

ARGONNE CANCER RESEARCH HOSPITAL
Chicago, Illinois

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BIOLOGY AND MEDICINE
PROGRAM BUDGET

FISCAL YEARS 1963, 1964 and 1965

April 1963

Operated by The University of Chicago
under

Contract No. AT(11-1)-69

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No.	
2. Project Title Summarization of Research at Argonne Cancer Research Hospital	189 No.		-
3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s)	8. Project Term: New Proj. Starting: Continuing:		
9. Man Years	FY 1963	FY 1964	FY 1965
(a) Scientific	57-1/2	65	67-1/2
(b) Other Tech.	50	54-1/2	54-1/2
Total	<u>107-1/2</u>	<u>119-1/2</u>	<u>122</u>
10. Costs	FY 1963	FY 1964	FY 1965
(a) Direct Salaries	696,200	910,600	1,041,100
(b) Materials, Services, Subcontracts	130,700	160,800	186,000
(c) Indirect Expenses	<u>1,673,100</u>	<u>1,848,600</u>	<u>2,004,900</u>
	<u>2,500,000</u>	<u>2,920,000</u>	<u>3,232,000</u>
Fallout Program:			
(a) Direct Salaries	5,000	5,200	-
(b) Materials, Services, Subcontracts	<u>31,100</u>	<u>4,800</u>	-
Total for Fallout Program	<u>36,100</u>	<u>10,000</u>	-
Combined Total	<u>2,536,100</u>	<u>2,930,000</u>	<u>3,232,000</u>
11. Reactor Concept: None	12. Materials: None		

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Summary

Accomplishments this Fiscal Year and Proposed Accomplishments for Next Fiscal Year

14. Scope of Work

We continue to maintain operation of the three supervoltage sources at a high standard of efficiency. Replacements and additions to improve stability and reliability of the Van de Graaff and the linear accelerator have materially aided in improving stable output during operation. A localizing device which has been applied to the linear accelerator will improve the accuracy of setting up patients for therapy. A new cobalt-60 source has been irradiated and will be substituted for the present source when the latter has decayed to below the desired maximum radiation output.

Studies using a small analog computer to evaluate methods of dose calculation and treatment planning on the lineac using two beams of radiation have demonstrated that this is a more flexible and adaptable system than was anticipated. When the large analog computer becomes available, we should be able to compute for up to 4 different beams of radiation, a method which will greatly facilitate treatment planning. Attempts will be made to apply these methods for treatment planning to the cobalt-60 machine.

The brain scanner has been tested and is ready for clinical application. The understanding and information compiled during the building of this facility have been invaluable in planning other work. The use of computer methods holds out great promise for refinement and perfection of planning of patient treatment and diagnostic methods, as well as in the designing of new scanning systems.

Comparative studies of the physical factors and biological effects of all three high energy sources continue both at the experimental level and in some cases in the Clinics. An increasing variety of patients has been treated on the supervoltage machines, and new methods of treatment planning are being sought. Rotational cobalt-60 therapy has been shown preferable to straight opposing ports for external irradiation to cancer of the cervix and gamma rays are being compared to electrons for treatment of bladder carcinoma. In cooperation with the Ear, Nose and Throat service, a randomly selected group of patients which includes most tumors of the head and neck is being treated in an attempt to compare the values of radiation therapy alone, preoperative radiation and postoperative radiation. Preoperative radiation is also being given to patients with carcinoma of the esophagus.

We also continue to examine various drugs and physical agents which may increase the effect of radiation on cancer without affecting the surrounding normal tissue. Animal experimentation has served as a guide to clinical treatment and to date 74 patients have been treated with combined colchicine and radiation, 40 with drug-induced hyperthyroidism and radiation, 30 with Actinomycin D and radiation, and 3 with fever and radiation. We are working on a refinement of the preliminary methods of screening agents which may prove useful, and are now using the incorporation of labeled amino acids to study growth patterns of hair in rodents before and

14. Scope of Work (Continued)

after irradiation. We plan to use this method to study Leurocristine, Velban, a number of alkylating agents and a number of halogenated pyrimidines. Studies of the effect of estrogen level on carcinoma of the breast are also being carried out.

Use of radioisotopes as interstitial sources of radiation on the treatment of malignancies continues as suitable patients present themselves. Substantial advances in the field of tumor detection may be expected from the methods of localization (immunologic and metabolic) and the advanced techniques of detection which are being developed.

Studies with Y^{90} pellets, sealed applicators and Pd^{103} continue and in addition a 50 mc Sr^{90} - Y^{90} applicator has been devised as a substitute for the Y^{90} implant used in destruction of the hypophysis. This applicator has been spectacularly successful in the hands of the neurosurgeons who use it to produce restricted destructive lesions of the spinal cord, particularly for the control of pain. Iodine-125 has a substantial but somewhat restricted usefulness. Iodine-125 diiodofluorescein is most successful for eye tumor localization; Tc^{99m} as pertechnetate for thyroid scanning is feasible with a 1000-fold reduction of dose to the gland, and liver scanning with technetium thiocyanate permits greatly increased isotope dosage with consequent reduction in collimator aperture and increased resolution. Cardiac output studies with this material are very promising. More than 150 liver scans have been performed in patients with a variety of liver diseases using Mo^{99} as tracer. We have found the resolution obtained greatly superior to that of Au^{198} and I^{131} . The use of labeled anti-fibrinogen for tumor localization has proved successful in a number of clinical cases. The work of the cardiovascular surgical group on cardiac output measurement and other diagnostic studies using external counting is being pursued from the point of view of better isotopes, detectors, analytical electronics and computer analysis of results.

Studies on the effects of radiation on the skin show that chronic long-term low irradiation with fast neutrons conspicuously retards growth of hair in mice, apparently without any other impairment of health. A newly modified method has been applied to the study of percutaneous absorption in the dog in which the amount of material absorbed can be measured in the venous blood leaving the region studied. The effect of x rays on this process will be studied. In metabolic studies on the skin the amounts of adenosine triphosphate (ATP) are being related to the number of cells in the skin and further evidence has been obtained on the accumulation of succinic acid. We hope to be able to examine the relationship between low ATP levels, atopic dermatitis, and irradiation.

The total-body counter, which was designed and built for metabolic studies in the human, is being used for studies of the metabolism of Ra^{226} , Sr^{85} , Ca^{47} , I^{131} , Mo^{99} and Mg^{28} in man, and for a study of the transport of simulated and actual fission products (fallout). The most valuable ways of using the 4 crystal detection assay of the counter are being explored and programed by use of the analog computer.

The radium study project carried out in conjunction with the Argonne National Laboratory and other laboratories, continues and we expect that a

14. Scope of Work (Continued)

joint publication will appear in 1963. Special attention will be devoted to: rate of elimination of radium, time elapsed since acquisition, degree of skeletal radiation damage, the time of earliest possible detection of significant damage and neoplasms. Data on Sr⁸⁵ and Ca⁴⁷ metabolism in man are being prepared for analysis on the analog computer.

Studies on transport and absorption of simulated fission products have been carried out on 30 persons. The turn-over time of Mo⁹⁹ in normal adults has been determined and studies are now being extended to cases of hepatocellular disease and carcinoma metastasis to the liver.

Purine metabolism in normal subjects and in patients with gout, xanthinuria and hematologic disorders have been studied using various precursors of the purine ring, uric acid and nucleotides labeled with C¹⁴.

The continuous C¹⁴O₂ monitor continues to be used in studies of normal carbohydrate metabolism and of patients with hyperlipemia, glucose-6-phosphate dehydrogenase deficiency, gout and diabetes mellitus. We expect to complete and publish a continuing study on carcinogenesis in mice.

Purification of sheep plasma erythropoietin has now proceeded to the point where it is 190,000 concentrated over the original plasma. Even at the high potency (about 1300 units per mg protein), there is evidence that it is still not pure. We have devised a new, sensitive fairly rapid assay which is dependent upon the action of the hormone on marrow cell cultures in vitro and are using them in studies of the mechanism of action of the material. This method will be employed for all assays except those using very crude material. New sources of the hormone will be sought.

Observations have been made on recovery of the stem cell compartment of the blood from damage by various chemotherapeutic agents -- nitrogen mustard, Actinomycin, bacterial polysaccharide and colchicine -- alone and in conjunction with irradiation. We are planning quantitative studies into the factors influencing the elaboration of the erythropoietin factor in rodents.

Studies on iron absorption in mice having different forms of experimentally-induced anemia indicate that anemia itself may be an important physiologic regulator of iron absorption. We have evidence which suggests that anemia, changes in body iron content, and changes in rate of erythropoiesis may have additive effects on absorption. We intend to examine further the mechanism by which anoxia, the acceleration of erythropoiesis in the bone marrow, and the plasma iron clearance rate affect the process. We will also use the effects of acute hepatic injury to examine the relationship which exists between liver disease and iron loading, and to evaluate the liver as a possible regulator of iron absorption.

We have shown that gastric acid secretion is not a critical factor in the pathogenesis of hypertransfusion-induced gastric ulceration in the rat, but that blood viscosity and other as yet undetermined factors are important. Experiments indicate that when red cells are intraperitoneally injected, they pass by local select pathways into the blood stream.

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14. Scope of Work (Continued)

Techniques are now being evolved to study the migration and function of lymphocytes.

A program recently initiated deals with the autoradiographic study of the replication of human chromosomes as evidenced by the time sequence of DNA synthesis in normal individuals. We expect to apply these methods to the study of chromosome replication in diseases with chromosome abnormalities, including chronic granulocytic leukemia and mongolism.

While studying the effect of natural and synthetic polynucleotides on the complement system and coagulation mechanism in the blood, we have found that the anticomplementary and anticoagulant properties of these substances depend upon their base composition and secondary structures. Polyinosinic acid has been found to have very potent anticomplementary effects and is also a reasonably potent anticoagulant, being able to affect both the first and second stages of the coagulation process. We are now interested in eliciting the structural basis for these properties.

Studies on postirradiation recovery of the blood-forming tissues in mice have been especially concerned with the developmental potential of cells in various sections of the tail, the effect of Nembutal^R anesthesia upon survival, and the relationship of thymectomy and Peyer's patch shielding to the immune reaction. We find that shielding the extreme tip of the tail, where the bone marrow contains no stem cells, does not protect against radiation death. The effects of temperature are being studied. Experiments with Nembutal indicate that mice which are irradiated and given rat marrow while still under anesthesia do not survive, although controls similarly treated, but un-anesthetized, do. The relationships between thymectomy, Peyer's patch shielding and the immune reaction have been explored in CF No. 1 mice thymectomized 4 days after birth. The work is being extended to animals thymectomized earlier than this.

We have been successful in the attempts to develop clones of cells from induced breast tumors in rats. "Toxins" produced by some bacteria have been found to inhibit growth of Sarcoma 37 in DBA/1 mice and these effects were increased by alternating the treatment with administration of Varidase.

Studies on the role of the spleen in the immune response suggest that extra splenic sites also form antibody. Antibody formation by the spleen rapidly reaches peak levels and ceases within a few days after antigen injection while formation by extra splenic sites approaches peak levels more gradually and is active for longer periods.

X ray studies indicate that passive transfer of antibody suppresses the immune response by inhibiting the response of the antibody-forming cells to antigens.

Patterns of cellular migration in the rat studied by means of tritium labeling suggest that lymphocytes migrating from the spleen to the lymph nodes following antigen stimulation, have a stem cell proliferative potential.

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REMARKS
**CANCER RESEARCH HOSP,
Biology & Medicine Program Budget
FY 63, 64, 65**

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REMARKS

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3/28/95			

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NAME OF REQUESTER **JANET ANDERSON** TELEPHONE NO. **708 252 8699** FTS DATE **3/28/95**

NAME AND ADDRESS OF AGENCY

(Include street address, building, room no. and ZIP Code)

1161838

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SIGNATURE **J. Anderson** DATE **3/28/95**

14. Scope of Work (Continued)

Experiments on the value of preirradiation treatment with AET or with PAPP indicate that both substances are able to reduce 30-day lethality in mice exposed to high energy electrons. It has previously been shown that AET administered before x rays enhances the ability of the immune mechanism to reject successfully transplanted leukemia in mice. Intraperitoneal injection was found to be more effective than oral administration.

The process of RNA formation in differentiated cells, and particularly in the cytoplasmic portions of these cells, is being studied in relation to the mechanism of cell differentiation. We have developed a method of studying the incorporation of isotopic precursors into cytoplasmic (microsomal) RNA, and have worked out the enzymatic pathway for the formation of 5-ribosyluridylic acid, which is a precursor of that RNA which is specific for the transfer of amino acids to the protein forming mechanism.

Studies on the properties of RNA polymerase and the mechanism whereby RNA molecules in vitro are assembled by this enzyme continue. We have achieved more extensive purification of RNA polymerase and evidence that in vitro both strands of DNA serve as templates for RNA synthesis. Double stranded RNA can be formed from enzymatically prepared RNA, and RNA polymerase will synthesize RNA with RNA primers as well as DNA primers. RNA molecules prepared with RNA polymerase are complementary in base composition to the RNA primers used.

It has been shown that Actinomycin inhibits the DNA-dependent RNA synthesis of intact cells and enzymes from mammalian and bacterial sources. This inhibition appears to account for the antibiotic and cytotoxic action of Actinomycin and is attributable to the fact that it is tightly bound to the DNA. In its turn this binding is absolutely dependent on the presence of guanine residues in the DNA primers.

The chemical synthesis of γ UMP and enzymatic synthesis of γ UTP have been accomplished; the biosynthesis and reaction of γ UDP glucose have been studied; and the incorporation of γ UTP into RNA by RNA polymerase has also been investigated.

Investigations in the field of steroid pharmacology include studies on the mechanism of hemolysis and fever production; the role of estrogenic hormones in immuno suppression in man and experimental animals; the use of estrogens in treatment of connective tissue diseases of the immune type, and of diseases characterized by lymphoid hyperplasia; and metabolic studies of the effects of massive estrogen administration in man. We have demonstrated the immuno suppressive effect of sex steroids in three immune situations, namely;--tubercular sensitivity; immune thyroiditis; and adjuvant arthritis in man. Clinical counterparts of these studies are being carried out in man.

Our future plans include facilities for full metabolic studies in steroid pharmacology. The work on steroid hemolysis will be completed, as will preliminary studies on the therapeutic use of intensive sex hormone therapy in rheumatoid arthritis and chronic lymphatic leukemia.

14. Scope of Work (Continued)

Another new project deals with the role of certain microbial inhabitants of the mouse's intestinal tract in maintaining its resistance to experimental Salmonella infection. This is important because infection with enteric pathogens like Salmonella is an important cause of death in animals exposed to mid-lethal doses of radiation.

ARGONNE CANCER RESEARCH HOSPITAL
 CONTRACT AT(11-1)-69
 BUDGET - F.Y. 1963
 06-09-01 - OPERATIONS

DIRECT PROGRAM ACTIVITIES BUDGET NO.	DIRECT COST		INDIRECT COST				TOTAL COST		
	DIRECT SALARIES MAN-YRS. AMOUNT	MATERIAL	TOTAL	SUPPLEMENTARY PROGRAM EXP.	HOSPITAL OPERATIONS	SERVICE UNITS AND FIXED CHARGED		TOTAL	
									TOTAL
1	4	19,900	2,100	22,000	10,000	20,000	14,500	44,500	66,500
2	6	39,000	10,000	49,000	22,300	44,500	32,300	99,100	148,100
3	5	28,600	2,000	30,600	14,000	27,800	20,100	61,900	92,500
4	8-1/2	59,600	6,000	65,600	29,900	59,600	43,200	132,700	198,300
5	1-1/2	10,800	8,000	18,800	8,600	17,100	12,400	38,100	56,900
6	8-1/2	48,800	3,200	52,000	23,700	47,300	34,200	105,200	157,200
7	3-1/2	27,000	6,000	33,000	15,000	30,000	21,700	66,700	99,700
9	3	20,900	2,000	22,900	10,400	20,800	15,100	46,300	69,200
11	6-1/2	44,000	4,000	48,000	21,900	43,600	31,600	97,100	145,100
12	3	23,800	1,000	24,800	11,300	22,500	16,300	50,100	74,900
13	4	29,900	4,000	33,900	15,500	30,800	22,300	68,600	102,500
14	6	39,800	45,000	84,800	38,700	77,100	55,800	171,600	256,400
15	7-1/2	43,800	8,000	51,800	23,600	47,100	34,100	104,800	156,600
16	6-1/2	26,600	6,100	32,700	14,900	29,700	21,500	66,100	98,800
18	5-1/2	25,600	4,000	29,600	13,500	26,900	19,500	59,900	89,500
19	3-1/2	29,400	2,000	31,400	14,300	28,500	20,700	63,500	94,900
20	5-1/2	42,000	3,000	45,000	20,500	40,900	29,600	91,000	136,000
22	3-1/2	34,000	3,500	37,500	17,100	34,100	24,700	75,900	113,400
23	5	37,500	2,000	39,500	18,000	35,900	26,000	79,900	119,400
24	3-1/2	28,900	1,800	30,700	14,000	27,900	20,200	62,100	92,800
25	1-1/2	8,400	1,500	9,900	4,500	9,000	6,500	20,000	29,900
26	4	13,000	2,000	15,000	6,800	13,600	9,900	30,300	45,300
27	2	14,900	3,500	18,400	8,600	16,900	12,200	37,700	56,100
TOTAL O6 OPERATION		696,200	130,700	826,900	377,100	751,600	544,400	1,673,100	2,500,000
FALLOUT PROGRAM		5,000	31,100	36,100	-	-	-	-	36,100
TOTAL OF ALL ACTIVITY		701,200	161,800	863,000	377,100	751,600	544,400	1,673,100	2,536,100

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ARGONNE CANCER RESEARCH HOSPITAL
BUDGET F. Y. 1963 - 06-09-01 - OPERATIONS
INDIRECT COST

1167842

	<u>MAN-YRS.</u>	<u>SALARIES</u>	<u>DIRECT MATERIAL</u>	<u>OTHER COSTS</u>	<u>TOTAL</u>
<u>Supplementary Program Activities</u>					
Isotope Pharmacy	-	-	40,000	-	40,000
Animal Farm	12	57,500	100,000	-	157,500
Electronics Shop	7-1/2	61,000	37,000	-	98,000
Machine Shop	8-1/2	57,500	6,500	-	64,000
Health Physics	2-1/2	10,700	6,900	-	17,600
Total - Suppl. Program	<u>30-1/2</u>	<u>186,700</u>	<u>190,400</u>	<u>-</u>	<u>377,100</u>
<u>Hospital Operations</u>					
Patient Exp. - Suppl. Service	-	-	-	286,000	286,000
Patient Exp. - Indirect	-	-	-	92,000	92,000
Interns and Residents	-	-	-	28,000	28,000
Nursing Services	39-1/2	170,500	9,000	-	179,500
Cost of Food Services	6-1/2	28,100	80,000	6,000	114,100
Housekeeping	-	-	-	52,000	52,000
Total	<u>46</u>	<u>198,600</u>	<u>89,000</u>	<u>464,000</u>	<u>751,600</u>
<u>Service Units and Fixed Costs</u>					
Steam, Electricity, and Gas	-	-	-	59,000	59,000
Telephone and Telegraph	-	-	-	17,000	17,000
Repairs and Maintenance	-	-	-	89,000	89,000
Housekeeping	9	36,800	14,100	-	50,900
Administration	9	67,200	20,300	-	87,500
Travel	-	-	-	26,000	26,000
Overhead	-	-	-	115,000	115,000
Fringe Benefits	-	-	-	100,000	100,000
Total - Service Units and Fixed Costs	<u>18</u>	<u>104,000</u>	<u>34,400</u>	<u>406,000</u>	<u>544,400</u>
Total Indirect Cost	<u>94-1/2</u>	<u>489,300</u>	<u>313,800</u>	<u>870,000</u>	<u>1,673,100</u>

ARGONNE CANCER RESEARCH HOSPITAL
 CONTRACT AT(11-1)-69
 BUDGET - F. Y. 1964
 06-09-01 - OPERATIONS

DIRECT PROGRAM ACTIVITIES	DIRECT COST			INDIRECT COST					TOTAL COST
	DIRECT SALARIES MAN-YRS. AMOUNT	DIRECT MATERIAL	TOTAL	SUPPLEMENTARY PROGRAM EXP.	HOSPITAL OPERATIONS	SERVICE UNITS FIXED CHARGES	TOTAL		
1	4	22,500	4,000	26,500	10,600	19,900	15,200	45,700	72,200
2	6-1/2	44,700	11,000	55,700	22,300	41,800	32,000	96,100	151,800
3	5	29,800	3,000	32,800	13,100	24,600	18,900	56,600	89,400
4	8-1/2	63,900	8,000	71,900	28,800	54,000	41,300	124,100	196,000
5	1-1/2	12,000	17,000	29,000	11,600	21,800	16,700	50,100	79,100
6	8-1/2	52,400	3,500	55,900	22,400	41,900	32,100	96,400	152,300
7	3-1/2	29,900	6,000	35,900	14,400	26,900	20,600	61,900	97,800
9	3	23,300	5,500	28,800	11,500	21,600	16,600	49,700	78,500
11	7-1/2	50,800	5,000	55,800	22,300	41,900	32,100	96,300	152,100
12	3	25,300	1,000	26,300	10,500	19,700	15,100	45,300	71,600
13	4	31,600	8,000	39,600	15,800	29,700	22,800	68,300	107,900
14	6-1/2	45,200	30,000	75,200	30,000	56,400	43,200	129,600	204,800
15	8	61,300	8,000	69,300	27,700	52,000	39,800	119,500	188,800
16	6-1/2	46,900	13,000	59,900	24,000	45,000	34,400	103,400	163,300
18	6-1/2	58,500	6,000	64,500	25,800	48,400	37,100	111,300	175,800
19	3-1/2	32,600	5,000	37,600	15,000	28,200	21,600	64,800	102,400
20	5-1/2	47,700	4,000	51,700	20,700	38,800	29,700	89,200	140,900
22	3-1/2	35,700	5,000	40,700	16,300	30,500	23,400	70,200	110,900
23	5	41,700	2,300	44,000	17,600	33,000	25,300	75,900	119,900
24	4	37,100	2,500	39,600	15,800	29,000	22,800	67,600	107,200
25	3-1/2	25,100	3,000	28,100	11,200	21,100	16,200	48,500	76,600
26	4	17,900	3,500	21,400	8,600	16,100	12,300	37,000	58,400
27	2-1/2	22,400	4,500	26,900	10,800	20,200	15,500	46,500	73,400
28	5-1/2	52,300	2,000	54,300	21,900	41,600	31,100	94,600	148,900
TOTAL O6 OPERATION FALLOUT PROGRAM	119-1/2 2	910,600 5,200	160,800 4,800	1,071,400 10,000	428,700 -	804,100 -	615,800 -	1,848,600 -	2,920,000 10,000
TOTAL OF ALL ACTIVITY	121-1/2	915,800	165,600	1,081,400	428,700	804,100	615,800	1,848,600	2,930,000

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ARGONNE CANCER RESEARCH HOSPITAL
BUDGET F.Y. 1964 - 06-09-01 OPERATIONS
INDIRECT COST

	MAN-YRS.	SALARIES	DIRECT MATERIAL	OTHER COSTS	TOTAL
<u>Supplementary Program Activities</u>					
Isotope Pharmacy	-	-	48,000	-	48,000
Animal Farm	12	60,500	110,000	-	170,500
Electronics Shop	10	75,700	39,000	-	114,700
Machine Shop	10	67,700	7,500	-	75,200
Health Physics	3	12,100	8,200	-	20,300
Total - Suppl. Program	<u>35</u>	<u>216,000</u>	<u>212,700</u>	-	<u>428,700</u>
<u>Hospital Operations</u>					
Patient Exp. - Suppl. Service	-	-	-	309,000	309,000
Patient Exp. - Indirect	-	-	-	102,000	102,000
Interns and Residents	-	-	-	32,500	32,500
Nursing Services	39-1/2	176,100	10,000	-	186,100
Cost of Food Services	6-1/2	28,900	85,000	6,500	120,400
Housekeeping	-	-	-	54,100	54,100
Total - Hospital Operation	<u>46</u>	<u>205,000</u>	<u>95,000</u>	<u>504,100</u>	<u>804,100</u>
<u>Service Units and Fixed Costs</u>					
Steam, Electricity, and Gas	-	-	-	60,500	60,500
Telephone and Telegraph	-	-	-	19,000	19,000
Repairs and Maintenance	-	-	-	90,500	90,500
Housekeeping	9	38,800	14,800	-	53,600
Administration	10	77,700	21,500	-	99,200
Travel	-	-	-	30,000	30,000
Overhead	-	-	-	125,000	125,000
Fringe Benefits	-	-	-	138,000	138,000
Total - Service Units and Fixed Costs	<u>19</u>	<u>116,500</u>	<u>36,300</u>	<u>463,000</u>	<u>615,800</u>
Total Indirect Cost	<u>100</u>	<u>537,500</u>	<u>344,000</u>	<u>967,100</u>	<u>1,848,600</u>

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ARGONNE CANCER RESEARCH HOSPITAL
 CONTRACT AT(11-1)-69
 BUDGET - F.Y. 1965
 06-09-01 - OPERATIONS

DIRECT PROGRAM ACTIVITIES	DIRECT COST		INDIRECT COST				TOTAL COSTS		
	DIRECT SALARIES MAN-YRS.	AMOUNT	DIRECT MATERIAL	TOTAL	SUPPLEMENTARY PROGRAM EXP.	HOSPITAL OPERATIONS		SERVICE UNITS FIXED CHARGES	TOTAL
1	4	25,000	5,000	30,000	11,700	20,800	16,500	49,000	79,000
2	6-1/2	48,100	12,000	60,100	23,400	41,700	33,100	98,200	158,300
3	5	30,900	6,500	37,400	14,500	26,000	20,600	61,100	98,500
4	8-1/2	66,600	6,000	72,600	28,200	50,400	40,000	118,600	191,200
5	1-1/2	12,900	19,000	81,900	12,400	22,100	17,600	52,100	84,000
6	8-1/2	56,000	4,500	60,500	23,500	42,000	33,300	98,800	159,300
7	3-1/2	29,900	7,000	36,900	14,400	25,600	20,300	60,300	97,200
9	3	25,800	6,500	32,300	12,600	22,400	17,800	52,800	85,100
11	7-1/2	53,800	6,000	59,800	23,300	41,500	32,900	97,700	157,500
12	3-1/2	26,900	2,000	28,900	11,200	20,000	15,900	47,100	76,000
13	4	35,400	9,000	44,400	17,300	30,800	24,500	72,600	117,000
14	5-1/2	55,000	30,000	85,000	33,100	59,000	46,800	138,900	223,900
15	8	67,600	9,000	76,600	29,800	53,200	42,200	125,200	201,800
16	6-1/2	49,900	14,000	63,900	24,900	44,300	35,200	104,400	168,300
18	8-1/2	80,800	8,000	88,800	34,500	61,600	48,900	145,000	233,800
19	3-1/2	35,800	6,500	42,300	16,500	29,400	23,300	69,200	111,500
20	5-1/2	52,500	5,000	57,500	22,400	39,900	31,700	94,000	151,500
22	3-1/2	35,700	6,000	41,700	16,200	28,900	23,000	68,100	109,800
23	5	41,700	3,000	44,700	17,400	31,000	24,600	73,000	117,700
24	4-1/2	40,800	3,500	44,300	17,200	30,700	24,400	72,300	116,600
25	3-1/2	28,000	4,000	32,000	12,400	22,200	17,600	52,200	84,200
26	4	42,700	5,500	48,200	18,700	33,500	26,500	78,700	126,900
27	2-1/2	28,000	5,000	33,000	12,800	22,900	18,200	53,900	86,900
28	6	71,300	3,000	74,300	29,000	51,700	41,000	121,700	196,000
TOTAL	122	1,041,100	186,000	1,227,100	477,400	851,600	675,900	2,004,900	3,232,000

ARGONNE CANCER RESEARCH HOSPITAL
BUDGET F.Y. 1965 - 06-09-01 - OPERATIONS
INDIRECT COST

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	<u>MAN-YRS.</u>	<u>SALARIES</u>	<u>DIRECT MATERIAL</u>	<u>OTHER COSTS</u>	<u>TOTAL</u>
<u>Supplementary Program Activities</u>					
Isotope Pharmacy	-	-	57,000	-	57,000
Animl. Farm	12	63,300	115,000	-	178,300
Electronics Shop	11	85,900	44,000	-	129,900
Machine Shop	11	78,700	8,500	-	87,200
Health Physics	3	15,100	9,900	-	25,000
Total - Suppl. Program	<u>37</u>	<u>243,000</u>	<u>234,400</u>	-	<u>477,400</u>
<u>Hospital Operations</u>					
Patient Exp. - Suppl. Service	-	-	-	328,000	328,000
Patient Exp. - Indirect	-	-	-	108,000	108,000
Interns and Residents	-	-	-	35,800	35,800
Nursing Services	39-1/2	185,000	11,000	7,000	196,000
Cost of Food Services	6-1/2	30,000	90,500	56,300	127,500
Housekeeping	-	-	-	56,300	56,300
Total - Hospital Operations	<u>46</u>	<u>215,000</u>	<u>101,500</u>	<u>535,100</u>	<u>851,600</u>
<u>Service Units and Fixed Costs</u>					
Steam, Electricity, and Gas	-	-	-	62,000	62,000
Telephone and Telegraph	-	-	-	20,000	20,000
Repairs and Maintenance	-	-	-	94,100	94,100
Housekeeping	9	40,700	15,500	-	56,200
Administration	10	83,800	22,800	-	106,600
Travel	-	-	-	30,000	30,000
Overhead	-	-	-	135,000	135,000
Fringe Benefits	-	-	-	172,000	172,000
Total - Service Units and Fixed Costs	<u>19</u>	<u>124,500</u>	<u>38,300</u>	<u>513,100</u>	<u>675,900</u>
Total Indirect Cost	<u>102</u>	<u>582,500</u>	<u>374,200</u>	<u>1,048,200</u>	<u>2,004,900</u>

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 1	
2. Project Title Chemical Studies of Erythropoietin		189 No. 1	
3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Eugene Goldwasser, Ph.D.	8. Project Term: New Proj. Starting: Continuing:		
9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	1	1	1
(b) Other Tech.	3	3	3
Total	4	4	4
10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	19,900	22,500	25,000
(b) Materials, Services, Subcontracts	2,100	4,000	5,000
(c) Indirect Expenses	44,500	45,700	49,000
(d) Equipment	-	-	-
Total	66,500	72,200	79,000
11. Reactor Concept: None	12. Materials: None		

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13. Dates and Titles of Publications (Other than Progress Reports)

Goldwasser, E., W. F. White and K. B. Taylor. On the Purification of Sheep Plasma Erythropoietin. In Jacobson, L. O. and M. Doyle, eds. Erythropoiesis. Grune and Stratton, New York, pp. 43, 1962.

Goldwasser, E., W. F. White and K. B. Taylor. Further Purification of Sheep Plasma Erythropoietin. Biochim. Biophys. Acta, 64: 487, 1962.

Dukes, P. P. and E. Goldwasser. Lack of Effect of Plasma Erythropoietin on Formate Incorporation into Nucleic Acids in vitro. Nature, 195, 1222, 1962.

Dukes, P. P. and E. Goldwasser. On the Utilization of Erythropoietin. In Jacobson, L. O. and M. Doyle, eds. Erythropoiesis. Grune and Stratton, New York, pp. 125, 1962.

14. Scope of Work

This project is concerned with the isolation, chemical identification and mode of action of the hormone erythropoietin. Evidence currently indicates that this material may provide a very important tool in the chemical study of the processes involved in differentiation of the stem cells of the red cell line.

15. Relationship to Other Projects

Leon O. Jacobson, M.D.	06-09-01	-	3
Clifford W. Gurney, M.D.	06-09-01	-	6

16. Technical Progress in Fiscal Year 1963

The purification of plasma erythropoietin has now proceeded, so that it is 190,000 times concentrated over the original plasma. Even at this high potency, about 1300 units/mg protein, there is evidence that it is not yet pure. We have demonstrated an in vitro effect in marrow cell cultures which makes it possible to have a sensitive, fairly rapid assay method and to study the mechanism of action of this material.

17. Expected Results in Fiscal Year 1964

We expect to be able to use the in vitro system for all assays except those with very crude materials and to start to explore details of the mechanism of action of erythropoietin. In addition, we will be looking for new sources of this hormone.

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Project No. 1 (Continued)

18. Expected Results in Fiscal Year 1965

By this time the purification problem should be completely finished and we expect to be studying the relation between structure and activity of this hormone, as well as having results related to the chemical mechanism of the differentiation of stem cells toward the red cell lineage.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 2	
2. Project Title Immunologic and Metabolic Factors in Neoplasia				189 No. 2	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963			
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Robert W. Wissler, Ph.D., M.D. Frank W. Fitch, Ph.D., M.D.		8. Project Term: New Proj. Starting: Continuing:			
9. Man Years		<u>FY 1963</u>		<u>FY 1964</u>	
(a) Scientific		3		3	
(b) Other Tech.		3		3-1/2	
Total		<u>6</u>		<u>6-1/2</u>	
10. Costs		<u>FY 1963</u>		<u>FY 1964</u>	
(a) Direct Salaries		39,000		44,700	
(b) Materials, Services, Subcontracts		10,000		11,000	
(c) Indirect Expenses		99,100		96,100	
(d) Equipment		-		-	
Total		<u>148,100</u>		<u>151,800</u>	
11. Reactor Concept: None		12. Materials: None			

1167850

13. Dates and Titles of Publications (Other than Progress Reports)

Wissler, R. W. Combined Effects of Antitumor Serum and other Therapy on the Growth and Appearance of Tumors (Studies on Heterologous Tumor Antibody). Estratto da Il Cancro - Periodico dell'Istituto di Oncologia di Torino. Anno XIV No. 5, 1, 1961.

Wissler, R. W. Effects of Specific Antibodies on Tissue Cells. Ann. Rev. Microbiol. 16, 265, 1962.

Wissler, R. W. Antibodies Against Cells. Bull. N. Y. Acad. Med. 38, 64, 1962.

Stone, M. J., K. Dzoga and R. W. Wissler. Combined Inhibitory Effect of Antitumor Antibody and an Oncolytic Virus on the Solid Ehrlich Tumor. Lab. Invest. 11, 306, 1962.

Gunderson, C. H., D. Juras, M. F. LaVia and R. W. Wissler. Tissue and Cellular Changes Associated with Antibody Formation in the Rat Spleen. J. A. M. A. 180, 116, 1962.

Wissler, R. W. and V. Kao. Immunohistochemical Studies of the Human Aorta (Abstract). Federation Proc. 21, 95, 1962.

Winebright, J. and F. W. Fitch. Antibody Formation in the Rat. I. Agglutinin Response to Particulate Flagella from Salmonella typhosa. J. Immunol. 89, 891, 1962.

Fitch, F. W. and J. Winebright. Antibody Formation in the Rat. II. Agglutinin Response to Soluble Flagellin from Salmonella typhosa. J. Immunol. 89, 900, 1962.

Haber, S. L. and R. W. Wissler. Effect of Vitamin E on Carcinogenicity of Methylcholanthrene. Proc. Soc. Exp. Biol. Med. 111, 774, 1962.

Goepp, R. and F. W. Fitch. Pathological Study of Oral Radiation Death in Mice. Rad. Res. 16, 833, 1962.

Goepp, R. A. and F. W. Fitch. Prevention of Death in Mice After Lethal Irradiation of the Head. Rad. Res. 1963. (In press).

Fitch, F. W. Effect of Splenectomy on the Agglutinin Response of the Rat. Federation Proc. 1963. (In press).

Rowley, D. A. and F. W. Fitch. Homeostasis of Circulating Hemolysin Formation in the Rat. Federation Proc. 1963. (In press).

14. Scope of Work

The problem of tumor-host balance will be studied both in the experimental animal utilizing carcinogen-induced tumors in inbred rats and in man searching for cancer cell cytotoxins and other circulating factors in individual human cancer patients. Investigations into the cellular dynamics and the control of the immune response will include further studies of the kinetics of cellular changes during antibody formation, of antigen localization and metabolism and of factors regulating antibody formation.

Investigations of tumor-host balance will include the following approaches:

- 1) Studies of the localization and specificity of antibodies against carcinogen-induced breast tumors grown in tissue culture.
- 2) Identification and isolation of cancer-cell cytotoxins in the serum of individual cancer patients.
- 3) Study of the tumor antigens of certain selected transplanted and induced tumors of the liver.
- 4) Anatomical and functional characteristics of tumors in relation to fibrinogen and anti-fibrinogen localization.

Investigations of the cellular dynamics and the control of the immune response will include the following approaches:

- 1) Study of antigen localization and metabolism at the tissue and cellular level utilizing a combination of radioisotope labeling and tracing with fluorescent immunohistochemistry.
- 2) Study of the migration and fate of antibody-forming cells in various organs using tritium-labeled thymidine.
- 3) Study of the various factors regulating the immune response including the role of antibody in the suppression of antibody formation after passive immunization and the role of persisting antigen in neonatal and adult immunological tolerance.
- 4) Study of the types of antibodies formed after immunization at different ages with various kinds of antigens.
- 5) Evaluation of the relative importance of cellular and humoral factors from the thymus in the development of the immune mechanism.
- 6) Study of the cellular reaction of the newborn animal to antigenic stimulation with particular emphasis on the fate of the antigen.

15. Relationship to Other Projects

Dr. Frank Fitch, using funds granted by USPHS Grant #AI-04197-02, will continue his studies of the functional activity and morphological characteristics of single antibody-forming cells at various times after antigen injection, utilizing the micromanipulation technique. Some aspects of the study of the role of passively administered antibody in the suppression of active immune response being done in collaboration with Dr. Donald Rowley of the Department of Pathology, will be supported by USPHS Grant #H-5667-03.

Most of the work on the projects outlined in Section 14 (preceding page) will be done in the Argonne Cancer Research Hospital. We will continue to use the Department of Pathology facilities for the histological, microbiological and serological work and for fluorescence microscopy and tissue culture; facilities for this type of work are not available in the Argonne Hospital. All animal work, irradiation, autopsies, surgery, radioisotope labeling of antigens and antibodies, and all radioactivity measurements are performed in the Argonne Hospital. Some training aspects of these studies are supported by an immunopathology training grant from the National Institutes of Health Institute of Allergy and Infectious Diseases (Grant #5-TI-AI-96).

16. Technical Progress in Fiscal Year 1963

Investigations of tumor-host balance: Progress is being made in developing better techniques for the detection of cytotoxins in the serum of human cancer patients. Sensitive biochemical assays of cell damage including inhibition of acid production and glucose metabolism are being investigated.

Attempts to develop clones of cells from carcinogen-induced breast tumors of rats have resulted in outgrowth of cells in 10 of the trials. Of these, 6 have been established as cell lines. The morphology and growth patterns of some of the cells are different but they all resemble fibroblasts. In one instance, initial growth was of epithelial cells but these eventually were overgrown by a fibroblastic cell type.

Studies on the tumor inhibitory effects of "toxins" produced by Strep-pyogenes and Serratia marcescens indicated that a single injection of these materials inhibited growth of sarcoma 37 in DBA/1 mice. Multiple injections alternating with administration of Varidase increased the inhibitory effects. Tumors from treated animals had peripheral inflammation, focal areas of necrosis, and numerous tumor giant cells; these findings were not noted in tumors from untreated animals.

Studies of "immunological enhancement" of Ehrlich tumor by administration of tumor specific antiserum indicated that the antiserum could be administered as long as 7 days after tumor transplantation and still cause enhanced tumor growth. A dose of antiserum that had no effect on the hematocrit was still effective in producing increased tumor growth.

Studies on the localization of fibrinogen and anti-fibrin antibodies in tumors included preliminary studies of a rat lymphosarcoma utilizing

16. Technical Progress in Fiscal Year 1963 (Continued)

I^{131} labeled anti-rat fibrin and anti-rat fibrinogen. In vivo and in vitro localization are being compared.

Investigations of the cellular dynamics and the control of the immune response: Certain phases of the studies of the role of the spleen in the immune response have been completed. They suggest that the spleen not only forms antibody but also permits extra-splenic sites to form antibody either by releasing immunologically functioning cells into the circulation or by altering the antigen and releasing it to other sites. It has become apparent that antibody formation by the spleen rapidly reaches peak levels and then abruptly ceases within a few days after antigen injection. Antibody formation by extra-splenic sites, however, appears to approach peak levels more gradually and remain active for prolonged periods.

The mechanism of the suppression of the immune response by passively administered antibody has been investigated further using cell transfer to x-irradiated recipients. These studies suggest that the passive antibody does not act only by preventing the antigen from reaching the antibody-forming site but rather modifies the cells in such a way that subsequent contact with antigen does not result in an immune response.

Studies on the patterns of cellular migration in the rat spleen occurring in response to antigenic stimulation indicate that tritium-labeled lymphocytes migrating from the spleen to lymph nodes have a stem-cell proliferative potential.

Preliminary studies on antigen metabolism and localization in the rat using I^{125} -labeled bovine gamma globulin given intravenously with S. typhosa endotoxin: the results indicate that under these conditions circulating antibody appears at a time when antigen is also present in the blood stream and that immune elimination does not occur. These observations are being pursued further.

In experiments preliminary to attempts to trace injected lymphocytes in mice, a strain-specific iso-antiserum has been produced utilizing intraperitoneal injection of pooled tissues in Freund's adjuvant. This anti-serum has been labeled with fluorescein and is now being fully evaluated.

17. Expected Results in Fiscal Year 1964

Investigations of tumor-host balance: We hope to apply more refined biochemical assays of humoral cytotoxicity as well as apply methods for measuring cellular cytotoxicity in the study of a selected group of human cancer patients.

We hope to be able to distinguish antigenic similarities and differences in the cultured cells of carcinogen-induced breast tumors of rats as compared to the normal tissue from which they were derived. Refined tissue culture methods including the use of feeder layers of hormone-producing cells and the use of media containing various hormones will be used in

17. Expected Results in Fiscal Year 1964 (Continued)

attempts to stimulate growth of epithelial tumor cells in vitro. Attempts will be made to suppress the fibroblastic cell growth by use of antisera against fibroblasts added to the media.

The antigenic components of carcinogen-induced and transplanted hepatic tumors of inbred mice will be studied utilizing combinations of cell fractionation, immunization of rabbits whose antibody response to "normal" antigens has been suppressed by passive administration of antibody against the "normal" antigens, and immunoelectrophoretic and gel-diffusion analysis.

Further studies on the "immunological enhancement" of tumor growth will include determination of organ and cellular localization of antibody labeled with I¹²⁵ and investigation of the histological changes in the tumor as well as in regional and distant lymphoid tissue.

Studies on the localization of labeled anti-fibrinogen in tumors will include use of fluorescent immunohistochemistry and electron microscopy to study vascular permeability in tumors.

Investigations of the cellular dynamics and the control of the immune response: There will be an intensified study of the fate, functional potential, and significance of cells entering the blood stream in response to antigenic stimulation in normal and irradiated animals including spleen-shielded, irradiated rats.

The study of the metabolism of bovine gamma globulin, bacterial flagella and perhaps other antigens administered to the rat will utilize I¹²⁵ labeling of the proteins. It will include measurement of antigen disappearance from the blood stream and determination of organ, tissue, and cellular distribution utilizing autoradiography and fluorescence immunohistochemistry as well as other techniques such as immunoelectrophoresis and chromatography for identification of antigens and antibodies.

Studies on the cellular migration patterns in the rat spleen in response to antigenic stimulation will include continued attempts to determine the immunological potential of the cells migrating from the spleen to lymph nodes. Methods to be used include direct and indirect fluorescent immunohistochemistry and bacterial adherence.

The duration of antibody formation by transferred spleen and lymph node cells will be studied. This investigation is prompted by previous work which indicates that the intact spleen forms antibody only briefly while extrasplenic sites continue to produce antibody for a long time.

Many studies indicate that antibodies are formed in the beta as well as gamma globulins. We will study the nature of the antibody globulins formed in response to various antigenic stimuli using starch block electrophoresis, DEAE cellulose column chromatography, immunoelectrophoresis and other techniques. The cellular sites of formation of the various antibody globulins will be studied using fluorescence immunohistochemistry.

17. Expected Results in Fiscal Year 1964 (Continued)

The importance of the thymus in the development of the immune mechanism has been clearly shown by others. It is still not clear, however, whether this effect is mediated by cells or by humoral factors. This will be studied using Millipore filter chambers in thymectomized newborn rats.

18. Expected Results in Fiscal Year 1965

Studies on host-tumor balance will continue into 1965. Work may have progressed to the point where attempts to alter growth of carcinogen and viral-induced neoplasms in inbred animals by immunological methods will be possible. Attempts to increase specificity of anti-tumor antibodies will probably involve use of various kinds of immunological tolerance to suppress the antibody response against normal tissue antigens. Studies in human cancer patients will probably involve further characterization of cytotoxic humoral substances.

Several aspects of the investigation of cellular dynamics and the regulation of the immune response will continue into 1965. These will include continuing studies of antigen metabolism in the immunologically tolerant animal as well as in the normal animal at the cellular and sub-cellular level. The role of antigen as well as antibody in regulating the antibody-forming mechanism will continue to be studied.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 3	
2. Project Title Studies on Recovery from Radiation Injury		189 No. 3	
3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi- annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Leon O. Jacobson, M.D. Eric L. Simmons, Ph.D.	8. Project Term: New Proj. Starting: Continuing:		
9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	2	2	2
(b) Other Tech.	3	3	3
Total	5	5	5
10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	28,600	29,800	30,900
(b) Materials, Services, Subcontracts	2,000	3,000	6,500
(c) Indirect Expenses	61,900	56,600	61,100
(d) Equipment	-	-	-
Total	92,500	89,400	98,500
11. Reactor Concept: None	12. Materials: None		

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13. Dates and Titles of Publications (Other than Progress Reports)

Jacobson, L. O., E. L. Simmons, E. K. Marks and E. O. Gaston. Recent Studies in Recovery from Radiation Injury after Transplantation of Heterologous tissue: Effect of Peyer's Patch Shielding in Irradiated Mice. Proc. VIIIth International Congress of Hematology, September 1960, Tokyo. Vol. I, pp. 8-9, Pan-Pacific Press, 1962.

Jacobson, L. O., E. K. Marks, E. O. Gaston and E. L. Simmons. Some Factors Influencing the Success of Foreign Hematopoietic Colonization. Studies on Transplantation using Transfusion-Induced Polycythemic Mice as Donor or Recipients. Proc. VIIIth International Congress of Hematology, September 1960, Tokyo. Vol. I, pp. 116-120, Pan-Pacific Press, 1962.

Filmanowicz, E., C. W. Gurney, N. Wackman and L. O. Jacobson. The Response of the Transfusion-Induced Polycythemic Mouse to Exogenous Erythropoietin. Proc. VIIIth International Congress of Hematology, September 1960, Tokyo. Vol. II, pp. 950-956, Pan-Pacific Press, 1962.

Jacobson, L. O. Sites of Formation of Erythropoietin. In Jacobson, L. O. and M. Doyle, eds. Erythropoiesis. Grune and Stratton, New York, pp. 69, 1962.

Jacobson, L. O. and S. Yachnin. Blood Transfusions: Their Uses and Abuses. World Wide Abstracts in General Medicine, 6, 8, 1963.

14. Scope of Work

We are continuing to investigate the mechanism of postirradiation recovery of blood-forming tissues following lead-shielding or the injection of bone marrow, spleen or embryo liver cell suspensions, since the application of this principle to the recovery of totally-irradiated human beings has been demonstrated. Repopulation is an important part of this recovery phenomenon, and the search for the cell types involved in the reconstitution of the blood-forming tissues in irradiated animals continues, in order to determine, if possible, the specificity of the stem cell precursors in the regenerative process. By techniques such as transplantation or shielding of hematopoietic tissue in various parts of the body, we are trying to determine whether functional differences exist between normally active and normally inactive marrow. Finally, the processes involved in differentiation and maturation of lymphoid tissue are being explored, since these cell types are critical in recovery from radiation injury and in homo- and heterotransplantation.

15. Relationship to Other Projects

Eugene Goldwasser, Ph.D.	06-09-01	-	1
Clifford W. Gurney, M.D.	06-09-01	-	6
Eric L. Simmons, Ph.D.	06-09-01	-	12

Project No. 3 (Continued)

16. Technical Progress in Fiscal Year 1963

Under normal conditions bone marrow in the tail of the mouse is inactive and does not contribute to the steady state. We have shown previously, however, that under stress situations such as total-body irradiation the marrow in an 11 mm segment that is 3 cm from the tip will proliferate and result in enhanced survival. We are continuing to explore the developmental potentiality of cells in various sections of the tail. Shielding of the extreme tip does not protect against radiation death. Similarly, marrow that is aspirated from the terminal section of the tail fails to save the life of lethally-irradiated mice, although marrow that is removed from sections closer to the body does promote recovery. Histological examination reveals that the marrow near the tip is composed of mature granulocytes and lymphocytes and lacks stem cells, although these are present as one proceeds to the base of the tail. The implications of environmental temperature to these findings is being explored.

In our studies on the effect of pentobarbital sodium (Nembutal^R) on the hematopoietic system, we have confirmed the findings previously reported for the dog that such anesthesia depresses peripheral lymphocyte count. When mice are irradiated with 950 r while under Nembutal anesthesia, immediate injection of rat bone marrow while still under anesthesia fails to save their life although such injections are efficacious in non-anesthetized mice.

CF No. 1 mice that were thymectomized 4 days after birth are still able to reject a foreign tumor, P-1534 lymphatic leukemia of the DBA/2 strain. Lead shielding of a single patch of Peyer of thymectomized mice during irradiation of the body followed by injection of rat bone marrow results in rejection of the foreign cells and death of the mouse. This indicates that the Peyer's patch of the thymectomized CF No. 1 mouse is still able to recolonize other lymphoid sites. Similarly, the injection of one million mesenteric lymph node cells for thymectomized mice following lethal irradiation of recipient mice with rat bone marrow therapy results in rejection and death as in control experiments.

17. Expected Results in Fiscal Year 1964

Attempts will continue using physiologic and other techniques to effect differential suppression of various cell types of the blood-forming tissue prior to its transplantation into irradiated recipients. We hope to determine the number and type of cells originally present in shielded tissues, to correlate this with the fate of homologous and heterologous transplants, and to elucidate the pattern of regenerated lymphoid tissue. We will attempt to find out whether a humoral mechanism controls the growth and differentiation of lymphoid tissue.

18. Expected Results in Fiscal Year 1965

It is expected that these studies will continue, since many problems of the cell types involved in bone marrow transplantation, the interactions that are involved in early as well as late immune disease, and the role of bone marrow grafts in the reconstitution of lymphatic tissue still remain to be solved.

Project No. 3 (Continued)

18. Expected Results in Fiscal Year 1965 (Continued)

We expect to follow up such leads as we may uncover relative to the site of origin and mode of action of specific humoral agents controlling lymphoid tissue. We also expect to continue to explore various means of inhibiting growth of lymphoid tissue, since the success or failure of homo- and heterologous bone marrow transplantation is dependent upon the functional state of these tissues.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 4
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2. Project Title Metabolic Studies in Human Beings	189 No. 4
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3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963
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5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois
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7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) George V. LeRoy, M.D.	8. Project Term: New Proj. Starting: Continuing:
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9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	5	5	5
(b) Other Tech.	<u>3-1/2</u>	<u>3-1/2</u>	<u>3-1/2</u>
Total	<u>8-1/2</u>	<u>8-1/2</u>	<u>8-1/2</u>

10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	59,600	63,900	66,600
(b) Materials, Services, Subcontracts	6,000	8,000	6,000
(c) Indirect Expenses	132,700	124,100	118,600
(d) Equipment	-	-	-
Total	<u>198,300</u>	<u>196,000</u>	<u>191,200</u>

11. Reactor Concept: None	12. Materials: None
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Schedule 189

Project No. 4

13. Dates and Titles of Publications (Other than Progress Reports)

LeRoy, G. V., J. L. Spratt and G. B. Ho. The Effect of Radiation on Intermediary Metabolism of the Rat. Presented at the Second International Congress on Radiation Research in Harrogate, England, August 7, 1962.

Tocus, E. C., G. T. Okita, J. P. Evans and S. Mullan. The Localization of Octoiodofluorescein-I¹³¹ in Human Brain Tumors. *Cancer*, 15, 153, 1962.

Okita, G. T. and J. L. Spratt. Determination of Radiotracer Stability of Tritium-Labeled Compounds in Biological Studies. In I.A.E.A. publication Tritium in the Physical and Biological Sciences. Volume II, Vienna, pp. 85, 1962.

Ezz, E. A., G. T. Okita and G. V. LeRoy. Metabolic Studies on Spontaneous Carcinogenesis in C3H Mice. In I.A.E.A. Proc. Conf. on the Use of Radioisotopes in Animal Biology and Medical Sciences. Academic Press, Inc., New York. 1963. (In press).

Okita, G. T. and E. A. Ezz. Biochemical Studies on Spontaneous Carcinogenesis: In Vivo Effects of Hormonal Changes on C3H Mice Bearing Hormone-Dependent Mammary Carcinoma. In the Proc. VIIIth Internatl. Cancer Congress. Moscow, 1962. (In press).

14. Scope of Work

The project has 2 objectives: (1) To investigate metabolic disorders in humans using C¹⁴-labeled compounds as tracers, and (2) To investigate the behavior of simulated particulate fallout in human volunteers.

15. Relationship to Other Projects

Part (1) in Section 14 cooperates with several other metabolic studies; and part (2) in Section 14 cooperates with Dr. Hasterlik using the whole-body counter.

16. Technical Progress in Fiscal Year 1963

- 1) Expansion of studies of hyperlipemia, glucose-6-phosphate dehydrogenase deficiency, gout and diabetes mellitus.
- 2) Progress in study of fallout.
- 3) Termination of carcinogenesis program (Okita)

Project No. 4 (Continued)

17. Expected Results in Fiscal Year 1964

- 1) Completion of Dr. Okita's phase of studies of carcinogenesis.
- 2) Further expansion of metabolic studies.
- 3) Completion of fallout studies.

18. Expected Results in Fiscal Year 1965

Continuation of metabolic studies.

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SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 5	
2. Project Title Brain Tumor Detection Research				189 No. 5	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963			
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Donald Charleston Paul V. Harper, M.D. Leon O. Jacobson, M.D.		8. Project Term: New Proj. Starting: Continuing:			
9. Man Years					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		1/2	1/2	1/2	
(b) Other Tech.		1	1	1	
Total		<u>1-1/2</u>	<u>1-1/2</u>	<u>1-1/2</u>	
10. Costs					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		10,800	12,000	12,900	
(b) Materials, Services, Subcontracts		8,000	17,000	19,000	
(c) Indirect Expenses		38,100	50,100	52,100	
(d) Equipment		-	-	-	
Total		<u>56,900</u>	<u>79,100</u>	<u>84,000</u>	
11. Reactor Concept: None		12. Materials: None			

1167864

13. Dates and Titles of Publications (Other than Progress Reports)

Beck, R. N. and D. B. Charleston. A Small Animal Scanning System. Internatl. J. Applied Rad. and Isotopes. 1963. (In press).

Charleston, D. Optimum Design of Scanning Systems. Presented at the Chicago Scanning Symposium at the University of Chicago, Chicago, Illinois, September 28-29, 1962.

Beck, R. N. Methods for Solving a Practical Design Problem for Brain Scanning. Presented at the Chicago Scanning Symposium at the University of Chicago, Chicago, Illinois, September 28-29, 1962.

14. Scope of Work

Work on the ACRH brain scanner for tumor location has been pursued in such a way as to permit optimization and evaluation of each function directly involved in producing basic information data for presentation and analysis. This method indicates that it is feasible to utilize this optimized and undistorted information for accurate quantitative measurements as well as for evaluation by means of computer techniques -- two processes, ignored previously, which could aid diagnostic interpretation directly.

15. Relationship to Other Projects

Paul V. Harper, M.D. 06-09-01 - 11

16. Technical Progress in Fiscal Year 1963

The mechanical construction of the brain scanning system has been completed and tested. Minor modifications and adjustments have been made. The performance is satisfactory in all ways. The unit was disassembled for undercoating, painting, engraving and anodizing. It has been re-assembled and is ready for operation as soon as an internal calibration feature can be incorporated. This unit is finished and awaits installation into the scanning apparatus. The patient cot has been modified and attached to the unit. The electronics system has been tested and installed. The unit is undergoing final test at this time. Three sets of focused collimators have been built and tested and are ready for use.

17. Expected Results in Fiscal Year 1964

Data logging, data manipulation and computer techniques will be utilized in conjunction with all scanning systems in the near future. Preliminary investigations have been made which prove it possible to use scanning information for quantitative evaluations.

Project No. 1 (Continued)

17. Expected Results in Fiscal Year 1964 (Continued)

With proper data logging equipment, it is possible to present the information to a programmed digital computer and extract additional useful information which is not obvious or available from conventional read-out systems.

18. Expected Results in Fiscal Year 1965

Specialized flying-spot scanners will be used to reduce, enhance, and quantitize information from film presentations. Further use for this technique will be found for blood cell counting; isodose plotting; information reduction; evaluation and calibration from films.

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SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 6	
2. Project Title Stem Cell Differentiation and Turnover				189 No. 6	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963			
5. Method of Reporting: Professional Journals and Semi- annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Clifford W. Gurney, M.D.			8. Project Term: New Proj. Starting: Continuing:		
9. Man Years					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		4	4	4	
(b) Other Tech.		<u>4-1/2</u>	<u>4-1/2</u>	<u>4-1/2</u>	
Total		<u>8-1/2</u>	<u>8-1/2</u>	<u>8-1/2</u>	
10. Costs					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		48,800	52,400	56,000	
(b) Materials, Services, Subcontracts		3,200	3,500	4,500	
(c) Indirect Expenses		105,200	96,400	98,800	
(d) Equipment		-	-	-	
Total		<u>157,200</u>	<u>152,300</u>	<u>159,300</u>	
11. Reactor Concept: None		12. Materials: None			

1167867

13. Dates and Titles of Publications (Other than Progress Reports)

DeGowin, R., D. Hofstra and C. W. Gurney. The Mouse with Hypoxia-Induced Erythremia, An Erythropoietin Bioassay Animal. *J. Lab. Clin. Med.*, 60, 846, 1962.

DeGowin, R., D. Hofstra and C. W. Gurney. A Comparison of Erythropoietin Bioassays. *Proc. Soc. Exp. Biol. Med.*, 110, 48, 1962.

Gurney, C. W., R. DeGowin, D. Hofstra and J. Byron. Applications of Erythropoietin to Biological Investigation. In Jacobson, L. O. and M. Doyle, eds. Erythropoiesis. Grune and Stratton, New York, pp. 151, 1962.

Gurney, C. W. Effect of Radiation on the Mouse Stem Cell Compartment In Vivo. *Perspectives in Biology and Medicine*. 1963. (In press).

Gurney, C. W. and D. Hofstra. Assessment of Actinomycin and Radiation Damage of Stem Cells by the Erythropoietin Tolerance Test. *Rad. Res.* 1963. (In press).

Gurney, C. W. Erythropoietin Tolerance Test: A Measure of Stem Cell Integrity (Abstract). *J. Lab. Clin. Med.*, 60, 880, 1962.

Marver, H. and D. Hofstra. The Contributions of Erythropoiesis to Porphyrin Excretion (Abstract). *Proc. Am. Fed. Clin. Res.* 1963. (In press).

Gurney, C. W. Dynamics of the Stem Cell Compartment. In I.A.E.A. Proc. Conf. on the Use of Radioisotopes in Animal Biology and Medical Sciences. Academic Press, Inc., New York. 1963. (In press).

Gurney, C. W. The Effect of Radiation on the Mouse Stem Cell Compartment In Vivo. Presented at the Second International Congress on Radiation Research in Harrogate, England, August, 1962.

Lajtha, L. G., R. Oliver and C. W. Gurney. Kinetic Model of a Bone-Marrow Stem-Cell Population. *Brit. J. Haematol.*, 8, 442, 1962.

Gurney, C. W., L. G. Lajtha and R. Oliver. A Method for Investigation of Stem-Cell Kinetics. *Brit. J. Haematol.*, 8, 461, 1962.

14. Scope of Work

The work continues to be concerned with the proliferative potential and the mechanism of homeostasis of the stem cell "compartment". By observing the damaging effects of radiation and chemotherapeutic agents, and rates of recovery from damage, we are able to develop hypotheses accounting for the regulation of normal growth of stem cells and the similarity or difference of action of various chemotherapeutic and radiation effects.

Project No. 6 (Continued)

15. Relationship to Other Projects

Eugene Goldwasser, Ph.D.	06-09-01	-	1 and 7
Leon O. Jacobson, M.D.	06-09-01	-	3
Eric L. Simmons, Ph.D.	06-09-01	-	12

16. Technical Progress in Fiscal Year 1963

During this year we have extended our observations on the sensitivity of the stem cell to chemotherapeutic agents - nitrogen mustard, Actinomycin, bacterial polysaccharide, and colchicine - alone and in conjunction with irradiation, and we have determined the patterns of recovery of the stem cell compartment in a few instances following single chemotherapeutic damage. We have continued our studies on the mechanism of production of plethora by hypoxia and have adapted these animals to the study of stem cell damage and recovery.

17. Expected Results in Fiscal Year 1964

During this year we will expand our observations on recovery of the stem cell compartment from damage by combined chemotherapy and irradiation. We also plan to study and obtain quantitative data on the duration and severity of stimulus required for the elaboration of the erythropoietic factor in rodents.

18. Expected Results in Fiscal Year 1965

We anticipate continuing our observations on stem cell proliferation following differentiation or destruction. As yet, very little is known about this important class of cells. The data we are obtaining and will continue to obtain for several years, will enable us to create a model accounting for the regulation of stem cell proliferation. Such a model can increasingly be based on experimental observations rather than guess or hypothesis.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 7	
2. Project Title Study of Biological Activity of Nucleic Acids				189 No. 7	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963			
5. Method of Reporting: Professional Journals and Semi- annual Report to the Atomic Energy Commission		6. Working Location: Chicago, Illinois			
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Eugene Goldwasser, Ph.D.		8. Project Term: New Proj. Starting: Continuing:			
9. Man Years					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		2	2	2	
(b) Other Tech.		<u>1-1/2</u>	<u>1-1/2</u>	<u>1-1/2</u>	
Total		<u>3-1/2</u>	<u>3-1/2</u>	<u>3-1/2</u>	
10. Costs					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		27,000	29,900	29,900	
(b) Materials, Services, Subcontracts		6,000	6,000	7,000	
(c) Indirect Expenses		66,700	61,900	60,300	
(d) Equipment		-	-	-	
Total		<u>99,700</u>	<u>97,800</u>	<u>97,200</u>	
11. Reactor Concept: None		12. Materials: None			

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Schedule 189

Project No. 7

13. Dates and Titles of Publications (Other than Progress Reports)

Heinrickson, R. L. and E. Goldwasser. The Enzymatic Synthesis of 5-Ribosyluridylic Acid. J. Biol. Chem., 238, PC485, 1963.

14. Scope of Work

The process of RNA formation in differentiated cells, in particular the cytoplasmic portion of such cells, may be related to the mechanism of cell differentiation and is being studied from this aspect.

15. Relationship to Other Projects

Samuel B. Weiss, Ph.D. 06-09-01 - 15

16. Technical Progress in Fiscal Year 1963

We have developed a method of studying the incorporation of isotopic precursors into cytoplasmic RNA (microsomal) which has removed any ambiguity resulting from the phenomenon of nucleotide binding. We have worked out the enzymatic pathway for the formation of 5-ribosyluridylic acid which is a precursor of that RNA which is specific for the transfer of amino acids to the protein-forming mechanism.

17. Expected Results in Fiscal Year 1964

We expect to be able to study the synthesis of amino acid transfer RNA by the cytoplasmic system and to pursue the study of RNA directed syntheses of specific ribonucleic acids.

18. Expected Results in Fiscal Year 1965

The relationship of cytoplasmic RNA synthesis to the specific formation of differentiated cell types will be studied, with the anticipation of a deeper understanding of cellular specificity.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 9
2. Project Title a) Purine Metabolism in Human Beings b) Metabolism of Trace Metals			189 No. 8	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission		6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Lief B. Sørensen, M.D., Ph.D.		8. Project Term: New Proj. Starting: Continuing:		
9. Man Years				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific		2	2	2
(b) Other Tech.		1	1	1
Total		<u>3</u>	<u>3</u>	<u>3</u>
10. Costs				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries		20,900	23,300	25,800
(b) Materials, Services, Subcontracts		2,000	5,500	6,500
(c) Indirect Expenses		46,300	49,700	52,800
(d) Equipment		-	-	-
Total		<u>69,200</u>	<u>78,500</u>	<u>85,100</u>
11. Reactor Concept: None		12. Materials: None		

1167872

Schedule 189

Project No. 9

13. Dates and Titles of Publications (Other than Progress Reports)

Sorensen, L. B. Specific Uptake of Molybdenum by the Liver (Abstract).
J. Lab. Clin. Med., 60, 1020, 1962.

Sorensen, L. B. Current Concepts of Gout and its Treatment. Med.
Clin. N. Am., 47, 169, 1963.

Sorensen, L. B. The Contribution of Radioisotope Scanning to the
Diagnosis of Liver Disease. Accepted for publication in Biochem. Clinics,
Vol. 1, International Symposium on Liver Diseases, 1963.

Sorensen, L. B. Mo⁹⁹, A New Isotope for Scintillation Scanning of
the Liver. To be published as an abstract in Gastroenterology and to be
presented at the Annual Meeting of the Am. Gastroenterological Association,
San Francisco, May 30 - June 1, 1963.

Sorensen, L. B. and M. Archambault. Visualization of the Liver by
Scanning using Mo⁹⁹ (Molybdate) as Tracer. Submitted for publication to
J. Lab. Clin. Med. 1963.

14. Scope of Work

1) Purine metabolism in normal subjects and in patients with gout,
xanthinuria and hematologic disorders have been studied using C¹⁴-labeled
materials, such as precursors of the purine ring, uric acid and nucleo-
tides.

2) The metabolism of molybdenum in man, the indispensability of this
trace metal (being an integrated part of the xanthine oxidase molecule),
and the use of Mo⁹⁹ as a tracer in scintillation scanning of the liver, have
been outlined.

15. Relationship to Other Projects

None

16. Technical Progress in Fiscal Year 1963

1) More than 150 hepatoscans have been performed in patients with a
variety of liver diseases using Mo⁹⁹ as tracer. The resolution obtained
with this isotope is superior to that of Au¹⁹⁸ and I¹³¹. The intracellular
localizations of molybdenum and xanthine oxidase in rat liver have been
determined by radioautographic and ultracentrifugal techniques. Injected
Mo⁹⁹ was incorporated as a non-dialyzable component of the xanthine oxi-
dase molecule.

1167873

16. Technical Progress in Fiscal Year 1963 (Continued)

2) Studies on purine metabolism continue. Interest at present is concentrated on the immediate precursors of uric acid, hypoxanthine and xanthine and the rare metabolic disorder, xanthinuria. Chromatographic separation of purines, ribosides and ribotides from urine and the particular patterns of excretions of these compounds in metabolic disorders and leukemia are being studied.

17. Expected Results in Fiscal Year 1964

1) Work on metabolism of molybdenum in man will continue and should be terminated by the end of Fiscal Year 1964. Comparative resolution of hepatoscans done with I¹³¹-labeled rose bengal and Mo⁹⁹ are under way. Work will start on the interrelationship of copper, molybdenum and tungsten (experimental molybdenum deficiency and molybdenosis). Work on purine metabolism will continue; it is hoped that metabolic studies using C¹⁴-labeled inosinic acid and other labeled nucleotides can be started in Fiscal Year 1964.

18. Expected Results in Fiscal Year 1965

Work along the same lines as outlined in Section 17 will be extended.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 11	
2. Project Title Clinical Application of Radioisotopes in Diagnosis and Treatment					189 No. 9
3. Budget Activity No. 06-09-01			4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Paul V. Harper, M.D.			8. Project Term: New Proj. Starting: Continuing:		
9. Man Years					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		3-1/2	3-1/2	3-1/2	
(b) Other Tech.		3	4	4	
Total		<u>6-1/2</u>	<u>7-1/2</u>	<u>7-1/2</u>	
10. Costs					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		44,000	50,800	53,800	
(b) Materials, Services, Subcontracts		4,000	5,000	6,000	
(c) Indirect Expenses		97,100	96,300	97,700	
(d) Equipment		-	-	-	
Total		<u>145,100</u>	<u>152,100</u>	<u>157,500</u>	
11. Reactor Concept: None		12. Materials: None			

1167875

Schedule 189

Project No. 11

13. Dates and Titles of Publications (Other than Progress Reports)

Endlich, H., P. V. Harper, R. Beck, W. Siemens and K. Lathrop. The Use of I¹²⁵ to Increase Isotope Scanning Resolution. Am. J. Roentgenol., Radium Therapy and Nucl. Med., 87, 148, 1962.

Fitch, F., J. Winebright and P. V. Harper. Iodine-125 as a Protein Label in Immunology. Science, 135, 1068, 1962.

Harper, P. V., G. Andros, K. Lathrop, W. Siemens and L. Weiss. Metabolism of Technetium-99m. Rad. Res., 16, No. 4, 1962.

Newell, F. W., S. Goren, H. Brizel and P. V. Harper. The Use of Iodine-125 as a Diagnostic Agent in Ophthalmology. Trans. Am. Acad. Ophthal. and Otolaryn., 66, 543, 1962.

Harper, P. V., G. Andros, K. Lathrop, W. Siemens and L. Weiss. Preliminary Observations on the Use of the Six-Hour Technetium 99m as a Biological Tracer. Presented at the Society of Nuclear Medicine meetings in Dallas, Texas, June, 1962 and published in Abstracts of meeting.

14. Scope of Work

Our use of radioisotopes as interstitial sources of radiation in the treatment of malignant tumors continues, special emphasis being placed on surgical application, which includes consideration of such features as ease of handling, ease of shielding, cost of preparation and availability. Those isotopes emitting soft x rays appear to be particularly useful.

Our interest in special diagnostic applications of radioisotopes emitting low energy gamma or x rays has been stimulated by the studies of Mr. Beck of our Electronics Group in the design of detection systems from this and other types of radiation.

Methods of localization, immunologic and metabolic, and advanced techniques of detection give promise of substantial advances in the field of tumor detection.

15. Relationship to Other Projects

Donald Charleston 06-09-01 - 5
Robert Beck
Leon O. Jacobson, M.D.

1167876

16. Technical Progress in Fiscal Year 1963

Studies with Y^{90} pellets, sealed applicators and Pd^{103} have continued as patients present themselves. In addition, the feasibility studies using a 50 mc Sr^{90} - Y^{90} applicator as a substitute for the Y^{90} implant in destruction of the hypophysis have been undertaken with a view to reducing complications. This same applicator has been spectacularly successful in the hands of the neurosurgical group in producing restricted destructive lesions of the central nervous system particularly for control of pain. I^{125} has proven to have a substantial but somewhat restricted usefulness. Eye tumor localization with I^{125} diiodofluorescein has been most successful. The use of Tc^{99m} as pertechnetate for thyroid scanning is feasible with a 1000-fold reduction of dose to the gland, and liver scanning with technetium thiocyanate permits greatly increased isotope dosage and consequent reduction in collimator aperture and increased resolution. Cardiac output measurements with this material are very promising. Tumor localization with tagged anti-fibrinogen confirms earlier conclusions of Bale and Spar.

17. Expected Results in Fiscal Year 1964

The new scanning system (Project 5) is on the point of becoming operational, so that there should be considerable stimulus to the related projects in exploration of various tagged compounds as scanning agents. The work with the cardiovascular surgical group on cardiac output measurement and other diagnostic studies using external counting is being pursued from the point of view of better isotopes, better detectors, better analytical electronics and computer analysis of results. The Oak Ridge group is investigating improved methods of rough processing cyclotron targets which should increase the availability and usefulness of Pd^{103} .

18. Expected Results in Fiscal Year 1965

In addition to the current projects, it is anticipated that the linear accelerator will, with its new electron gun (which should increase the average beam current by a large factor (100 or 1000)), become a significant source of short-lived radioisotopes such as Oxygen-15, or Iodine-123 and many others which will open new avenues of investigation.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 12	
2. Project Title Radiobiologic Studies on Tumor Transplantation and Immune Processes		189 No. 10	
3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Eric L. Simmons, Ph.D.	8. Project Term: New Proj. Starting: Continuing:		
9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	2	2	2
(b) Other Tech.	1	1	1
Total	<u>3</u>	<u>3</u>	<u>3</u>
10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	23,800	25,300	26,900
(b) Materials, Services, Subcontracts	1,000	1,000	2,000
(c) Indirect Expenses	50,100	45,300	47,100
(d) Equipment	-	-	-
Total	<u>74,900</u>	<u>71,600</u>	<u>76,000</u>
11. Reactor Concept: None	12. Materials: None		

1167878

13. Dates and Titles of Publications (Other than Progress Reports)

Thompson, J. S., E. L. Simmons and D. Hofstra. Studies on the Immunologic Unresponsiveness During the Secondary Disease Period of Lethally Irradiated Mice Protected by Homologous Bone Marrow. *J. Immunol.*, 89, 62, 1962.

Simmons, E. L., J. S. Thompson and J. M. Randi. Reduction in Secondary Disease by Injection of Homologous Lymphoid Cells (Abstract). *Rad. Res.*, 16, 569, 1962.

Simmons, E. L. and O. Lartigue. Protective Effect of AET (S, 2-aminoethylisothiuronium) on the Immune Mechanism of X-irradiated Mice. *Proc. Conf. on Modification of Radiation Injury by Bone Marrow Transplantation and Chemical Protection. Ann. N. Y. Acad. Sci.* 1963. (In press).

14. Scope of Work

The experimental study of the basic changes which result when hematopoietic cells are injected for post-irradiation therapy, or when blood-forming tissues are shielded, is of continuing importance from the practical viewpoint of protection against lethal radiation, as well as making possible the medical usage of higher dosages of radiation for treating existing leukemias or metastasized tumors. The changes in the immune response offer an excellent tool for investigating tumor sensitivity and rejection, transplantation mechanism, and factors affecting growth, migration, and differentiation of cells. The effective use of radiation in killing tumor cells within the body could be greatly enhanced by chemicals 1) that could protect surrounding tissues but not tumor cells, or 2) that would potentiate the action of ionizing radiation on cancer cells. It is important to explore the basic radiobiologic action of such experimental drugs when combined with irradiation on normal as well as tumor tissues.

15. Relationship to Other Projects

Leon O. Jacobson, M.D.	06-09-01	-	3
Melvin L. Griem, M.D.	06-09-01	-	19
Lawrence H. Lanzl, Ph.D.	06-09-01	-	23

16. Technical Progress in Fiscal Year 1963

The ability to protect CF No. 1 female mice against high energy (30 MeV) electrons from the linear accelerator by pre-irradiation injection of S,2-aminoethylisothiuronium (AET) and of p-aminopropiophenone (PAPP) has been compared with the effects in mice irradiated with 250 KvP x rays. This investigation has relevance to at least three significant radio-protective problems. These are; first, the extent to which a selected agent can modify the response of a biological system to high energy

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16. Technical Progress in Fiscal Year 1963 (Continued)

electrons (which is also of interest in space medicine); second, the relative effectiveness of two different types of radioprotective agents in modifying the response of a biological system to this type of radiation; the third, the relative effectiveness of one type of radioprotective agent compared in systems exposed to two different types of radiations -- electrons and x rays. Our experiments indicate that pre-irradiation treatments with AET or with PAPP are able to reduce 30-day lethality in mice exposed to high energy electrons.

CF No. 1 mice are normally resistant to lymphatic leukemia of the DBA/2 mouse, but will succumb if weakened with low doses of x rays. In earlier experiments we found that pretreatment with AET intraperitoneally before dosages from 300 r to 900 r enhanced the ability of the immune mechanism to reject successfully the transplantation of leukemoid cells. Subsequent experiments have explored the effectiveness of AET when administered orally, using thiolated gelatin as the vehicle. When AET was given intraperitoneally, the dose reduction factor (DRF) was 1.7, while protection of the intestine only by oral administration resulted in a DRF of 1.2; with both modes of administration the DRF for leukemic deaths were comparable to the DRF obtained from mortality curves of AET-protected mice not challenged with leukemia. Subsequent experiments will determine whether AET can protect a single lymphoid nodule such as a patch of Peyer, and elevate the dose of 650 r that is necessary to abolish its immune response.

17. Expected Results in Fiscal Year 1964

Supralethally irradiated (950 r) mice die by the 12th day, and even if acute death is prevented by injections of homologous bone marrow, such mice may succumb between the 30th and 120th days of a secondary wasting disorder. However, when a single patch of Peyer is protected while the remainder of the mouse is x irradiated, and injections of homologous or heterologous bone marrow are given, an extremely rapid 5- to 6-day death pattern results. The respective role of host and of graft will be explored, and experiments with killed foreign bone marrow cells (sonicated or x irradiated) as well as with non-murine antigens such as *S. typhi* vaccine and sheep RBC will attempt to determine the nature of the immunologic interaction involved. Using the Peyer's patch test system, we will attempt to clarify whether the proliferating cells are capable of responding to particulate and soluble antigens. The ability of the lymphoid system to recognize and reject embryonic cells and also bone marrow from closely related genetic strains belonging to the same histocompatibility group will be determined.

Investigation of the radiobiologic action of experimental drugs when combined with irradiation on normal as well as tumor tissues will be continued in order to clarify their mode of action.

18. Expected Results in Fiscal Year 1965

Investigation of the ability of pure electrons from the linear accelerator to control experimental tumors, and possible enhancement of such treatment by combination with chemicals, will await the present screening of such drugs with x irradiation. The shielding of specific blood-forming tissues during irradiation, with ensuing seeding from the site, as well as the injection of cell preparations to totally-irradiated hosts, will continue to provide excellent research tools for exploring the specificity of cell development, ensuing tissue differentiation, and the immunologic changes that follow irradiation. This approach will continue to provide basic answers that will contribute to our understanding of the mechanics of transplantation, secondary irradiation disease, and tumor immunity.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 13	
2. Project Title Therapeutic Application of High Energy Sources					189 No. 11
3. Budget Activity No. 06-09-01			4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) James W. J. Carpenter, M.D.			8. Project Term: New Proj. Starting: Continuing:		
9. Man Years					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		2	2	2	
(b) Other Tech.		2	2	2	
Total		<u>4</u>	<u>4</u>	<u>4</u>	
10. Costs					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		29,900	31,600	35,400	
(b) Materials, Services, Subcontracts		4,000	8,000	9,000	
(c) Indirect Expenses		68,600	68,300	72,600	
(d) Equipment		-	-	-	
Total		<u>102,500</u>	<u>107,900</u>	<u>117,000</u>	
11. Reactor Concept: None		12. Materials: None			

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13. Dates and Titles of Publications (Other than Progress Reports)

Lanzl, L. H. and J. W. J. Carpender. Adapted and expanded, Moving Field Radiation Therapy, by Wachsmann, F. and G. Barth, Chicago. The University of Chicago Press, 1962.

Carpender, J. W. J. Moderator of Panel Discussion on Supervoltage at the American Radium Society, New York City, April 2-4, 1962.

Carpender, J. W. J. Head and Neck Cancer. Submitted for presentation at the Muncie Academy of Medicine, Muncie, Indiana, April 10, 1962.

Carpender, J. W. J. Head and Neck Cancer. Submitted for presentation at the May Day Clinic, St. Anthony Hospital, Rockford, Illinois, May 9, 1962.

Carpender, J. W. J., L. S. Skaggs, L. H. Lanzl and M. L. Griem. Radiation Therapy with High-Energy Electrons Using Pencil Beam Scanning. Am. J. Roentgenol., Radium Therapy and Nucl. Med. 1963. (In press).

14. Scope of Work

An increasing variety of patients has been treated on supervoltage machines. In cooperation with the Ear, Nose and Throat Service, a randomly selected group of patients, which includes examples of most tumors of the head and neck is being treated by radiation alone, preoperative radiation, and postoperative radiation, the objective of the study being to estimate the validity of these methods of treatment.

15. Relationship to Other Projects

Eric L. Simmons, Ph.D.	06-09-01	-	12
Lester S. Skaggs, Ph.D.	06-09-01	-	14
Melvin L. Griem, M.D.	06-09-01	-	19
Lawrence H. Lanzl, Ph.D.	06-09-01	-	23

16. Technical Progress in Fiscal Year 1963

It is hoped that the installation of the new klystrons for the linear accelerator will allow treatment at higher energy levels. Preoperative therapy of carcinoma of the esophagus has been added to the preoperative lung cancer study.

Project No. 13 (Continued)

17. Expected Results in Fiscal Year 1964

We shall continue to make a comparison of patients treated in the past with 250 Kv with those treated by means of supervoltage, with a view to establishing the relative values of these methods of therapy.

18. Expected Results in Fiscal Year 1965

It is hoped that by this time the comparative studies will show whether or not there is any advantage in preoperative radiation.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 14	
2. Project Title High Energy Sources - Development and Operation				189 No. 12	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963			
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Lester S. Skaggs, Ph.D.			8. Project Term: New Proj. Starting: Continuing:		
9. Man Years					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		1-1/2	1-1/2	1-1/2	
(b) Other Tech.		4-1/2	5	5	
Total		<u>6</u>	<u>6-1/2</u>	<u>6-1/2</u>	
10. Costs					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		39,800	45,200	55,000	
(b) Materials, Services, Subcontracts		45,000	30,000	30,000	
(c) Indirect Expenses		171,600	129,600	138,900	
(d) Equipment		-	-	-	
Total		<u>256,400</u>	<u>204,800</u>	<u>223,900</u>	
11. Reactor Concept: None		12. Materials: None			

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13. Dates and Titles of Publications (Other than Progress Reports)

Carpender, J. W. J., L. S. Skaggs, L. H. Ianzl and M. L. Griem.
Radiation Therapy with High Energy Electrons using Pencil Beam Scanning.
Am. J. Roentgenol., Radium Therapy and Nucl. Med., 1963. (In press).

Skaggs, L. S. and S. Savic. Use of an Analog Computer to Calculate
Treatment Dose for Multiple Fields (Abstract). Radiology, 80, 116, 1963.

14. Scope of Work

To provide radiation facilities from the 2-MeV Van de Graaff,
cobalt-60 therapy machine, and 50-MeV linear accelerator for the treatment
of malignant disease; and for studies in radiobiology and dosimetry.

15. Relationship to Other Projects

Eric L. Simmons, Ph.D.	06-09-01	-	12
J. W. J. Carpender, M.D.	06-09-01	-	13
Melvin L. Griem, M.D.	06-09-01	-	19
L. H. Ianzl, Ph.D.	06-09-01	-	23

16. Technical Progress in Fiscal Year 1963

Efforts have been continued to improve the stability and reliability
of operation of the high energy sources. The Van de Graaff continues to
show the high reliability resulting from the change to a sealed tube and a
servo controlled filament. The last tube installed is still operating at
200 hours beyond the warranty period of 1000 hours. A new ion chamber has
been added to the machine and minor modifications made to the charging
system inside the tank.

New thyratrons of higher voltage rating have been installed in the
linear accelerator. These make it possible to achieve full energy output
with two tubes in series and eliminate some of the problems that would re-
sult from having to operate three of the old thyratrons in series. A new
beam energy monitor and new klystron power output meters have been
developed and installed. A new stabilized D.C. power source has been in-
stalled to supply the beam deflecting magnets. Additions have also been
made to the dose monitoring system. These materially aid the operator in
maintaining more stable output during operation.

Two new klystrons have been obtained from Stanford University and both
are being installed. An attempt was made to obtain commercial klystrons
but it appears that tubes of proven reliability and reasonable cost are
still about two years in the future. Since the old klystrons will certainly
not last that long, it was necessary to return to Stanford for the old type
of tube. Several improvements have been made, however, such as all-metal

Project No. 14 (Continued)

16. Technical Progress in Fiscal Year 1963 (Continued)

gaskets and ion pumping systems. A new dummy microwave load has been procured which will permit klystrons to be completely processed and tested before installation on the accelerator. This will decrease the time required for change over to a new tube.

A new high current injector has been procured and preparations are under way for its installation.

A small analog computer was set up to study this method of dose calculation and treatment planning. While its capability was limited to two beams of radiation, it adequately demonstrated the value of the system and showed it to be more flexible and adaptable than had been anticipated. An almost infinite variety of beams of various sizes, shapes and angles of incidence are easily simulated and are combined in any amount or orientation with respect to the patient's body.

A new localizing device was developed and applied to the linear accelerator to improve the accuracy of setting up patients for therapy.

17. Expected Results in Fiscal Year 1964

The installation of the high current injector should be completed during the year, and the production of short-lived isotopes started. A feasibility study will also be started on the production of 20-40 MeV x rays for therapy.

A large general purpose analog computer will become available and will be used to compute up to 4 different beams of radiation. Greater flexibility and accuracy in simulating the actual conditions of radiation therapy is expected. An attempt will also be made to use the computer to calculate and plan radiation treatment using the rotating beam of the cobalt-60 machine.

A method of accurately projecting an anatomical cross section of the body from the collection in Eycleshymer and Schoemaker - "A Cross-Section Anatomy" will be sought. It is desired that elliptical (i.e., non-uniform) magnification of the sections be made so that they can be fitted to the lateral and anterior-posterior dimensions of the patient determined clinically. The projected cross sections will then be used to more accurately locate the tumor area with respect to recognizable anatomical features.

Installation of a very stable source of radiofrequency on the linear accelerator is proposed. This would use newly developed techniques now commercially available and would improve the energy stability of the machine.

Project No. 14 (Continued)

18. Expected Results in Fiscal Year 1965

Further improvements in reliability, stability, accuracy of dosimetry and accuracy in treatment planning and patient positioning are expected for all the high energy machines. Efforts will be directed toward production of an x ray beam from the linear accelerator if preliminary studies are encouraging. The cobalt-60 source will be replaced by a newly irradiated source to return the radiation output to the design maximum.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 15
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2. Project Title The Biosynthesis of Ribonucleic Acid	189 No. 13
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3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963
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5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois
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7. Person in Charge: Dr. L. O. Jacobsón Principal Investigator(s) Samuel B. Weiss, Ph.D.	8. Project Term: New Proj. Starting: Continuing:
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9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	5-1/2	6	6
(b) Other Tech.	2	2	2
Total	<u>7-1/2</u>	<u>8</u>	<u>8</u>

10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	43,800	61,300	67,600
(b) Materials, Services, Subcontracts	8,000	8,000	9,000
(c) Indirect Expenses	104,800	119,500	125,200
(d) Equipment	-	-	-
Total	<u>156,600</u>	<u>188,800</u>	<u>201,800</u>

11. Reactor Concept: None	12. Materials: None
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13. Dates and Titles of Publications (Other than Progress Reports)

Weiss, S. B. Biosynthesis of Ribopolynucleotides. Federation Proc. 21, 120, 1962.

Nakamoto, T. and S. B. Weiss. The Biosynthesis of RNA: Priming by Polyribonucleotides. Proc. Natl. Acad. Sci., 48, 880, 1962.

Geiduschek, E. P., J. W. Moohr and S. B. Weiss. The Secondary Structure of Complementary RNA. Proc. Natl. Acad. Sci., 48, 1078, 1962.

14. Scope of Work

We are continuing with our studies on the properties of RNA polymerase and the mechanism of how RNA molecules are assembled by this enzyme. We are primarily concerned with the in vitro synthesis of RNA molecules that may have biological activity in other systems.

15. Relationship to Other Projects

None

16. Technical Progress in Fiscal Year 1963

1. More extensive purification of RNA polymerase.
2. Evidence that in vitro both strands of DNA serve as templates for RNA synthesis.
3. The demonstration that double stranded RNA can be formed from the enzymatically prepared RNA.
4. The demonstration that RNA polymerase will synthesize RNA not only with DNA primers but with RNA primers as well.
5. The demonstration that the RNA molecules prepared with RNA polymerase are complementary in base composition to the RNA primers used.

17. Expected Results in Fiscal Year 1964

We hope to gain insight into how certain specific RNA molecules, such as "transfer" RNA, is made and to determine the specific nature of the RNA products formed with DNA primers.

18. Expected Results in Fiscal Year 1965

The research program outlined in Sections 14 and 17 will be continued.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 16
2. Project Title Total-Body Counting Facility		189 No. 14
3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963	
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois	
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Robert J. Hasterlik, M.D.	8. Project Term: New Proj. Starting: Continuing:	

9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	1-1/2	1-1/2	1-1/2
(b) Other Tech.	5	5	5
Total	<u>6-1/2</u>	<u>6-1/2</u>	<u>6-1/2</u>

10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	26,500	46,900	49,900
(b) Materials, Services, Subcontracts	6,100	13,000	14,000
(c) Indirect Expenses	66,100	103,400	104,400
(d) Equipment	-	-	-
Total	<u>98,800</u>	<u>163,300</u>	<u>168,300</u>

11. Reactor Concept:
None

12. Materials:
None

1167891

Schedule 189

Project No. 16

13. Dates and Titles of Publications (Other than Progress Reports)

Hasterlik, R. J., C. E. Miller and A. J. Finkel. Carcinoma of the Mastoid and Paranasal Sinuses in Radium-Bearing Patients. In the Proc. VIIIth Internatl. Cancer Congress. Moscow, 1962. (In press).

Hasterlik, R. J., A. J. Finkel and C. E. Miller. The Late Effects of Radium Deposition in Man. Presented at the Second International Congress on Radiation Research in Harrogate, England, August, 1962.

14. Scope of Work

This facility, designed for metabolic studies in the human, is being used for the study of the transport and absorption of simulated and actual fission products, as well as for studies on the metabolism of Ra^{226} , Sr^{85} , Ca^{47} , I^{131} , Mo^{99} and Mg^{28} in man.

The four crystal array makes possible variations in crystal arrangement necessitated by levels of isotope used, localization of isotope in patient, and other geometric considerations. The University of Chicago 7090 Computer has been programmed and yields information concerning optimization of counts with various crystal arrays with the aforementioned geometric variables.

15. Relationship to Other Projects

The human Ra study project is carried on in close cooperation with the ANL project. Intercalibration of this facility for I^{131} counting will be carried out with other U. S. facilities.

16. Technical Progress in Fiscal Year 1963

Studies on the transport and absorption of simulated fission products have been carried out on 30 persons. Studies on the metabolism of Ca^{47} have been completed on approximately 10 persons. The total-body facility has been used to determine the turn-over time of Mo^{99} in the normal adult and studies are now being extended to those with hepatocellular disease and carcinoma metastasis to the liver.

Project No. 16 (Continued)

17. Expected Results in Fiscal Year 1964

The work on fission products, Ra, Mo, Ca, Sr, I, and Mg metabolism will continue. Experiments will be carried out with discrete sources at varying positions in phantoms in order to solve the problem of Compton scattering in relation to size of person counted, location of isotopes, and in the presence of two or more radioisotopes. The Division of Biological Sciences Computer Facilities will be used in the solution of these problems. This problem should be solved in Fiscal Year 1964.

18. Expected Results in Fiscal Year 1965

Attention will be directed to metabolic studies of other isotopes not available for use at present because of the present deficiencies connected to problems of scattering.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 18	
2. Project Title Steroid Studies in Man				189 No. 15	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963			
5. Method of Reporting: Professional Journals and Semi- annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Attallah Kappas, M.D.		8. Project Term: New Proj. Starting: Continuing:			
9. Man Years		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		4-1/2	5-1/2	7-1/2	
(b) Other Tech.		1	1	1	
Total		<u>5-1/2</u>	<u>6-1/2</u>	<u>8-1/2</u>	
10. Costs		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		25,600	58,500	80,800	
(b) Materials, Services, Subcontracts		4,000	6,000	8,000	
(c) Indirect Expenses		59,900	111,300	145,000	
(d) Equipment		-	-	-	
Total		<u>89,500</u>	<u>175,800</u>	<u>233,800</u>	
11. Reactor Concept: None		12. Materials: None			

1167894

13. Dates and Titles of Publications (Other than Progress Reports)

Lazar, A. W., R. L. Landau and A. Kappas. Metastatic Carcinoma of Parathyroid and Persistent Hyperparathyroidism. Arch. Pathol., 72, 484, 1961.

Angevine, J. M., A. Kappas, R. L. DeGowin and B. Spargo. Renal Tubular Inclusions of Lead Poisoning. Arch. Pathol., 73, 486, 1962.

Jones, H. E. H., A. Kappas and I. M. Roitt. The Effect of Endocrine Factors on the Production of Experimental Allergic Thyroiditis. Acta Endocrinol., 40, 63, 1962.

Palmer, R. H., P. B. Glickman and A. Kappas. Pyrogenic and Inflammatory Properties of Certain Bile Acids in Man. J. Clin. Invest., 41, 1573, 1962.

Palmer, R. H. and A. Kappas. Fever-Producing Action of Steroids. Med. Clin. N. Am., 47, 101, 1963.

14. Scope of Work

Studies on steroid pharmacology continue as follows: 1) studies on mechanism of hemolysis and calorigenesis of steroid pyrogens, 2) studies on immuno-suppression in man and experimental animals by estrogenic hormones, 3) use of estrogen in therapy of connective tissue diseases of the immune type, 4) therapeutic use of intensive estrogen therapy in diseases characterized by lymphoid cell hyperplasia and 6) metabolic studies with massive estrogen administration in man.

15. Relationship to Other Projects

None

16. Technical Progress in Fiscal Year 1963

The immuno-suppressive effect of sex steroids has been examined and demonstrated in 3 immune contexts: 1) tubercular sensitivity, 2) auto-immune thyroiditis, 3) adjuvant arthritis in man. Clinical counterparts of the latter studies are being carried out in patients.

17. Expected Results in Fiscal Year 1964

It is expected that facilities for full metabolic studies in our laboratories will be established before or in 1964; studies on steroid hemolyses will be completed; as will preliminary studies on the therapeutic use of intensive sex hormone therapy in rheumatoid arthritis and chronic lymphatic leukemia.

Project No. 18 (Continued)

18. Expected Results in Fiscal Year 1965

1. The studies of the group in general steroid pharmacology will be expanded as will clinical and metabolic studies related to our steroid pharmacology work. It is hoped that these studies will provide a useful new therapeutic approach to auto-immune disease as well as malignant disease of the lymphoid system. The group will expand to four physicians and will require increased laboratory space, the services of a full time Ph.D. chemist and four technicians.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 19
2. Project Title Potentiation of Radiation Effect with Modifiers				189 No. 16
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission		6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Melvin L. Griem, M.D. Klaus Ranniger, M.D. Fred Malkinson, M.D. Harold G. Sutton, M.D.		8. Project Term: New Proj. Starting: Continuing:		
9. Man Years				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific		2-1/2	2-1/2	2-1/2
(b) Other Tech.		1	1	1
Total		<u>3-1/2</u>	<u>3-1/2</u>	<u>3-1/2</u>
10. Costs				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries		29,400	32,600	35,800
(b) Materials, Services, Subcontracts		2,000	5,000	6,500
(c) Indirect Expenses		63,500	64,800	69,200
(d) Equipment		-	-	-
Total		<u>94,900</u>	<u>102,400</u>	<u>111,500</u>
11. Reactor Concept: None		12. Materials: None		

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13. Dates and Titles of Publications (Other than Progress Reports)

Griem, M. L. and K. Ranniger. Modification of the Radiation Effect on Hair Roots of the Mouse by Actinomycin. Rad. Res., 17, 92, 1962.

Jefferson, E. H., A. C. Kienzle and M. L. Griem. Microwave Heating as an Adjunct in the Experimental Control of Tumors in Mice (Abstract). Rad. Res., 16, 1962.

Griem, M. L. and F. D. Malkinson. Modification of Radiation Response of Tissue by Colchicine: Preliminary Clinical Evaluation. In Proc. VIII Internatl. Cancer Congress. Moscow, 1962. (In press).

Malkinson, F. D., M. L. Griem, D. M. Phillips and P. H. Morse. 2-Mercaptoethylamine Protection of X ray Induced Dysplasia in Mouse Hair. Rad. Res. 1963. (In press).

Carpender, J. W. J., L. S. Skaggs, L. H. Lanzl and M. L. Griem. Radiation Therapy with High Energy Electrons using Pencil Beam Scanning. Am. J. Roentgenol., Radium Therapy and Nucl. Med. 1963. (In press).

14. Scope of Work

We are continuing to examine various drugs and physical agents which may increase the effect of radiation on cancer. By proper selection of these agents, it may be possible to increase the effect of radiation within the malignancy without doing any damage to the surrounding normal tissue. Animal experimentation serves as a guide to clinical treatment of patients with a variety of malignancies. Seventy-four patients have been evaluated clinically with combined colchicine and radiation; 40 patients with the combined use of induced hyperthyroidism and radiation, and 30 patients with combined use of Actinomycin D and radiation. Fever and radiation have been used on 3 patients.

Investigation is continuing on the effect of estrogen level on carcinoma of the breast. Currently under development is a method of assay using gas chromatography.

15. Relationship to Other Projects

Eric L. Simmons, Ph.D.	06-09-01	-	12
James W. J. Carpender, M.D.	06-09-01	-	13
Lester S. Skaggs, Ph.D.	06-09-01	-	14
Stephen Rothman, M.D.	06-09-01	-	22
Lawrence H. Lanzl, Ph.D.	06-09-01	-	23

16. Technical Progress in Fiscal Year 1963

One of the problems facing this group has been the screening of a number of drugs rapidly, using the microscopic hair indicator system. The microscopic evaluation of hair has proved satisfactory, but we have felt that some form of isotope labeling of this rapidly growing tissue might better indicate the degree of radiation injury. A number of amino acids are incorporated into growing hair and using these radioactive amino acids, it is possible to study the growth pattern before and after radiation injury. This technique should eliminate observer bias and increase the sensitivity and accuracy of determinations.

17. Expected Results in Fiscal Year 1964

Using these labeling techniques on a rodent hair, we plan to screen Leurocristine, Velban, a number of the alkylating agents, and a number of the halogenated pyrimidines. We also plan to continue the feasibility of the assay of estrogen levels in the urine, using gas chromatography for separation and quantitation of the various urinary steroids.

The results of animal experimentation on the rodent hair indicator system and tumors will be applied to patients with various advanced malignancies.

18. Expected Results in Fiscal Year 1965

By use of the above screening techniques, we hope to find a number of other drugs and physical agents which should be investigated clinically. Both Actinomycin D and colchicine have proved beneficial in pilot studies and consideration should be given to setting up a random clinical study of these drugs.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 20
2. Project Title The Late Effects and Metabolism of the Bone-seeking Radioelements		189 No. 17
3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963	
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois	
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Robert J. Hasterlik, M.D.	8. Project Term: New Proj. Starting: Continuing:	

9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	2-1/2	2-1/2	2-1/2
(b) Other Tech.	3	3	3
Total	<u>5-1/2</u>	<u>5-1/2</u>	<u>5-1/2</u>

10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	42,000	47,700	52,500
(b) Materials, Services, Subcontracts	3,000	4,000	5,000
(c) Indirect Expenses	91,000	89,200	94,000
(d) Equipment	-	-	-
Total	<u>136,000</u>	<u>140,900</u>	<u>151,500</u>

11. Reactor Concept: None	12. Materials: None
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Schedule 189

Project No. 20

13. Dates and Titles of Publications (Other than Progress Reports)

None

14. Scope of Work

The radium study project carried out in conjunction with groups at the Argonne National Laboratory continues. Re-measurement of radium content of all persons previously studied (approximately 300) will be done as well as total skeletal radiography. It is hoped that correlations can be drawn between rate of elimination of radium, time elapsed since acquisition, degree of skeletal radiation damage, and other parameters, as well as the earliest possible detection of significant orthopedic damage and neoplasms. Studies on the relative retention rates of Ra, Sr, and Ca are being carried forward.

15. Relationship to Other Projects

In conjunction with Argonne National Laboratory

16. Technical Progress in Fiscal Year 1963

Data collected on Sr⁸⁵ and Ca⁴⁷ metabolism in man have been assembled and are being reduced on the Division of Biological Sciences computer for which a program has been written. The National Institutes of Health have granted the Division's request for an analog computer facility and our data on Ca and Sr metabolism are being prepared for compartment analysis on the analog computer.

Summaries of the radium patient studies have been prepared (not completed) for inclusion in the joint card index kept by Professor Robley Evans at M. I. T.

Case histories and studies on the radium patients have been organized preparatory to publication of the mass of radium data.

17. Expected Results in Fiscal Year 1964

Publication of the radium studies will be accomplished. It is hoped to restudy all radium patients. Studies of the metabolism of radium in man will be carried out.

It is hoped to study the metabolism of uranium isotopes in man (in conjunction with Dr. R. Bernard of the Radiological Physics group, Oak Ridge National Laboratory).

18. Expected Results in Fiscal Year 1965

The above studies will be continued.

1167901

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 22	
2. Project Title The Effects of Ionizing Radiation on the Skin		189 No. 18	
3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Stephen Rothman, M.D.	8. Project Term: New Proj. Starting: Continuing:		
9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	3	3	3
(b) Other Tech.	<u>1/2</u>	<u>1/2</u>	<u>1/2</u>
Total	<u>3-1/2</u>	<u>3-1/2</u>	<u>3-1/2</u>
10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	34,000	35,700	35,700
(b) Materials, Services, Subcontracts	3,500	5,000	6,000
(c) Indirect Expenses	75,900	70,200	68,100
(d) Equipment	-	-	-
Total	<u>113,400</u>	<u>110,900</u>	<u>109,800</u>
11. Reactor Concept: None	12. Materials: None		

1167902

13. Dates and Titles of Publications (Other than Progress Reports)

Rothman, S. Medical Research in Africa. Arch. Dermatol., 85, 311, 1962.

Rothman, S. Some Remarks on Moricz Kaposi and on the History of Kaposi's Sarcoma. Acta Union Internat. Contre Cancer, 18, 322, 1962.

Rothman, S. Remarks on Sex, Age and Racial Distribution of Kaposi's Sarcoma and on Possible Pathogenetic Factors. Acta Union Internat. Contre Cancer, 18, 326, 1962.

Rothman, S. Some Clinical Aspects of Kaposi's Sarcoma in the European and North American Population. Acta Union Internat. Contre Cancer, 18, 364, 1962.

Kim, Y. P., K. Adachi and D. C. Chow. Leucine Aminopeptidase in Candida Albicans. J. Invest. Dermatol., 38, 115, 1962.

Adachi, K. and D. C. Chow. A New Simplified Method for Perfusing Dog Skin. J. Invest. Dermatol., 39, 299, 1962.

Malkinson, F. D. and S. Rothman. Percutaneous Absorption. J. Jadassohn's Handb. Haut- Geschlechtskv., Suppl., Vol. 1, Part 3, Berlin, Springer Verlag, 1963, pp. 90.

Santoianni, P. and S. Rothman. Deoxyribonucleic Acid Microdetermination in Human Epidermis. J. Invest. Dermatol. 1963. (In press).

Rothman, S. and A. L. Lorincz. Defense Mechanisms of the Skin. Ann. Rev. Med. 1963. (In press).

DeBersaques, J. On the Mechanism of Keratin Formation and the Influence of X rays. Proc. XIIth Internatl. Congr. Dermatol. (In press).

Rothman, S. Differences in Types of Keratinization Anomalies (Letter to the Editor). Arch. Dermatol., 87, 2, 1963.

14. Scope of Work

The effects of ionizing radiation on specific metabolic processes of the skin are being investigated. Presently studied processes are: keratinization and growth of hair, levels of adenosine triphosphate (ATP) and adenosine triphosphatase in normal, diseased and irradiated skin, succinic acid accumulation, and effect of x ray irradiation on percutaneous absorption.

15. Relationship to Other Projects

Melvin L. Griem, M.D. 06-09-01 - 19

16. Technical Progress in Fiscal Year 1963

a) Long-term irradiation of mice with fast neutrons in low daily dosages (0.15 r/day for 650 days) resulted in a conspicuous retardation of hair growth without any other sign of impairment of health.

b) ATP levels in skin tissue are now being related to DNA content of the specimen so that the amounts of ATP can be expressed in their relation to number of cells. Estimation of ATP-ase has been adapted for use in skin tissue; this enzymatic activity will also be expressed in relation to DNA.

c) Further evidence of succinic acid accumulation in human skin was obtained. Some specimens showed inhibition of the oxidation of succinic acid by succinic dehydrogenase; this effect seems to be exerted via the inhibition of sulfhydryl groups.

d) Percutaneous absorption has been studied with a newly modified method in the dog: the substance is applied to the shaved skin of the inner surface of the thighs under standard conditions and the amount of absorbed material is measured in the outflowing venous blood of the cutaneous branch of the femoral vein. Reproducible patterns of absorption curves have been obtained.

17. Expected Results in Fiscal Year 1964

a) We expect to establish the dose-effect relationship of low-intensity-long-term fast neutron irradiation and its damaging effect on hair growth. We expect to find out about the action mechanism by microscopic studies.

b) In a human skin disease, called atopic dermatitis, there is an exaggerated vasoconstrictor tendency which could be caused by low ATP tissue levels or increased ATP-ase activity because ATP is a potent physiological vasodilator. We expect to obtain corresponding analytical results and normalization by ionizing radiation because the manifestations of this disease are favorably influenced by x ray treatments.

c) The nature of the sulfhydryl inhibition by skin extracts will be studied in normal and abnormal skin.

d) The effect of local x ray irradiations on percutaneous absorption will be studied with the method described above.

e) Esterification of cholesterol by normal and diseased human epidermis will be studied.

18. Expected Results in Fiscal Year 1965

Continuation of the above program.

1167904

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago	Contract No. AT(11-1)-69	Task No. 23	
2. Project Title Physical and Biological Investigations of High-Energy Radiation Directed Toward Therapy		189 No. 19	
3. Budget Activity No. 06-09-01	4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi- annual Report to the Atomic Energy Commission	6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Lawrence H. Lanzl, Ph.D.	8. Project Term: New Proj. Starting: Continuing:		
9. Man Years	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific	3	3	3
(b) Other Tech.	2	2	2
Total	5	5	5
10. Costs	<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries	37,500	41,700	41,700
(b) Materials, Services, Subcontracts	2,000	2,300	3,000
(c) Indirect Expenses	79,900	75,900	73,000
(d) Equipment	-	-	-
Total	119,400	119,900	117,700
11. Reactor Concept: None	12. Materials: None		

Schedule 189

Project No. 23

13. Dates and Titles of Publications (Other than Progress Reports)

Brizel, H. E., L. H. Lanzl and E. M. Duthorn. A Comparison of Techniques for Parametrial Irradiation Using Cobalt-60. Am. J. Roentgenol., Radium Therapy and Nucl. Med., 89, 101, 1963.

Lanzl, L. H. High-Energy Moving Field Electron Beam for Cancer Therapy. In Proc. VIII Internatl. Cancer Congress. Moscow, 1962. (In press).

Lanzl, L. H. and J. W. J. Carpender. Adapted and expanded, Moving Field Radiation Therapy, by Wachsmann, F. and G. Barth, Chicago. The University of Chicago Press, 1962.

Carpender, J. W. J., L. S. Skaggs, L. H. Lanzl and M. L. Griem. Radiation Therapy with High-Energy Electrons Using Pencil Beam Scanning. Am. J. Roentgenol., Radium Therapy and Nucl. Med. 1963. (In press).

14. Scope of Work

The purposes of this project are to evaluate the physical factors and biological effects of the various parameters of the scanning beam from the linear accelerator and to compare the biological effects of electrons with those of the more conventionally used ionizing radiations. The project also aims at the development of new methods of treatment planning on all the supervoltage equipment. In addition, work is being undertaken to determine bone-mineral content and muscle-fat ratio in living systems.

15. Relationship to Other Projects

Eric L. Simmons, Ph.D.	06-09-01	-	12
Lester S. Skaggs, Ph.D.	06-09-01	-	14
Melvin L. Griem, M.D.	06-09-01	-	19
(N. Strandjord, M.D. - not on Argonne Hospital staff).			

16. Technical Progress in Fiscal Year 1963

We completed a study comparing techniques for parametrial irradiation using cobalt-60 and a heterogeneous phantom. Work is continuing on the film isodensity plotter which is semi-automatic and of the electro-mechanical type.

We carried out a digital computer calculation of the distribution of energy deposited by the pencil beam of high-energy electrons from our linear accelerator. The basic block diagram defining the step-by-step calculation and the determination of the most accurate multiple scattering cross-section has been completed.

1167906

17. Expected Results in Fiscal Year 1964

We expect to complete a comparative study of various ways to treat bladder carcinoma with gamma rays and electrons; to complete a study of an alternate way of specifying half-value layers for characterizing the energy of x ray beams; to carry out a biological study using dysplastic hairs to evaluate skin sparing effects of high-energy electrons; to improve the method of energy calibration of the linear accelerator; to complete iso-density plotter development and put it into use in patient treatment planning.

18. Expected Results in Fiscal Year 1965

We expect to complete an automatic patient contour plotter coupled with a transmission ion chamber reader for use with cobalt-60 unit and to start clinical trials with the unit. We hope to complete digital computer study on distribution of energy deposited by the pencil beam of high-energy electrons from our linear accelerator, and establish the usefulness of bone-mineral and muscle-fat ratio measurements by completing clinical trials.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 24	
2. Project Title Studies in Hematology				189 No. 20	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963			
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Richard K. Blaisdell, M.D.			8. Project Term: New Proj. Starting: Continuing:		
9. Man Years					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		3	3	3	
(b) Other Tech.		<u>1/2</u>	<u>1</u>	<u>1</u>	
Total		<u>3-1/2</u>	<u>4</u>	<u>4</u>	
10. Costs					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		28,900	37,100	40,800	
(b) Materials, Services, Subcontracts		1,800	2,500	3,500	
(c) Indirect Expenses		62,100	67,600	72,300	
(d) Equipment		-	-	-	
Total		<u>92,800</u>	<u>107,200</u>	<u>116,600</u>	
11. Reactor Concept: None		12. Materials: None			

1167908

Schedule 189

Project No. 24

13. Dates and Titles of Publications (Other than Progress Reports)

Blaisdell, R. K. Ionizing Radiation and Human Leukemia. Postgraduate Med., 31, A-61, 1962.

14. Scope of Work

The program is concerned with 4 studies:

- 1) Hypertransfused gastric ulceration in the rat.
- 2) Peritoneal transfer of red cells.
- 3) Lymphocyte behavior.
- 4) An autoradiographic study of the replication of human chromosomes.

15. Relationship to Other Projects

None

16. Technical Progress in Fiscal Year 1963

- 1) Gastric acid secretion is not a critical factor in the pathogenesis of hypertransfusion-induced gastric ulceration in the rat; blood viscosity and as yet undetermined local factors in the stomach are important.
- 2) Intraperitoneal red cells do not pass diffusely through the peritoneal membrane into the circulation, but through local select pathways.
- 3) Techniques for studying the peculiar migration and function of lymphocytes are being perfected.
- 4) We are at present studying the time sequence of DNA synthesis in normal chromosomes.

17. Expected Results in Fiscal Year 1964

During Fiscal Year 1964 we expect to continue exploration of any hitherto unknown factors which may be uncovered and to apply the techniques which have been developed and elaborated, to their study. In the human chromosome studies we hope to apply our methods to studies of chromosome replication in diseases with chromosome abnormalities, including chronic granulocytic leukemia and Mongolism.

1167909

Project No. 24 (Continued)

18. Expected Results in Fiscal Year 1965

Our 1965 program depends very largely on the success of our 1964 studies, and will be developed on this basis. The chromosome studies will be facilitated and extended as suitable material appears in the Clinics.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 25
2. Project Title Studies on the Regulation of Iron Absorption				189 No. 21
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission		6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Gerald A. Mendel, M.D.		8. Project Term: New Proj. Starting: Continuing:		
9. Man Years				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific		1/2	2-1/2	2-1/2
(b) Other Tech.		1	1	1
Total		<u>1-1/2</u>	<u>3-1/2</u>	<u>3-1/2</u>
10. Costs				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries		8,400	25,100	28,000
(b) Materials, Services, Subcontracts		1,500	3,000	4,000
(c) Indirect Expenses		20,000	48,500	52,200
(d) Equipment		-	-	-
Total		<u>29,900</u>	<u>76,600</u>	<u>84,200</u>
11. Reactor Concept: None		12. Materials: None		

1167911

13. Dates and Titles of Publications (Other than Progress Reports)

Mendel, G. A. Erythropoiesis and Iron Absorption. In Jacobson, L. O. and M. Doyle, eds. Erythropoiesis. Grune and Stratton, New York, pp. 347, 1962.

Mendel, G. A. and R. J. Weiler. Studies on the Regulation of Iron Absorption in Experimental Hypoplastic and Iron Deficiency Anemias (Abstract). J. Clin. Invest., 41, 1384, 1962.

Mendel, G. A. Studies on the Regulation of Iron Absorption. Proc. Inst. Med., Chicago, 24, 100, 1962.

Mendel, G. A. and R. J. Weiler. Observations on the Gastrointestinal Absorption of Iron in Experimental Hypoplastic and Iron Deficiency Anemias. Presented at the 9th Congress of the International Society of Hematology, Mexico City, September 1962. (In press).

14. Scope of Work

The purpose of these studies is to define the mechanism by which iron is absorbed and the physiologic factors which influence this process. Studies now in progress deal with the effects of acute hepatic injury on iron absorption and a search for humoral factors which may influence the absorptive process.

An understanding of the factors that influence absorption is of importance in the understanding of the pathogenesis of iron deficiency and the iron storage disorders; in the understanding of erythrokinetics; and may lead to a better understanding of absorptive processes and membrane transport in general.

15. Relationship to Other Projects

Eugene Goldwasser, Ph.D.	06-09-01	-	1
Clifford W. Gurney, M.D.	06-09-01	-	6

16. Technical Progress in Fiscal Year 1963

During the past year, iron absorption was studied in mice having different forms of experimentally induced anemia (hypoplastic, iron lack, hemolytic and post-hemorrhagic). The results of these studies indicate that anemia per se has a marked influence on the absorption of iron that is independent of the effects of alterations in the rate of erythropoiesis and body iron content; and that anemia, of itself, may be an important physiologic regulator of iron absorption.

16. Technical Progress in Fiscal Year 1963 (Continued)

Evidence has been accumulated which suggests that anemia, changes in body iron content, and changes in the rate of erythropoiesis have effects on the absorptive process that are to some extent additive.

17. Expected Results in Fiscal Year 1964

Studies programed for the coming year deal with:

- 1) Further investigation of the mechanism by which anoxia results in increased iron absorption, since evidence now indicates that this is independent of increased red cell production.
- 2) Further investigation of the means by which acceleration of erythropoiesis in the bone marrow influences the absorptive structures of distant mucosal cells.
- 3) An assessment of the effect of changes in the plasma iron clearance rate on iron absorption.
- 4) Investigation of the effects of acute hepatic injury on the absorptive process in order to evaluate the relationship that exists between liver disease and iron-loading and to evaluate the liver as a possible regulator of iron absorption.

18. Expected Results in Fiscal Year 1965

Continuation of the studies outlined above.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 26
2. Project Title Cyclic Nucleotide Biosynthesis, Pseudouridylic Acid Metabolism Mechanism of Actinomycin Action				189 No. 22
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi- annual Report to the Atomic Energy Commission		6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Murray Rabinowitz, M.D.		8. Project Term: New Proj. Starting: Continuing:		
9. Man Years				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific		2	2	2
(b) Other Tech.		2	2	2
Total		<u>4</u>	<u>4</u>	<u>4</u>
10. Costs				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries		13,000	17,900	42,700
(b) Materials, Services, Subcontracts		2,000	3,500	5,500
(c) Indirect Expenses		30,300	37,000	78,700
(d) Equipment		-	-	-
Total		<u>45,300</u>	<u>58,400</u>	<u>126,900</u>
11. Reactor Concept: None		12. Materials: None		

1167914

Schedule 189

Project No. 26

13. Dates and Titles of Publications (Other than Progress Reports)

Rabinowitz, M. and Goldberg, I. H. Differential Utilization of Pseudo-UTP and UTP by RNA Polymerase. Federation Proc., 21, 1962.

Goldberg, I. H. and M. Rabinowitz. Inhibition of DNA-Dependent RNA Synthesis by Actinomycin D in Mammalian Cell Extracts. Science, 136, 315 1962.

Reich, E., M. Rabinowitz and I. H. Goldberg. Structure Activity Correlations of Actinomycin and Their Derivatives. Nature, 196, 743, 1962.

Goldberg, I. H., M. Rabinowitz and E. Reich. Basis of Actinomycin Action. I. DNA Binding and Inhibition of RNA-Polymerase Synthetic Reactions of Actinomycin. Proc. Natl. Acad. Sci., 48, 2094, 1962.

Goldberg, I. H., M. Rabinowitz and E. Reich. Basis of Actinomycin Action. II. Effect of Actinomycin on the Nucleoside Triphosphate Inorganic Pyrophosphate Exchange. Proc. Natl. Acad. Sci., 49, 226, 1963.

Goldberg, I. H. and M. Rabinowitz. Inhibition of RNA Polymerase by 6-Azauridine Triphosphate. Biochim. Biophys. Acta. 1963. (In press).

Rabinowitz, M. and I. H. Goldberg. Glycogen Synthesis and Other Reactions of Pseudouridine Diphosphate Glucose. J. Biol. Chem. 1963. (In press).

Goldberg, I. H. and M. Rabinowitz. Comparative Utilization of Pseudouridine Triphosphate by RNA Polymerase. J. Biol. Chem. 1963. (In press).

Sasse, L., M. Rabinowitz and I. H. Goldberg. Synthesis of Polypseudouridylic Acid by Polynucleotide Phosphorylase (Abstract). Federation Proc. 1963.

14. Scope of Work

A study of the mechanism of Actinomycin inhibition of RNA synthesis has been in progress. In addition, the mechanisms of pseudouridylic acid incorporation into transfer RNA is being studied. The role of cyclic nucleotides in cell metabolism is also under study.

15. Relationship to Other Projects

None

16. Technical Progress in Fiscal Year 1963

The chemical synthesis of ψ UMP and enzymatic synthesis of ψ UTP has been accomplished. The biosynthesis and reaction of ψ UDP-glucose have been studied. The incorporation of ψ UTP into RNA by RNA polymerase has also been investigated. The mechanisms of Actinomycin inhibition of RNA synthesis by binding of DNA has been elucidated. The site of binding to DNA has also been investigated and binding to guanosine shown.

17. Expected Results in Fiscal Year 1964

Further elucidation of the mechanisms of SRNA synthesis and of incorporation of pseudouridylic acid into SRNA is planned.

18. Expected Results in Fiscal Year 1965

Continuation of current project.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 27
2. Project Title The Biologic Properties of Polynucleotides				189 No. 23
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission		6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) Stanley Yachnin, M.D.		8. Project Term: New Proj. Starting: Continuing:		
9. Man Years				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific		1	1-1/2	1-1/2
(b) Other Tech.		1	1	1
Total		<u>2</u>	<u>2-1/2</u>	<u>2-1/2</u>
10. Costs				
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries		14,900	22,400	28,000
(b) Materials, Services, Subcontracts		3,500	4,500	5,000
(c) Indirect Expenses		37,700	46,500	53,900
(d) Equipment		-	-	-
Total		<u>56,100</u>	<u>73,400</u>	<u>86,900</u>
11. Reactor Concept: None		12. Materials: None		

1167917

13. Dates and Titles of Publications (Other than Progress Reports)

Yachnin, S. Studies on the Antigenicity of Natural and Synthetic Polynucleotides (Abstract). J. Clin. Invest., 41, 1414, 1962.

Yachnin, S. Non-Antigenicity of Synthetic Polynucleotides and Apurinic Acid. Nature, 195, 1319, 1962.

Jacobson, L. O. and S. Yachnin. Uses and Abuses of Blood transfusions. World Wide Abstracts in General Medicine, 6, 8, 1963.

14. Scope of Work

Attempts to produce biological "transformation" in mammalian species by means of heterologous RNA injection have been unsuccessful, and this phase of the project is more or less dormant at present. However, interesting observations have been made on the effects of polynucleotides on the complement and coagulation systems *in vitro*. The anti-complementary and anticoagulant properties of natural and synthetic polynucleotides have been found to depend both upon base composition, and secondary structure and these phenomena are being intensively explored.

15. Relationship to Other Projects

None

16. Technical Progress in Fiscal Year 1963

Polyinosinic acid has been found to be a very potent anticomplementary substance, as little as 0.007 μmol P polymer being capable of inhibiting 1 C'₅₀ HU. The anti C' activity of poly I can be reversed stoichiometrically by poly A and poly C which form hydrogen bonded helices with poly I. Mixed polymers of I + U and U + G also have anti C' activity, their potency being related to their I and G contents. Poly I is also a reasonably potent anticoagulant and is able to affect both the first (thromboplastin generation) and 2nd (prothrombin conversion) stages of the coagulation process.

17. Expected Results in Fiscal Year 1964

At present we are most interested in the structural basis of the anti C' activity of synthetic polynucleotides. It appears that some extended sequence of G or I in the polymer molecule is necessary for this activity. We are interested in establishing the minimum length of this sequence and are approaching this problem by means of selective enzymatic degradation of mixed polymers.

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18. Expected Results in Fiscal Year 1965

The potency of poly I as an anti C' substance in vitro raises questions as to 1) its effect in vivo (for example, on passive cutaneous anaphylaxis) and 2) its effect on certain hemolytic states in man such as the C' dependent hemolysis in paroxysmal cold and nocturnal hemoglobinurias.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 28	
2. Project Title Resistance to Experimental Salmonella Infection				189 No. 24	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963			
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission			6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) C. Phillip Miller, M.D.			8. Project Term: New Proj. Starting: Continuing:		
9. Man Years					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Scientific		-	3-1/2	4	
(b) Other Tech.		-	2	2	
Total		-	5-1/2	6	
10. Costs					
		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>	
(a) Direct Salaries		-	52,300	71,300	
(b) Materials, Services, Subcontracts		-	2,000	3,000	
(c) Indirect Expenses		-	94,600	121,700	
(d) Equipment		-	-	-	
Total		-	148,900	196,000	
11. Reactor Concept: None		12. Materials: None			

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13. Dates and Titles of Publications (Other than Progress Reports)

None

14. Scope of Work

Previous work has shown that the oral administration of streptomycin (or penicillin) is followed by a marked (about 100,000-fold) increase in the mouse's susceptibility to infection with streptomycin resistant Salmonella enteritidis inoculated by mouth, the natural route of infection.

Among the changes in the enteric microflora resulting from the antimicrobial action of the drug, the most important seems to be the elimination of certain obligate anaerobes belonging to the genus Bacteroides. Susceptibility of antibiotic treated mice can be significantly reduced by reestablishing Bacteroides in the intestinal tract.

Material removed from the large intestine of normal, untreated mice contains a heat stable, readily dialyzable substance which effectively inhibits multiplication of Salmonella in the test tube. Similar material from streptomycin treated mice does not. Chemical examination of intestinal content of untreated, control mice shows it to contain acetic and butyric acids in concentrations which in the test tube effectively inhibit multiplication of Salmonella. These two acids are metabolic products of Bacteroides. After streptomycin treatment, the concentrations of these two acids in intestinal content fall below inhibitory levels.

15. Relationship to Other Projects

None

16. Technical Progress in Fiscal Year 1963

Recent findings suggest that additional factors are involved in the susceptibility of streptomycin treated mice; viz., a change in the pH of intestinal content and an increase in the concentration of lactic acid. This acid in sufficient concentration is able to counteract the inhibitory effect of the two fatty acids on multiplication of Salmonella in the test tube. Under investigation are: 1) the mechanism of the inhibitory activity of acetic and butyric acids on multiplication of Salmonella; 2) the nature of the interference with this inhibitory activity by lactic acid; and 3) the members of the enteric microflora responsible for their production.

17. Expected Results in Fiscal Year 1964

It is hoped that results of the current studies will provide information which can be applied to a systematic investigation in vitro of the ecology of the enteric microflora; i.e., the interrelationship of its bacterial constituents growing together in various combinations and under controlled conditions in continuous cultivation.

SCHEDULE 189

ADDITIONAL JUSTIFICATION FOR OPERATING COSTS

Argonne Cancer Research Hospital
Field Office or Laboratory

06-Biology and Medicine
Program

1. Contractor University of Chicago		Contract No. AT(11-1)-69		Task No. 29
2. Project Title Fallout Studies			189 No. 25	
3. Budget Activity No. 06-09-01		4. Date Prepared: April 15, 1963		
5. Method of Reporting: Professional Journals and Semi-annual Report to the Atomic Energy Commission		6. Working Location: Chicago, Illinois		
7. Person in Charge: Dr. L. O. Jacobson Principal Investigator(s) George V. LeRoy, M.D. Robert J. Hasterlik, M.D. John H. Rusty, M.D.		8. Project Term: New Proj. Starting: Continuing:		
9. Man Years		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Scientific		0	0	0
(b) Other Tech.		2	2	0
Total		2	2	0
10. Costs		<u>FY 1963</u>	<u>FY 1964</u>	<u>FY 1965</u>
(a) Direct Salaries		5,000	5,200	-
(b) Materials, Services, Subcontracts		31,100	4,800	-
(c) Indirect Expenses		-	-	-
(d) Equipment		-	-	-
Total		36,100	10,000	-
11. Reactor Concept: None		12. Materials: None		

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Schedule 189

Fallout Studies

13. Dates and Titles of Publications (Other than Progress Reports)

None

14. Scope of Work

Investigation of metabolism of simulated particulate fallout, and samples of authentic fallout.

15. Relationship to Other Projects

Uses resources of Dr. Hasterlik's whole-body counter.

16. Technical Progress in Fiscal Year 1963

Examination of behavior of authentic fallout, and nine varieties of simulated particulate fallout, consisting of glassy microspheres containing Cs¹³⁴, Ba¹³³, and Sr⁸⁵, respectively. Further investigation of solutions of Cs¹³⁴Cl, and Sr⁸⁵Cl.

17. Expected Results in Fiscal Year 1964

A reasonable description of translocation and elimination of Cs and Sr by normal volunteers. Project will terminate in Fiscal Year 1964.

18. Expected Results in Fiscal Year 1965

None

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**CANCER RESEARCH HOSP.
Biology & Medicine Program Budget
FY 63, 64, 65**

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3/28/95

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J. Anderson

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