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Form NY00-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Medical Research	2. Date Prepared: 1960	Revision No.
3. Sub-Title:		
4. Budget Activity No. 06-01-02, 06-03-01, 06-03-02	5. Budget Item No.	6. Contractor's No.
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 of Project: Continuing	

SUMMARY

REPOSITORY Brookhaven Nat'l Lab
COLLECTION Form 189 - Med. Dept. 1950-61
BOX No. _____
FOLDER _____

4002168

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Title: Medical Research - Summary (06-01-02; 06-03-01; 06-03-02)

18. Operating Costs (In Thousands of Dollars)	Estimated 1960	Estimated 1961	Estimated 1962
Labor (including Benefits)	1,238	1,525	1,798
Materials, Travel, etc.	370	440	496
Development Subcontracts, Special Proc.	5	28	28
Total Direct	1,613	1,993	2,322
Special Power	-0-	-0-	-0-
Reactor and/or Accelerator Usage	86	95	96
Technical Services (from BNL Service Units)	198	233	268
General & Administrative Overhead	785	869	944
Total	2,682	3,190	3,630
Capital Equipment (Obligations-for information only)	211	240	280

19. Plant & Equipment Directly Required (Obligations-Shown here for information only)

	Estimated 1960	Estimated 1961	Estimated 1962
(A) Construction (In Thousands of Dollars)			
(B) Equipment (In Thousands of Dollars)	211	240	280

FY 1961 equipment will probably include the following special items which will be utilized by more than one medical activity: C^{14} Analyzer - $9,000; Prep Ultra Centrifuge - $8,000; Auto Record Scintillation Spectrometer - $6,500.

FY 1962 equipment will probably include the following special items which will be utilized by nore than one medical activity: Scanning Instrumentation - $12,000; Multi-channel Analyzer (4000 ch.) - $30,000; Whole Body Counting Equipment - $40,000.

20. Direct Man Power No. of Man Years	Estimated 1960	Estimated 1961	Estimated 1962
Scientists, Research Associates	38.5	45.5	48.0
Visiting Scientists	13.0	14.5	18.5
Scientists - Total	51.5	60.0	66.5
Technical	107.0	125.5	144.0
Administrative & Services	18.5	22.5	25.0
Total	177.0	208.0	235.5

21. Comments

REPOSITORY Brookhaven Natl Lab
COLLECTION From 189 Med Dept. 1950-61
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ASSOCIATED UNIVERSITIES, INC. - BROOKHAVEN NATIONAL LABORATORY

MEDICAL RESEARCH - SUMMARY

Page No.	Activity No.	Project Title	F. Y. 1960 Cost in Thousands	F. Y. 1960 Direct Man-Years Scientific Staff	F. Y. 1960 Scientific Vis.	F. Y. 1960 Scientific Tot.	F. Y. 1960 Total	F. Y. 1961 Cost in Thousands	F. Y. 1961 Direct Man-Years Scientific Staff	F. Y. 1961 Scientific Vis.	F. Y. 1961 Scientific Tot.	F. Y. 1961 Total	F. Y. 1962 Cost in Thousands	F. Y. 1962 Direct Man-Years Scientific Staff	F. Y. 1962 Scientific Vis.	F. Y. 1962 Scientific Tot.	F. Y. 1962 Total
06- 7	06-01-02-a	Radioactive Elements in Organs and Tissues of Man	155	2.9	0.4	3.3	10.5	170	3.2	0.5	3.7	11.8	195	3.4	0.6	4.0	13.0
06-16	06-01-02-b	Radioactive Isotopically Labeled Cells for Predictions of Life Span, Functions & Progeny	470	5.0	3.3	8.3	32.5	525	5.7	3.4	9.1	35.9	600	6.0	4.4	10.4	40.6
06-32	06-01-02-c	Hematology & Clinical Management of Radiation Injury	105	1.5	-	1.5	8.3	110	1.8	-	1.8	8.4	125	1.8	0.1	1.9	9.3
06-37	06-01-02-d	Radiation Effects on Immunity and Allergy	170	2.4	-	2.4	11.6	190	2.8	-	2.8	13.3	215	2.9	0.3	3.2	15.0
06-46	06-01-02-e	Radioisotopic Tracing of Total and Intermediate Carbohydrate Metabolism	240	3.6	0.4	4.0	15.3	270	4.0	0.4	4.4	17.2	305	4.2	0.7	4.9	19.3
06-54	06-01-02-f	Radioisotopes for Study of Protein and Nitrogen Metabolism	185	3.8	2.3	6.1	13.0	200	4.3	2.4	6.7	14.5	230	4.5	3.1	7.6	16.3
06-62	06-01-02-g	Radioisotopic Labeled Hormones to Determine Action Sites	75	0.9	1.8	2.7	5.7	80	1.1	1.9	3.0	6.4	95	1.1	2.1	3.2	7.0
06-66	06-01-02-h	Special Projects (Marshall Islands, etc.)	100	0.9	1.3	2.2	3.6	115	1.1	1.4	2.5	5.0	125	1.1	1.7	2.8	5.5
06- 6	06-01-02	Medical Research - Total	1,500	21.0	9.5	30.5	100.5	1,660	24.0	10.0	34.0	112.5	1,890	25.0	13.0	38.0	126.0
06-74	06-03-01-a	Neutron Capture Therapy	485	8.5	1.9	10.4	29.9	635	11.3	2.3	13.6	41.1	720	12.2	2.6	14.8	46.6
06-84	06-03-01-b	Vitamin & Amino Acid Metabolism in Neoplasia and Normality	27	1.0	0.2	1.2	2.2	30	1.0	0.3	1.3	2.4	35	1.0	0.4	1.4	2.6
06-87	06-03-01-c	Labeled Proteins for Metabolic Observations in Cancer Evaluation	225	1.0	0.4	1.4	13.4	290	1.2	0.4	1.6	17.5	335	1.3	0.5	1.8	19.8
06-73	06-03-01	Cancer Research - Total	737	10.5	2.5	13.0	45.5	955	13.5	3.0	16.5	61.0	1,090	14.5	3.5	18.0	69.0
06-90	06-03-02-a	Maps of Metal Pathways with Special Reference to Trace Metals & Central Nervous System Diseases	400	6.3	1.0	7.3	28.3	515	7.2	1.3	8.5	31.0	585	7.7	1.6	9.3	36.5
06-98	06-03-02-b	Selective Single Elemental & Colligative Activation	45	0.7	-	0.7	2.7	60	0.8	0.2	1.0	3.5	65	0.8	0.4	1.2	4.0
06-89	06-03-02	Medical Research - Total	445	7.0	1.0	8.0	31.0	575	8.0	1.5	9.5	34.5	650	8.5	2.0	10.5	40.5
		MEDICAL RESEARCH - TOTAL	2,682	38.5	13.0	51.5	177.0	3,190	45.5	14.5	60.0	208.0	3,630	48.0	18.5	66.5	235.5

Form NY00-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title:		
4. Budget Activity No. 06-01-02, 06-03-01, 06-03-02	5. Budget Item No.	6. Contractor's No.
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 of Project;~~ Continuing	

REPOSITORY Brookhaven Nat'l Lab.
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SUMMARY

The research program of the Medical Department concerns itself with the biological effects of radiation and in particular with particle radiation arising intracellularly with a range of a cell radius or a cell diameter and wherein the energy release is over a very short track. The researches thus are, and must be concerned inherently with studies of precise cell site localization, kinetics of distribution and redistribution, metabolism of organic compounds, function of inorganic compounds, and the effects of excited atoms on the stability of large molecules or complexes. Advantage is sought of special situations wherein specific products or devices are concerned which may be applicable to medical therapy. Diagnostic studies in the widest sense are carried out on suitable disease states under study in the hospital. Such studies are concerned primarily with elucidation of the nature of the disturbance and the proper selection of individuals in a general population for a uniform response rather than with specific diagnostic routines for use in a large general medical clinic, although the latter is kept in mind.

The overall scope of the medical program will not change markedly in any budget year; however, in any given year the emphasis will be on 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: Since the work is part of the Department's continuing program, break-throughs will be exploited when warranted with imagination and determination. In other instances, the knowledge will be brought to the attention of collaborators or others for further development elsewhere.

Specifically, the program contains several component parts which relate the general program as outlined above to the several fields of medicine. The continuing intensive exploration of particle radiation of short range has brought out the necessity for further dosimetric and instrumental developments. In the application of a therapeutic procedure such as neutron capture therapy, it becomes important to know the effect of a single fission event on a single cell so that the probability of biological effect can be estimated by a summation of knowledge of the probability of the capture reaction occurring together with the probable atomic distribution of the boron in the tissue of interest. Thus, it becomes important to know dose effects in terms not of tissue volumes but of cell populations of varying types, closely intermingled, and for the larger part of their metabolism, carrying on identical biochemical reactions. Hence, from time to time greater emphasis must be placed upon differing particle bombardments, for example cosmic rays, ionizing products from boron-10 capture of slow neutrons, neutrons and charged particles.

To elucidate effects, and intimate knowledge must be obtained of cell, organ, or tissue, and of entire mammalian metabolism so that not only is the specific reaction known and identifiable, but its relation and interrelationship to a whole host of other reactions is clearly understood. While this is necessary to assess effects, other knowledge, together with a precise statement of the laws governing passage across cell membranes, must be sought out and established so that specific isotopes may be placed in specific situations in order to observe specific effects. To the general area of knowledge concerned with such target placement, the term "selective kinetics" has been applied.

(See continuation sheet)

It is clear that capability to place and fix an atom on a specific cellular target without diversion, wandering, or delay implies a concise knowledge which in the reverse could be employed to remove an atom from a cell, organ or tissue effectively and expeditiously and without engendering harm to the body as a whole or its constituent parts. While much work will be concerned with specific body constituents added under experimental conditions, it is clear that additional useful, extremely accurate, and rapid analytical methods are necessary. In part they will be pioneered through the further adaptation of machines, devices, and products of nuclear physics to the solution of specific biological, analytical problems. The exploration and development of activation analysis is an example of this effort.

The medical research program now in existence covers the following broad lines of investigation, all of which are closely integrated operationally.

06-01-02 - Radiation Effects on Biological Systems-- Medical Research

- 06-01-02-a Radioactive Elements in Organs and Tissues of Man
- 06-01-02-b Radioactive Isotopically Labeled Cells for Predicitions of Life Span, Functions and Progeny
- 06-01-02-c Hematology and Clinical Management of Radiation Injury
- 06-01-02-d Radiation Effects on Immunity and Allergy
- 06-01-02-e Radioisotopic Tracing of Total and Intermediate Carbohydrate Metabolism
- 06-01-02-f Radioisotopes for Study of Protein and Nitrogen Metabolism
- 06-01-02-g Radioisotopic Labeled Hormones to Determine Action Sites
- 06-01-02-h Special Projects:
  1. Educational Conferences
  2. Marshallese Survey
  3. Summer Student Institute
  4. Occupational Medicine Clinic

06-03-01 - Beneficial Applications of Atomic Energy--~~Cancer~~ Brookhaven Nat'l Lab. Research

- 06-03-01-a Neutron Capture Therapy COLLECTION From 189 Med. Dept. 1950 - 61
- 06-03-01-b Vitamin and Amino Acid Metabolism ~~in Neoplasia and Normality~~ BOX NO.
- 06-03-01-c Labeled Proteins for Metabolic ~~Observations in Cancer~~ FOLDER Evaluation

06-03-02 - Beneficial Applications of Atomic Energy--Medical Research

- 06-03-02-a Maps of Metal Pathways with Especial Reference to Trace Metals and Central Nervous System Diseases
- 06-03-02-b Selective Single Elemental and Colligative Activation

The heading of "Special Projects", 06-01-02-h, gives details of certain self-contained projects carried out by the Department, such as the operation of an occupational medicine clinic, educational conferences and other educational activities, and the continuing medical study of the Marshall Islanders. While very important and significant in their own right, they derive from staff competence gained by Brookhaven experience rather than basically providing that experience for the scientists concerned. Costs for operating the occupational medical clinic are included in the general and administrative costs of the Laboratory and are distributed as Indirect Expense. On the other hand, costs for such Special Projects as the Marshallese studies are included in the costs of Radiation Effects with the major expense being borne by AEC Activity 06-01-02.

The program of the Medical Department can be divided into two components, (1) which may be called the intramural program which is carried out by the regular full time staff at Brookhaven and, (2) the extramural program which is a joint venture between the regular full time staff at Brookhaven and a non-salaried research collaboration staff working part-time, intermittently at Brookhaven but

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(See continuation sheet)

carrying on much of their research at their home institutions. Included in the extramural program are the educational activities of the Department. These range from lectures given to institutions and societies to an annual conclave in which attendance is by invitation only and one person from a specific discipline in each medical school of the United States and Canada is invited. This endeavor particularly well emphasizes the point that in publicizing its research the Department inextricably blends its investigative work into its educational program. The conclaves cover specific, clinical, financial, and administrative phases of this new area of medical science on which the Department can offer guidance and counsel.

In 1952 the definitive plan for the ultimate staffing of the Medical Department was presented and approved in principle. It was agreed the professional staff should be 49 physicians with an adequate supporting technical staff. In FY 1959, the professional staff level exclusive of the physicians in the Industrial Medicine Group was 41, in FY 1960 it was 40, in FY 1961 the level should return to about 49.

The Medical Department has now developed its program in outline. During FY 1960 and FY 1961 there should logically be an increase in intensity of work on most of the basic division 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 Mn^{56}; (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 shortlived isotopes in gaining a better understanding of cancer therapy; (5) the effects of radiation as a carcinogenic and mutagenic agent with particular reference to the usefulness of whole body counting techniques 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 in two main areas: (1) the biological effects and medical implications of radiation exposure and (2) the reactor program which in turn is composed of two parts: (a) the design of a Medical Research Reactor and its component parts, and (b) the use of reactors in medical research and therapy. The importance of the first is exemplified by the present controversy on the effects of fallout. An additional whole-body counter, a multiple-foci chrono-intensity detector, and additional animal facilities will enable the increased staff productively to work on these problems. The importance of the problem regarding reactors is pointed up by the number of reactors built, under construction 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.

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Form NYOO-230
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-UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title:		
4. Budget Activity No. 06-01-02	5. Budget Item No.	6. Contractor's No.
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: See Individual Project Proposals	11. Starting Date of Project: Continuing	

SUMMARY

14. Related Projects:

The general, broad subject covered by this activity is under investigation at other U.S. and foreign research institutions. However, to the best of our knowledge, the specific conceptual approach and techniques of this BNL program are in most cases not being utilized at other laboratories and are frequently beyond the capabilities of other research centers.

REPOSITORY Brookhaven Natl Lab
COLLECTION Item 189 Med. Dept. 1950-61
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Title: Medical Research 06-01-02

18. Operating Costs (In Thousands of Dollars)	Estimated 1960	Estimated 1961	Estimated 1962
Labor (including Benefits)	676	777	919
Materials, Travel, etc.	227	244	272
Development Subcontracts, Special Proc.	3	19	19
Total Direct	906	1,040	1,210
Special Power	-0-	-0-	-0-
Reactor and/or Accelerator Usage	46	47	47
Technical Services (from BNL Service Units)	109	121	142
General & Administrative Overhead	439	452	491
Total	1,500	1,660	1,890
Capital Equipment (Obligations - for information only)	120	105	110

19. Plant & Equipment Directly Required (Obligations - shown here for information only)

	Estimated 1960	Estimated 1961	Estimated 1962
(A) Construction (In Thousands of Dollars)	—		
(B) Equipment (In Thousands of Dollars)	120	105	110

FY 1961 equipment obligations for this activity include a proportional part of the total obligation for special items which will be utilized by more than one medical activity. (see Medical Research Summary) - $10,800.

In addition the following special item will probably be acquired for this activity: B^{12} Counting System - $10,000.

FY 1962 equipment obligations for this activity include a proportional part of the total obligation for special items which will be utilized by more than one medical activity. (see Medical Research Summary) - $26,000.

20. Direct Man Power	Estimated 1960	Estimated 1961	Estimated 1962
No. of Man Years			
Scientists, Research Associates	21.0	24.0	25.0
Visiting Scientists	9.5	10.0	13.0
Scientists - Total	30.5	34.0	38.0
Technical	58.0	65.5	73.5
Administrative & Services	12.0	13.0	14.5
Total	100.5	112.5	126.0

REPOSITORY Brookhaven National Lab.

21. Comments

COLLECTION Form 189 Medical Dept. 1950-61

BOX No

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Form NY00-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Radioactive Elements in Organs and Tissues of Man		
4. Budget Activity No. 06-01-02	5. Budget Item No. 06-01-02-a	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-01-02-a Radioactive Elements in Organs and Tissues of Man (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	155	170	195
Direct Man-Years			
Staff	2.9	3.2	3.4
Visitors	0.4	0.5	0.6
Scientific	3.3	3.7	4.0
Other	7.2	8.1	9.0
Total	10.5	11.8	13.0

The human body normally contains radioactivity. The significance of the radiation exposure coming from these radioisotopes is dependent upon the element, its biochemical effects, its cellular location, and the nature of its radioactive emissions. Since evolution has occurred in the presence of small amounts of radiation, the exposure resulting from these so called naturally occurring radioactive isotopes is presumed to be within tolerance limits. It is clear, however, that with the development of atomic energy man's environment in terms of radiation exposure is changing. Further contamination of the environment by a wide spectrum of radioactive elements, some of which will gain access to the interior of the body, will undoubtedly occur. The significance, or indeed the presence of this body contamination remains to be discovered. To determine the amount, and attempts to deduce the significance of radioactive isotopes in the human body from whatever source is the concern of this study.

06-01-02-a-(1) Whole Body Counting Facility and Radiochemistry Laboratory

REPOSITORY Brookhaven Natl Lib.

Persons in Charge: S. H. Cohn and J. S. Robertson

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12. & 13. Objectives and Overall Description:

BOX No.

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The Brookhaven National Laboratory whole-body counting unit, patterned after the system developed at Argonne National Laboratory employs a single NaI (Tl) crystal detector. In order to achieve a high signal-to-noise ratio with the low signal levels demanded by safe tracer concentrations, a steel room is used to suppress background radiation. The walls, ceiling and floor of this 6' x 7' x 9' room are formed of 6" steel, and the inner walls are lined with 0.125" Pb, 0.040" Cd and 0.040" Cu. At the present time, the radiation detector is a 4" x 5" sodium iodide crystal used in conjunction with a 5" photomultiplier tube. The gamma spectrum is obtained with a Penco 100-channel pulse-height analyzer.

Patients are counted for a 10-minute period while seated in a standardized position which provides a fixed geometry. The detector is located over the abdomen, equidistant from the back and the seat of the chair. The gamma emitting isotopes in each patient are determined prior to administration of the labeled albumin material or radioactive ion such as Na. The gamma spectra are measured at various time intervals. The amount of activity is determined by measurement of

(See continuation sheet)

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12. & 13. Objectives and Overall Description: (contd.)

the area under the curve of the photopeaks of the predominant gamma energies, less the background activity for these channels.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

Construction of the whole-body counting facility and its gamma spectrometer and a low-level radiochemical laboratory and a low-level anticoincidence type beta counter have been completed and are now in use. These facilities have come into wide use in various research programs, and the research programs using these facilities are hereby listed.

1. Whole body counting facility

A. I^{131} labeled albumin, I^{131}-beta globulin, I^{131} Thyroglobulin and I^{131} turnover studies in control and diseased patients.

B. Na^{22} turnover studies in control and hypertensive patients maintained on various salt intakes.

C. Sr^{85} and Zn^{65} uptake and kinetics in patients with bone disease (in collaboration with Montefiore Hospital).

2. Radiochemistry laboratory

A. Analysis of Sr^{90} in urine and food samples obtained from the 1959 Medical Survey of the Marshall Islands.

Details of these projects will be found in 06-01-02-f, 06-01-02-i, 06-03-01-b, 06-03-01-c and 06-03-02-a.

Related to these projects are the following: Attempts to correlate the neutron-induced gamma activities with the neutron dose received by patients treated with neutrons in the neutron-capture therapy program. A number of individuals were counted to determine the body burdens of internally-deposited radium as well as a number of people accidentally exposed to radioactive material.

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COLLECTION [illegible] Med Dept 1950-61
BOX No.
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16. Expected Results This Fiscal Year - 1961:

In Fiscal Year 1961 the following program will be prosecuted.

A survey of representative groups of persons with the whole-body gamma spectrometer will be undertaken in order to provide data on the level of internally deposited radionuclides in the population. Clinical studies will be continued, employing gamma emitters such as Sr^{85}, Na^{22}, and possibly, Ca^{47}. Emphasis will be placed on skeletal mineral metabolism in various disease states of the patient. In addition, a number of collaborative studies will continue, involving the determination of the turnover rates of labeled protein and other radionuclides in various disease states. The low-level radiochemistry service will be continued, primarily for the determination of levels of Sr^{90}. Studies on the growth and metabolism of bone will be continued using animals, particularly the effect of both external radiation and radiation from internally-deposited radionuclides (Sr^{90}) on the rates of accretion and exchange of skeletal minerals. Investigation will be made of the possibility of in vivo Sr^{90} counting by suitable modification of the whole body counting facility to utilize the Bremsstrahlung effect. The object is to develop a technique for external Sr^{90} counting which will be suitable for a population survey similar to that planned for gamma-emitting radionuclides. Many of the biological half-times for radionuclides in the whole body and in various tissues should be re-evaluated. Whenever appropriate, this problem will be investigated with the use of the whole-body and gamma spectrometer facilities.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

06-01-02-a-(2) Gastric Secretion of Halides

Persons in Charge: J. S. Robertson, R. L. Cranny

12 & 13. Objectives and Overall Description:

It has previously been established elsewhere that the gastric mucosa and the salivary glands concentrate iodine and other halides, but the variation with time of the amount of radioactive iodine present in the stomach following intravenous injection of the radioactive iodine has not been well documented. Study of the rates of secretion of iodine and other halides by the stomach under various conditions have therefore been undertaken with the expectation that such information would be of value in three areas: i) in contributing to knowledge of the physiology of the stomach and in further elucidating the mechanism by which the stomach secretes hydrochloric acid, ii) in assessing the possibility that variations in the concentration of iodine by the stomach could affect the interpretation of thyroid iodine uptake studies because of the competition between the thyroid and the stomach for iodine, and iii) in providing a better basis for calculating the dose of radiation delivered to the gut where large therapeutic doses of iodine are administered to patients.

Studies of the gastric secretion of iodine by rats were begun by J. S. Robertson and S. H. Cohn at the NRDL (both investigations are presently at BNL) in 1954 and were continued at BNL during the summer of 1956 by J. S. Robertson, P. W. Durbin (a research collaboratory from Berkeley) and D. Sohn (a summer student). The 1956 studies involved simultaneous injection of I^{131}, Br^{82}, Cl^{38}, and At^{211} in pairs. Analysis of the as-yet unpublished data indicated that to some extent the apparent differences in the gastric secretion rates of the various halides are actually due to differences in absorption rates.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960

Study of the problem of gastric secretion of the halides was resumed in FY 1960 with attention directed to getting more detailed time variation curves for the I^{131} content of the stomachs of rats, and to evaluating the effects of age and of recent feeding versus non-feeding for 12 hours prior to the study. The I^{131} content of the thyroid, kidneys, blood and carcass was determined simultaneously. Points were obtained at intervals of 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, and 24 hours following intravenous injection of I^{131}. Three hundred and fifty rats have been studied. These studies were extended to 6 patients with malignant conditions, with I^{132} being used instead of I^{131} in order to keep the dose of radiation within the accepted limits. In the patients, I^{132} was administered intravenously, blood samples withdrawn serially, and the counting rates over several parts of the body including the thyroid and the stomach were obtained at intervals with an in-vivo scintillation counting system. The maximal iodine activity in the stomach occurs at about 1 hour after administration.

16. Expected Results This Fiscal Year - 1961

There is still a backlog of data to be analyzed, but no further data acquisition is contemplated. The project will be terminated because of Dr. Cranny's non-continuation and until another assistant interested in this problem is acquired.

17. Expected Programs and Results for Next Fiscal Year - 1962

No activity.

Brookhaven Natl Lab
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06-01-02-a-(3) The Mathematical Basis for the Interpretation of the Behvaior of Tracers

Person in Charge: J. S. Robertson

12 & 13: Objectives and Overall Description:

Although the basic principles by which the behavior of radioactive tracers to the behavior of the systems into which the tracers are introduced are well established, their application to particular biological problems involves assessment of the pertinent assumptions, construction of applicable mathematical models, and a continuing back-and-forth exchange of information and ideas between those who are collecting data and those who are analyzing the data. There are also areas in which the theoretical treatment itself requires extension, including a search for better mathematical techniques.

A review article published in 1957 summarized the status of the theoretical approach to studies of the kinetics of tracers in biological systems at that time and included original contributions to the procedures for applying the basic principles to practical problems. The methods of mathematical analysis have been applied in numerous tracer studies conducted in the Medical Department.

The difficulty of choosing among several possible mathematical models by desk computations helped establish a need for methods of machine computation. An analogue computer capable of handling 4 compartments in the steady state was built and used in several studies such as in the evaluation of model systems suggested for use in the interpretation of radio-manganese studies then underway. Construction of a more versatile computer capable of handling 8 compartments was begun.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960

One of the major problems for which analysis was attempted is the kinetics of tritiated thymidine behavior observed in the bone marrow. A completely satisfactory model is yet to be achieved but the theoretical work has provided suggestions for further experiments. Another problem has been the kinetics of iodinated proteins, which is complicated by the fact that degradation of the labeled proteins introduces free iodine into the system under study and the detection methods used do not distinguish between free and bound iodine. The recently completed larger analogue computer has been useful in approaching these problems. This computer is designed principally for analysis of steady-state compartmented systems with equal rates of flow in the two opposing directions between each pair of compartments. In addition to the practical problems mentioned, the computer has had use in extending the theoretical analysis to more complicated systems. For study of the labeled protein degradation, operational amplifiers were used as one-way pumps.

REPOSITORY Brookhaven National Lab.
COLLECTION Iowa 189 Med. Dept. 1950-61
BOX No.
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16. Expected Results This Fiscal Year - 1961

It is very difficult to predict the future in this field because what will be done depends in a large degree upon what problems arise, and this in turn depends as much or more upon the actual data to be obtained than upon preconceived notions of what to expect. Among the foreseeable applications are further studies of the kinetics of tritiated thymidine, of the radioactive halides used in the gastric secretion studies, and of various electrolytes. Further development of the analogue computer to increase its flexibility for handling non-steady-state problems is contemplated. Further development of the methods for storing and displaying experimental data in the computer system is also desired.

Certain experimental data on solvent transfer rates across semi-permeable membranes have been interpreted by others as indicating that tracers do not

(See continuation sheet)

16. Expected Results This Fiscal Year - 1961 (Contd)

accurately follow the non-labeled components in the case of somatic flow. An alternative explanation that suggests itself is that the uni-directional flux has been overestimated because of incorrect assumptions regarding the nature of the osmotic process and the value of the driving force. Studies of diffusion at high pressures, i.e., about 1000 atmospheres, would help resolve the controversial issues involved by testing the question of whether the chemical activity of water is the driving force for diffusion.

17. Expected Programs and Results for Next Fiscal Year - 1962

This is a long-term continuing project. Expansion will occur only after equipment has been received and assembled, and if results prove to be of significance.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Jnm 189 Med. Dept. 1950-61
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06-01-02-a (4) Radiation Induced Carcinogenesis

Persons In Charge: C.J. Shellabarger, V. P. Bond, E. P. Cronkite, and S.W.Lippincott

12 & 13. Objectives and Overall Description:

It is known that large doses of radiation, under certain not-well-defined conditions, may produce neoplasia. As the result of an accidental discovery some four years ago, this Laboratory has developed a biological system to study the induction of mamary neoplasms of the rat by sub-lethal x or gamma radiation. It is proposed to combine the findings already made, and described below, and with future experiments, partially described below, to learn more about the mechanism of tumor induction by radiation in a long-range program.

Many of the experiments involve the study of exposed rats for a period of 12 to 24 months. Thus it is difficult to show clearly fiscal year by year accomplishments.

Before the Fiscal Year 1959, it was demonstrated that young virgin female Sprague-Dawley rats respond to a single sub-lethal, total body, x or gamma radiation exposure with an incidence of rats with one or more neoplasms of the breast that is 60 to 80 times higher than non-exposed rats of the same age -- approximately one year of age.

In Fiscal Year 1959, the following results were obtained when the rats were studied for approximately 1 year after exposure. 400 r of x-ray to females, an 80% incidence, ovariectomized females, males, and castrate males, a 25% incidence, non-exposed rats of the same age with the same surgical treatments, a 0-2% incidence. The response was linear between 25 and 400 r, above 400 r the incidence did not increase. When female rats were exposed to partial body exposure, more than 90% of the breast neoplasms appeared under the area of the x-ray beam.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

400 r of x-ray induced 70 per cent of the female rats to show one or more breast neoplasms when given as a single dose, or divided in 5 or 18 equal doses. Pregnancy, lactation, thyroid hormone, and a thyroid blocking agent did not change the response to 400 r. Estrogen reduced tye incidence in rats exposed to 400 r from 70% to 30%.

16. Expected Results This Fiscal Year - 1961:

The response of Long-Evans male and female rats to 400 r will be completed and compared to the results obtained with Sprague-Dawley rats. The study of the effects of 400 r as divided doses given over 4 months to female Sprague-Dawley rats has begun and will be completed.

17. Expected Programs and Results for Next Fiscal Year - 1962:

Approximately 5 years and 2500 rats have gone into these studies and the following facts are becoming apparent. Neoplasia of the rat breast occurs more often in exposed than in non-exposed rats; this effect is dose-dependent; effect is at least in part dependent upon direct radiation exposure of the breast tissue; and the effect is in part independent of the time over which the radiation exposure occurs. It is proposed to extend these studies, as facilities permit, to investigate the factors that influence radiation exposed tissue to develop neoplasia.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION From 189 Med. Dept. 1950-61
BOX No
FOLDER

06-01-02-a (5) Distribution of Technetium in Animals

Persons in Charge: C. J. Shellabarger

12 & 13. Objectives and Overall Description:

Through the cooperation of the Hot Laboratory (M. W. Greene) Tc^{99} has become available for biological studies. This element is not stable, it is only radioactive and is produced by fission. There are Tc isotopes that have a half-life of many thousand years, however the istope Tc^{99} has a half-life of six hours. Tc is a member of the VII group in the periodic table. Since it had been reported that another member of this group, Re, was concentrated in hen eggs, Tc^{99} was given to 10 laying hens by the subcutaneous route. Tc^{99} radioactivity was detected in eggs laid by these hens. It has not yet been determined if this is a process peculiar to these chemical elements or is part of a general metabolic process resident in egg production.

Iodine is concentrated by the thyroid gland and becomes part of the thyroid hormone. Other members of the VII group of elements are concentrated by the thyroid gland, Mn, Re, Br, At, but not utilized in the synthesis of thyroid hormone. Tc^{99} was investigated, using approximately 150 rats, in all cases Tc^{99} was concentrated by the thyroid gland. In these experiments, I^{131} was found in the thyroid gland in larger amounts than Tc^{99}, and these results are compatible with the hypothesis that although Tc^{99} is concentrated by the gland, Tc^{99} is not utilized in the synthesis of thyroid hormone.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

The mechanism of concentration of iodine and other members of the VII group of elements is not understood. By using conventional techniques, chemical and biological, the thyroidal concentration of Tc^{99} and I^{131} in animals was investigated in an effort to learn more about this mechanism.

16. Expected Results This Fiscal Year - 1961:

This project will not be continued.

17. Expected Programs and Results for Next Fiscal Year - 1962:

No Activity.

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

06-01-02-a (6) Isotope Localization

Person in Charge: J. S. Robertson

12 & 13. Objectives and Overall Description:

The present methods of isotope localization detection depend upon scanning the area of interest with a collimated crystal or crystals which are moved mechanically. A particularly useful system of this type involves the use of a coincidence circuit and two crystals moving synchronously on opposite sides of the body to locate positron emitters. There is a need for a much more rapid method for acquiring the same information.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

Construction of a 4906-channel pulse-height analyzer by the Electronics Division of BNL was in progress. This device will make it feasible to record coincidence counts in any pair of up to 64 detectors on each side. This will make it possible not only to eliminate mechanical scanning, but will improve the efficiency of the method by recording coincidences not only between directly-opposite crystals but between any pair of crystals.

16. Expected Results This Fiscal Year - 1961:

Construction of a multiple crystal detection system, probably with only 10 cyrstals on each side in the first model, is contemplated. When completed, this will be used in localization studies involving several positron-emitting isotopes such as As^{76} and I^{124} which are known to or may be expected to localize in tumors. The theoretical problem of interpreting the two-dimensional display of information which the 4096-channel analyzer will provide, in terms of the real three-dimensional system has not yet been solved and will be attacked. It may be necessary to resort to a three-dimensional analog method of displaying the data.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Form 189 Med. Dept. 1950
BOX No.
FOLDER
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4002183

06-01-02-a-(7) Blood Clearance Rates of Injected Isotopes

Persons in Charge: S. H. Cohn and S. Fine.

12. & 13. Objectives and Overall Description:

Data on the very early clearance of radioactive elements from the blood stream are difficult to obtain. Special equipment and techniques may aid in obtaining data of this nature, particularly in regard to the alkaline earth elements.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

In 1960 a scintillation counter has been designed so that the counting equipment can be placed directly in the circulatory system of the dog.

16. Expected Results This Fiscal Year - 1961:

In 1961 development of this equipment with the addition of rate meters with fast time constants and fast recorders should make it possible to obtain an instantaneous and continuous record of blood clearance of isotopes of the alkaline earth group. This program is expected to end during this fiscal year.

17. Expected Programs and Results for Next Fiscal Year - 1962:

No activity.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Inm 189 Med. Dept. 1950-61
BOX No.
FOLDER

Form NYOO-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Radioactive Isotopically Labeled Cells for Predictions of Life Span, Functions and Progeny		
4. Budget Activity No. 06-01-02	5. Budget Item No. 06-01-02-b	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-01-02-b Radioactive Isotopically Labeled Cells for Predictions of Life Span, Functions and Progeny-(Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	470	525	600
Direct Man-Years			
Staff	5.0	5.7	6.0
Visitors	3.3	3.4	4.4
Scientific	8.3	9.1	10.4
Other	24.2	26.8	30.2
Total	32.5	35.9	40.6

Man and all mammals came ultimately from a single cell. During embryonic growth and continuing until maturity, cell differentiation is predominant as well as multiplication. The specific factors affecting cell differentiation are unknown but are believed to be controlled by specific chemical substances. These substances, while not necessarily identical with the genetic material, may interact with it to produce new cell types, thereafter consistently reproducing. It is of the greatest importance to learn how this genetic material is transmitted from one cell to another and how it may be altered so that in the one instance a new species arises whereas in the other a neoplasm arises. Radioisotopic labeling provides a possible means but it must be firmly established that the radioisotopic label itself does not affect the process observed. Varieties of labels providing different energy inputs may give insight into the answers to both questions.

06-01-02-b-(1) Tritiated Thymidine Study of Cellular Contribution of the Periosteum to Bone Growth, Fracture Repair as a Function of Age and to Localize the Factors Responsible for Stimulating Bone Cell Proliferation Following Trauma.

Persons in Charge: E. A. Tonna, E. P. Cronkite, E. A. Usenik.

12. & 13. Objectives and Overall Description:

Studies have been made on histochemical changes (phosphatases, respiratory enzymes, sulfated mucopolysaccharides and cytological changes (population of osteoblasts and mitochondrial complement, changes in mitochondrial morphology, etc) from birth to old age in the femoral periosteum of rats and mice and at different periods after healing. It had been established during 1958 and 1959 that there is a marked reduction in the elements listed above with increasing age.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

REPOSITORY Brookhaven Natl Lab.
COLLECTION Trm 189 Mid Oct. 1960-
BOX No.
FOLDER

(See continuation Sheet)

Project Title: Tritiated Thymidine Study of Cellular Contribution of the Periosteum to Bone Growth, Fracture Repair as a Function of Age and to Localize the Factors Responsible for Stimulating Bone Cell Proliferation Following Trauma 06-01-02-b-(1)

15. Accomplishments Last Fiscal Year - 1960:

The use of tritiated thymidine was initiated in 1960 and it was shown that the periosteum significantly contributes to the growth and changing architecture of bone in mice and rats. During the period of active growth, it has been shown by the thymidine technique, that the periosteum significantly contributes to the changing architecture and growth of the bone. Previously it had been felt that most of the cellular contribution to growth came from the epiphyseal plate. This has been conclusively shown not to be true and that the area of periosteum adjoining the ends of the bone significantly contributes to the remodeling. These studies have been completed and are in the process of publication. Fracture studies have been initiated and it has been found that factors connected with the fracture rapidly shifts the quiescent periosteal cells in the mid shaft and throughout the shaft from this quiescent state to active proliferation of DNA commencing approximately 12 hours after the fracture. The kinetics of periosteal growth and function in repair are underway.

16. Expected Results This Fiscal Year - 1961:

During 1961 studies are going to be initiated on the influence of hormones, vitamins, radiation etc. on bone growth, development and repair utilizing approximately 250 mice and 100 rats and selected dogs for some studies. If and when the humoral or cellular factor that is liberated by a fracture which stimulates quiescent periosteal cells to DNA synthesis and proliferation is determined, chemical studies will be initiated to characterize this stimulatory factor. The studies on bone, growth, repair, proliferation will be continued indefinitely.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Iron 159 Med. Dept. 1950-61
BOX No.
FOLDER

4002186

06-01-02-b-(2) Studies of the Metabolic Pathways of DNA and its Precursors in Radiation Injury and During Radio and Chemotherapy

Persons in Charge: E. P. Cronkite, V. P. Bond, H. Johnson, S. Killmann, P. Reizenstein, E. A. Tonna and E. Usenik

12. & 13. Objectives and Overall Description:

Knowledge of the degradation pathways of labeled DNA in normal and malignant cells is vital to evaluation of radiation injury and certain types of therapy just as the metabolic pathways of DNA precursors are vital to understanding normal and neoplastic cell growth. More complete data are needed on the availability, time and fate of injected tritiated thymidine in patients and animals.

Prior to 1959, the following were established: 1) Plasma clearance of tritiated thymidine in degradation pathways in normal and in patients with leukemia. 2) In collaboration with Oak Ridge National Laboratory, the excretion of beta aminoisobutyric acid in the Y-12 patients was shown. 3) In patients in the hospital at Brookhaven, the excretion of labeled beta aminoisobutyric acid was shown following the administration of tritiated thymidine. 4) The excretion patterns of beta eminoisobutyric acid in leukemics during and between therapeutic regimes have been established. 5) The excretion of beta aminoisobutyric acid has been correlated with low mitotic index (low cell turnover) and with a possible shunt of thymine to beta aminoisobutyric acid suggesting a constant endogenous level of thymidine production and a spillover into the thymidine - BAIBA pathway when the DNA synthetic pathway is blocked or eradicated.

During 1959, the data collected and listed above was written up and published in a series of reports that have been either accepted or are published. In the above studies excretion was followed serially over many weeks in 25 patients with diverse blood dyscrasias, the 5 Y-12 casualties, 12 irradiated dogs, 24 irradiated guinea pigs, and 60 irradiated rats.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

As clinical material becomes available for appropriate studies in expanding the knowledge on the metabolism on thymidine, its relation to beta aminoisobutyric acid and degradation products of DNA in normal and malignant states will be undertaken. During 1960 they have continued at about the same rate but not expanded.

16. Expected Results This Fiscal Year - 1961:

The status of this work will be evaluated again during 1961 and these studies will probably be terminated during 1961.

17. Expected Programs and Results for Next Fiscal Year - 1962:

No activity.

REPOSITORY Brookhaven Natl Lab
COLLECTION Form 189 Med. Dept. 1950-61
BOX No.
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06-01-02-b-(3) Attempt at Complete Solution of Kinetic Model for Bone Marrow Cell Proliferation

Persons in Charge: P. Reizenstein, E. P. Cronkite, V. P. Bond, J. S. Robertson, S. A. Killmann

12. & 13. Objectives and Overall Description:

A number of techniques are employed currently to estimate the proliferation rate of human and animal bone marrow cells. Such techniques include the determination of relative number of cells or mitotic indices in different morphological cell compartments; determination of the tritiated thymidine labeling index, degree of labeling, and increment increase of labeling index in different morphological bone marrow cell compartments; and turnover rate of erythrocytes or leukocytes in the circulating blood compartment. The application of a single technique will usually yield insufficient information to obtain both the size and turnover rate in the different cell compartments. However, as indicated by the frequent use of the word "index", ratios will instead be obtained which are often complicated functions of the size of the compartment studied and the flow rates out of and into this compartment.

It has long been planned to pool all the data obtained from all the techniques mentioned, in order to see whether a complete solution can be achieved. An attempt is being made to construct a suitable kinetic model with equations describing the data obtained with the single techniques. By introducing numbers for these data, obtained during earlier experiments, a preliminary attempt will be made to see whether or not the system can be solved. If it is possible to obtain a solution, an experiment is planned, employing simultaneously in one single patient all the techniques mentioned. If the experiment is successful, it is conceivable that the size of the different cell compartments, the flow rates between them, and, consequently, the times spent in these compartments, can be given in absolute figures for the first time.

During 1958, in vitro and in vivo tritiated thymidine labeling studies were performed on 2 patients in hemopoietic equilibrium. The crude mitotic index and specific index was worked out in a series of 12 normal young males.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

During FY 1960, the completion of the model has been started.

16. Expected Results This Fiscal Year -1961:

When the mathematical model is considered satisfactory, further studies will be performed upon 1-6 patients in hemopoietic equilibrium in whom it is appropriate to administer tritiated thymidine intravenously. In large animals, comparable studies, probably in 6 dogs, will be performed. It is probable that if this approach is successful that the model and its experimental testing will act as the basis for the design of further experiments for many years to come.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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

06-01-02-b-(4) In Vivo Studies with H^3 Thymidine, H^3 Cytidine and $S^{35}O_4$.

Persons in Charge: E.P.Cronkite, V.P. Bond, S.A. Killmann, P. Reizenstein, E.A. Tonna, E.A. Usenik, J.Bateman, L. Feinendegen, N. Ordartchenko and A. Tsuya.

12 & 13. Objectives and Overall Description:

Labeling cells with H^3 thymidine at the time of synthesis of DNA prior to mitosis enables one to study migration, pathways, cell transformation, proliferation rates and capabilities, life span, and function of these cells in human beings and animals. Particular attention has been given to normal hematopoiesis and selected leukemias and lymphomatour diseases of man and dogs.

Labeling RNA with H^3 cytidine enables one to follow the relationship of RNA turnover to cell proliferation, function, and transformation, particularly in hematopoieses and during induction of antibody formation.

Prior to 1959, labeling of nucleated normal hematopoietic cells in 120 mice, 24 guinea pigs, 100 rats, 12 dogs, 2 patients in hemopoietic equilibrium was accomplished, and 13 patients with blood dyscrasias were studied. During 1959, further studies have been performed on 4 patients with blood dyscrasias (1 multiple myeloma and 3 leukemias) and the data collected prior to 1959 has been analyzed and submitted and accepted for publication. It has been shown that the turnover time of megakaryocytes by tritiated thymidine labeling is of the order of 10 days. The turnover time for the orthochromatic normoblast is approximately 20 hours and for the metamyelocyte is approximately 26 hours. The time to flow from the most immature granulocytopoietic precursor to the segmented neutrophil in the peripheral blood is of the order of 9 days. The upper limit for time in the peripheral blood of the neutrophil is 28 hours.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

REPOSITORY Brookhaven Nat'l Lab
COLLECTION Tonn/89 Med. Dept. 1950-61
BOX No.
FOLDER

15. Accomplishments Last Fiscal Year - 1960:

These studies continued in FY 1960 with the goal of obtaining a total description of the kinetics and a model for hemopoiesis that will supply a base for further definitive studies on the regulation of blood cell production and its disturbance in normal and diseased individuals. These studies will continue indefinitely and at least for a period of the next 5 years.

The possible hazard of radiation injury by tritiated thymidine limits the use of this material in patients with leng life expectancy because of the unknown carcenogenic effect and because of the unknown role of possible genetic effects transmitted by procreation. In FY 1960, it was shown that tritiated thymidine in doses of 0.05 to 0.5 μc/gram are adequate for the labeling of spermatogenesis in the mouse yet this level of radioactivity did not produce any detectable radiation injury as judged by the Oakberg technique for depletion in the spermatocyte population 60 hours after labeling. Doses in excess of μc/gram begin to show detectable interference with spermatogenesis. This work has been completed and published and further studies on spermatogenesis are not contemplated. Comparable studies on H^3 thymidine radiation injury on lymphocytopoiesis were initiated in FY 1960 and are continuing. The Trowell technique of pyknotic lymphocyte counts has been used to indicate that in doses in excess of 5 μc/gram approaches an injury produced by approximately 75 rad external x-ray in rats.

The very small per cent of circulating lymphocyte cells which synthesize DNA is uniform throughout all mammals studied including patients. The implication of the low labeling both in vitro and in vivo indicate that most small lymphocytes are non-dividing cells and that they have a life span probably in excess of 100 days. The medium and large lymphocytes turnover rapidly with generation times less than 24 hours. Studies on life span and potentialities of the lymphocyte in patients and in animals are continuing. To date there have been studies performed on 2 normal individuals and 18 individuals with various types of blood dyscrasias. Eleven dogs have been studied by cannulation of the thoracic duct

(See Continuation Sheet)

4002189

15. Accomplishments Last Fiscal Year - 1960 (Cont'd.):

lymph and serial sampling of the lymph after repetitive injections of tritiated thymidine. There is a continual outpouring of immature DNA synthesizing cells from lymphatic vessels into the blood stream. Their fate and function are in part obscure. However, in studies on rats in which a high fraction of lymphocytes were labeled by repetitive injections of thymidine, the medium and large lymphocytes were approximately 100 per cent labeled and the small lymphocytes approximately 30 per cent labeled. In animals so labeled sterile information has been produced and there is an outpouring of these labeled cells into this area with a subsequent transformation into histocytes, and fibroblasts thus indicating a probable potentiality of the large and medium lymphocyte to be transformed into other cells and subsequent mitosis in the production of fibroblastic barriers to inflamation.

No leukemia or blood dyscrasia studied so far has a greater labeling index than normal hematopoietic tissue hence the generation time is probably longer in these diseases. In the case of multiple myeloma the low mitotic index of approximately 1 in 5000 cells and 1 per cent labeling with thymidine suggest a doubling time of perhaps as long as 300 days. Similar observations have been made in chronic myelocytic leukemia (3 cases), chronic lymphocytic leukemia (6 cases) and acute leukemia (2 cases). Cancer therapy has, in general, been predicated upon the assumption of aberrant accelerated growth. Chemical agents are aimed at mitosis and DNA synthesis. Certain neoplastic diseases respond to radiotherapy and various chemical agents in a manner that suggests the predication is correct. Others do not respond. Often the limiting factor in therapy is the suppression of normal hematopoiesis. The usual explanation is that of differential sensitivity the neoplasm being less sensitive than the normal tissue thus the antimitotic and anti DNA synthetic agents may produce more damage to normal cells than to the neoplastic cell. However, with identical intrinsic sensitivities, more cells will be killed in the tissue in which a greater proportion of its generative cycle is spent in DNA synthesis and mitosis. Hence the characterization of the various stages of the cell generative cycle for normal cells and malignant cells is essential for selection of therapy and design of research for further development of anticancer agents.

The nature of the cellular response - cell proliferation vs. cell transformation - in antibody production remains unanswered. The combination of DNA labeling, RNA labeling, autoradiography and cytochemical study of lymph nodes, spleen, and bone marrow may resolve these problems. Cell transformation studies have been performed using dogs and guinea pigs. In these studies to date 11 dogs, 24 guinea pigs and 120 rats have been used. Circulation has been interrupted to the lower half of the body while it is being maintained by extracorporeal circulation. Tritiated thymidine is injected intravenously in the upper half. After one hour the circulation is reestablished. In addition approximately 100 parabiotic rats have been studied in which the label is introduced into 1 parabiont with the circulation occluded to the other and then labeled cells searched for in the other parabiont. Similarly cross circulation studies have been performed in rats from a labeled donor to an unlabeled recipient. In the cross circulation studies, and the parabiotic studies it has been found that labeled precursor cells are present in the labeled portion of the blood and hemopoietic tissues. With time, more labeled medium and large lymphocytes appear in the marrow of the lower extremities. Later, labeled plasma like cells, reticulum cells and rarely myeloblast - promyelocytes are seen. No labeled erythrocytic precursors have been found as yet. The experiments do not prove cell transformation from "lymphocytes" to "plasma" and "reticulum" cells but suggest this possibility. Migration and transformation to granulocytic precursors is unlikely since only ~~a rare myelocyte may be seen in~~ the peripheral blood normally. To date there is no evidence to support the concepts of Yoffey on transformation of small lymphocytes ~~into any line of hematopoiesis~~.

REPOSITORY Brookhaven Natl. Lab.
COLLECTION Hem. Res. Prot. 1960-61
BOX No. 8
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RETENTION

16. Expected Results This Fiscal Year - 1961:

The studies on human malignant blood dyscrasias will continue through 1960 and will be expanded in 1961 with the acquisition of staff commensurate with the complicated problems of handling of the patients and the study of hundreds of radioautographs.

In addition to the practical problems of defining growth potentials of normal and cancer cells, there remain many problems on the control mechanisms that maintain a normal steady state equilibrium in hematopoiesis. Intimately connected with this is the identification of stem cells, detection of cell transformation, function and fate that are not yet resolved. These problems will be approached on

(See Continuation Sheet)

16. Expected Results This Fiscal Year - 1961: (Cont'd.)

a collaborative endeavor between Dr. Marcel Bessis, Paris, France, and this Laboratory. Further collaborative work has been initiated with Dr. Charles Sondhaus of the Radiation Laboratory, University of California to better characterize the flow of cells from one compartment to another in the process of multiplication and maturation.

The work on cellular response in antibody production will continue. Clinical studies particularly on leukemias and lymphomatous disease will be accentuated through FY 1961 and FY 1962, with the acquisition of staff, both professional and technical, to undertake the expanded nature of the work.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for F.Y. 1961 is expected to be continued.

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

06-01-02-b-(5) Kinetics of Injected and Absorbed Vitamin B_{12} in Man.

Persons in Charge: E.P. Cronkite, P. Reizenstein, E.A. Usenik, S.H. Cohn, C. Rosenblum, Research Collaborator from the Merck Co., and J.S. Robertson.

12 & 13. Objectives and Overall Description:

Vitamin B_{12} plays an important role in several fundamental metabolic processes, but its human requirement is unknown. In previous studies performed at BNL during 1958-59 on B_{12} excretion, it was established that the probable half time for turnover of vitamin B_{12} is of the order of 1 year. Similar studies had been performed elsewhere by Dr. Reizenstein before joining the staff. Therefore a study of the whole body turnover rate and of turnover rate in various body compartments has been programmed to utilize the whole body counter and specific radio chemical studies for determining whether cobalt remains in vitamin B_{12} and is thus an indicator of the true turnover rate of the vitamin.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

In FY 1960, activities in this program were relatively limited. However, B_{12} turnover studies indicated that current preparations for parenteral use are excreted too rapidly.

16. Expected Results This Fiscal Year - 1961:

In order to study simultaneously the turnover rate of naturally occurring, absorbed vitamin and that of therapeutically employed, parenteral vitamin, B_{12} labeled with two different isotopes will be employed in a series of 6 patients. Gamma spectrometry in the whole body counter, and in single compartments such as plasma and liver will be employed to follow isotope turnover over several months. With the acquisition of the data the models will be constructed for the three compartments studied and analyzed by use of the analogue digital computers.

In an effort to find a suitable vitamin B_{12} preparation with a depot effect, the turnover in man of the naturally occurring B_{12} analog hydroxycobalamin will be studied. Like the previous investigation, this study is planned as a double tracer experiment with long time gamma spectrometry of several body compartments as well as the whole body. These studies will be performed upon a series of at least six patients. Independent studies at Merck and Company, Rahway, New Jersey, and in Stockholm, Sweden, have indicated a possible difference between naturally occurring, absorbed vitamin B_{12} on one hand, and injected B_{12} on the other. Therefore, the chemical stability of the two substances will be compared, using a double-tracer technique in a series of 4 dogs. The whole body studies, maintenance of the animals and injection of the isotopes will be carried on at Brookhaven. The isotope present in the tissues at the time of sacrificing the animals will be identified with a tracer-dilution technique at the Merck and Company Laboratories.

The experimental portion of this project should be completed during FY 1961. However, the analysis of data and final interpretation will probably take an additional year.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 ~~is expected to be~~ continued.

Brookhaven Natl Lab
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06-01-02-b-(6) Comparison of the Enzymatic Activity of Commercially Available Hyaluronidases Towards the Removal of Sulfated Mucopolysaccharide Complex of Cartilage.

Persons in Charge: E. A. Tonna

12 & 13. Objectives and Overall Description:

In previous studies several histochemical procedures have been employed for the localization of mucopolysaccharides in tissue. These studies required control sections which were treated with hyaluronidase for the removal of sulfated mucopolysaccharides.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

During FY 1960 a variety of commercial hyaluronidases were tested and results compared. Findings indicated that variations in enzyme application will be necessary because of differences in commercial preparations. As yet, there has been no standardization of a method to be used nor are the optimal time periods of incubation known that would consistently and adequately remove mucopolysaccharides from tissue sections.

16. Expected Results This Fiscal Year - 1961:

During FY 1961 standardization in the application of hyaluronidases from tissues for histochemical and autoradiographic applications will be undertaken. Sections of cartilage taken from rats previously given S^{35} sulfate will be incubated in the various enzyme solutions for various time periods and the treated sections will then be stained with colloidal iron for mucopolysaccharides and toluidine blue for metachromasia. The removal of the dye staining will be followed histophotometrically. Additional S^{35} tissues will be used for quantitative autoradiographs. The removal of mucopolysaccharides by treatment with hyaluronidases will be evaluated by grain counting. It is hoped that in the ensuing 2 years this investigation will standardize the application of the enzymes listed above for the removal of mucopolysaccharides from tissue for histochemical application and thus open up quantitative studies on bone and cartilage metabolism which are not now currently available.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for F.Y. 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
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06-01-02-b-(7) Studies on the Cytochemical Mechanisms of Bone Growth and Repair During Aging, and Skeletal Pathology Including Tumor and Cancer Formation

Persons in Charge: E. A. Tonna and E. P. Cronkite

12. & 13. Objectives and Overall Description:

These studies are directed at obtaining fundamental information on the biochemistry of cells taking part in vital activities leading to the growth and repair of bone and at ascertaining the deviation of the normal biochemistry of these cells as a result of skeletal pathology. In attempts to alleviate many of the pathological conditions which are associated with the skeletal system, there is the need of obtaining fundamental cytochemical information on the role of bone cells and their activities in the normal animals, and which, in turn, this information can be used as a base line for comparison and a better study of skeletal pathology.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

These studies were begun in 1960. Use of tritium labeled thymidine combined with histochemical techniques on the formation of osteoclasts of bone from young and old mice has revealed that these cells take their origin directly from the osteoblastic cells and not from osteogenic cells. Experiments have begun on young rats, with the intention of following the population, both irradiated and non-irradiated, in an effort to learn more about the effects of radiation on skeletal maturation and pathology.

16. Expected Results This Fiscal Year - 1961:

During Fiscal Year 1961 the following studies are planned:

1. To study the contribution of the various cells and tissues to fracture healing using tritium labeled thymidine on rats, from birth to old age.

2. The mode of osteoclast formation, disappearance and histochemical role using tritium labeled thymidine.

3. The localization, distribution and function of ATP-ase in bone formation during aging.

4. Protein formation in osteoblasts using H-labeled amino acids.

5. Development of combined radioisotope methods with histochemical techniques to allow more precise quantitative analyses of the stained cell and time components.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
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06-01-02-b-(8) Intranuclear Irradiation with Tritium

Person in Charge: J. S. Robertson

12 & 13. Objectives and Overall Description:

This program concerns itself with theoretical aspects of the irradiation of cellular components by the localization of tritium-labeled substances. Earlier calculations were concerned with describing the radiation dose distribution pattern about a point source of tritium, and have been published.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

The previous calculations were used to help explain variations seen in the resolution and image spread of autoradiographs of tissue sections and smears labeled with tritium. The results of these computations have been published.

16. Expected Results This Fiscal Year - 1961:

Calculations directed toward comparing the radiation dose patterns delivered by tritium-labeled substances which localize in the chromatin material, with those which do not so localize, and with physically-equivalent radiation from x-rays and gamma-ray sources are contemplated. No patients, no animals and no isotopes are needed for this phase of the work. Experimental data for comparison with the calculated results are expected to be made available from work by Bond and Cronkite of the BNL Medical Department.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
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06-01-02-b-(9) Dynamics of Incorporation of Nucleic Acid Precursors into Cellular Components

Persons in Charge: V. P. Bond, L. E. Feinendegen, and W. W. Shreeve

12. & 13. Objectives and Overall Description:

The current concern of this study is to measure by autoradiographic and biochemical techniques the time rate of incorporation of tritium labeled nucleic acid precursors into subcellular structures of cells. These data are valuable as basic studies on cell activity and proliferation, and as models for studying irradiation effects on the cell cycle. Standard biochemical procedures have not allowed clear definition of the precise site and time of synthesis of DNA, RNA or protein within the cell. High resolution autoradiography with tritium - labeled precursors, and cell fractionation and other biochemical techniques make it possible to localize accurately the sites of synthesis within the cell.

HeLa and Osgood and rabbit kidney culture cells have been used in this work and the time course of distribution of label after administration of tritium labeled cytidine has been characterized by autoradiographic and biochemical techniques. Preliminary work on other precursors (labeled ribose, deoxyribose, acetaldehyde and thymidine), has been performed. Radioactivity from labeled cytidine was shown first to go to the nucleus, then to the nucleoli and to the cytoplasm, and also out into the medium.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

The labeled material coming out into the medium was found to be a low molecular weight material that could be reincorporated into the RNA and DNA of cells. The macromolecular RNA tritium and the tissue culture cell was found to be metabolically stable, while the acid soluble RNA was found to have a high turnover rate within a generation time. A number of experiments indicated that beside the nuclear cytidine larger nucleic acid components are incorporated into DNA during DNA synthesis time. This observation was extended to the mammalian organism. Experiments in rats demonstrate utilization of RNA components for DNA synthesis in hemopoietic tissue. Work continues to determine the origin of these precursors, whether they are derived from DNA synthesizing cells, or whether they are obtained by intercellular exchange.

16. Expected Results This Fiscal Year - 1961:

Work will be continued and extended to confirm the apparent stability of RNA in the HeLa cell, and to study further the use of intermediate "RNA" acid soluble fractions, and released low molecular weight labeled material for DNA synthesis. Work is projected to determine the origin of RNA components that label DNA in the mammalian cell, to see whether they are derived from the DNA synthesizing cell or whether they are obtained by intercellular exchange. Studies with the millipore chamber will be instituted to further study the possibility of a common acid soluble pool of RNA in the mammal. The objective of these studies is to characterize the course and inter - relationship of RNA and DNA synthesis in normal and malignant cells.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
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06-01-02-b-(10) The Temporal Relationships of Deoxyribonucleic Acid Synthesis to Mitosis and the Generative Cycle in Human Cancer Cell (HeLa) Cultures.

Persons in Charge: R. M. Drew and R. B. Painter

12. & 13. Objectives and Overall Description:

The investigation of time relationship of the several components of the generative cycle, utilizing tissue culture of HeLa cells with tritiated thymidine yield data on the activity and proliferation of cell populations and serve as a model to study radiation effects on cell cycles.

During 1959 information concerning the variability in cell DNA synthetic time within different populations of mammalian cells has been obtained. The DNA synthetic time, the resting phase between DNA synthesis and mitosis and the post-mitotic resting phase for HeLa and the HeLa S3 clone cells have been determined. In comparing the aspects of DNA physiology of S3 and HeLa cell cultures, the latter has shown, repeatedly, the persistence of a very small percentage of cells with extremely long DNA synthetic time.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

In 1960 these studies have been expanded to include observations which have to do with (1) the rate of incorporation of tritiated thymidine into DNA; (2) the linearity of the rate of DNA synthesis; and (3) the extent of synchrony of DNA synthesis. Valuable information concerning the transport rate of tritiated thymidine across the cell membrane has been obtained. The amount of isotope incorporated into DNA depends primarily on the rate of polymerization, i. e., on the DNA synthetic rate. Data obtained on the synchrony of chromosomal replication in the cell indicate that DNA synthesis is going on in the majority of the chromosomes in one cell at the same time during most of the 6 hour synthetic period. However, it appears that initiation or cessation of DNA synthesis may not occur in all the chromosomes at exactly the same time.

16. Expected Results This Fiscal Year - 1961:

These studies will be continued on normal and malignant cells, and the information obtained will serve as a model for experiments testing the effects of external irradiation on DNA synthesis.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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06-01-02-b-(11) The Pathogenesis of Atherosclerotic Lesionx

Persons in Charge: S. Spraragen, V. P. Bond, L. K. Dahl

12 & 13. Objectives and Overall Description:

This program concerns itself with the possible role of endothelial hyperplasia as an etiological factor in atherosclerosis. Previous research in this field has not adequately evaluated this problem.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

The possible role of hyperplasia in the pathogenesis of atherosclerotic lesions was investigated, using rabbits, on an atherogenic diet, and employing tritiated thymidine and autoradiography to indicate DNA synthesis within individual cells (and thus capability of division). Initial attempts at in vitro labeling of aortic tissue were not successful. Following in vivo administration of tritiated thymidine, occasional cells of the aortic media and intima in normal rabbit was observed to be labeled. No detectable increase in the number of labeled cells was found after one month of cholesterol feeding; however no macro- or microscopic evidence of atherosclerosis was found at this time. The studies are being extended to other time intervals, to other species, and to additional isotopically labeled materials (Calcium-45, tritium-labeled cytidine) to indicate further the metabolic state of the tissue. In particular, the possible role of calcium and Vitamin D in the etiology of atherosclerosis will be investigated.

16. Expected Results This Fiscal Year - 1961

The general program described above will be continued.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program described above will be continued.

REPOSITORY Brookhaven Nat'l Lab
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06-01-02-b-(12) The Effect of Intracellular Incorporation of Tritiated Thymidine on Mammalian Cell Survival and Cell Cytology.

Person in Charge: R. M. Drew

12 & 13. A determination of the cytological and lethal effects of intranuclear tritiated thymidine is needed to study the mechanism of action of short range particle radiation effects within the nucleus of cells and to evaluate the potential hazard of tritiated thymidine, now widely used in chemical and biological investigations. This study utilizes the tissue culture technique making use of HeLa cells.

The lethal action of this radioactive isotope on dividing mammalian cells has been demonstrated and been shown to be a function of the dose and specific activity. As a result of radiation damage there is a marked alteration in the cytological appearance of cells and abortive colonial growth. Tritiated Thymidine concentrates radioactivity largely only in the most radiosensitive region of cells, i.e., the nucleus. Therefore, the killing effect is reasonably attributed to nuclear damage by beta irradiation coming from the decay of the tritium portion of the thymidine incorporated by the nucleus.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960.

During 1960 a comparison of the radiobiologic effects of tritium labeled thymidine and tritium labeled cytidine after incorporation into HeLa cells in tissue culture is being made. Since the tritiated cytidine is incorporated into the nucleic acids of both nucleus and the cytoplasma white tritiated thymidine is incorporated only into the nucleus, the distribution of radioactivity producing radiation damage can be compared.

16. Expected Results This Fiscal Year - 1961:

The above studies will be continued and extended to include mutational effects at low doses of intranuclear radiation, and to include the effects of other labeled nucleic acid precursors.

17. Expected Programs and Results for Next fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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06-01-02-b-(13) DNA Synthesis and Turnover Activity in the Mouse Embryo

Persons in Charge: V. P. Bond and M. Atlas

12. & 13. Objectives and Overall Description:

Tritiated Thymidine provides a useful tool, when combined with the autoradiographic technique, to establish the cell turnover time of embryological tissues, and to estimate the DNA synthesis rate.

In previous work approximately 40 pregnant mice in various stages of gestation were injected intraperitoneally with tritiated thymidine, and the animals were sacrificed 24 hours following injection for examination of the embryos. No incorporation of tritiated thymidine was noted prior to the establishment of embryonic circulation on approximately the 11th day of gestation, following which varying degrees of incorporation in the various fetal structures was noted. The time of appearance, and the intensity of label was noted for each type of embryonic tissue.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

During 1960 the investigations were extended to study the uptake of tritiated thymidine in embryonal tissues in fetuses at different degrees of maturity as a function of hours following tritiated thymidine administration to the mother. These studies are presently being analyzed to determine the approximate turnover rates of the individual tissues.

16. Expected Results This Fiscal Year - 1961:

Reading of the tissues and analysis of the data will continue in 1961, and such additional tissue as may be necessary to characterize turnover rates will be obtained. It is anticipated that these studies will be continued.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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Form NYOO-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Hematology and Clinical Management of Radiation Injury		
4. Budget Activity No. 06-01-02	5. Budget Item No. 06-01-02-c	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-01-02-c Hematology and Clinical Management of Radiation - (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	105	110	125
Direct Man-Years			
Staff	1.5	1.8	1.8
Visitors	-	-	0.1
Scientific	1.5	1.8	1.9
Other	6.8	6.6	7.4
Total	8.3	8.4	9.3

One of the major effects following radiation exposure is the profound depression of formed elements of the blood. Understanding of the factors that control the circulating levels of the formed elements of the blood must go hand-in-hand with, or proceed, the understanding of the effect of radiation on these processes in health and diseased states.

06-01-02-c-(1) Clinical Management of Radiation Injury

Persons in Charge: E. P. Cronkite, V. P. Bond, E. A. Usenik, V. Perman, D. Sorenson and A. Nielsen

12. & 13. Objectives and Overall Description:

Hemostasis in irradiation injury by transfusion of fresh platelets is an accomplished fact. The mechanism of action of the platelets remain obscure. $S^{35}O^{4}$ labeling of platelets, coupled with autoradiographic techniques suggests that a definite platelet-endothelial interaction may occur.

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14. Related Projects:

See 06-01-02- Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

Attempts to label RNA with tritiated cytodine have been successful in an effort to study this problem. Unfortunately the turnover of RNA in the megakaryocytes was so rapid that it is an ineffective method of labeling platelets.

In the lethal doses range the major cause of death are the sequelae of suppression of bone marrow function. An understanding of this and both substitution and specific therapy are the basis of successful management of radiation injury. A series of 24 dogs exposed to an LD_{90-100} dose of irradiation, were treated by a combination of fresh blood transfusions, platelet concentrates and antibiotics. A very significant improvement in mortality was obtained following this dose of irradiation. When the dose of irradiation was increased by 50 to 75 r into the absolute lethal dose range, this mode of therapy was no

(See continuation sheet)

15. Accomplishments Last Fiscal Year - 1960: (contd.)

longer satisfactory. The dogs which have survived this exposure are being studied now by stressing hemopoietic tissues to evaluate whether residual radiation injury will inhibit their capacity to regenerate following stresses such as severe bleeding. In performing the preceding studies it was necessary to have a blood donor colony of typed dogs varying between 20 and 40 animals.

The capacity of irradiated bone marrow to synthesize DNA and the duration of mitotic abnormalities are under study. This work was commenced in 1958 and 1959 and has been followed in 120 rats, 6 dogs, and on the patients irradiated accidentally in the Y-12 accident in conjunction with the Hospital Division, Oak Ridge Institute of Nuclear Studies.

16. Expected Results This Fiscal Year - 1961:

Extracorporeal circulation is expected to be developed as a technique to study the effect of radiation on life span and function of irradiated blood cells. In addition organ perfusion, techniques will be developed as a means of studying the relation between peripheral levels of leukocytes and platelets and their production or removal by specific organs.

During 1960, further developmental work on extracorporeal circulation and the development of techniques for irradiating blood in an external shunt in order to determine the effect of irradiation directly upon circulating blood cells will be expanded. Approximately 24 dogs will be used in this study and when leukemic cows, swine, or dogs are found, this mode of irradiation of circulating leukocytes will be tested to see if it is therapeutically effective in reducing the number of circulating leukocytes. This work is in the developmental stage and will extend over a period of 3 to 6 years.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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06-01-02-c-(2) Study of Fate and Function of In Vitro and In Vivo Labeled Mononuclear Cells.

Persons in Charge: V.P. Bond, L. Feinendegen, E. Usenik and R. Stoner.

12 & 13. Objectives and Overall Description:

It was shown in this laboratory in 1958 that some circulating mononuclear cells labeled with thymidine and thus presumably are capable of proliferation. Previous studies have indicated that bone marrow cells are protective in acute radiation injury, and there are indications that circulating cells may be protective against radiation damage and may be immonologically competent. In FY 1959, efforts were made to study the fate and function of the label circulating mononuclear cells. Initial efforts to transfuse labeled blood were not successful because of the small number of labeled cells transfused. Parabioyic animals were used, and in a total of approximately 15 pairs, it was shown that labeled cells do get across into an unlabeled recipient animal. Some evidence was accumulated to indicate that the mononuclear cells might be capable of transformation into myeloid precursors; however this could not be demonstrated with certainty. Studies with parabiotic animals were discontinued because of difficulty with the development of "runt" disease in one of the parabionts.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

Efforts were made to transfuse blood from labeled donors into unlabeled normal and unirradiated recipients, using the transfer of venous blood, and employing a technique of connecting donor and recipient animal either artery-to-vein, or artery-to-artery. Again, it was not possible to get blood across in quantities sufficient to allow one to follow labeled cells in the recipient animal. Since it was thought that most of the labeled cells in the peripheral blood is derived from the thoracic duct, a direct transfusion of thoracic duct lymph from labeled donors was carried out into recipient normal and irradiated animals. Large numbers of labeled cells are seen in the recipient by this technique. These cells early appear to be lymphocytic in character; however with the passage of time they become more and more plasma - cell-like in character. It is not clear whether transformation into plasma cell - like cells has occurred, or whether plasma cell precursors in sufficient number are actually present in the thoracic duct lymph. These studies are being extended, and massive transfusion of labeled cells in the peripheral blood of a number of donors is being transfused into recipient animals in an effort to uncover the fate and function of these cells.

16. Expected Results This Fiscal Year - 1961:

These studies will be continued, and will be modified with regard to the times of observation, the preparation of the recipient animal, and the nature of the injected preparation. It is anticipated that these studies will continue until the ultimate fate of the labeled cells is determined, or until it is determined that no significant change in cell type occurs.

It seems definite that the use of tritiated thymidine should allow a definite answer to the question of possible cell transformation.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined in FY 1961 is expected to be continued.

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Project Title: Effects of Radiation on DNA Synthesizing Cells in Marrow and Peripheral Blood. 06-01-02-c-(3)

06-01-02-c-(3) Effects of Radiation on DNA Synthesizing Cells in Marrow and Peripheral Blood.

Persons in Charge: V.P. Bond, A. Tsuya, T. M. Fliedner and E. P. Cronkite

12 & 13. Objectives and Overall Description:

While a good deal of investigative work has been devoted to the study of changes in DNA synthesis following irradiation, most of these studies have dealt with entire organ systems in which changes observed could be on the basis of an actual effect on DNA synthesis, or an indirect effect mediated through changes in cell population, or effects on mitosis itself. The use of tritiated thymidine and autoradiography makes it possible to study the effects of radiation on DNA synthesis at the cellular level, and to determine the effects of radiation on the proliferative potential of dividing cells. In FY 1959 rats and dogs were exposed to radiation, following which short term or "flash" labeling of both the bone marrow and peripheral blood was carried out by either in vivo or in vitro techniques. Results indicated marked changes in the number of labeled circulating cells, that appeared to be correlated with periods of degeneration and regeneration. Studies of bone marrow indicated that the apparent effect on DNA synthesis could be accounted for in part by an actual effect on the process of DNA synthesis, and in part by an effect on mitosis itself.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

These studies were extended, and a series of approximately 70 rats were studied quantitatively following exposure to radiation. In addition to labeling index, the mitotic index and the total marrow cellularity was determined. These studies indicated a profound effect of radiation on total cellularity in the bone marrow, and indicated that in addition to an effect on mitosis, there was a direct cell loss during both DNA synthesis phase and the inter-mitotic rest phases. Grain counts indicated also some effect on the process of DNA synthesis itself. These studies have been extended to study the effect of radiation on amimals who have received a single injection of tritiated thymidine just prior to exposure. These studies should yield data on the effects of radiation on the kinetics of bone marrow proliferation. Studies have been initiated on the effects of neutron irradiation on the labeling of bone marrow cells in the mouse.

16. Expected Results This Fiscal Year - 1961:

Slides obtained in studies carried out during 1960 will continue to be read, and the date will be analyzed. Studies will be continued in which labeled bone marrow and peripheral blood from donor animals is injected into recipient irradiated animals in an effort to determine the types of cells responsible for bone marrow protection in the irradiated animal.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined in FY 1961 is expected to be continued.

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06-01-02-c-(4) Characterization of Erythroid Precursors

Persons in Charge: V.P. Bond, L. Feinendegen and C. Sondhaus

12 & 13. Objectives and Overall Description:

It has been well recognized that morphology does not constitute an adequate criterion for characterization of the various erythroid precursor forms. In this laboratory autoradiographic methods have been developed to indicate the degree of DNA synthesis within a cell. By differential extraction methods, it is possible to determine the degree of RNA synthesis in progress. Dr. Sondhaus of the Donner Laboratory, a research collaborator, has studied methods of quantifying the amount of nucleic acid and of hemoglobin within the single cell, and is now prepared to carry out such studies at his laboratory in California. With a collaborative endeavor, it should now be possible to attempt to correlate these various quantitative indices with the morphologic appearance of erythroid precursor cells.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

This work was initiated in FY 1960. Preliminary work was carried out to determine the feasibility of carrying out such a project. Dog bone marrow slides were prepared, and the separate analyses done by the two laboratories, were carried out. It now appears definite that the multiple determinations indicated can be carried out on an individual cell basis, and that for the various erythroid precursors, it will be possible to determine morphology, size of cell and nucleus, DNA content, and the hemoglobin content.

16. Expected Results This Fiscal Year - 1961:

Studies will be continued in the dog until completely satisfactory methods have been worked out. It is anticipated and hoped that when the work on the dog has been completed, that it will be possible to do studies on human bone marrow.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined in FY 1961 is expected to be continued.

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Form NYOO-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Radiation Effects on Immunity and Allergy		
4. Budget Activity No. 06-01-02	5. Budget Item No. 06-01-02-d	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-01-02-d Radiation Effects on Immunity and Allergy - (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	170	190	215
Direct Man-Years			
Staff	2.4	2.8	2.9
Visitors	-	-	0.3
Scientific	2.4	2.8	3.2
Other	9.2	10.5	11.8
Total	11.6	13.3	15.0

Radiation depresses antibody production while at the same time anaphylactic allergy is enhanced. During the recovery period of antibody production anaphylactic allergy may decrease to normal levels. Presumably a single system of protein synthesis and cell reactivity is responsible for this paradox. The concern of this study is to investigate antibody production, particularly in regard to the effects of radiation.

06-01-02-d-(1) Depressant Effect of Acute Exposure, Divided Acute Exposure and Chronic Exposure to Radiation on Antibody Formation

Persons in Charge: R. D. Stoner and W. M. Hale (Collaborator from U. of Tennesse)

12. & 13. Objectives and Overall Description:

This study was initiated in FY 1959 to compare the depressant action of cobalt ^{60} γ-radiation on the secondary tetanus antitoxin response in mice when equal total doses of radiation are delivered by single acute exposure, divided acute exposures and by chronic or continuous exposure. Several exploratory experiments were done to test the radiosensitivity of the secondary antibody response to total doses of 400 rads and 800 rads when radiation was delivered at dose rates of 4 rads per hour and 2,400 rads per hour. Preliminary findings indicated that the antibody forming mechanism was more radiosensitive when radiation was delivered by chronic exposure or in divided exposures when compared to the depressant effect of the total dose delivered by acute exposure.

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14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

A series of 9 experiments were carried out in study of the effects of total doses of 100, 200, 300, 400, 500, 600 and 800 rads on antibody formation. A detailed study was done concerning the temporal relationships between time of radiation, total dose, dose rate and time of administration of the secondary antigenic stimulus after irradiation. When post irradiation time of injection of

(See continuation sheet)

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15. Accomplishments Last Fiscal Year - 1960: (contd.)

the antigen after a single acute exposure was delayed to correspond to the delay encountered with chronic exposure and divided acute exposures there was little difference in the sensitivity of the secondary antibody response with regard to dose rate. A report of this study is being prepared for publication.

16. Expected Results This Fiscal Year - 1961:

Several exploratory experiments will be carried out in this study of temporal relationships and radiation dose rate on the radiosensitivity of the primary antibody response.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Natl Lab
COLLECTION Form 189 Med. Dept. 1950-61
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06-01-02-d-(2) Comparative Radiosensitivity of the Primary and Secondary Responses

Persons in Charge: R. D. Stoner, W. M. Hale (Research Collaborator) University of Tennesse, K. Packer and M. McIlwee.

12 & 13. Objectives and Overall Description:

Antibody formation is greatly inhibited when animals are exposed to ionizing radiation prior to immunication with a primary or booster antigenic stimulus. It is generally assumed that the primary and secondary antibody responses are equally sensitive to radiation.

This study compares the depressant effect of Cobalt^{60} γ radiation on the primary and secondary tetanus antitoxin responses in mice.

Several preliminary experiments indicated that the primary antibody response may be more radiosensitive than the secondary antibody response. Further work showed that whole-body exposure to doses of 50, 100, 200 and 300 rads increasingly suppressed the primary antibody response to fluid toxoid given 1 hour after radiation, whereas doses of 300, 400 and 600 rads were needed to produce a correspondingly depression of the secondary response.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

In another series of experiments, equivalent depression of the primary and secondary response from titers obtained in non-irradiated control animals indicated that the primary antibody response was approximately three times as radiosensitive as the secondary antibody response. Similar results were obtained when a primary stimulus of adsorbed toxoid was given 1 hour after irradiation. An immediate radiosensitivity of the primary response was obtained when fluid toxoid was injected 1, 3 and 6 hours after exposure to 200 rads. Depression of the secondary response occurred only when the antigen was injected 6, 12 and 24 hours after irradiation. The data indicate that the cells concerned with acceptance of the primary antigenic stimulus may be more radiosensitive than the cells involved in the secondary antibody response.

16. Expected Results This Fiscal Year - 1961

A series of experiments will be carried out in an attempt to identify the cells involved in the primary and secondary antibody response.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Hist. Rpt. Med. Dept. 1960-61
BOX No.
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06-01-02-d-(3) Enhancing Effect of Radiation on Anaphylaxis

Person in Charge: R. D. Stoner

12 & 13. Objectives and Overall Description:

The severity of anaphylactic shock in mice is increasingly enhanced for several weeks after exposure to ionizing radiation. Although several antihistaminic agents, Thephorin and Ambodryl, prevent fatal anaphylaxis in irradiated mice, these agents do not appear to act specifically against histamine. This study is being extended in an attempt to explain the mechanisms involved in increased susceptibility to anaphylaxis after irradiation. Earlier experiments were completed studying the enhancing effect of chronic exposure to γ-radiation on anaphylactic shock and a paper was published on this topic.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

No activity took place during this fiscal year.

16. Expected Results This Fiscal Year - 1961

A series of experiments will be carried out in an attempt to modify or enhance fatal anaphylaxis in irradiated mice with various chemical agents.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for FY 1961 is expected to be continued.

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

06-01-02-d-(4) Immune Mechanisms in Homologous and Heterologous Disease

Persons in Charge: R. D. Stoner, V. P. Bond

12 & 13. Objectives and Overall Description:

Post irradiation transfusion of mouse and rat bone marrow protects recipient mice against lethal doses of whole body radiation. Mice protected with homologous or heterologous marrow demonstrate recovery of the hematopoietic system followed by a secondary loss of weight and wasting frequently resulting in death during the second month after irradiation. It has been postulated that the wasting disease and delayed deaths result from antibody production by the donor bone marrow against host tissues.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960

An immunological study was started in an attempt to determine the ability of bone marrow cells to produce antibody against specific antigens when transplanted into irradiated animals. In preliminary experiments it has not been possible to demonstrate antibody production by heterologous bone marrow cells in mice previously exposed to 650 and 850 rads. Evidence for antibody formation by bone marrow cells was obtained, however, only when isologous (same strain) mouse cells were transferred to irradiated mice.

16. Expected Results This Fiscal Year - 1961

A series of experiments will be carried out to explore the immune reactions that may be involved in heterologous and homologous disease.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Hrn 189 Med. Dept. 1950-61
BOX No. _____
FOLDER _____

06-01-02-d-(5) Antibody Absorption on Guinea Pig Ileum

Person in Charge: G. Terres

12 & 13. Objectives and Overall Description:

The nature of the binding between antibody and tissue is being studied to learn more about the quantitative relationship between the amount of antibody absorbed and the degree of sensitization.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960

Antibody was labeled with I^{131}. Normal guinea pig ileum was soaked in the protein and the amount of radioactivity absorbed was measured as well as the degree of sensitization thus attained. The sensitization was measured by the Schultz-Dale reaction. It has been found that the amount of antibody is proportional to the concentration of protein used and conforms to a Langmuirian isotherm. The sensitivity as determined by the Schultz-Dale reaction is proportional to the amount of protein (antibody) absorbed.

16. Expected Results This Fiscal Year - 1961

The study will be terminated with the analysis of the experimental data.

17. Expected Programs and Results for Next Fiscal Year - 1962

No activity.

REPOSITORY Brookhaven Nat'l Lab
COLLECTION Form 189 Med. Dept. 1950-6
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06-01-02-d-(6) Acquired Immune Tolerance to Crystalline Bovine Serum Albumin

Person in Charge: G. Terres

12 & 13. Objectives and Overall Description:

This study is based on the finding that animals neonatally exposed to an antigen become specifically immunologically tolerant or unresponsive to the antigen. Data accumulated will provide insight into the normal immune response, into antibody synthesis, and into the mechanism initiating auto-immunity and particularly to the fundamental mechanism by which native proteins are recognized and thus fail to elicit an antibody response.

In earlier studies, mice were exposed soon after birth to crystalline bovine serum albumin and acquired immune tolerance to bovine serum albumin was demonstrated which lasted several weeks. This tolerance was demonstrated by the lack of anaphylactic response to a challenge following suitable sensitizing injections.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960

Mice were exposed to the antigen during the first two weeks of life. At six weeks of age the mice were re-exposed to the antigen and subsequently challenged. Mice similarly treated were bled. To the serum was added I^{131} BSA and the gamma globulin precipitated with ammonium sulfate (Farr technique). The per cent radioactivity precipitated (antigen-antibody complexes) was determined. Only 2 of the 61 mice injected during the first two weeks of life were anaphylactically shocked at the challenge. In contrast 44 of the 60 control mice (litter mates not injected during the first two weeks of life) were anaphylactically shocked. Similar results were obtained using the above mentioned Farr technique. Thus only 2 of 17 mice treated at birth with BSA had circulating antibodies when sensitized and bled at 8 weeks of age, while 14 of 22 control mice had circulating antibody following the same treatment.

16. Expected Results This Fiscal Year - 1961

The experimental portion of this study will cease during the current fiscal year.

The analysis of these experiments will be carried into the next fiscal year after which this project will be terminated.

17. Expected Programs and Results for Next Fiscal Year - 1962

No further activity.

REPOSITORY Brookhaven Nat'l Dept.
COLLECTION Form 189 Med. Dept. 1950-61
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06-01-02-d-(7) Immune Degradation

Persons in Charge: G. Terres, W. Wolins

12 & 13. Objectives and Overall Description:

The concern of this study is to characterize the kinetics of the antigen-antibody reaction in vivo in order that a method may be developed to investigate diseases in which an auto-immune mechanism has been implicated.

In FY 1959, antigen was labeled with I^{131} and mice were passively sensitized with rabbit anti-serum. The amount of antigen degraded at an accelerated rate was a function of the amount of antigen and antibody used. With one antiserum, the initial rapid degradation phase was followed by one in which the antigen was degraded at a rate slower than in normal mice. Preliminary studies were also started with horse and mouse anti-serum.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

During the current fiscal year the reverse experiments are being done. In these experiments the antibody is labeled and its degradation followed as a function of the amount of antigen used. An experiment is also planned in which the antigen is labeled with I^{131} and the antibody with I^{133}. This study will be completed this fiscal year except for analysis of data.

16. Expected Results This Fiscal Year - 1961

Analysis of the experimental data will be completed and the project will be terminated.

17. Expected Programs and Results for Next Fiscal Year - 1962

No further activity.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Frm 189 Med Dept 1950-61
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06-01-02-d-(8) Studies on the Turnover of I^{131} Labeled Thyroglobulin

Persons in Charge: W. Wolins, G. Terres, S. Cohn, C. J. Shellabarger

12 & 13. Objectives and Overall Description:

It has been reported that circulating autoantibodies are present in patients with various thyroid diseases and that autoantibodies can be produced in animals. Thus the concept that antibodies to naturally occurring proteins may precipitate certain diseases or be present in certain diseases has arisen and is the concern of this study.

During FY 1959, attempts were made to completely remove any source of thyroglobulin from rats by radiothyroidectomized embryos and to compare these animals against control, intact rats for their capacity to degrade I^{131} rat thyroglobulin and I^{131} serum albumin. No large differences were noted between the two groups, although complete analysis of the study was not completed.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960

The animal results have been subjected to further analysis. Human thyroglobulin extracted from surgically removed thyroid tissue has been iodinated with I^{131} and used to study its turnover in a variety of thyroid abnormalities. It is expected that increased degradation of the antigen will be associated with demonstrable anti-thyroglobulin in the serum. It is especially desirable to determine the turnover of the antigen in hypothyroid states unassociated with circulating anti-thyroglobulin. Accelerated degradation of the antigen in such a situation would imply that auto immune states can induce pathology in the absence of demonstrable antibody. These experiments will terminate in FY 1960.

16. Expected Results This Fiscal Year - 1961

No activity.

17. Expected Programs and Results for Next Fiscal Year - 1962

No further activity.

REPOSITORY Brookhaven Nat'l Lab
COLLECTION Form 189 Med. Dept. 1950-61
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Form NY00-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Radioisotopic Tracing of Total and Intermediate Carbohydrate Metabolism		
4. Budget Activity No. 06-01-02	5. Budget Item No. 06-01-02-e	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-01-02-e Radioisotopic Tracing of Total and Intermediate Carbohydrate Metabolism

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	240	270	305
Direct Man-Years			
Staff	3.6	4.0	4.2
Visitors	0.4	0.4	0.7
Scientific	4.0	4.4	4.9
Other	11.3	12.8	14.4
Total	15.3	17.2	19.3

Carbohydrate metabolism may be modified in various disease states, and by some hormones and drugs. The utilization of C^{14} or tritium labeled carbohydrates aids in the study of the rate and metabolic pathways of the synthesis and degradation of carbohydrates. Since carbohydrate metabolism and fat metabolism are interrelated, a new program has been started to investigate the hormonal regulation of fat metabolism in the radiation syndrome. Further studies on the kinetics and molecular specificity of sugar transfer across cell membranes utilizing labeled materials aid the understanding of carbohydrate metabolism.

06-01-02-e-(1) Studies on Diabetic and Non-diabetic Human Subjects

Persons in Charge: W. W. Shreeve, R. C. De Meutter and R. Schwartz

12. & 13. Objectives and Overall Description:

The rates and metabolic pathways of glucose formation are being studied, utilizing C^{14} labeled compounds, under various hormonal, nutritional and drug influences in both normal and diseased patients. These studies involve mainly analyses of C^{14} content in human blood glucose after administration of 2 or 3-C^{15} lactate or 2-C^{14} pyruvate. The purpose is to disclose metabolic pathways of hepatic glucose formation and the effects of diabetes, insulin, and sulfonylureas on rates of the various pathways and conversions. Approximately 12 studies were done on 6 patients, which included about 150-175 total hospital days. Technical work included the chromatographic purification of blood glucose as well as blood lactic acid, followed by C^{14} analyses of various carbon constituents. C^{14} analysis was done by gas counting of CO_2 and also some liquid scintillation counting of organic compounds. Insulin and tolbutamide were found to have an early and substantial effect on decreasing C^{14}-glucose output by the liver. Findings also indicate some major pathway of glucose formation other than the Embden-Meyerhof reactions.

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14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

(See continuation sheet)

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15. Accomplishments Last Fiscal Year - 1960:

Accomplishments of the current fiscal year include studies of blood glucose formation from C^{14}-labeled precursors. Four studies have been done including three new patients (about 50 hospital patient days). This study will continue, probably accumulating 100-150 hospital days for the fiscal year. A new feature of this study is the continuous analysis of breath $C^{14}O_2$ for the first few hours following C^{14} administration in order to better evaluate the oxidative fate of the administered compound. This feature was made possible by purchase of an ionization chamber-type flow counter. The apparatus has been used with all patients since its receipt in September 1959 and is satisfactory for present purposes except that a print out timer for the integrator will have to be added in order to make possible a permanent record of cumulative C^{14}.

Further studies of C^{14}-bicarbonate metabolism were carried out in the first part of this year. These studies will probably be continued with the utilization of the new continuous breath $C^{14}O_2$ analyzer.

An intermittent study of ketone body formation from 1-C^{14}-acetate conducted 2 or 3 years ago has been pursued by further analysis of urine samples. In addition to more reliable and extensive analysis of the C^{14} content of ketone bodies, it has been incidentally observed that diabetics of different types or the same diabetics with or without glucocorticoid administration have markedly changed ratios of acetoacetic to beta-hydroxybutyric acid in the urine. This interesting finding may be followed up by studies in which column chromatographic separations of the acids are a key feature.

During the final two months of this year, another research collaborator (Dr. Robert Schwartz) worked in association with W. W. Shreeve and R. C. De Meutter on a study of bicarbonate metabolism and kinetics by injecting $NaHC^{14}O_3$ intravenously into two diabetic humans and analyzing changes in $C^{14}O_2$ content of breath, artery, and vein. Na^{22} and T-1824 were also used as tracers to compare body compartment distributions with that of C^{14}. The study provided further evidence for significant pools of miscible CO_2 in the intracellular fluids.

16. Expected Results This Fiscal Year - 1961:

It seems possible that this year will see extension of the glucose formation study with diabetic humans to some other C^{14}-labeled precursors, e.g., some amino acids. Some hormonal influences on the important process of glucoenogenesis from protein may then be studied more directly. Chromatographic separation of blood amino acids may be done in connection with this study. An apparatus which could be potentially very valuable and useful in this sort of study is a continuous liquid scintillation C^{14}-analyzer which can be applied to chromatographic column techniques. This apparatus might also be useful in further studies of the formation of interconversion of acetoacetic and beta-hydroxybutyric acids as affected by adrenal cortical steriods.

If analyses of breath $C^{14}O_2$ become more extensive and critical in the interpretation of bicarbonate kinetics or the oxidation of labeled compounds, it may be advisable to consider supplementing the present apparatus for C^{14} analysis with the infrared gas analyzer for $C^{12}O_2$ analyses, which would permit direct computation and plot $C^{14}O_2$ specific activities.

This is a continuing program and no large expansion is anticipated.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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06-01-02-e-(2) Animal Studies of Sugar Metabolism

Persons in Charge: W. W. Shreeve, L. Feinendegen and F. C. G. Hoskin

12. & 13. Objectives and Overall Description:

The possibilities of utilizing certain species with specialized needs for energy derived from glucose have been investigated. Also, utilization of tissue culture techniques, where the sources of compounds needed for cellular metabolism can be controlled closely, are being studied.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

Dr. F. C. G. Hoskin, Research Collaborator from Columbia University, under guidance of W. W. Shreeve, spent the first two months of this year initiating a study of pathways of carbohydrate utilization in the electric eel in order to relate the unique form of energy produced to the metabolic reactions underlying it. Techniques in the use of C^{14}-labeled glucose and analysis of $C^{14}O_2$ evolved from tissues incubated with it were learned while at Brookhaven and the study continued later at Columbia University in Dr. David Nachmansohn's laboratory. The Brookhaven phase of this study has been completed. Whether more work at Brookhaven needs to be done will depend upon the results from the study to be completed elsewhere.

Use of regenerating rat liver systems over the past 3 years has shown that at least part of deoxyribose in DNA had an origin different from ribose in RNA. This project has been completed and it is not expected to be reactivated.

Along with the nucleosides T-thymidine and T-cytidine, some labeled sugars (T-deoxyribose and C^{14}-ribose) have been presented to tissue culture cells. The essential finding was that deoxyribose was a poor precursor of DNA, while ribose was converted extensively to both RNA and DNA.

During the current year this study has continued. Ribose was found to be readily incorporated with a pattern of nucleic acid formation similar to that of T-cytidine. Free deoxyribose was not significantly taken into DNA or RNA. These studies involved column and paper chromatographic separation and radioautographic detection of tracers.

16. Expected Results This Fiscal Year - 1961:

These studies will be continued at the same level of effort for the next year and are not to be expanded in the future.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
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06-01-02-e-(3) Radiation Physiology of Blood Lipids and Adipose Tissue

Persons in Charge: I. Schwartz, A. Debons and L. Gidez (Research Collaborator) from Albert Einstein Medical School.

12. & 13. Objectives and Overall Description:

Effects of radiation on the storage and transport forms of body fat represent little explored facets of radiation physiology. Because fat is a major and mobile body constituent, an investigation of the changes in lipid structure, mobilization and metabolism resulting from various forms of radiation would be of interest per se and may bring new insight into the nature of radiation toxicity.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

Standard methods for extraction and analysis of lipids have been set up and used in experiments to study effects of adipose tissue and whole body irradiation (1000 r) in rats and dogs. Lipids from blood sampled during these experiments have been extracted, rectified, frozen and stored, pending satisfactory collaborative arrangements for final fractionation of the extracts by silicic acid and gas chromatography. All rats not sacrificed on the day of irradiation were given an intraperitoneal injection of acetate-1-C^{14} three hours before sacrifice on the second or third post-irradiation day. The in vivo incorporation of acetate into adipose and hepatic fatty acids and particularly into hepatic cholesterol was found to be greatly increased in the irradiated as compared to the control animals. In addition, we have made and used a preparation of albumin bound C^{14}-labeled palmitic acid as an in vivo label for the pool of non-esterified fatty acids in experiments to be described below.

16. Expected Results This Fiscal Year - 1961:

Plans for the next group of experiments will depend on the results of the lipid analysis of the samples from our current study. If radiation induces a qualitative or quantitative change in the major classes of transport lipid or in the fatty acid pattern within any of these classes, radiation effects on the chemical composition of storage and structural lipids will be studied and attempts made to isolate any abnormal lipids.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Natl Lab
COLLECTION Hum 189 Med. Dept. 1950-61
BOX No.
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06-01-02-e-(4) Radioisotopic Analysis of Lipid Metabolism and Transport in the Blood

Persons in Charge: I. Schwartz, A. Debons, and L. Gidez (Research Collaborator, Albert Einstein Medical School)

12. & 13. Objectives and Overall Description:

The availability of isotopic fatty acids has greatly facilitated the study of the mobilization, transport and utilization of body fat. Only recently it has become clear that the non-esterified fatty acid (NEFA) fraction of plasma is a highly important metabolic fuel which alone can supply as much as 50% of the total energy requirement of fasting human beings. (This fact was established directly by determination of $C^{14}O_2$ in expired air after administration of C^{14}-labeled NEFA to man and dogs.) Thus the NEFA fraction of plasma is capable of delivering energy to working cells at a rate equal to and possibly exceeding the caloric flux available from glucose. What is even more interesting is the fact that delivery of NEFA from storage is regulated to supply caloric deficits arising when the total energy requirement exceeds the energy made available from carbohydrate metabolism. This regulation is rapid, sensitive and involves versatile attributes of adipose tissue that were unsuspected until very recently. It is of considerable importance to make use of isotopic fatty acids to characterize the nature of this regulation not only because of its central position in caloric hemeostasis, but also because of the high probability that an unregulated flow of NEFA from storage is the cardinal defect which causes diabetic ketosis.

Studies begun elsewhere on the regulation of the plasma concentration of NEFA have been continued at Brookhaven. In addition, an attempt to develop a more suitable lipid label than C^{14} for studies in humans. One promising possibility which is uniquely adapted to the facilities of BNL is the use of O^{18} which can be determined after proton radioactivation as F^{18}.

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14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

The mechanism by which thyroid hormone elevates the concentration of non-esterified fatty acids in plasma was studied in dogs by comparing the clearance of C^{14}-labeled palmitic acid before and after the administration of l-triiodothyronine (T_3). Within 5 hours after an intravenous injection of one milligram the rate of disappearance from the plasma of palmitic acid-1-C^{14} was increased although the total concentration of NEFA in the plasma had doubled, thus extending previous observations in man. When a uniform concentration of labeled NEFA was maintained by a constant infusion, the administration of T-3 was followed in 5 hours by a significant decrease in specific activity. It is concluded, therefore, that although the thyroid hormone increases the rate of removal of NEFA from the blood, its predominant effect is to enhance the release of fatty acids from tissue stores.

A related series of studies dealt with the effect of thyroid hormone on the in vivo NEFA-genic response to adrenalin in humans and on the in vitro lipolytic response to adrenalin of isolated rat adipose tissue. In the tests on the human subjects, adrenalin evoked a significantly greater and more prolonged elevation of the Plasma NEFA level when the patients were receiving from 0.1 to 0.2 mg of l-triiodothyronine (T_3) than was observed in control periods during which no thyroid was given. Similarly in the in vitro experiments, adipose tissue from hyperthyroid rats showed an exaggerated release of NEFA in response to epinephrine; whereas adipose tissue from hypothyroid animals showed little or no release of NEFA in response to an identical challenge with epinephrine. These studies show that thyroid hormone is essential for what is probably a key process for integrating the requirement for lipid substrate by metabolizing cells and the supply of such substrate from storage. In fact, they establish for the first time a clear role for the thyroid hormone in the regulation of fat mobilization.

It has been observed consistently that whenever l-triiodothyronine increases the basal metabolic rate, it also increases the plasma NEFA level. In sharp

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15. Accomplishments Last Fiscal Year - 1960: (cont'd)

contrast, d-triiodothyronine, which has little or no effect on oxygen consumption, proved to be without effect on the plasma NEFA level and without influence on epinephrine-induced NEFA production. These findings indicate that the increased plasma NEFA concentration of hyperthyroid subjects reflects the accelerated mobilization of fat required to support their excessive metabolic requirement.

During the latter study, it was noted that although d-T_3 had little or no effect on metabolic rate and fatty acid mobilization, its depressive effect on the level of serum cholesterol was fully comparable to that of l-T_3. This finding clearly separates the general metabolic (calorigenic) action of thyroid hormone from its action on cholesterol metabolism and suggests that thyronines devoid of calorigenic action, such as d-T_3, are worthy of study in relation to the general problem of atherosclerosis as well as for their potentially useful pharmacologic effects in man.

Preliminary experiments have been carried out to investigate the hypocholesterolemic effect of thyroid hormone, the most obscure aspects of which is the nature of the hormone influence of cholesterol absorption. Rats with lymph fistulas were prepared and given approximately 50 mg of a preparation of cholesterol-4-C^{14} by stomach tube. The total amount and specific activity of cholesterol absorbed into the lymph over a 24 hour period was determined in normal controls and in 2 groups of animals chronically pretreated with l-T_3 and with d-T_3, respectively. In the normal animals the peak of absorption was sharp and occurred at 6 hours. The specific activity of the lymph cholesterol was strikingly lower than the administered cholesterol-4-C^{14}, showing that there had been an endogenous dilution of the administered labeled cholesterol which can only be accounted for by the existence of a large endogenous pool of cholesterol in the intestinal wall. In contrast, in the thyroid-treated animals, the ratio of the specific activity of the lymph cholesterol to the specific activity of the administered cholesterol was very much higher than in the controls, showing that the thyroid hormone acts in some manner to reduce the endogenous intestinal mucosal pool of cholesterol. This fact is further documented by the finding that the total amount of cholesterol absorbed is reduced by 50 per cent or more in the thyroid-treated animals as compared with the controls.

Additional clinical studies include the use of liquid formula feedings. Because of the increasing general use of formula diets in metabolic studies as well as in the evaluation and therapy of obesity and hypercholesterolemic states, evaluation has been made of the major clinical consequences of prolonged maintenance of patients on these regimens, giving particular attention to the obese patient on a low daily intake of protein. Obese patients losing weight on formulas providing as little as 21 grams of milk protein per day achieve nitrogen balance within 6 weeks, despite a century of nutritional tradition (but no critical data) to the contrary. Potassium balances paralleled nitrogen balances; sodium balances depended on sodium intake which is being varied in a variety of ways in order to determine whether or not fat people have a characteristic abnormality in the regulation of the volume or composition of body fluid. Liver function studies carried out on these patients were all normal except for the findings of abnormal BSP retention in 3 patients on admission, of increasing BSP retention in all patients during the first month on caloric deficit and of decreasing BSP retention with continuing weight reduction thereafter, ultimately reaching values below those on admission in the cases of those who had abnormal elevation and to the same levels in the case of those that did not. This finding of improved liver function draws attention to the relation of obesity and fatty infiltration of the liver and tends to deemphasize the importance of the present so-called optimal level of dietary protein intake especially during restriction of total calories. Measurements of renal, pancreatic, gastric, parotid gland function as well as a limited endocrine survey were all within normal limits during the course of the study.

Measurement of body composition by isotope dilution have been carried out but the results have not yet been analyzed. Relevant to this category of studies are: (1) the possibility of making direct estimates of body fat in man by isotope dilution studies using a radioactive inert gas, such a krupton, the oil:water partition ratio of which is 30:1; and (2) the obvious superiority of the whole body counter over balance techniques for estimation of the retained amount of the administered isotope.

Two clinical studies have been initiated in collaboration with Dr. Gidez. One is concerned with the in vivo transformation of palmitic acid-1-C^{14}, 8,9-H^3 into so-called "essential" fatty acids in man; the second involves an appraisal

(See continuation sheet)

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15. Accomplishments Last Fiscal Year - 1960: (cont'd)

of the metabolic role of unsaturated fatty acids, particularly linoleic acid, in man.

In collaboration with Dr. Shreeve and Dr. De Meutter who are studying incorporation into glucose C^{14} derived from C^{14}-labeled glycolytic and Krebs cycle intermediates, we are observing C^{14} incorporation from these substrates into human serum lipids and cholesterol.

16. Expected Results This Fiscal Year - 1961:

Related studies on the hormone influence of cholesterol absorption will be studied in patients. For the human studies we will try to obtain and use O^{18}-labeled cholesterol, which can be analyzed by radioactivation (P-N reaction converting O^{18} to F^{18}). In the course of this work, we hope to introduce the use of O^{18} (in conjunction with this specific radioactivation procedure) as a sterol and lipid label. This label would be especially valuable for metabolic work in humans since the isotope is stable in vivo and rendered radioactive only for analytical purposes after the experimental samples have been removed.

It is planned to extend the work involving C^{14} in both the normal man and diabetic patient and that these experiments will reveal significant aspects of the interplay between lipid and carbohydrate metabolisms in normal and diabetic man.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Iron 189 Med. Dept. 1950-61
BOX No
FOLDER

06-01-02-e-(5) Transfer of Sugars Across Cell Membranes

Person in Charge: P. G. Le Fevre

12. & 13. Objectives and Overall Description:

During the past 3 years, studies on the mechanism of sugar transfer across the boundary membrane of the mammalian red blood cell have been carried out.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

Theoretical calculations derived from two current interpretations of kinetic data on net sugar transfers have led to application of isotopic tracer methods providing decisive means for discriminating between the 2 proposed hypotheses. Previous kinetic studies have all dealt with net transfers in response to gross concentration gradients. The saturation kinetics found with D-glucose and related monosaccharides have been attributed either to operation of a special sugar carrier system or to nonspecific depression of cell permeability by surface alterations at high sugar concentrations. The latter hypothesis predicts a tracer glucose exchange rate which is only a small fraction of that predicted by carrier theory. Therefore, C^{14} glucose equilibration in both directions was studied in thick suspensions of human erythrocytes. The speed of tracer equilibration in comparison with the speed of net transfer was 50 to 100 times greater than would be found in a diffusion process; these high fluxes are consistent with the carrier theory, provided that a glucose-carrier affinity appreciably higher than that previously estimated is assumed.

Concerning the molecular specificity in sugar transfer systems, the conformational type of biological stereospecificity discovered in the human red cell was extended to other monosaccharide transfer systems, with special attention to the mouse Krebs ascites tumor cell. Appropriate chemical methods have been developed for improved quantification of the partial results reported from other laboratories. Estimation of the specific carrier constants in this cell, which will permit consideration of the correlation with molecular conformational stabilities, is beginning. The related problem of the reversible combination of these systems, in erythrocytes and ascites tumor cells, with phloretin, stilbestrol, hexestrol, and other such diphenolic competitive inhibitors, has been extensively studied. Various correlations have been drawn with respect to minor rearrangements in these diphenolic molecules and alterations in the composition of the medium, as factors in the degree to which the agents become fixed to the cells.

The experimental portion of these studies will be completed during FY 1960.

16. Expected Results This Fiscal Year - 1961:

Final analyses of the experimental data will be completed and this program is expected to terminate.

17. Expected Programs and Results for Next Fiscal Year - 1962:

No activity.

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

Form NYOO-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared:	Revision No.
3. Sub-Title: Radioisotopes for Study of Protein and Nitrogen Metabolism		
4. Budget Activity No. 06-01-02	5. Budget Item No. 06-01-02-f	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-01-02-f Radioisotopes for Study of Protein and Nitrogen Metabolism - (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	185	200	230
Direct Man-Years			
Staff	3.8	4.3	4.5
Visitors	2.3	2.4	3.1
Scientific	6.1	6.7	7.6
Other	6.9	7.8	8.7
Total	13.0	14.5	16.3

The use of labeled proteins for an evaluation of the nutritive state of intact organisms will continue to be explored. C^{14} and tritium labeled compounds give information on a nutritive condition and food utilization, and further demarcate broad pathways into which come and go many other elements. For example, tritium emits very weak beta particles with a range less than cellular dimensions. Thus, this isotope is useful for locating labeled compounds as well as possibly localizing radiation effects within a given cell or part of a given cell.

06-01-02-f-(1) Mechanisms of DNA Synthesis

Persons in Charge: W. L. Hughes, S. L. Commerford, and R. C. Krueger

12. & 13. Objectives and Overall Description:

Many radiobiological effects can be traced ultimately to damage to the genetic material, DNA. Studies with tritiated thymidine at BNL before 1959 have suggested a template mechanism whereby genetic information is duplicated and then divided equally between the two daughter cells during cell division. These observations have been made autoradiographically at the chromosomal level and therefore have shown only how the DNA complex, the chromosome, is duplicated. In order to examine this process at the level of individual DNA molecules other technics must be developed. A promising approach is by labeling the DNA with heavy atoms which will make possible its separation in a centrifugal field.

During FY 1959 a beginning on this problem was made by showing that the thymidine analogue, bromo-deoxyuridine, could be incorporated into DNA.

REPOSITORY Brookhaven Nat'l Lab.

14. Related Projects:

COLLECTION from 189 Med Dept. 1950-1961

See 06-01-02 - Medical Research - Summary Sheet

BOX No.

FOLDER

15. Accomplishments Last Fiscal Year - 1960:

During F.Y. 1960 these studies have been extended to the heavier analogue, iodo-deoxyuridine. However, most studies to date have been with radioactive material in tracer amounts (see succeeding project). In addition the technic

(See continuation sheet)

06-01-02-f-(5) Studies on the Glycoprotein Orosomucoid

Persons in Charge: E. A. Poponoe and M. Maxfield

12 & 13. Objectives and Overall Description:

Among the plasma proteins, the low molecular weight, acidic glycoproteins are more or less unique in that no specific functions have yet been attributed to them. It is unlikely, however, that they are mere chance constituents. The concentration in the plasma of one of these glycoproteins, orosomucoid, is markedly elevated in a number of apparently unrelated conditions including pregnancy, rheumatoid arthritis and various neoplastic diseases. In neoplastic diseases, in fact, the plasma orosomucoid level can be used as an indication of the patient's response to therapy. When treatment has been successful, the level drops.

The most interesting aspects of the structure of orosomucoid would appear related to its carbohydrate moiety and this in turn should bear on its function. Previously it has been found to contain 40% of a carbohydrate containing 17 terminal sialic acid residues each linked to a galactose in the carbohydrate as a glycoside.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

During the past year unsuccessful attempts were made to probe further into the structure of the carbobydrate portion of the molecule using a variety of enzymes known to hydrolyze galactosides. However, attempts to whittle away the protein part of the molecule have been more successful. An unidentified flavobacterium which has been isolated by Dr. Drew, of BNL, will grow on a medium containing orosomucoid and inorganic salts. During this growth about 90 per cent of the polypeptide part of the glycoprotein is removed leaving the carbohydrate part apparently unchanged, and still firmly attached to a small peptide. An amino acid analysis of this residual material showed that it is composed predominantly of aspartic acid and theonine with lesser amounts of glutamic acid, proline, and glycine and traces of several other amino acids.

16. Expected Results This Fiscal Year - 1961:

During Fiscal Year 1961 attempts will be made to degrade this product further either by chemical or enzymatic means and thus ultimately to identify the amino acid to which the carbohydrate is attached. As time permits, it is hoped also to use the experience gained with orosomucoid to make parallel studies on certain other mucoproteins. Most likely candidates for this study are an alpha$_2$-glyoprotein which can be isolated in a pure state from human plasma, and the urinary mucoprotein which is already under study in this Department.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab
COLLECTION Form 189 Med. Dept. 1950-61
BOX No.
FOLDER

06-01-02-f-(4) Metabolism of C^{14} - labeled amino acids by Trichinella Spiralis Larvae.

Person in Charge: L. V. Hankes and R. D. Stoner

12 & 13. Objectives and Overall Description:

Investigation of the problems of trichinosis as studied with radioactive compounds yields information on host-parasite relationships.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

Specifically, the effects of an active trichinella infection on host metabolism were investigated. In vitro turnover studies of labeled proteins and carbohydrates were studied in Trichinella larvae, utilizing larvae cultures in chemically defined media. The larvae were labeled in the host by feeding mice diets containing C^{14}-labeled amino acids. Tissue and blood components were analyzed for C^{14} to assess the effects of parasitic infection on host metabolism. Although the data have been collected, analysis and interpretation will not be complete until FY 1961.

16. Expected Results This Fiscal Year - 1961:

Activity during this year will be limited to the analysis and interpretation of the experimental data.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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

06-01-02-f-(3) Plasma Protein Metabolism

Persons in Charge: W. L. Hughes
F. Gregoire (Research Collaborator in Residence from Belgium),
A. Scanu (Research Collaborator from Cleveland Clinic),
L. Ledoux (Research Collaborator from Centre d'Etude l'Energie Nucleaire, Brussels, Belgium)

12 & 13. Objectives and Overall Description.

Serum albumin has been labeled with tritium, serum lipoproteins have been labeled with radioiodine, α lipoprotein has been labeled with I^{131} and the dynamics of its dissociation into lipid and protein moieties has been studied.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960

The above described program was continued into FY 1960, and the ease and reversibility of this process indicated the importance of α-lipoprotein in lipid transport and metabolism. Ribonuclease has been similarly labeled with iodine and found to rapidly distribute extravascularly after i.v. injection as well as concentrating in the kidneys.

16. Expected Results This Fiscal Year - 1961

In FY 1961 further studies on lipoproteins and on the mechanism of renal concentration of ribonuclease are planned.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for FY 1961 is expected to be continued.

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

Project Title: The Preparation and Use of Tritiated Compounds for Biomedical Studies. 06-01-02-f-(2)

06-01-02-f-(2) The Preparation and Use of Tritiated Compounds for Biomedical Stud.

Persons in Charge: W. L. Hughes, H. A. Johnson, R. Painter, L. E. Feinendegen, R. C. Krueger (Research Collaborator - Univ. of Connecticut) S. L. Commerford (Research Collaborator in residence from National Institute of Health), D. Gitlin (Research Collaborator from Harvard University), M. Rodriguez (Research Collaborator from John Hopkins Univ.)

12 & 13. Objectives and Overall Description:

The value of H^3-thymidine in following the dynamics of cell proliferation was demonstrated in FY 1958 and has initiated a number of projects in the following years. Its invention as a method of localizing radiation within the radio-sensitive volume of the cell's nucleus has largely been ignored in view of its many tracer applications. Nevertheless, in sufficient dosage it can produce radiation damage. This was first demonstrated in tissue culture in FY 1958 and extended to mice in FY 1959, 1960, where it has been shown that temporary sterility and thymic weight loss can be produced. The sterilizing effect has been correlated with that of x-rays - 1 μc of H^3-thymidine per gram of body weight being about equivalent to 2 r of x-rays per day.

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960 :

During FY 1960 Iodo-deoxyuridines (IDU) labeled with I^{131} and I^{133} have been prepared as thymidine analogues. The gamma radiation of these isotopes permits metabolic measurements outside the body in the intact organism. It has been shown that IDU is a specific analogue of thymidine, like the latter being incorporated only into DNA. This property has been utilized to study in vivo rates of DNA synthesis in various organs of mice and the inhibitory effects of x-rays which were discernible with as little as 10 r. The use of both I^{131} and I^{133} - labeled IDU in the same animal permitted the measurement of changes in the rate of DNA metabolism produced by experimental procedures uncomplicated by the individual variations observed between animals. This technic proved particularly useful in studying the mouse sarcoma which normally showed a high but variable rate of IDU incorporation. The tumor proved to be much less radiosensitive than the intestinal epithelium but the per cent inhibition was quite similar to that of bone marrow for the same x-ray dose.

16. Expected Results This Fiscal Year - 1961:

During FY 1961 it is planned to survey by the IDU technic a variety of procedures used in cancer therapy looking for differential effects on DNA synthesis in the tumor vs. normally proliferating tissues of the host. Also IDU labeled with the position-emitting I^{124} will be prepared in an attempt to locate tumors by coincidence scanning of the anihilation radiation emitted from the isotope built into DNA. (Note: The volume of work contemplated with IDU and its close relation to cancer suggest that a new project should be initiated in this field, see proposed joint project by Hughes and Farr.)

The preparation of tritiated compounds which was interrupted in 1959 by the move to the new building will be resumed in FY 1961 when adequate facilities are available. The preparation of biochemicals labeled at high specific activities for autoradiographic studies has proven particularly fruitful in studying nucleic acid metabolism and attempts will be made to extend this to the study of proteins. (Serum albumin of relatively high specific activity was prepared in FY 1959, but thus far has not yielded any autoradiographic results.)

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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

15. Accomplishments Last Fiscal Year - 1960: (contd.)

of density gradient centrifugation has been applied to the separation of protein molecules of different densities; iodinated albumin has been separated from normal albumin and investigation of the immune reaction has suggested that density gradient centrifugation may be a promising method of separating complexes of antigen and antibody.

16. Expected Results This Fiscal Year - 1961:

During FY 1961 it is planned to extend density gradient centrifugation to the analysis of DNA from cells grown in the presence of large amounts of iododeoxyuridine. The new "heavy" DNA should thus be readily resolvable permitting a variety of studies on kinetics, mechanisms and radiation effects.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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

06-01-02-f-(6) Collagen Formation Studied with Isotope-Labeled Amino Acids.

Persons in Charge: D.D. Van Slyke, E. A. Popenoe

12 & 13. Objectives and Overall Description:

Collagen, the structural protein that binds the tissues of animals together, constitutes 30 to 40 per cent of mammalian body protein. It is involved in the pathological changes of the "collagen diseases" and the changes of aging. The formation and metabolism of collagen in rats was studied before and during FY 1959 with the use, as a tool, of C^{14}- and H^3-labeled lysine. Hydroxylysine is unique among protein amino acids in combing two properties: it occurs only in collagen and, as shown by previous studies in this laboratory, it is formed from only one source, lysine. Lysine from food proteins is hydroxylated in the tissues and the hydroxylysine thus formed is incorporated into the collagen. Hydroxylsine itself, when administered labeled with H^3, was found not to be incorporated. Hence it appears that hydroxylysine formation from lysine does not occur before incorporation. The question remains, whether the formation of hydroxylysine from lysine occurs at the moment of incorporation, or whether it follows. The question whether one amino acid can be transferred into another after incorporation into the protein molecule is of importance in the general problem of protein metabolism. If hydroxylation of lysine occurs at the moment of incorporation of C^{14}-labeled lysine, the carbons of the lysine and hydroxylysine in the collagen must have from that moment equal C^{14} specific activities. A final answer to the question whether this occurs has not yet been reached.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

During 1960 when collagen was isolated by conventional methods, that obtained an hour after injection of C^{14}-labeled lysine showed hydroxylysine carbon with only 70 per cent as great C^{14} activity as lysine from the same collagen preparation. The figure slowly increased towards 100 per cent during subsequent days. The course of the change made it appear probable that hydroxylysine formation from lysine in fact was completed at the moment of incorporation, and that the excess C^{14} activity of the lysine over the activity of the hydroxylysine in the collagen during the first hours after the lysine injections was due to the incomplete removal of other proteins from the collagen preparations by the conventional methods of purification.

16. Expected Results This Fiscal Year - 1961:

To obtain a final solution of the problem during 1961 the experiments performed in FY 1960 will be repeated with refinements in the purification of the collagen.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined in FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Trm 189 Med. Dept. 1950-61
BOX No. _____
FOLDER _____

06-01-02-f-(7) Use of Radioactive Iodine to Improve Methods for Determination of Protein-Bound Iodine in Serum.

Persons in Charge: D. D. Van Slyke, L. V. Hankes and O. P. Foss

12 & 13. Objectives and Overall Description:

Normal human serum contains an average of 6 parts of iodine per 100 million, 1 part being inorganic iodide, while the other 5 parts are in thyroid hormone attached to the plasma proteins. The measurement of this protein-bound iodine is important in diagnosis of thyroid disease. Because of the minute amounts of iodine involved reliable analytical results are obtained only with exceptional precautions.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

With the help of tracer amounts of I^{131} conditions for the successive steps of the analysis, viz., precipitation and washing of the proteins containing the protein-bound iodine, incineration of the proteins with alkali, extraction of iodide from the ash, estimation of the iodide by its effect in catalyzing the reduction of cerate by arsenite, and the reagents used with each step, have been tested in detail with variations to find optimal conditions for each. As a result losses of iodine which could, by former procedures be as great as 30 per cent, have been reduced consistently to less than 5 per cent, and the procedure has been simplified so that an analyst in a day can finish many more determinations. This project was conducted during 1959-60 and has now been terminated.

16. Expected Results This Fiscal Year - 1961:

No activity.

17. Expected Programs and Results for Next Fiscal Year - 1962:

No activity.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Irvin 189 Med. Dept. 1950-61
BOX No. _____
FOLDER _____

Form NYOO-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared: May 1960	Revision No.

3. Sub-Title: Radioisotopic Labeled Hormones to Determine Action Sites

4. Budget Activity No.	5. Budget Item No.	6. Contractor's No.
06-01-02	06-01-02-g	

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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing

06-01-02-g Radioisotopic Labeled Hormones to Determine Action Sites - (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	75	80	95
Direct Man-Years			
Staff	0.9	1.1	1.1
Visitors	1.8	1.9	2.1
Scientific	2.7	3.0	3.2
Other	3.0	3.4	3.8
Total	5.7	6.4	7.0

The mechanism of action, particularly at the molecular level of hormones remains obscure. The deficiency, excess, or qualitative abnormality of hormones is correlated with major disease processes such as diabetic ketosis, atherogenic changes in blood lipids, and diabetes insipidus secondary to radiation or other factors. The preparation of hormones labeled with low energy, alpha or beta-emitting, isotopes would make it possible to study, at the subcellular and molecular level, the crucial questions in endocrinology underlying these important clinical problems.

REPOSITORY Brookhaven Nat'l Lab.
COLLECTION Form 189 Med. Dept.
BOX No. 1950-61
FOLDER

06-01-02-g-(1) Mechanism of Hormone Action

Persons in Charge: I. Schwartz, A. Debons, C. Fong, L. Silver, H. Johnson, E. P. Cronkite, L. K. Dahl, and E. Popenoe.

12. & 13. Objectives and Overall Description:

Although there is extensive literature and considerable activity in the field of endocrine biochemistry and physiology, little, if anything is known about the chemistry of hormone-receptor interactions. It is believed that studies of such interactions at the molecular level are feasible now because it is possible to label and prepare biologically-active derivatives of pure hormones of known chemical structure, and because the nature of the physiological action of some important peptide hormones has been recently so precisely defined. For example, it is now clear the antidiuretic hormone of the posterior pituitary alters amphibian membranes and the mammalian distal nephron to bring about an increased hydrodynamic flow in response to a transmembrane or transtubular osmotic gradient. This is accomplished either by the dilatation of "pores" or by expansion of a water-filled lattice in these membranes. An impressive array of evidence has accumulated to indicate that one of the major actions of insulin is to alter the permeability to sugars of the membranes of insulin-sensitive cells. A study of the relation between the mechanism of antidiuretic activity and the bonding of vasopressin to kidney and other tissues; a study of the bonding of insulin to its receptors in muscle and adipose tissue; and a study of the effects of radiation on the correlated chemical and biological activities of these receptor sites in both vasopressin-sensitive and insulin-sensitive tissues has been initiated.

(See continuation sheet)

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14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

1. Lysine vasopressin and arginine vasopressin were purified from partially-processed mixed hog and beef pituitary powder by counter-current distribution and ion exchange chromatography. Both hormones were labeled with H^3 by the Wilzbach procedure, freed of exchangeable tritium, repurified from the mixture of radiation degradation products and shown to have retained biological activity.

2. Using these purified labeled hormones evidence has been obtained that arginine vasopressin is attached at its renal receptor site through a disulphide bond. This formation of a mixed hormonereceptor disulphide proved to be specific for renal tissue and could not be demonstrated in the ADH-insensitive kidney or in the soluble proteins precipitated from normal challenged kidney. Thus, this chemical bond appears to bear an important relation to the mechanisms of the antidiuretic activity of vasopressin. This finding represents the first description of a chemical bond formed between a hormone and a target organ and suggests the value of further exploring the significance and specificity of this bond in relation to the ultimate action of the hormone on membrane permeability.

3. Experiments to determine the nature of the bonding of I^{131}-labeled insulin to insulin-receptors in rat diaphragm and adipose tissue invariably resulted in a significant release of radioactivity only after procedures which specifically disrupt disulphide bonds, thus suggesting that what we have found for vasopressin may be a general phenomenon applicable to all disulphide peptide hormones which act on cell membrane permeability. It must be noted, however, that in the case of insulin, our findings cannot be interpreted with the same confidence as in the case of vasopressin until we have pinpointed the location of isotopic labels within the insulin molecule at least with reference to the A and B chain.

4. I^{131}- labeled vasopressin has been prepared and recovered as a chromatographically and electrophoretically homogeneous entity with approximately 1/1000 of the biological activity of native or tritiated ADH. Studies of the turnover of both I^{131}-ADH and H^3-ADH are now in progress in dogs and in humans with and without abnormalities of water and electrolyte metabolism. These studies of ADH turnover will supply critical data bearing on the nature of the homeostatic regulation of the quantity or volume of body fluids.

5. In collaboration with Dr. Johnson, Dr. Cronkite and Dr. E. M. Darmady we are attempting to localize I^{131}-vasopressin and H^3 vasopressin and I^{131} insulin autoradiographically. In first experiments, we demonstrated a clear cut specific localization of insulin in the first part of the proximal convoluted tubule, and this finding is of considerable interest because this is the precise site where glucose was found to be reabsorbed.

6. The effects of self-irradiation on beta and gamma emitting isotope derivatives of vasopressin was studied by following the change with time in potency of cold ADH as compared with H^3-ADH and I^{131}-ADH. Lysine vasopressin-H^3 sustained an approximately 10% loss of hormonal potency over a 1 year period of storage at -30°C. On the other hand, I^{131}-AVP did not lose potency during the period required for the I^{131} to decay to levels of less than 0.1% of the original radioactivity. In fact the hormonal potency of the I^{131}- AVP may have increased during storage. If this unexpected finding can be substantiated by assays of preparations with higher specific activity, this phenomenon will constitute a possibly unique instance of enhanced biological activity as a consequence of isotope decay. This phenomenon, although odd at first consideration, is not implausible since the decay of I^{131} to Xe^{131} results in the formation of a chemically inert gas which may simply free the hormone of the markedly inhibitory influence of its attached iodine and restore the native form of its tyrosyl residue.

7. The use of activation technique, specifically neutron activation, is being developed as a labelling procedure as well as an analytical procedure. Arginine vasopressin has been exposed to neutron fluxes in the range of 2.5×10^{13}. Destruction of the hormone was almost complete, but the trace amounts of "activated" hormone that were detected by bioassay of chromatographic eluates approximated in specific activity that which is theoretically predicted from maximal activation of the Sulfur^{34} content of the hormone.

(See continuation Sheet)

REPOSITORY Brookhaven Natl Lab
COLLECTION Ann Rpt Med. Dept. 1960-61
BOX No. 8

15. Accomplishments Last Fiscal Year - 1960: (contd.)

8. The bladder of the toad, Bufo Marinus is being used as a model for the ADH-receptive zone of the mammalian kidney, since it is a simple ADH-responsive membrane, consisting of a single layer of mucosal cells supported on a small amount of connective tissue. This membrane is ideally suited for continuation and extension of studies of hormone-receptor interaction and of the effects of radiation on receptor function. The ADH has a striking action on its permeability by altering the structure of a diffusion barrier in its wall, not affecting its metabolic processes including those metabolic processes coupled to active transport of sodium. This finding is consistent with the suggestion that a hormone-receptor thioldisulphide exchange reaction underlies the critical change, i.e., partial disruption of cross-linking in the teritary structure of the receptor protein, which enlarges the membrane area available both for free diffusion and hydrodynamic flow of water. The finding also suggests that in the course of study of the effect of radiation on the functional integrity of the ADH-receptor system of this tissue, a radiation dose range should be found which will affect differentially its structural and metabolic properties.

16. Expected Results This Fiscal Year - 1961:

An attempt to develop neutron activation as a procedure for labeling vasopressin, insulin and possibly other biologically important molecules for which labeling by synthesis would be impractical or impossible will be made. The preparation of synthetic labeled vasopressin derivatives with the aims of identifying the groups essential to binding of hormone to receptor and of learning the sequence of reactions that accounts for initial fixation of the hormones, specificity of its attachment and the ultimate critical chemical reaction that brings about its physiological action will continue. The design of the bonding experiments will be similar to but in general more extensive than those already developed. The work with insulin will be carried out along similar lines except that the experiments will involve receptors in muscle and adipose tissue and that it will be necessary to pinpoint the isotopic labels within the insulin molecule.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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

06-01-02-g-(2) Biochemical and Physiological Activity of the Thyroid Hormones and Their Analogues.

Persons in Charge: C.J. Shellabarger and R.C. Mason. (Research Collaborator) from Seton Hall.

12 & 13. Objectives and Overall Description:

It was discovered in this Laboratory some five years ago that there is a species difference between birds and mammals in their response to thyroxine and 3,5,3' triiodothyronine. Attempts to exploit this finding, in terms of the mechanism of action of the thyroid hormones have continued utilizing various analogues of the thyroid hormones, animals, labeled hormones, and experimental design.

During earlier studies, it became clear that 3,5,3' triiodothyronine possesses all of the qualities of thyroxine although these two thyroid hormones differ quantitatively according to the system studied to estimate their biological activity. Specifically, the finding that thyroxine was no more potent than triiodothyronine in birds but much less potent than triiodothyronine in mammals and amphibia was confirmed.

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

During F.Y. 1960, analogues of thyroxine proved to be less potent than analogues of triiodothyronine when tested in amphibia and mammals. In an effort to understand the mechanism that allows one thyroid hormone to be more potent than the other thyroid hormone, the following three studies were initiated:

1. Studies to learn more about the biochemistry of the thyroid hormones. Analogues of the thyroid hormones as synthesized by R. Pitt-Rivers are sent to this Laboratory and screened for biological potency using the stimulation of metamorphosis as the endpoint. Promising compounds are then tested in other classes of vertebrates using various indices of potency. This program is in the data collecting stages; as more information is acquired it may be possible to assign biological properties to chemical configuration of the thyroid hormones.

2. With Dr. R.C. Mason (Research Collaborator, Seton Hall, College of Medicine) the requirement of thyroid hormones needed for the action of male and female hormones on secondary sex characters is being studied. It would appear that no thyroid hormone is required for androgen to act upon the seminal vessicles of the rat, but thyroid hormone is required for androgen to act on the chick comb. Similar studies are continuing, utilizing analogues of thyroid hormone and various androgens and estrogens in both birds and mammals.

3. A continuation of studies begun at the National Institute for Medical Research, London, includes the study of the mechanism of transport of thyroid hormones in the blood of birds and mammals. Using I^{131} labeled thyroxine (T-4) and 3,5,3' triiodothyronine (T-3) studies to determine the half-time in the blood of these two thyroid-hormones of birds is underway. In contrast to mammals where T-3 has a much shorter half-time than T-4, in birds the half-times are similar. Attempts to modify these half-times by infusion of thyroxine-binding protein, a serum protein absent in birds, is to be attempted.

16. Expected Results This Fiscal Year - 1961:

It is proposed to continue and terminate these studies in the next fiscal year.

REPOSITORY Brookhaven Natl Lab

17. Expected Programs and Results for Next Fiscal Year - 1962:

COLLECTION Form 189 Med. Dept. 1950-61

No activity.

BOX No

4002234

Form NY00-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Radiation Effects on Biological Systems - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Special Projects		
4. Budget Activity No. 06-01-02	5. Budget Item No. 06-01-02-h	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-01-02-h Special Projects (Marshall Islands, etc.) - Summary

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	100	115	125
Direct Man-Years			
Staff	0.9	1.1	1.1
Visitors	1.3	1.4	1.7
Scientific	2.2	2.5	2.8
Other	1.4	2.5	2.7
Total	3.6	5.0	5.5

06-01-02-h-(1) Educational Conferences

Persons in Charge: L. E. Farr and S. W. Lippincott

12. & 13. Objectives and Overall Description:

A stated effort of the Department, which has arbitrarily been termed an educational effort, is the organization of at least one special conference for selected invitees each year in conjunction with the Division of Biology and Medicine of the Atomic Energy Commission. These conclaves are, in general, for educators to examine with active investigators specific responsibilities in the field of atomic medicine. The exact format of the conclave is altered in each case to meet the specific needs of the group concerned.

Participation is by invitation only with no substitutions, and the objective is to provide two full days of discussion and demonstration dealing with a special field of medicine in which the visitiors are engaged. Members of the Brookhaven Medical Department staff give talks as a basis for discussion as well as demonstrations of various devices in atomic energy programs useful in the field of medicine the guests represent. The first of these conclaves, held March 15 and 16, 1956, and entitled "A Critique of Present Knowledge and Investigations of the Effects of Radiation Upon the Central Nervous System," was attended by physiologists, pathologists, neuropathologists, clinicians and biochemists interested in the central nervous system. The second conclave, "The Responsibility of the Chairman of the Department of Pathology for Training, Research, and Hospital Practice in the Field of Nuclear Energy," was held February 6 and 7, 1958.

The third of these conferences was held on December 15 and 16, 1958 to which all Deans of Medical Schools in the United States and Canada were invited to discuss, and hear discussed by BNL personnel and eminent authorities selected from various organizations, "The Impact of Atoms on Medical Science and Education." Approximately 75 per cent of the invitees attended and the conference was adjudged most successful.

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(See continuation sheet)

14. Related Projects:

See 06-01-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

The fourth conclave was held October 26 and 27, 1959, and was entitled, "Nuclear Medicine in Surgical Research and Practice," and was attended by chairmen of the Departments of Surgery of American and Canadian Medical Schools, each of the conclaves has been very well attended and discussion has been spirited.

16. Expected Results This Fiscal Year - 1961:

A fifth conclave on "Pediatricians, the Child and Atomic Radiation," is planned for the fall of 1960.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined above is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
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06-01-02-h-(2) Marshallese Survey

Persons in Charge: R. A. Conard

12 & 13. Objectives and Overall Description:

In March 1954 following the 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 medical teams under the auspices of the Division of Biology and Medicine of the Atomic Energy Commission. These studies are under the sponsorship of the Medical Department, Brookhaven National Laboratory and Dr. Robert A. Conard has been appointed by the Laboratory as chief of the Marshall Islands study project, and is in charge of organizing and carrying out the annual medical surveys of these people in the Marshall Islands. Much valuable information has been and is being obtained on the effects of fallout radiation on human beings which is being made available to the medical profession and scientific world through publications.

Reports have been published on the findings of surveys made at the following times after exposure: initial examination, 6 months, 1 year, 2 years, 3 years, and 4 years. The data from the 5 year post-exposure survey is in the process of being analyzed.

The early effects of the radiation exposure were as a result of sub-lethal gamma radiation, extensive beta burns, and absorption of radioisotopes. The gamma radiation caused significant depression of their blood forming organs during the two months following exposure recovered from these effects of their exposure with the exception of their blood platelets, whose mean level is still slightly below the level of the unexposed comparison population, but within the normal range. Of greater concern now is the possible development of late effects of radiation based on knowledge gained from animal studies and from limited experience with human beings. Some of these effects which may possibly appear in the Marshallese are: increased incidence of malignancies, development of opacities of the lens of the eyes and genetic changes, other less well defined effects might be noted in retrospect but no significant examination program can be conducted about them. These effects have not yet been observed in the Marshallese but continued close medical supervision is considered necessary in order to detect and carry out treatment of any diseases that may develop as soon as they might appear. To this end, a cancer detection program must be instituted in the surveys. This will include careful observation of the residual scars of beta burns for signs of malignant change. In the Japanese exposed to the atomic bombings an increased incidence of leukemia, which reached a peak between 5 and 10 years after exposure, was noted. Therefore, the next five years may be a critical period for the development of radiation induced leukemia in the Marshallese, and annual surveys for leukemia are essential in order that a possible case be not missed, since the average time from diagnosis to death in some forms of leukemia is less than a year. Certain examinations, however, will be necessary on an annual basis such as physical examinations, cancer survey and hematological examinations.

In view of the above stated facts, continued examination of the Rongelap people is considered necessary on a yearly basis until such time as it is the medical concensus that examinations may be reduced in frequency. This matter has been discussed at some length with medical experts in this field, many of whom have participated in past surveys.

As a result of recent conferences with Trust Territory officials, including Dr. H. H. Macdonald, Director of Public Health, the Trust Territory has agreed to take a more active part in the surveys. This is considered a very important step forward and has many favorable aspects.

14. Related Projects:

REPOSITORY Brookhaven Nat'l Lab

See 06-01-02 Medical Research - Summary Sheet

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15. Accomplishments Last Fiscal Year - 1960:

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Details of the March 1960 survey were worked out with Dr. Macdonald of the Trust Territory. The survey involved only a brief examination of the exposed Rongelapese including one WBC and differential count. A limited number of urine

(See Continuation Sheet)

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15. Accomplishments Last Fiscal Year - 1960: (Cont'd.)

samples were collected for radiochemical analyses. It is anticipated that this survey required only a few days at Rongelap.

16. Expected Results This Fiscal Year - 1961:

Definite plans have only been made through the 1961 survey. During that survey a more complete examination schedule is planned including growth and development studies of the children, leukemia and cancer survey, complete routine hematological survey, use of the steel room for carrying out gamma spectroscopy, and collection of urine samples for radiochemical analyses to be carried out at Brookhaven National Laboratory.

17. Expected Programs and Results for Next Fiscal Year - 1962

Though specific plans for the 1962, 1963, 1964 surveys have not been made, it is likely that these surveys will not be of too large scope in view of the alternating schedule referred to above. For instance such studies as gamma spectroscopy, growth and development studies and ophthalmological studies may be carried out on alternate years. Certain examinations, however, will be necessary on an annual basis such as physical examinations, leukemia and cancer survey and hematological examinations.

Precise figures cannot be given at this time on the number of personnel participating from the United States. This will depend entirely on the number of personnel the Trust Territory can furnish. It seems likely that the number of personnel from the United States will probably range from 6 to 15 in any one future survey. Although the number of individuals going to the Marshall Islands will decrease, the volume of analysis of specimens sent from the Marshall Islands to the United States is not expected to decrease.

REPOSITORY Brookhaven Nat'l Lab.
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06-01-02-h-(3) Summer Student Institute

Persons in Charge: L. E. Farr and W. W. Shreeve

12 & 13. Objectives and Overall Description:

The role of the Brookhaven National Laboratory in Medical education has been evaluated as follows:

BNL should center its major educational efforts upon physicians of faculty rank because thereby information is multiplied and young faculty members may, as a result of such experiences, elect a research-academic career as contrasted to a practice-academic career. This program must be carried out in such a fashion that for the exceptional student opportunities to participate in the work of the BNL medical program will remain open.

Careful study and consideration of the problems for several years has led to the conclusion that for medical students the most effective, appropriate and efficient extension of Brookhaven to undergraduate medical education would be accomplished by giving a highly modified version of a Medical School course at Brookhaven. By this means the student can be given a suitable and proper introduction to the broad problems of nuclear medicine from public health to patient care, from nuclear physics to disease prognosis. If, however, such a course were given by Brookhaven Staff alone it would divert BNL physicians from their basic research. Therefore, the course should be given by a Faculty assembled from Medical School Faculties, by men skilled in conducting teaching of medical students and by men interested in the field of atomic energy. The faculty in turn will be Research Collaborators in the Medical Department participating with BNL scientists in research as do all other Research Collaborators in the Department. Thereby diversion is prevented and an actual reinforcement of program is attained. Since the course will be a responsibility of Faculty and it is the decision of the School to grant credit for the same, it places the student in exactly the same relationship to Brookhaven as when he is performing thesis work at B.N.L. By control of course content, it can be assured that proper experiences are given ranging from Laboratory manipulations of radioisotopes to waste disposal, hot laundry and personal physical examinations. By encouraging use of Brookhaven Medical Department personnel in lectures but limiting lectures by any given individual to two, the main reliance cannot be placed on BNL Staff yet their lectures will give the real impact to the course. Utilization of wards by the Faculty for student rounds including whole body counter usage will be wholesome for all. Participation should be by allotment to Medical Schools on some basis which has yet to be established and which will be rotated in a manner to provide various medical schools with a chance to participate. Obviously some experience must be obtained to determine instrumentation needs, intensity of course and hours required of the Faculty.

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COLLECTION Trm 189 Med. Dept. 1950's
BOX No.
FOLDER

14. Related Projects:

See 06-01-02 Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

It is clear that no firm commitment should be made in regard to any new variant of the student program without experience that would indicate the value of the new approach. It is equally clear that such an experiment cannot be carried out jointly with 85 medical schools but that the best experimental approach is to find one medical school which is favorable to the idea and then to explore it for one or two years after which conclusions may be drawn and a course for further action plotted. The many details requiring agreement made it clear that if anything were to be accomplished during the summer of 1959, it had to be done with a single medical school ready and willing to participate in such an educational experiment. Dr. John Truslow, Dean of the University of Texas, indicated a willingness to carry on the necessary experimental study. A three man curricula committee from Texas visited Brookhaven March 30th and 31st to establish jointly with Brookhaven Medical Department members curriculum content. Eight students and three faculty members were chosen for the first joint BNL-Medical School Course in Principles in Nuclear Medicine to run June 28 to July 31, 1959 at Brookhaven.

A course of lectures and laboratory sessions was worked out by the two groups. Members of the Brookhaven Staff were called upon for lectures in their special

(See Continuation Sheet)

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15. Accomplishments Last Fiscal Year - 1960: (Cont'd)

fields, and laboratory facilities were made available under the direction of scientists or technical staff members of this Department working with the University's faculty members. A very successful five-week intensive study and training period was enthusiastically carried out by the eight students selected and the three visiting faculty members.

Certainly the procedure must be explored further with particular reference to means for making it available simultaneously to a number of medical schools. The whole development is under intensive study by the Medical Department Staff members concerned.

16. Expected Results This Fiscal Year - 1961:

During the coming year it is planned to develop the Medical Student Institute on a four school basis for Fiscal 1962. The administrative details for faculty selection and course integration into the various schools are numerous. It is not planned to increase the numbers of students participating until past experience has indicated the optimal format. This endeavor is of importance since it permits medical schools not having atomic energy projects to participate in active work in nuclear medicine both on the faculty and student level and is accomplished with existing facilities. The response thus far from Deans acquainted with the project has been enthusiastic.

17. Expected Programs and Results for Next Fiscal Year - 1962:

By Fiscal 1962, it is hoped administrative arrangements can be completed for several schools to participate. Perhaps one Medical School will be invited to participate in the course, as previously described.

REPOSITORY Brookhaven Nat'l Lab
COLLECTION Item 189 Med Dept. 1950 61
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06-01-02-h-(4) Occupational Medicine Clinic

Person in Charge: R. A. Love.

The largest Laboratory-supported activity of the Medical Department is the Occupational Medicine Clinic. This organization provides to the Laboratory as a whole the necessary industrial medical services for proper operation. The work of the clinic has risen steadily with each year of the Laboratory's operation and the ultimate size of the operation cannot yet be determined. The total number of visits to the occupational medicine clinic during Fiscal 1959 was 15,127 as compared to 13,133 in Fiscal 1958. Similarly, the total number of X-ray examinations increased from 2,005 to 2,236.

Man-years and costs are not included above, but are part of the General and Administrative costs of the Laboratory and are distributed as Indirect Expense.

REPOSITORY Brookhaven National Lab.
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Title Cancer Research 06-03-01

18. Operating Costs (In Thousands of Dollars)	Estimated 1960	Estimated 1961	Estimated 1962
Labor (including benefits)	350	467	551
Materials Travel, etc.	89	122	139
Development. Subcontracts, Special Proc.	1	6	6
Total Direct	440	595	696
Special Power	-0-	-0-	-0-
Reactor and/or Accelerator Usage	25	30	30
Technical Services (from BNL Service Units)	56	70	80
General & Administrative Overhead	216	260	284
Total	737	955	1,090
Capital Equipment (Obligations - for information only)	56	55	85

19. Plant & Equipment Directly Required (Obligations - shown here for information only)

	Estimated 1960	Estimated 1961	Estimated 1962
(A) Construction (In Thousands of Dollars)			
(B) Equipment (In Thousands of Dollars)	56	55	85

FY 1961 equipment obligations for this activity include a proportional part of the total obligation for special items which will be utilized by more than one medical activity. (see Medical Research Summary) - $10,700.

FY 1962 equipment obligations for this activity include a proportional part of the total obligation for special items which will be utilized by more than one medical activity. (see Medical Research Summary) - $41,000.

20. Direct Man Power	Estimated 1960	Estimated 1961	Estimated 1962
No. of Man Years			
Scientists, Research Associates	10.5	13.5	14.5
Visiting Scientists	2.5	3.0	3.5
Scientists - Total	13.0	16.5	18.0
Technical	29.0	39.5	45.5
Administrative & Service	3.5	5.0	5.5
Total	45.5	61.0	69.0

21. Comments

REPOSITORY Brookhaven Nat'l Lab

COLLECTION From 189 Med. Dept. 1950-61

BOX No

FOLDER

4002242

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Form NYOO-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Beneficial Applications of Atomic Energy - Cancer Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Neutron Capture Therapy		
4. Budget Activity No. 06-03-01	5. Budget Item No. 06-03-01-a	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-03-01-a Neutron Capture Therapy - (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	485	635	720
Direct Man-Years			
Staff	8.5	11.3	12.2
Visitors	1.9	2.3	2.6
Scientific	10.4	13.6	14.8
Other	19.5	27.5	31.8
Total	29.9	41.1	46.6

Neutron Capture Therapy originated at Brookhaven National Laboratory and to date all patients treated and experimental animals studied have been observed at either the Brookhaven Graphite Research Reactor or the Medical Research Reactor. The very large general project consists of numerous component parts in which major endeavor is carried out largely within a single discipline. The design and operation of reactors for medical purposes is a project which includes besides Medical Department members, staff from Health Physics and Instrumentation, Physics, Nuclear Engineering and Reactor Operations. The inter-relationship between devices as engineered and usefulness in medical fields are being explored both on site and off site by appropriate consultations with other reactor engineering groups largely from commercial companies. The effects achieved by neutrons of different energies and particularly the regional tolerance of such exposure is a continuing study. While no limits can yet be set, the surprising tolerance to thermal neutrons of the central nervous system increases considerably the medical interest in reactor design and performance. As part of this general problem the exploration is expected to expand to effects of particles derived from other machines and interactions of other particles such as mesons. Use of such procedures in control of neoplasia or its generation will also come under view.

06-03-01-a-(1) Neutron Capture Therapy of Glioblastoma Multiforme

Persons in Charge: L. E. Farr, Y. L. Yamamoto, O. D. Easterday, E. E. Stickley, J. S. Robertson and S. W. Lippincott

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12. & 13. Objectives and Overall Description:

Neutron capture therapy is an experimental radiation treatment of cancer which utilizes intracellular generation of heavy particles in neoplastic cells. It is based upon empirical demonstrations at Brookhaven of ability to destroy cancer by prompt disintegration of boron-10 following thermal neutron capture. This is carried out in such fashion that although the target atom boron-10 is distributed in both neoplastic and normal cells, the disintegration effect is killing only in cancer cells because it has been observed that such selectivity exists at a given time interval after injection. This is not dependent upon tumor-normal tissue ratios.

(See continuation sheet)

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12. & 13. Objectives and Overall Description: (contd.)

The application of thermal neutron capture reactions to therapy of malignant tumors becomes increasingly attractive with our increasing experience and markedly improved results. Boron-10 appears to be a very satisfactory capture element. The procedure is still complicated though much less so than two years ago.

14. Related Projects:

See 06-03-01 - Cancer Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

During the past year results on seven patients became available for study. In the most adequately treated patient, one with sarcoma of the vascular system of the brain stem and cerebellum, the results showed almost complete destruction of the sarcoma and failure to regrow over a nine-month interval. One patient with glioblastoma still survives after 18 months following a single treatment. This survival period far surpasses any previously attained in control of this disease by neutron capture therapy. Successful turn back of skin flaps was shown capable of preventing a previously troublesome skin lesion.

16. Expected Results This Fiscal Year - 1961:

The general program outlined above is expected to be continued with further careful probes planned as rapidly as they can be evaluated.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab
COLLECTION Form 189 Med. Dept 1950-61
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4002244

06-03-01-a-(2) Neutron Capture Therapy Effectiveness and Tissue Effects of Thermal Neutron Exposures

Persons in Charge: L. E. Farr, Y. L. Yamamoto, S. W. Lippincott, W. Calvo

12 & 13. Objectives and Overall Description:

In the development of a new therapeutic procedure two facts must be clearly shown (1) that the procedure indeed accomplishes its purpose; and (2) that the procedure causes no serious additional damage. To determine the answer in part to both these questions a very ambitious project was undertaken in FY 1960 to study the entire brains of persons given neutron capture therapy together with a reasonable number of comparison patients. Through serial sections, appropriate staining and histologic study the presence or absence of effects in both neoplasm and normal structures are expected to be demonstrated.

14. Related Projects:

See 06-03-01 Cancer Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

A study of twenty celloidin embedded specimens from patients receiving therapy was started in FY 1960. An additional twenty specimens from a comparison group are ready for evaluations, while seventeen specimens await a survey of results before final plans for them are made.

The results will undoubtedly add new knowledge concerned with the reliability of diagnosis, the mode of tumor spread, effectiveness of the treatment and effect of both tumor and treatment on non-affected regions of the brain. It is expected that these data will become basic for all subsequent studies in this field both by BNL and others.

16. Expected Results This Fiscal Year - 1961

During FY 1961 it is anticipated that the studies on the first 20 patients will be completed and readied for publication.

The results of histopathological and topographical studies in 17 cases indicated that higher neutron flux is necessary in order to treat deep-lying intracranial neoplasms. Since the new Medical Research Reactor is operational, the treatment of a new series of patients was started late in FY 1960 with higher neutron exposures, twice the neutron dose used previously. Clinical and histopathological studies of a new series of cases will be pursued, and greater effectiveness of the treatment is anticipated.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for 1961 is expected to be continued.

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06-03-01-a-(3) Neutron Capture Therapy Procedures in Control of Tumor

Person in Charge: L. E. Farr

12 & 13. Objectives and Overall Description:

A tumor induced through the use of methyl cholanthrene in the brain of the mouse is transplantable and is highly invasive. For seven years it has been used at BNL as a test tumor in the study of maneuvers for neutron capture therapy and the evaluation of certain concepts in this therapeutic procedure.

14. Related Projects:

See 06-03-01 Cancer Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

During the past year this transplantable tumor has been used both as an intracerebral transplant and as an intramuscular transplant. Effectiveness of neutron exposure has been explored with variations in (1) time of exposure after boron injection, (2) total neutron exposure, (3) total dose of boron. This is in an attempt to determine the parameters which may be expected to be required for successful conclusion of patient therapy. Effectiveness does not parallel tumor-brain ratio. A tumor boron concentration is most effective in the period of 20 to 30 minutes post-injection. Total neutron exposure, 10^{11} per cm^2 is required throughout the tumor for a cure. A boron dose of 25 mg/kg gave a 96% cure and 50 mg/kg gave a 100% cure.

Mice with intramuscular transplants treated after reaching the large size of 12 to 16 mm diameter have been observed up to two years after treatment. Tumors can be made completely to disappear after a single exposure to neutron capture therapy. No recurrence of the tumor has been observed. No other tumors occurred at the site and the normal structures about the tumor at time of treatment show no scarring, altered cytological structure, or loss of functions as a result of this experience.

16. Expected Results This Fiscal Year - 1961

The general program outlined above will be continued.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined above is expected to be continued.

REPOSITORY Brookhaven Nat'l Lab.
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FOLDER _____

06-03-01-a-(4) Medical Research Reactor Studies

Persons in Charge: E. E. Stickley, S. Fine

12.& 13. Objectives and Overall Description:

Following erection of the Medical Research Reactor, extensive testing, adjustment, and even modification have been found to be necessary and desirable so that the most effective neutron stream, possible with minimal contamination, could be developed. Criteria used have been judged first from the standpoint of the best interests of the patients to be treated, and second in terms of adequate protection of the necessary clinical and technical personnel.

Besides general use in many of the medical program activities, a number of specific projects depend completely upon the reactor as a neutron source. These include: (1) Physical measurement of neutron distribution in animals with Medical Research Reactor (Y. L. Yamamoto, S. Fine, S. H. Cohn and E. E. Stickley); (2) Neutron spectroscopy of biological materials (S. Fine and H. Bollatin); (3) Development of additional ancillary research facilities (C. G. Amato, E. E. Stickley and J. S. Robertson) and (4) Neutron spectrum analysis (E. E. Stickley and J. S. Robertson).

14. Related Projects:

See 06-03-01 Cancer Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

The MRR has been brought into successful engineering operation as a new tool in a new field. The appropriate application of the reactor will require an intensive effort toward its development into an increasingly effective instrument and must be continued for some time to come. Its first few months of use have been a variety of exploratory standardization procedures with small animals and a few with human subjects. The physical evaluation of the reactor output and the development of suitable equipment for neutron and isotope irradiations have occupied the bulk of the operating schedule. Available techniques with activation foils and with ionization chambers have been applied.

Physical dosimetry studies of the Medical Research Reactor with animals are being continued. Initial experiments on induced activity dosimetry of the Medical Research Reactor have been completed.

Neutron spectroscopy of elements has been conducted by the physics group of Brookhaven National Laboratory for a number of years. Dr. H. Bollatin, an associate of the late Dr. Donald Hughes, started to run biological materials in the fast chopper. Initial sample holders have been constructed, and initial runs of absorption spectra of biological materials have been completed at the fast chopper facility.

During FY 1960 an intensive program directed toward characterizing the various radiations (thermal and fast neutrons, gamma rays) in the external beam of the Medical Reactor was initiated. This program relied principally on the activation of various metallic foils as threshold detectors for neutrons of various energies. A quite detailed picture exists now of the neutron spectrum as a function of various operating conditions and of configurations of materials in the beam path within the reactor.

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16. Expected Results This Fiscal Year - 1961

The study of reactor output is to be extended and improved, while other approaches utilizing neutron spectrometers and solid-state detector systems are being added.

In the MRR program for the immediate future, the work toward full characterization of the quality and quantity of the emergent radiations will increase.

(See continuation sheet)

16. Expected Results This Fiscal Year - 1961 (cont'd)

The means of controlling each of the causative factors in the reactor will be studied further in all of the irradiation areas and at the short-lived isotope production ports as well. An irradiation loop for rapid activation analysis procedures is also to be installed.

To achieve full exploitation of the new and unique capabilities of the Medical Research Reactor, the development of special equipment and calibration procedures is essential. The work of first importance will be the establishment of methods for physical mensuration in the next series of neutron capture therapy trials. Dosimetric analysis in tissue equivalent phantoms must progress along with the clinical and animal work, using activation detectors, ionization chambers, semi-conductor and other solid-state devices, and other useful instruments. Apparatus for producing and exploring the diagnostic and therapeutic possibilities of short-lived isotopes must be improved and new types developed. It is expected that the major part of these investigations will be carried out in the same irradiation rooms used for the neutron exposure procedures, whether for patients or in animals. The activation analysis potentialities of the MRR will for the most part be based on the rapid handling of tissue sample at the reactor face, the detector being the only segment of the counting equipment to be kept in the reactor building. Utilization of the broad beam exposure cell will begin after some further measurements of the mixed radiation field present in it have been performed; its actual usefulness will be enhanced when further radiation filters and screens are devised. This particular space should provide for whole-body radiation studies of the hazards and general effects of the several constituents of reactor-originated and reactor-mediated patterns of radiation.

It is proposed to continue the experimental work on neutron spectroscopy in biological materials with a view to obtaining the absorption cross section of the biological samples at various neutron energies, and to determine whether this technique is of value in searching for trace elements in biological materials. Neutron absorption and neutron diffraction in various energy ranges will be investigated.

It is planned to fabricate, install, and shield a short-lived isotope loop. This device will include provision for therapeutic administration to patients to make full use of the potentialities of the Medical Reactor for applications which do not involve direct neutron irradiation of patients.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for FY 1961 is expected to be continued.

REPOSITORY Brookhaven National Lab
COLLECTION Form 189 Med. Dept. 1950-61
BOX No
FOLDER

06-03-01-a-(5) General Radiation Effects of Accelerator Generated Neutrons

Persons in Charge: J. L. Bateman, V. P. Bond

12. & 13. Objectives and Overall Description:

Biological effects of monoenergetic neutrons at selected energies have been studied using a tritium target in the 3 Mev Van de Graaff machine in the Physics Department. Weight loss in mouse spleen and thymus, and reduction in the number of spermatogonia in mouse testis have served as measures of effect.

14. Related Projects:

See 06-03-01 Cancer Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

Relative biological effectiveness (RBE) in the 0.43 - 1.80 Mev range (compared to 250 KVP X-ray) has been evaluated with spleen and thymus. Results show an RBE of 4.6 for spleen at 0.43 Mev, decreasing to 3.3 at 1.80 Mev. Corresponding values for thymus are 4.2 and 3.0. Testis exposures to neutrons of the same energies have been made and results are pending.

Exploration down to 60 kev neutron energy with testis suggests an RBE of 8 or more at this level, with an area of considerably reduced effectiveness between this and 0.43 Mev.

16. Expected Results This Fiscal Year - 1961:

Further study in the low energy range with spleen, thymus and testis is planned. Study of other biological endpoints in the above-mentioned energy ranges is intended, in addition to evaluation of other neutron energies up to 14 Mev.

17. Expected Program and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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06-03-01-a-(6) Toxicity and Pharmacology of Target Elements and Compounds

Person in Charge: O. D. Easterday

12 & 13. Objectives and Overall Description:

The toxicity and pharmacology of the target elements and their parent compounds which are employed in the neutron capture therapy research have assumed an important position relative to the experimental investigations of this therapeutic procedure. The objective of the toxicological and pharmacological investigations is to study and evaluate new elements and compounds containing these elements employing the techniques and principles of this scientific discipline for possible use in the neutron capture therapy program. These studies are required for several reasons: (1) to determine if the elements or compound has possibilities for neutron capture therapy, (2) to determine the degree of safety associated with the new material, (3) to determine its general pharmacology and (4) to utilize pharmacological mechanism and principles to manipulate or direct the material to the desired locus.

14. Related Projects:

See 06-03-01 Cancer Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

Several of the accomplishments that may be cited are: the pharmacology and toxicity of a new compound, sodium pentaborate decahydrate, have been continued; the investigations of sodium pentaborate decahydrate have progressed to the point where expanded studies concerned with evaluating its effectiveness in tumor-bearing animals and in patients having intracranial neoplasms are currently in progress; complexing agents other than d-glucose have been investigated and the data are currently being evaluated -- a new series of compounds containing the target elements, lithium and boron, are being studied toxicologically. Additional instrumentational developments were made on the remotely controlled injection equipment used to administer the neutron capture agent to the patients.

16. Expected Results This Fiscal Year - 1961

The main new objective for the next fiscal year is to commence physical, chemical, toxicological and pharmacological studies on a new series of organic compounds containing the target elements boron.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for FY 1961 is expected to be continued.

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

06-03-01-a-(7) Solubility of Organo-Boron Compounds

Person in Charge: J. S. Robertson

12. & 13. Objectives and Overall Description:

In the exploration of the use of various boron compounds for neutron capture therapy, it is highly desirable to know the optimal ratio of the concentrations of the boron compounds and other substances in the solution to be injected.

14. Related Projects:

See 06-03-01 - Cancer Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

Phase system studies of the Na-borate-glucose-water system were conducted in the lower concentration region (up to 10 grams each of Na-borate and glucose in 100 ml of water). Investigation of the phase system for higher concentrations of the Na-borates and of other organo-boron compounds is proposed.

During FY 1960, phase-system studies were extended to the higher concentrations of Na-borate and glucose (over 10 grams each of Na-borate and glucose per 100 ml of water).

16. Expected Results This Fiscal Year - 1961:

The studies of boron compounds will be continued in 1960-1961 with applications to new compounds as they are developed for application to neutron capture therapy.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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06-03-01-a-(8) Chemical Dosimeters for Depth-Dose Studies with Thermal Neutrons

Persons in Charge: V. P. Bond, E. E. Stickley, G. Taplin

12 & 13. Objectives and Overall Description:

These studies were initiated in FY 1960. The purpose is to provide a more reliable means of measuring radiation patterns in studies with thermal neutrons. This is an area of importance to a number of biological and medical problems in which technical difficulties arise from the presence of a mixture of interfering radiations. The small size of chemical dosimeters and the possibility of adjusting their structure and content to give controlled response to each of the several constituents of the radiation field are their outstanding advantages.

14. Related Projects:

See 06-03-01 Cancer Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

In the previous depth-flux measurements in this laboratory and elsewhere, thermal neutron levels have been made principally with gold foil activation techniques, and to a lesser extent by the use of tissue equivalent ionization chambers. In the present studies, Dr. Taplin has worked extensively with a system of chemical dosimetry using halogenated hydro-carbon systems, and in collaboration, B-10 and Lithium-6 have been added to the system. The system has been developed to where it appears possible to obtain meaningful readings with the boron and lithium present. The increase in reading with the boron and lithium present is due almost exclusively to the recoil of heavy particles liberated in the process of thermal neutron capture, and thus it is possible to establish the distribution of this dose with depth by placing chemical dosimeters with and without added lithium or boron at various depths in a phantom. Preliminary experiments have been carried out; however, some difficulties with a "sink" effect, and with apparently impurities in the glassware has complicated interpretation of the data. These difficulties are being remedied, and it is anticipated that accurate depth dose curves can be obtained in the near future.

16. Expected Results This Fiscal Year - 1961

In FY 1961 it is anticipated that the studies will be continued until satisfactory depth-dose patterns for thermal neutrons and for the heavy particles from thermal neutron capture are determined.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for 1961 is expected to be continued.

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4002252

Form NYOO-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Beneficial Applications of Atomic Energy - Cancer Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Vitamin and Amino Acid Metabolism in Neoplasia and Normality		
4. Budget Activity No. 06-03-01	5. Budget Item No. 06-03-01-b	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-03-01-b Vitamin and Amino Acid Metabolism in Neoplasia and Normality - (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	27	30	35
Direct Man-Years			
Staff	1.0	1.0	1.0
Visitors	0.2	0.3	0.4
Scientific	1.2	1.3	1.4
Other	1.0	1.1	1.2
Total	2.2	2.4	2.6

There is evidence that the urinary levels of metabolites of certain vitamins may vary in several neoplastic diseases. The metabolites of tryptophan are examples. Further, it has been suggested that certain of these metabolites possess carcinogenic activity. The study of the metabolism of tryptophan to niacin would be advanced by the synthesis of H^3 and C^{14} labeled intermediates so that the metabolism of tryptophan could be better understood, in health and disease and the possible carcinogenic activity of the compounds found in the urine of patients with certain diseases could be studied better if labeled compounds were available, specifically, the pentose sugar found in pentosuria.

06-03-01-b-(1) Metabolism of Tryptophan

Persons in Charge: L. V. Hankes, R. R. Brown, R. Kawashima, P. Carson and L. Anderson

12. & 13. Objectives and Overall Description:

In the past few years attention has been focused on the cancerous amino acid (tryptophan metabolism in neoplastic disease). The recent evidence that 3-hydroxyanthranilic acid, a tryptophan metabolite, exhibits carcinogenic activity in producing a mouse bladder tumor has made it more essential to establish the structure of the intermediate compounds in the pathway from 3-hydroxyanthranilic acid to the products, quinolinic acid and niacin.

REPOSITORY Brookhaven Nat'l Lab

14. Related Projects:

See 06-03-01 - Cancer Research - Summary Sheet.

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15. Accomplishments Last Fiscal Year - 1960:

During the fiscal year 1960 metabolism studies were conducted with 3-hydroxyanthranilic acid-1-C^{14} and para-aminobenzoic acid-1-C^{14} in normal mice and mice having spontaneous mammary tumors, brain tumors or ascites tumors. The injection of these compounds into mice and the subsequent collection of labeled CO_2 and

(See continuation sheet)

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15. Accomplishments Last Fiscal Year - 1960: (contd.)

urinary metabolites, such as quinolinic acid and nicotinic acid, provided information for the design of future patient experiments with this type of disease. Work on the synthesis of tryptophan-5-C^{14} was continued and it is nearing completion. The synthesis of a sufficient quantity of high specific activity carboxyl-C^{14}-labeled 3-hydroxyanthranilic acid for patient experiments has been initiated and it is nearing completion as is the synthesis of a large quantity of carboxyl-labeled 3-methoxy-2-nitrobenzoic acid. This latter compound is the starting material for the synthesis (with aid of collaborators) of a large quantity of 3-hydroxykynurenine-4-C^{14}, which will be used in neoplasia patient studies.

During the past year metabolism studies were conducted with 3-hydroxyanthranilic acid-1-C^{14}, carboxyl-labeled-3-hydroxyanthranilic acid and 5-hydroxyanthranilic acid-1-C^{14}. The quantities of these compounds synthesized were very limited, and in quantities only large enough for animal studies. Techniques were developed for labeling tryptophan and kynurenine with tritium in large quantities for use in human neoplastic disease studies. The synthesis of tryptophan-5-C^{14} was started and this material will be used in patient studies. The synthesis of para-aminobenzoic acid-1-C^{14} was concluded and plans made for the study of its metabolism. Studies were continued on the mechanism of converting 3-hydroxyanthranilic acid into the vitamin, niacin. In the process of these rat metabolism studies it was discovered that the number one carbon of 3-hydroxyanthranilic acid becomes the number two carbon of acetate. This is a previously unknown source of acetate in the body. The C^{14} of 5-hydroxyanthranilic acid-1-C^{14} was found to be rapidly and quantitatively excreted in urine.

16. Expected Results This Fiscal Year - 1961:

During the next year the studies of the metabolism of tryptophan and 3-hydroxyanthranilic acid in various disease state patients will be continued with experiments designed to determine the nature of the urinary products of these compounds in the urine of normal and diseased man. There is evidence of variations in the metabolism of anthranilic acid and quinolinic acid in some disease states in humans. The large-scale synthesis of carboxyl-C^{14}-labeled anthranilic acid and carboxyl-3-C^{14}-labeled quinolinic acid is planned for studies of the metabolism of these compounds in normal and diseased humans.

The synthesis of tryptophan-5-C^{14}, carboxyl-labeled 3-hydroxyanthranilic acid, 3-hydroxykynurenine-4-C^{14} and kynurenine-4-C^{14} are to be continued. It is planned to continue studies of tryptophan metabolism in brain tumor patients, ante and post boron-neutron treatment. It is planned to initiate the synthesis of tryptophan 7-C^{14} to study the conversion of the seven carbons of tryptophan into the number one carbon of acetate in humans with neoplastic disease and diabetes.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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06-03-01-b(2) Studies of Pentosuria

Person in Charge: L. V. Hankes

12 & 13. Objectives and Overall Description:

This program concerns itself with studies of pentosuria.

14. Related Projects:

See 06-03-01 Cancer Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960

The nature and source of the pentosugar appearing in urine of patients with pentosuria is unknown. C^{14} labeled-I-inositol provided by a collaborator will be administered to a patient with this disease and the urine will be studied for metabolites for the administered compound during FY 1960.

16. Expected Results This Fiscal Year - 1961

The direction in which the study branches out will be dictated by information gathered in the current year.

17. Expected Programs and Results for Next Fiscal Year - 1962

The general program outlined for FY 1961 is expected to be continued.

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COLLECTION Form 189 Med. Dept. 1950-61
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Form NY00-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Beneficial Applications of Atomic Energy - Cancer Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Labeled Proteins for Metabolic Observation in Cancer Evaluation		
4. Budget Activity No. 06-03-01	5. Budget Item No. 06-03-01-c	6. Contractor's No.
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: S. W. Lippincott	11. Starting Date of Project: Continuing	

06-03-01-c Labeled Proteins for Metabolic Observation in Cancer Evaluation

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	225	290	335
Direct Man-Years			
Staff	1.0	1.2	1.3
Visitors	0.4	0.4	0.5
Scientific	1.4	1.6	1.8
Other	12.0	15.9	18.0
Total	13.4	17.5	19.8

12. & 13. Objectives and Overall Description:

This clinical study has been underway for four years, with the first year having been spent on animal investigation preparatory to the clinical work now in progress. The objective is to determine whether patients with various neoplastic diseases have the same or different rates of turnover (degradation) for I^{131} labeled proteins obtained from normal individuals and for those obtained from cancer patients. If, in man, a difference in turnover rates could be established this might be used as a laboratory test to assist the physician in detecting the individual who has cancer. At present there is no blood test which is capable of detecting cancer in the early stages so that if a test were to be devised it would be of immediate clinical usefulness.

Both labeled albumin and globulin have been used in these investigations. These proteins have been fractionated in this Laboratory and the homogeneity determined by ultracentrifugation and electrophoresis before labeling. The patient series is now 100 with many of these patients having died during the course of observations. The total number of turnover studies to date is 177, with some patients having had up to six turnover studies, in which event a patient may have been followed from about 15 to 30 months. Two principle observations have resulted from these turnover studies (1) in multiple myeloma there is a striking correlation between excessive catabolism of gamma globulin and the presence of a circulatory abnormal component with similar electrophoretic mobility and (2) in metastatic cancer of breast origin (15 cases) the turnover rate of gamma globulin fractionated from cancer patients is much more rapid than that of globulin fractionated from normal individuals. These observations have led to the two new approaches cited below.

14. Related Projects:

See 06-03-01 - Cancer Research - Summary Sheet

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15. Accomplishments Last Fiscal Year - 1960:

Customarily the degradation rate of I^{131} labeled normal albumin (or globulin) in man has been determined from plasma or serum concentration curves and/or from urinary excretion data. During this last year the former method has been compared in two patients (with different diseases) with a new method employing the in vivo whole-body counting technique (gamma spectrometer) which permits measurement of very low levels of an internally deposited gamma emitter. In the first patient the half-lives of the I^{131} labeled albumin were 19 and 19.5 days respectively and in the second patient 15 and 15.4 days. This new procedure makes possible the clinical investigation of turnover of albumin with the administration of as little as one or two microcuries of the radioisotope used. The inconvenience to the patient of multiple blood sampling and to the investigator of tedious radiochemical analyses of excreta are eliminated. The applicability of this technique to other proteins is being investigated.

16. Expected Results This Fiscal Year - 1961:

It is conceivable that the more rapid turnover rates of gamma globulin from cancer patients noted above may be due to degradation at the tumor sites (or site), thus it would be desirable to localize this if possible. Therefore the next step to be undertaken is the labeling of the respective proteins by I^{124} (in addition to further observations with I^{131}). I^{124} is a positron emitter and its annihilation radiation enables coincidence counting that could be used in conjunction with a mechanical scanning technique of the patient. This possibility is to be explored in the near future.

This clinical study requires expert nursing care and assistance as well as detailed laboratory investigations in each patient. Both in and outpatients have to be followed regularly. By the nature of the patients' illness the hospital care and service is extensive.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The metabolic studies being carried out on patients with various cancer diseases will in 1962 include more work with I^{124} labeling than with I^{131}. Dr. Baker, in charge of the Cyclotron, after reviewing the English literature on the production of I^{124}, has been successful in bombarding antimony with alpha particles and producing I^{124}. In the chemical division of the Hot Laboratory, this product has been cleaned up to a large extent, and the first small batch of I^{124} has been made available. It is possible now to get a large enough amount in terms of millicuries to label the protein fractions that have heretofore been labeled with I^{131}. Arrangements have been made with Dr. William Sweet, Professor of Neurosurgery at Harvard, to do the initial study with him because he has a positron scanner that he has been using to detect neoplasms in the brain in patients given radioactive arsenic. Both arsenic and I^{124} are positron emitters and thus the preliminary study, before attempting to get a positron scanner here, can be carried out on a Research Collaborator basis.

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UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Beneficial Applications of Atomic Energy - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title:		
4. Budget Activity No. 06-03-02	5. Budget Item No.	6. Contractor's No.
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: See Individual Project Proposals	11. Starting Date of Project: Continuing	

SUMMARY

14. Related Projects:

The general, broad subject covered by this activity is under investigation at other U.S. and foreign research institutions. However, to the best of our knowledge, the specific conceptual approach and techniques of this BNL program are in most cases not being utilized at other laboratories and are frequently beyond the capabilities of other research centers.

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UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Beneficial Applications of Atomic Energy - Medical Research		2. Date Prepared: Revision No. May 1960
3. Sub-Title: Maps of Metal Pathways with Special Reference to Trace Metals and Central Nervous System Diseases.		
4. Budget Activity No. 06-03-02	5. Budget Item No. 06-03-02-e	6. Contractor's No.
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: See individual sub-division proposals	11. Starting Date Continuing	

06-03-02-a Maps of Metal Pathways with Special Reference to Trace Metals and Central Nervous System Diseases. - (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	400	515	585
Direct Man-Years			
Staff	6.3	7.2	7.7
Visitors	1.0	1.3	1.6
Scientific	7.3	8.5	9.3
Other	21.0	22.5	27.2
Total	28.3	31.0	36.5

The pathways of distribution, the site of primary and secondary accumulation, the factors affecting partition, and the regulation of total body content of metals, particularly trace metals, in health and disease is the concern of this study. These data are of the greatest importance in the development of diagnostic procedures and understanding of significance of measures designed to influence specific metals in the body. Emphasis is placed on the short half-life isotopes permitting precise physical studies. Manganese and sodium have been chosen as the basic reference metals because of their differing distribution in various body systems and compounds.

06-03-02-a-(1) Maps of Metal Pathways with Reference to Central Nervous System.

Persons in Charge: G.C. Cotzias, D.C. Borg, A.J. Bertinchamps, E.R. Hughes and P.S. Papavasiliou.

COLLECTION Brookhaven Nat. Lab. Item 184 Mid Dept 1950-61

12 & 13. Objectives and Overall Description: BOX No. _____

Animal experimentation has shown that a diet deficient in trace metals, notably manganese, results in irregularity or deficiency of coordination of the muscular system. Observations of humans exposed to manganese ore dusts showed the development of a clinical picture identical to Parkinsonism. These two conditions might constitute prototypes for the elucidation of spontaneously occurring human diseases characterized by the above symptomatology.

Thus radioisotopes of manganese and of other related elements were thought to be useful tools for bedside studies. It was found, however, that the literature contained little information relative to distribution, accumulation and partition of such isotopes relative to the pathways which they pursue, or relative to the control of total body content of trace metals. Since these parameters are indispensable in the elucidation of patterns in health and disease, they have constituted the subject of this project.

Short-lived isotopes are emphasized (1) because of their usefulness in repetitive testing, (2) because of their availability and ease of handling at Brookhaven and (3) because of their unique role in activation analysis (vide infra). Although

(See Continuation Sheet)

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12 & 13. Objectives and Overall Description (Cont'd.):

many metals have been studied, manganese has been the reference metal and is the only one discussed here.

14. Related Projects:

See 06-03-02 - Medical Research - Summary Sheet

15. Accomplishments Last Fiscal Year - 1960:

Prior to 1959, the blood disappearance rate of injected manganese isotopes had been studied in rats, rabbits and humans using $Mn^{56}SO_4$. This was found to be profound and rapid. The element was taken up by tissues rich in mitochondria as determined by the dissection of many animals and the external scanning of 14 in-patients. Mitochondria from rat liver were therefore isolated and found to contain the minimal value of about 40% of the total liver Mn^{56}. In view of the techniques this indicated an almost total early accumulation of the isotope in these organelles. Since the behavior of the isotope was otherwise identical in man and animals, its disappearance from human blood was explored as a measure of total body mitochondrial functions.

In FY 1960, the ideas on manganese disappearance from human blood were tested on a patient suffering from thyrotoxicosis, a condition characterized by marked mitochondrial activity. This test was encouraging in that it was concordant with our notions; it will be pursued further in FY 1961 utilizing more patients. Treatment of these patients and the resulting reduction of thyroid tissue with I^{131} offers an opportunity for study of a gradually corrigible mitochondrial dysfunction, utilizing Manganese isotopes.

Manganese has been accepted as a cofactor of many enzyme actions too numerous to list. However this element could be substituted for in all those systems by other elements, including magnesium. If this were true in vivo manganese would have no role in the living animal. Therefore the specificity of the pathway of this element was studied in mice by trying to substitute, to dislodge or to affect the turnover of previously injected manganese isotopes with stable metals suspected of having the capacity to do so. Radio-manganese was exquisitely sensitive to stable manganese, totally insensitive to other metals.

Some efforts were begun to study the specificity of the manganese pathway in humans. In three patients, injected radiomanganese was initially exquisitely sensitive to manganese loads. These tests showed, however, a diminishing sensitivity of the kinetics of radiomanganese to manganese feedings with passing time. This suggested the synthesis of metallo-organic compounds of manganese in the body. It is hoped that these studies will be completed in 1960.

The above findings led to the discovery of a human porphyrin containing manganese instead of iron. This has now been demonstrated in 16 patients and several rabbits. Preliminary data show (1) that this porphyrin is very similar to synthetic manganiprotoporphyrin in many of its properties and (2) that it may also occur in cells other than red cells, notably liver.

The specific behavior of manganese in the body suggested the existence of a specific carrier mechanism in human plasma, a mechanism capable of sharp discrimination between manganese and other metals. Such a mechanism was discovered in the plasma of one patient and confirmed in seven further trials. The carrier mechanism involves (1) a Beta plasma globulin, probably different from the iron carrying one, (2) a change in the valence of manganese from either 2^+ or 4^+ to a level in between, which must be the unstable form 3^+. This mechanism is specific for manganese and manganese only.

These observations are considered as a real turning point in this work. In 1960, this novel transport mechanism is being studied in several patients because (1) it is a new type of system, (2) it puts manganese studies on a sound clinical basis and (3) it is a highly specific mechanism.

The excretion of manganese was found to be biliary in mice and rats. The excretion patterns in normalcy are grossly different from those of manganese overloads. When used as a bio-assay, this pattern showed many "normal" foods to be overloaded with manganese.

(See Continuation Sheet)

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15. Accomplishments Last Fiscal Year - 1960: (Cont'd.)

This work will be published in 1960 and will be extended to investigate more food stuffs and the mechanism of the biliary excretion.

Patients fell into two categories with regard to total body manganese turnovers; slow ones and fast ones. The fast ones were treated Parkinsonians, the one patient with thyrotoxicosis and the three patients given manganese supplements. The slow ones were two patients with Wilson's disease, one patient with Friedreich's ataxia, one patient with Apresoline Disease and most of the untreated Parkinsonians. However, two control patients straddled the two populations and one untreated Parkinsonian was fast. No conclusions can, therefore, be reached as yet and the study is being extended in 1960 and beyond.

Since Phenothiazine drugs seemed to have the above-mentioned effects on patients with Parkinsonism, they were tested for their capacity to bind manganese. They were found to make 2:1 complexes with manganese of a valence higher than 2^+ and lower than 4^+, a story similar to the one of the Beta globulin mentioned above. These complexes occur in the presence of tissues. Their in vivo role will be further studied in FY 1961.

The chemical properties of the manganese-phenothiazine complexes that underlie the specificity of their action in vivo are being investigated also. These complexes may serve further as model systems to study "the chemical foundation of metal specificity shown by more complex biological" systems. Preliminary results of optical spectroscopic and electron paramagnetic resonance studies indicate that the unique behavior of such systems are best explained by considering certain quantum chemical properties of the metal ions and of the other reactants. This area of research will be pursued further in FY 1961 and 1962.

A study of the homeostatic control of manganese by the body was initiated. Mineral corticoids were found thus far to be ineffectual while glucocorticoids, amazingly enough, had profound effects on Mn^{54} kinetics in mice and rats. This will be continued in FY 1961.

Accomplishments of the past year (FY 1960) include:

1. Analysis of tissues and their constitutents for trace metals by neutron activation analysis, to be continued in FY 1961 and 1962.

2. Total body radioactivity studies in man, mice and rats, to be continued in FY 1961 and 1962.

3. The excretory patterns of metals under normal conditions and metabolic stress. These will be studied further in FY 1961 and 1962.

4. The fact that a pharmacological agent, the tranquilizer chlorpromazine acts primarily, if not exclusively, by binding trivalent manganese. This has generated interest in other agents acting similarly. Hormones are being tested in that regard.

5. The induction of irreversible ataxia in offspring of manganese-deficient mothers is being studied in mice.

6. Cyclopentadienyl manganese carbonyl has been proposed as an anti-knock agent in gasolines. Since it is a fat soluble manganese compound, it is of great physiological interest even without regard to public health considerations. The Ethyl Corporation of America supplied samples and chemical information. We have contacted Dr. Robert A. Kehoe of Cincinnati relative to his toxicological studies with this compound. We anticipate severe "Parkinsonian" syndromes in animals and high concentrations in the basal ganglia following exposure. The concentration will be followed by neutron activation of the element manganese.

7. The fast disappearance rate of injected manganese salt (which has been correlated with entrance into the mitochondria) has been slowed down by pharmacological agents of the phenothiazine class (Thorazine).

8. Although the manganese pathway through the body was found to be specific for that element, it was confirmed in animals that strontium is interchangeable with calcium in some body pools. The surprising discovery has been made that magnesium greatly accelerates the turnover of strontium. Since magnesium is primarily

(See Continuation Sheet)

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REPOSITORY Brookhaven Natl Lab
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15. Accomplishments Last Fiscal Year - 1960: (Cont'd.):

intracellular, this has focussed our attention to intracellular strontium, a hitherto neglected fraction of this element. Beryllium is being studied in the same context.

9. Zinc seems to be susceptible to replacement by cadmium in the animal body. This is not evidenced by any acceleration of the turnover of zinc but only by abnormal partition of Zn^{65} after Cd administration. Zinc concentration was discovered to be under homeostatic control: there is a positive feed-back and negative feed-back mechanism of the excretion and absorption, respectively, of zinc. Cadmium is under no evident control. This indicates that cadmium is potentially a very subtle poison indeed, and also that the sites of cadmium-binding are not sites of transmission of homeostatic signals, regardless of whether in a given animal they happen to be occupied by cadmium, zinc or any other metal.

10. It now appears that the manganese porphyrin which was isolated from red cells of the human is not the only such porphyrin in the body. Work in progress suggests that there are also manganese porphyrins other than that of the hemoglobin variety.

11. The biliary excretion of manganese is studied further relative to its pattern which suggests two separate pathways of excretion. Kinetic evidence suggests that there exists in the liver a specific pool of small-capacity and a large non-specific pool for this element. These pools are being correlated with the two paths of biliary excretion, the second of which is operational only after metabolic loading.

12. The patterns found in patients with central nervous system disease following administration of manganese tracers are being analyzed. It is now safe to state that two populations of patients are becoming evident: those with slow, or with fast turnover rates. Common denominators are becoming apparent, but their present enumeration is unsafe.

13. Steriod hormones appear to bind manganese in the animal body. Their administration produces dramatic alterations of the partition pattern of this element in the bodies of mice. This finding is suspected of being a clue to the action of steroids and is being studied intensively.

16. Expected Results This Fiscal Year - 1961:

The general program described for FY 1960 will be continued.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program previously outlined will be continued.

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06-03-02-a-(2) Relationship of Salt (Sodium Chloride) to High Blood Pressure In Man.

Persons in Charge: L. K. Dahl, W. Gordon, L. Silver, S. Spraragen and M. Smilay

12 & 13. Objectives and Overall Description:

Since 1952, the role of salt in the hypertension of man has been explored at Brookhaven. Studies have been carried out of the hypertensive process of (a) salt restriction and salt addition, (b) weight loss and weight gain, (c) the addition of potassium and magnesium salts to the diet. Using these techniques, the following parameters have been measured: (a) changes in blood pressure and heart size, (b) changes in body pools of sodium, potassium, chloride, magnesium, and water, as measured by the isotopes Na^{24}, K^{42}, Br^{82}, Mg^{28}, and H^3, (c) changes in sensitivity to the catecholamine, nor-epinephrine, (d) changes in adrenocortical function, (e) electrolyte losses from the skin.

In addition, epidemiological studies have been made both on Brookhaven National Laboratory personnel and a Japanese farm village near Hiroshima, which suggest that hypertension is significantly more frequent among individuals on a high salt intake (above 10 gms per day) than among those on a low salt diet (about 5-6 gms per day).

In 1959 a study of exaggerated natriuresis after hypertonic $Na^{24}Cl$ infusion in patients with hypertension was carried out. The phenomenon of exaggerated natriuresis following infusions of hypertonic saline in hypertensive patients is well established. The influence of antecedent salt intakes on this response has been of interest as well as the possibility that individuals with and without hypertension might call upon different body pools of sodium after this stimulus. To this end, 11 hypertensive and 6 non-hypertensive adult subjects were studied for two or more periods during each of which the daily salt intake was held constant at 0.3, 4.3, 8.3 or 12.3 gms. After metabolic equilibrium on each level of salt intake had been established, small infusions of 5% $Na^{24}Cl$ were made and measurements of Na^{23} and Na^{24} in plasma and urine carried out for the next 24 hours. This study has been completed and the results are as follows: (1) On equivalent salt intakes hypertensives during the first three hours following the infusion usually excrete more urinary sodium than do non-hypertensives. (2) Some non-hypertensives respond like hypertensives. (3) The magnitude of the natriuretic response can be changed drastically by antecedent variations in salt intake; the higher the salt intake the greater the response and vice versa, but at equal levels of salt intake the response of the hypertensive is generally greater than that of the non-hypertensive. However, a normotensive on a high salt intake responds in a fashion similar to or greater than, that of a hypertensive on a lower salt intake. (4) The specific activity of urine and blood was the same in hypertensive and non-hypertensive, suggesting that the sodium was probably mixed in similar fashion in the body.

14. Related Projects:

See 06-03-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

In 1960 studies were begun of factors affecting sodium turnover in the human with the aid of the whole body counter. It has become possible to study the biological half-life of sodium in patients with and without hypertension who are under strict metabolic control. Patients on constant diets are given 1-3 microcuries of Na^{22}, and after equilibration with the isotope has been established, the regimen is modified in a single respect. This extensive time-consuming program is still in progress and no single parameter has been fully explored. The following preliminary observations have been made on 12 patients:

(1) By appropriate increases in the NaCl intake, the biological half-life of sodium can be changed from more than 200 days to less than 8 days; (2) Keeping sodium intake constant, increments in the potassium intake materially shorten the biological half-life of sodium.

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(See Continuation Sheet)

4002263

16. Expected Results This Fiscal Year - 1961:

This work will be continued at approximately the same level in FY 1961 during which time other factors affecting either hypertension or sodium metabolism will be tested by this technique.

The recently acquired animal whole-body counter will be exploited primarily to see whether changes in the biological half-life of Na^{22} can be related to the induction or maintenance of experimental hypertension.

The observation that chronic salt-feeding results in hyperlipemia in dogs and rats will be studied in detail using C^{14} labelled lipids and lipid precursors in an effort to define the mechanism by which this phenomenon is effected. The well-known inter-relationship between hypertension and atherosclerosis will be explored using the technique of salt feeding to produce both hypertension and hyperlipemia.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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17. Expected Programs and Results for Next Fiscal Year - 1962 (cont'd)

These studies will be made primarily with Na^{22}, using the whole-body counter, under various sodium loads. Factors known to affect either hypertension or sodium turn-over will be tested systematically. Since a study on one patient requires continuous observations for approximately 2 to 6 months, progress will necessarily be slow.

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FORM NY00-230
(1-60)

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE
PROJECT PROPOSAL AND AUTHORIZATION

1. Project Title: Beneficial Application of Atomic Energy - Medical Research	2. Date Prepared: May 1960	Revision No.
3. Sub-Title: Selective Single Elemental and Colligative Activation		
4. Budget Activity No. 06-03-02	5. Budget Item No. 06-03-02-b	6. Contractor's No.
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: See Individual Sub-division Proposals	11. Starting Date of Project: Continuing	

06-03-02-b Selective Single Elemental and Colligative Activation - (Summary)

Cost and Personnel Data (for information only)

	1960	1961	1962
Total Operating Cost (In Thousands)	45	60	65
Direct Man-Years			
Staff	0.7	0.8	0.8
Visitors	-	0.2	0.4
Scientific	0.7	1.0	1.2
Other	2.0	2.5	2.8
Total	2.7	3.5	4.0

The term "activation by neutrons" refers to the fact that neutrons induce radioactivity in those elements that possess the property of "capturing" neutrons. The induced radioactivity is then analyzed for the qualitative and quantitative elements present in samples of biological and medical interest. These activation techniques of analysis are directed toward situations where no satisfactory chemical physical, or biological methods of analysis presently exist.

06-03-02-b-(1) The Development of Methods Permitting Selective Activation of Single Elements for Colligative Activation of Groups of Elements

Persons in Charge: G. C. Cotzias, P. S. Papavasiliou, D. C. Borg and J. S. Robertson

12. & 13. Objectives and Overall Description:

The development of these methods depends upon: (1) studies of the neutron fluxes that reach the center of containers in which samples of medical interest are irradiated and studies of shielding in order to gain advantage of threshold energies of known nuclear reaction, (2) development of instrumentation permitting the direct reading of specific radiations. With the aid of coincidence counting and a 100 channel pulse height analyzer, the manganese peak was made visible in the presence of large amounts of sodium, potassium and chloride. Potassium can be seen directly and can be measured in .1 ml samples of blood with an accuracy of 1 per cent.

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14. Related Projects:

See 06-03-02- Medical Research - Summary Sheet.

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15. Accomplishments Last Fiscal Year - 1960:

During FY 1960 a method was developed (Papavasiliou and Cotzias) which permits the accurate estimation of manganese in biological materials, but this employs destruction of the sample and chemical separation of the Mn^{56} isotope produced by activation of tissue samples in the reactor. 0.05 ml of blood (= 1 x 10^{-3} gm of manganese) are adequate for both accurate and precise analysis.

(See continuation sheet)

Project Title: The Development of Methods Permitting Selective Activation of Single Elements for Colligative Activation of Groups of Elements 06-03-02-b-(1)

15. Accomplishments Last Fiscal Year - 1960: (contd.)

The effort to distinguish radiations emanating from trace metals in intact tissues following their neutron activation has been temporarily halted by the low resolution of present equipment, which cannot differentiate the small peaks of the trace metals from the enormous peaks of the macroconstituents (Na, Cl, K).

16. Expected Results This Fiscal Year - 1961:

The study of radiation emanating from trace metals in intact tissue will probably be renewed with new instrumentation presently in the stage of planning and design, and studied in FY 1961.

Beginning in FY 1961 it is hoped to utilize the Medical Reactor for an examination of the potentialities of these activation techniques. With the nuclear fluxes soon to be available, the measurement of manganese in .2 ml samples of blood can be made with a 10 per cent precision. Most trace metals cannot be quantitated in clinical samples as of the present. The Medical Reactor is calculated to solve these problems.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined for FY 1961 is expected to be continued.

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06-03-02-b-(2) Localization of the Site of Action of Goldthioglucose by Radioactivation of Gold.

Persons in Charge: I. Schwartz, A. Debons and E. P. Cronkite.

12 & 13. Objectives and Overall Description:

Although it has been shown that goldthioglucose injections in mice produce a syndrome of hyperphagia and obesity similar to the obesity produced by stereotactic hypothalamic lesions, investigators have not agreed as to whether or not goldthioglucose itself produces hypothalamic lesions. It is contended that the toxic gold moiety destroys the satiety-integrating neurones after being selectively accumulated by virtue of the special affinity of these cells for glucose. These important observations and the theory based upon them can be tested critically by radioautographic localization and tissue assay for gold in experimental animals treated with goldthioglucose and control animals treated with other goldthiocompounds. Because of the short half-life of $Gold^{197}$ and the extended duration of treatment required to produce the goldthioglucose syndrome, the only means for the definitive localization of this isotope in the brain is by neutron activation of tissue removed from adequately treated animals.

14. Related Projects:

See 06-03-02 - Medical Research - Summary Sheet.

15. Accomplishments Last Fiscal Year - 1960:

A method to take advantage of the high resonance capture peak of Au^{196} at neutron energies around 5 e.v. has been discussed. Cadmium foil was used to diminish the activation of interferring tissue components such as Na, K and Cl and thus to reduce the background for the subsequent direct tissue analysis. It was found that Au^{197} could be determined in the presence of brain tissue in amounts well under 1 microgram per sample and that the induced radioactivity was linear over the range of Au concentrations tested, i.e. 1 to 100 gamma per sample.

16. Expected Results This Fiscal Year - 1961:

The analysis of brain tissue obtained from mice who have been rendered hyperphagic and obese by treatment with goldthioglucose in order to define the locus and timing of the gold accumulation is planned. On the basis of these experiments, we will be able to plan the development of a procedure for neutron activation of gold in histological sections for radioautography. The total amount of Au^{196} in any section may be too small for clear radioautographic discrimination of Au^{197} from interferring tissue consitituents. If so, we will explore the possibility of shielding the sections for reduction of background as accomplished in our tissue assays.

17. Expected Programs and Results for Next Fiscal Year - 1962:

The general program outlined in FY 1961 is expected to be continued.

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