesthetic agent concentrated to the greatest extent in the adrenal gland followed by the central nervous system. Additional studies are planned using this radioactive isotope in May and June, 1953.

3. The treatment of glioblastoma multiforme.
Dr. W. H. Sweet et al, Massachusetts General Hospital.

The Brookhaven aspects of this project are detailed elsewhere. The collaboration consists of preradiation studies on patients, and their postradiation evaluation, as well as extensions of toxicological observations on boron administration.

4. The possible therapeutic effects of radiolanthanum chloride upon pleural or peritoneal carcinomatous effucions.
The distribution of rare earth isotopes other than lanthanum having different half-lives and radiation spectra when injected as chelate compounds.
Dr. Daniel Laszlo et al, Montefiore Hospital.

This collaboration is projected for 1954. Radiation studies will be done at Brookhaven. Chemical studies and postradiation evaluation of patients at collaborating institution.

E. The use of radioactive isotopes to evaluate disease states and the therapy thereof.
Drs. L. K. Dahl, B. G. Stall III, C. G. Foster, J. L. Gamble, Jr.

12. Radioactive isotopes may find one of their greatest uses in medicine in the evaluation of a patient's condition and the effectiveness of the therapy. This requires careful study of the disease mechanisms and development of isotopic compounds capable of yielding the desired information. The use of I^{131} in thyroid disease is one type of example, but this is unique by virtue of the avidity of thyroid for iodine. In most instances the approach will be through evaluation of the cardiovascular-renal system, the gastrointestinal system or some other body component where specific measurements can be made. Short-lived isotopes should be particularly useful in these adaptations.

13. -The distribution of body water and its solutes in body compartments and factors affecting the movement of these constituents.
-The effects of isotopic radiation on physiology and histology of body systems and the exploration of the use for medical purposes of short-lived radioactive isotopes.

14. Patients with Graves disease were evaluated, treated and re-evaluated. By the use of Na^{24} sodium distribution anomalies in the nephrotic syndrome were found.

15. The above studies continued and a comprehensive study was begun of hypertension and the relationship of body electrolytes to control of the disease has been begun. Na^{24} is the element being first explored. To date ~~data~~ in patients with hypertension the Na^{24} studies have shown that the decrease in total exchangeable body sodium which follows sodium restriction is not correlated with decrease in blood pressure.

16. Studies will continue.

ogical assay methods for individual amino acids have been set up together with specific chemical methods to permit selection of best methodology for each experimental study. Ion exchange columns in conjunction with a fraction cutter have been set up to isolate the individual amino acids from biological mixtures.

16. The study will continue.

D. **The mechanisms of protein synthesis and degradation in the intact animal body as elucidated by radioactive labelled proteins, precursors and products.**
Drs. D. D. Van Slyke, F. M. Sinex, L. V. Hankes, P. E. Carson, Jr., L. Gidez, L. E. Farr.

12. The mechanisms by which amino acids are used in the synthesis of protein are not known and it is of particular interest to try to explain why no recognizable intermediates have been found between amino acids and protein; to search for these intermediates and to isolate them if they be demonstrable; to study the metabolism of amino acids with specific reference to their oxidation, storage and incorporation into protein; to study the effects of hormones and other homeostatic mechanisms on amino acid metabolism; and to study the relationship of intra- and extracellular free amino acid concentration as well as other factors related to the incorporation of C^{14} labelled amino acid into tissue protein. To use this knowledge to help explain certain disease phenomena and to explore the effects of radiation on the biochemical systems having to do with protein synthesis, degradation and distribution in the body. In addition to the above there are being developed methods for free amino acid analysis by fraction cutting and chromatography in addition to those already available for patient study.

13. -Utilization of thermal neutrons from the reactor to determine their biological effects, their application to medical therapy and their effects on biological, biochemical, cytological and physiological systems.
-The distribution of body water and its solutes in body compartments and factors affecting the movement of these constituents.
-The effects of isotopic radiation on physiology and histology of body systems and the exploration of the use for medical purposes of short-lived radioactive isotopes.
-The use of radioactive isotopes to evaluate disease states and the therapy thereof.

14. One paper was published on the effect of insulin on the incorporation of carbon 14 into the protein of rat diaphragm. Methods were established and experiments begun on other parts of the problem.

15. To provide adequate supplies of properly labelled l-lysine synthesis of the amino acid is being attempted. Chemical synthesis was explored but an enzymatic synthesis treating l-lysine with bacterial lysine dicarboxylase in the presence of C^{14} bicarbonate has yielded small amounts of properly labelled lysine. Of C^{14} labelled alanine administered to rats, 54% was oxidized within one hour and about 28% was found incorporated in protein of liver, muscle and plasma within the same period. Microbiol-

13. -Utilization of thermal neutrons from the reactor to determine their biological effects, their application to medical therapy and their effects on biological, biochemical, cytological and physiological systems.
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14. Standards of treatment for thyroid cancer patients were established and there was established validity of tracer administration to enable prediction of radiation delivered to the hematopoietic system. Methods were established to study immune mechanisms and preliminary dosages were worked out. Studies were begun on the use of Cl^{38} as a palliative treatment in carcinomatosis and explorations made looking toward clinical use of argon 41.

15. The period during which an animal remains refractory to immune stimuli after isotopic radiation and the dose required has been worked out. Testing is now under way to determine specific roles played by various organs concerned with anti-body productio The series of patients treated with Cl^{36} for fluid accumulation has been enlarged and studies with krypton 87 have been carried out on similar patients. Adenomatous changes of the thyroid have been found in some rats exposed to radiation from I^{131}. Studies have been continued on the control of metastatic thyroid cancer. It has been shown that krypton 87 may suppress formation of acid by the stomach without significant histological changes.

16. Studies will be continued in all productive areas.

C. **The effects of isotopic radiation on physiology and histology of body systems and the exploration of the use for medical purposes of short-lived radioactive isotopes.**
Drs. L. E. Farr, J. S. Robertson, D. C. Tosteson, J. L. Gamble, Jr. R. D. Stoner, J. T. Godwin, C. G. Lewallen, C. G. Foster, C. J. Shellabarger, J. E. Rall, H. L. Conn, Jr.

12. Administration of radioactive isotopes for diagnostic and therapeutic purposes is dependent not only on a full knowledge of the pathways these substances may take in the human body but on a precise knowledge of their effects, metabolic, physiological and cytological, on the tissues which may be exposed to radiation. The avoidance of undesirable effects and enhancement of desired effects is being sought. Experience must range from partly established bases such as use of I^{131} in treatment of thyroid disease and malignancy to explorations on the use of radioactive gaseous isotopes exhibiting certain specific types of physiological and radiological behavior. The study is a broad one and includes the below listed projects:

1. The local control of fluid accumulation associated with carcinomatosis by radiation with short-lived radioactive isotopes such as Cl^{36} (35 min.), A^{41} (108 min.) and Kr^{87} (74 min.)

2. The suppression of gastric acidity with Kr^{87} and A^{41}.

3. The long term histological effects on rats of I^{131} given in doses equivalent to those used for thyroid ablation in patients and to control Graves disease.

4. The histological effects of local radiation on human tissues from internally administered isotopes as in fluid accumulations associated with carcinomatosis and in treatment of thyroid disease and malignancy.

5. Systemic and thyroid effects of I^{131} administered to patients with angina and Graves disease.

6. Control of metastatic thyroid carcinoma with I^{131} especially with reference to increasing tumor avidity for radioactive iodine.

7. Pituitary cytology and its relation to pituitary function, radiation effects and pituitary-thyroid inter-relationships.

8. The effects of radioactive isotope administration on kidney function.

9. Histological changes following localized isotopic beta and gamma radiation in malignant and normal structures.

10. The effects of isotopic radiation on the immune mechanisms with respect to viral, bacterial, toxic and parasitic agents.

14. Methods were developed using the older means of studying body water distribution and certain comparisons were made with Na^{24}.

15. Methods were developed for using Cl^{38}, Br^{82}, Cl^{36} in the measurement of a certain fraction of body water and the validity of such measurements established by comparison with inulin and sucrose measurements simultaneously. Extensive data were obtained on the movement of Na^{24} and K^{42} across the red cell membrane and factors were uncovered which may be significant in affecting this movement in sickle cell anemia. Tracer theory was further developed in accordance with needs for prediction of fast moving components in neutron capture experiments. Several publications have been prepared.

16. The studies will be developed and extended during this interval.

B. The distribution of body water and its solutes in body compartments and factors affecting the movement of these constituents.
Drs. J. S. Robertson, L. E. Farr, J. L. Gamble, Jr., D. C. Tosteson, C. G. Foster, C. G. Lewallen, E. T. Dunham.

12. The use of radioactive isotopes and particularly the use of stable elements which may capture thermal neutrons rests upon available knowledge regarding the distribution of these compounds within the body and the rates at which they move through the various body compartments. In capture therapy it is necessary to develop precise knowledge regarding the fast components in such movements and the barriers which may exist. Much information can be gained by a better knowledge of edema formation and control. The use of radioactive tracers appears to be the best way to obtain desired knowledge and newer short-lived isotopes are being studied to see if by their employment better methods can be developed. The study is being prosecuted through the projects given below:

1. Equilibrium rates of Na^{24} and other electrolytes in edematous and non-edematous patients.

2. Distribution of Cl^{38} Br (stable), Br^{82}, Na^{24} and Cl^{36} in extra- and intracellular fluids.

3. Transfer of Na and K across the red cell membrane with particular reference to sickle cell anemia.

4. Disappearance of Na^{24}, Cl^{36}, Cl^{38}, K^{42}, antipyrine and tritium in various states of thyroid function.

5. Application of tracer theory in analysis of the kinetics of electrolytes in physiological systems.

13. -Utilization of thermal neutrons from the reactor to determine their biological effects, their application to medical therapy and their effects on biological, biochemical, cytological and physiological systems.
-The effects of isotopic radiation on physiology and histology of body systems and the exploration of the use for medical purposes of short-lived radioactive isotopes.
-The mechanisms of protein synthesis and degradation in the intact animal body as elucidated by radioactive labelled protein precursors and products.
-The use of radioactive isotopes to evaluate disease states and the therapy thereof.

11. Effects of neutron radiation of receptor animals on tumor transplantability in mice with especial reference to brain tumors.

12. Neutron depth dose measurements in tissue equivalent phantoms comparing collimated and divergent beams.

13. Design of apparatus to facilitate therapeutic and experimental medicine uses of the Brookhaven reactor.

14. Tissue pathology of organs and tumors exposed to neutron radiation during capture therapy of patients with brain tumors.

15. Tissue changes in mice exposed to neutron radiation with and without administration of capture elements.

16. Tissue cytology in mice exposed to various dosages of compounds used and proposed for neutron capture studies.

17. Analysis of tissue for trace elements by activation by thermal neutron capture.

18. The effects of thermal neutron radiation on protein synthesis and degradation in rats.

19. The effects of neutron capture induced radiation on bacterial cells and their products.

13. The distribution of body water and its solutes in various body compartments and movement between these compartments.

The effects of isotopic radiation on physiology and histology of body systems and the exploration of the use ~~of~~ for medical purposes of short-lived radioactive isotopes.

The mechanisms of protein synthesis and degradation in the intact animal body as elucidated by radioactive labelle protein precursors and products.

14. A beginning was made in the use of the reactor for brain tumor therapy. The feasibility of the procedure was established and the immediate need for certain types of additional information was shown.

15. A series of ten patients with brain tumor was completed with boron 10 capture therapy. Clinical results were apparent in eight of the ten patients suggesting a retardation of tumor growth. The procedure does not seem to alter the blood-brain

barrier through these exposures. Tissue equivalent phantoms have been made and the isodose neutron curves are being worked out. An experimental glioblastoma multiforme has been developed in mice which it is hoped will provide a suitable experimental model for development of better procedures. Histological changes believed to be characteristic of intense high energy radiation presumed to be of capture origin have been noted in specimens examined. A method is being worked out for suitable boron analysis in blood and tissues. Preliminary data on neutron dosage tolerated by intact animals have been obtained. Facilities have been constructed using a side port of the reactor for instrumentation and certain small animal studies. Designs have been made for a facility at the Medical Department's high flux port permitting its use for animal experimentation with the reactor at constant power. Several publications are being prepared dealing with various aspects of the study.

16. The projects will be developed, explored and utilized further as additional data become available. Explorations are being carried out looking toward adding one or two university hospitals in addition to the Massachusetts General Hospital to the cooperating group.