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FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
APPLICATION FOR GRANT-IN-AID

NUMBER: (Do not write in this space)

Date May 1, 1950

THE SURGEON GENERAL,
Public Health Service,
Washington 25, D. C.

(Extension Application for Grant O-396(C2))

Application is hereby made for a grant-in-aid in the amount of \$ 117,207.43 for the period from January 1 1951 through December 31 1951, inclusive,* for the purpose of conducting a research project on the following subject: Give only brief descriptive title of project:

Physiology of patients with cancer and experimental therapy of cancer

TITLE OF PRINCIPAL INVESTIGATOR: Dean of the Medical School and Professor of Pediatrics	NAME OF PRINCIPAL INVESTIGATOR: Dr. Francis Scott Smyth
ADDRESS OF PRINCIPAL INVESTIGATOR: University of California School of Medicine Medical Center, San Francisco 22, California	
GIVE TITLE OF FINANCIAL OFFICER TO WHOM CHECK SHOULD BE MAILED: Vice-President - Business Affairs	NAME OF FINANCIAL OFFICER: Mr. James E. Corley
GIVE ADDRESS OF FINANCIAL OFFICER: 250 Administration Building, University of California Berkeley 4, California	

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant-in-aid may be revoked in whole or in part at any time by the Surgeon General, provided that a revocation shall not include any amount obligated previous to the effective date of the revocation if such obligations were made solely for the purposes set forth in this application; (3) that all reports of original investigations supported by any grant-in-aid made as a result of this request shall acknowledge such support; and (4) that if any patentable discoveries or inventions are made in the course of the work aided by any grant received as a result of this application, the applicant will, in consideration of such grant, refer to the Surgeon General of the Public Health Service, for determination, the question, of whether such patentable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

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Name of institution University of California School of / **Medicine**

(TYPE name and title of official authorized to sign for institution) Robert G. Sproul
President of the University

[Signature] PERSONAL SIGNATURE of the official authorized to sign for the institution

* This period is not to exceed 1 year.

Budget Bureau No. 68 - 2249.3

PAGE 1

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APPLICATION FOR GRANT-IN-AID
 6-396(02)
 Budget proposed for the year 1/1/51 through 12/31/51

NUMBER: (Do not write in this space)

PERSONNEL (1(a) cont.)

	Per No.	Per Annum	Total
Ward Nurses:			
Day Duty (4)	220.00	2,640.00	10,560.00
Night Duty (4)	230.00	2,760.00	11,040.00
Dietitian (1)	260.00	3,120.00	3,120.00
Ward Helpers (3)	175.00	2,100.00	6,300.00
Orderlies (4)	190.00	2,280.00	9,120.00
Kitchen Helpers (3)	173.50	2,082.00	6,246.00
Secretary (1)	200.00	2,400.00	2,400.00
Janitor (1)	185.00	2,220.00	2,220.00
			(51,006.00)

The above represents the actual number of people on our personnel rolls. The per annum figure represents the entrance salary for a beginning employee. No professional (M.D. or Ph.D.) personnel are employed on these funds.

Allowance for yearly honor merit increase for personnel:

Nurses	1,800.00
Dietitian	120.00
Ward Helpers	720.00
Orderlies	840.00
Kitchen Helpers	720.00
Secretary	360.00
Janitor	240.00

This figure represents increases already in effect and for increases anticipated for the period of this budget. (4,800.00)

General Assistance:

Relief Dietitian (1)	(yearly basis) @ \$1.269 hr.	960.00
Dietitian, relief	(1 mo. period) @ \$1.269 hr.	220.00
Kitchen Halper, relief	(3 mo. period) @ \$1.001 hr.	520.50
Ward Helper, relief	(3 mo. period) @ \$1.010 hr.	525.00
Orderly, relief	(3 mo. period) @ \$1.096 hr.	570.00

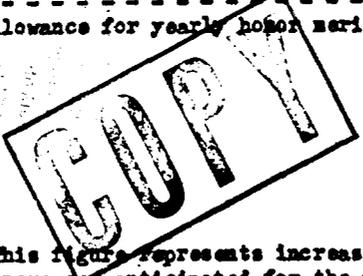
Allowance for accumulated vacation leave for personnel on permanent status (based on 1 month period):

Nurses (8)	1,800.00
Dietitian (1)	270.00
Ward Helpers (3)	585.00
Orderlies (4)	820.00
Kitchen Helpers (3)	581.00
Secretary (1)	230.00
Janitor (1)	205.00

Matching contributions to the State Employees Retirement System at 5% of total gross non-academic salaries, plus a \$4.00 service charge for each participant. (5,131.40)

TOTAL..... \$65,223.90

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APPLICATION FOR GRANT-IN-AID

C-396(62)

NUMBER: (Do not write in this space)

Budget proposed for the year 1/1/51 through 12/31/51

CONSUMABLE SUPPLIES NEEDED (1(a) cont.)

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	<u>TOTAL</u>
Supplemental food for diets: 15 patients @ \$0.65 per day, 365 days	3,559.00
Drugs, including fluids, antibiotics, heparin	8,219.00
Surgical Dressings	1,278.00
Kitchen Equipment, expendable	230.00
Glassware, syringes, surgical supplies, catheters	1,526.00
Surgical Instruments, enamelware, replacement items for permanent equipment on hand	841.00
X-ray film, photographic supplies	552.00
Linens replacements	774.00
Household supplies (soap, paper towels, lysol, etc.)	627.00
Minor repairs and maintenance of equipment	248.00
Total.....	\$17,554.00

These items are based on actual expenses incurred during past full year of operation. No additional permanent equipment is requested. Many items not covered by this request for the operation of the research ward are to be covered by the anticipated grant from the University of California of \$16,000.

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**BUDGET SUMMARY COMPARISON SINCE ESTABLISHMENT
OF RESEARCH WARD**

	C-396(R) 1948 1/	C-396(C&CS) 1949	C-396(C2) 1950	C-396(C3) 1951
Personnel.....	35,150.56	54,111.00	60,732.00	68,223.90
Permanent Equipment.....	14,196.00	2,877.50	—	—
Consumable Supplies.....	5,500.00	14,495.00	12,743.00	17,854.00
Contractual-Bed space...	18,246.50	18,450.65	20,422.00	22,447.50
Other Expenses.....	400.00	—	—	—
Overhead.....				
TOTAL.....	\$ 79,372.50	\$ 97,128.85	\$ 101,408.76	\$ 117,207.43 2

- 1/ The research ward was actually opened on July 6, 1948.
 - 2/ As seen from the budget, the increase of \$15,798.67 is due to three major factors: (a) merit and other increases in salaries, as authorized by the University, (b) increased cost of reimbursement for beds to Laguna Honda Home from \$3.72 to \$4.10 per day per bed, and, (c) an additional \$5,000 is requested for drugs such as antibiotics, fluids, etc., which were underestimated last year.
- plus the State Employment Retirement System contributions, as agreed by the United States Public Health Service and the Secretary of the Regents of the University of California.

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List all support, including that from own institution, on this or related research projects from sources other than Public Health Service

TITLE OF PROJECT	SOURCE	AMOUNT	YEARS OF SUPPORT	
			From	to
PREVIOUS				
Laboratory	Univ. of California School of Medicine	\$ 5,000.00	1/47	6/30/47
Research Ward	Univ. of California State Funds	18,000.00	11/47	6/30/48
Laboratory	Univ. of California School of Medicine	3,000.00	7/1/47	6/30/47
Research Ward - Isotope Unit	Univ. of California State Funds	7,000.00	11/47	6/30/48
Research Ward - Pathology Unit	Univ. of California State Funds	10,000.00	11/47	6/30/48
Research Ward	Univ. of California State Funds	12,500.00	7/1/48	6/30/47
Laboratory	Ditto	4,500.00	7/1/48	6/30/47
Research Ward - Isotope Unit	Ditto	9,500.00	7/1/48	6/30/47
Research Ward - Pathology Unit	Ditto	7,200.00	7/1/48	6/30/47
CURRENT				
Research Ward and Laboratory	Univ. of California State Funds	15,000.00	7/1/49	6/30/50
Research Ward - Isotope Unit	Ditto	7,400.00	7/1/49	6/30/50
Research Ward - Pathology Unit	Ditto	11,000.00	7/1/49	6/30/50
Research Ward	Damon Runyon Fellowship	500.00	7/1/49	6/30/50
PENDING				
Research Ward and Laboratory	Univ. of California State Funds	16,000.00	7/1/50	6/30/50
Research Ward - Isotope Unit	Ditto	5,000.00	7/1/50	6/30/50
Research Ward - Pathology Unit	Ditto	11,000.00	7/1/50	6/30/50

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APPLICATION FOR GRANT-IN-AID
 PROPOSED PLAN (Continuation Sheet)

NUMBER: (Do not write in this space)

4(a). Specific Aims of Project. The specific aim of the project is clinical research in cancer. With the cancer patient as the focal point of the investigations, the work is oriented along four broad approaches: (1) Experimental therapy, providing clinical material for other studies as well as permitting evaluation of such procedures on neoplastic diseases; (2) Physiology, particularly cardiovascular and respiratory physiology of patients with neoplastic diseases; (3) Biochemistry, including metabolic studies on cancer patients, and investigations of specific biochemical reactions; and, (4) The study of protein fractions of cancer and normal tissues of human and animal origins, utilizing physicochemical and immunochemical techniques.

4(b). Method of Procedure. Patients for investigation are selected through the Consultative Tumor Board of the University of California School of Medicine, by referral of physicians of the Bay Area. Such patients as are not applicable for curative therapy by surgery or irradiation are evaluated for their applicability to experimental procedures. For admission to the research ward, each patient signs a release which indicates that the patient understands that he will be used for experimental work, and that he agrees to this and to a necropsy (See attached Release Form). Each patient receives a full clinical and pathology work-up, an observation period, and is then applied toward one or another of the investigations underway at the Laboratory (see Progress Report). Each investigative program on patients is reviewed by the Cancer Board of the University of California School of Medicine for its clinical safety.

4(c). Relationship of Anticipated Results to General Problems in the Field. The results of the investigations, since they are of work being done on patients, is directly applicable to the clinical management of patients with cancer. The chief interests of the Laboratory, however, are the study of the biology, physiology and biochemistry of human cancer, with particular emphasis on how the presence of various neoplastic diseases affects the human host.

4(d). Facilities Available. The Laboratory and its research ward occupy two floors of a wing of the Laguna Honda Home. This space was made available by arrangement between the University of California and the San Francisco Department of Public Health; the Laboratory will move to its new quarters at the Medical Center toward the end of 1952. Two-thirds of the area is occupied by laboratories, including 2 clinical biochemical laboratories, 1 hematology laboratory, 1 protein chemistry and immunochemistry laboratory, 1 clinical isotope laboratory, 1 biochemical isotope laboratory, 1 physiology laboratory and an animal room. The pathology laboratory (supported by University of California funds) is in another area. All these laboratories and the research ward are fully equipped for their designated work. Special equipment includes: electrophoresis (Amico), preparatory ultracentrifuge (Spinco), microchemical assembly (Kirk), and a full clinical physiology complement of strain-gage indicators, recording oximeters, oscillographs, electroencephalograph etc.

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APPLICATION FOR GRANT-IN-AID
PROPOSED PLAN (Continuation Sheet)

NUMBER: (Do not write in this space)

5(a). Previous Work Done on This (or closely related) Project. The Laboratory of Experimental Oncology was initiated in January 1947 and the research ward, which is supported by Grant C-396, was opened on July 6, 1948. The attached project report indicates the lines of investigation being undertaken and the publications indicate the segments of work which have been pursued to the point of publication.

5(b). Personal Publications Pertaining to this Problem. The list of 19 publications which have appeared or have been submitted during the past year are given in the progress report. Five additional papers are in the process of preparation. At least 40 copies of reprints of all publications have been submitted to the National Cancer Institute and the National Institutes of Health and additional reprint copies are not being submitted with this application at this time.

6(a). Results Bearing on This Project Obtained by Others. The wide program being undertaken at the Laboratory of Experimental Oncology would refer to such an extensive review of previous literature in cancer research that it is considered inappropriate to include this here. The paper entitled, "Experimental chemotherapy in neoplastic diseases" by Shimkin and Bierman (Radiology, 53:518-529, October, 1945 for example, lists 64 references on this segment of the program alone.

It is believed that some specific investigations were first initiated at this Laboratory. These include: (1) the effects of virus infections on clinical cancer, which is now also being studied at the Memorial Hospital in New York, (2) intra-arterial catheterisation including the use of chemotherapeutic agents by this route which is now also being explored at Georgetown University at Washington, D.C., and, (3) accentuation upon the exploration of cardiovascular effects of cancer.

6(b). Publications by Others on Related Work. Refer to 6(a). The listing of references from the literature for this wide program would be too extensive to justify inclusion here. References to publications by others on similar or related work are, of course, always included in the publications.

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (Do not use this space)

CONTRACTING AGENCY: FEDERAL SECURITY AGENCY, PUBLIC HEALTH SERVICE

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TITLE OF PROJECT:
Physiology of patients with cancer and experimental therapy of cancer

Give names, departments, and official titles of PRINCIPAL INVESTIGATOR(S) and ALL OTHER PROFESSIONAL PERSONNEL engaged on the project.

Dr. Francis S. Smyth, Dean of Medical School & Professor of Pediatrics
 Dr. Michael B. Shimkin, Clinical Professor of Experimental Oncology
 Dr. Howard R. Bierman, Assoc. Clinical Professor of Experimental Oncology

NAME AND ADDRESS OF INSTITUTION:

University of California School of Medicine
 Medical Center, San Francisco 22, California

APPLICANT - DO NOT USE THIS SPACE

SUMMARY OF PROPOSED WORK - (200 words or less - Omit Confidential data)

In the Program of Exchange of Information summaries of work in progress are exchanged with government and private agencies supporting research in medical and related fields and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objective of the Laboratory is clinical research in cancer. With the cancer patient as the focal point of investigation, the work is oriented along four broad approaches: (1) Experimental therapy, providing clinical material for other studies as well as permitting evaluation of such procedures on neoplastic diseases; (2) Physiology, particularly cardiovascular and respiratory physiology of patients with neoplastic diseases; (3) Biochemistry, including metabolic studies on cancer patients, and investigations of specific biochemical reactions; and (4) The study of protein fractions of cancer and normal tissues of human and animal origin, utilizing physicochemical and immunochemical techniques.

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Grant C-396(C2)

LABORATORY OF EXPERIMENTAL ONCOLOGY

ANNUAL REPORT 1949-1950

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 University of California, Berkeley, CA 94720.

Project Title: Physiology of patients with cancer and
 experimental therapy of cancer.

Project Director: Francis S. Smyth, M.D.
 Dean of the Medical School and
 Professor of Pediatrics

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C-396(C2)

LABORATORY OF EXPERIMENTAL ONCOLOGY

ANNUAL REPORT 1949-1950

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The Laboratory of Experimental Oncology is a member of the
 Cancer Research Center at the University of California at Berkeley.
 The Laboratory was established in 1947 as the first of its kind
 in the United States. It is a part of the Department of
 Biological Chemistry and the School of Public Health. The Laboratory
 is a part of the University of California at Berkeley. It is located in the
 Biological Chemistry Building, 740 University Hall, Berkeley, California.
 An arrangement between the University of California and the Department
 of Public Health, San Francisco.

The objective of the Laboratory is clinical research in cancer
 with the cancer patient as the focal point of investigation. The work is
 oriented along four broad approaches: (1) Experimental therapy,
 providing clinical material for other studies as well as permitting
 evaluation of such procedures on neoplastic diseases; (2) Physiology,
 particularly cardiovascular and respiratory physiology of patients
 with neoplastic diseases; (3) Biochemistry, including metabolic studies
 on cancer patients, and investigations of specific biochemical reactions;
 and (4) The study of protein fractions of cancer and normal tissues of
 human and animal origin, utilizing physicochemical and immunological
 techniques.

Reference is made to the Annual Reports of the Laboratory of
 Experimental Oncology for 1947-48 and 1948-49, which present fully the
 administrative and research developments during the first two years of
 activity. Further progress is being achieved in all major segments
 of the program. The personnel, finances, physical facilities and equipment
 remain at approximately the same levels as in 1948-49.

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First admissions	132	132
Readmissions	151	151
Total admissions	283	283
Discharges	142	141
Patient days	3,715	3,351
Mean daily census	10.3	12.2
Out-patient visits	388	249
Deaths	23	27
Autopsies	35	27
Surgical pathology	119	60

Additional patients, estimated at 50 per cent of the above.

are seen and studied at other hospitals in San Francisco. Many patients, of course, are used for more than one experimental study.

The investigations being reported are the work of the professional staff of the Laboratory, ably assisted by the technical, nursing, clerical and custodial personnel. The professional staff includes:

- Dr. Michael B. Spinkin, Chief of the Laboratory
- Dr. Howard R. Bierman, Internist and physiologist
- Dr. Leo R. Melcher, Immunochemist
- Dr. Joseph Shack, Biochemist
- Dr. Bernard Shacter, Biochemist
- Dr. Nellie Eallday, Biochemist
- Dr. Kenneth S. Dod, Research fellow (ACS)
- Dr. Keith H. Kelly, Research fellow (Damon Runyon)
- Dr. Serafeim Maseuredis, Research fellow (ASO-KOI)
- Dr. Paul Ortega, Resident in pathology
- Mr. Morris Sable, Physicist

Many investigations were and are being carried out in collaboration with other Departments of the University of California School of Medicine, particularly including:

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The mean in the above table relative to the length of survival of untreated patients with aplastic disease was reviewed (25). The duration of life, determined from the time of onset of clinical symptoms, appears to be a reproducible function of function and may be very long in untreated patients with cancer. This is particularly true of patients with carcinoma of the breast and with leukemia or lymphoma. About approximately 15 per cent survive for 5 years or longer.

1. Duration of chronic myelogenous leukemia.

Records on 212 patients with chronic myelogenous leukemia compiled from San Francisco hospitals between 1910 and 1949 were reviewed. In conformity with data in the literature, the length of life in these patients was statistically the same in 1940-49 as it was before 1940 and therapy with irradiation was not reflected by a significant prolongation of life (26).

2. Duration of leukemia in children.

A survey of all of clinical case records on lymphatic leukemia in children, available at the University of California Hospital. A group of 10 patients who were untreated had an average life span of 5.8 months. A similar group of 17 treated by radiation had a mean life span of 5.8 months. A group of

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...anti-folic acid compounds and methotrexate, and the average life span of patients with
 ...months ... which has been ... while the average
 life span was in the neighborhood of 3 to 5 months. This survey suggests
 that the anti-folic acid compounds may have little to do with the
 longer survival obtained in childhood leukemia with this agent, or that
 the clinical reactions are not manifested in prolongation of life.

B. Effect of virus infections on neoplastic growth.

The hypothesis that certain viruses with intracellular existence may
 accumulate in tumors and adversely affect their growth, because
 neoplasms represent an embryonal type of growth, a program was initiated
 on the effect of induced virus infections in patients with neoplastic
 diseases. Since Dr. W. D. Hanson has now left the University of California
 new arrangements for these studies were made with Dr. E. R. Lennette of
 the Virus Laboratory, State of California Department of Public Health.

Five adult patients with far-advanced carcinoma, two of the
 stomach, one of the kidney, one of the parotid gland, and one male with
 infected intravenously with lymphopathic venereum virus culture, and
 eggs (obtained from Dr. Pale of Squibb Laboratories). Only two of these
 patients survived long enough for a minor rise in the titer of antibody.

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to lymphoma or psittacosis. No objective effects on the
 were observed in these two patients, but further data are
 obviously necessary.

Seven children with acute leukemia as well as one adult with
 lymphatic leukemia were injected with filtered suspensions of spleens
 of cats bearing the feline agranulocytic virus. Four children survived
 long enough for clinical observations. In all of these, there was a
 mild elevation of temperature and a marked drop in the white count
 approximately one month after the inoculation. Four of the children
 and the adult had nondescript skin rashes following the inoculation.
 Apparent temporary remissions of the disease were observed in three of
 the children, but no long-term beneficial effects were obtained.

An almost complete remission of acute leukemia for three to
 four weeks was seen in a child with lymphatic leukemia who spontaneously
 developed chicken-pox while being studied on the research ward. A
 14-year-old boy with lymphatic leukemia developed a hemolytic staphy-
 lococcus septicemia and had such a complete remission of the disease
 for about 2 months that the original diagnosis was questioned. The
 child eventually died of leukemia. It is believed that this field of
 investigation should be continued and expanded, and it is anticipated
 that the studies will be resumed during the forthcoming year. No
 publications have been prepared on these limited observations.

C. Effect of hypophysectomy on neoplastic growth. Interest
 was aroused in a study of interruption of hypophyseal function in cases
 of advanced melanoma because of the clinical experience that melanomas

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entered after division of the optic crossing, which would produce
 bilateral hemianopia. Further attempts will be made when suitable
 cases become available. No publications have resulted from the data
 thus far available.

D. Intra-arterial catheterization. The afferent artery to
 a tumor represents one point of attack upon the neoplastic growth.
 During the past year techniques have been devised which make it possible
 to enter arteries leading to specific viscera by introducing and
 passing catheters from the carotid, brachial or femoral arteries. The
 coeliac axis, hepatic artery and other vessels can be entered by such
 catheterizations and the blood supply of the specific viscera outlined
 by means of radio-opaque substances introduced through the catheter.
 Distortions of the vascular pattern are seen with metastatic lesions
 to the liver. This addition to arteriography may have diagnostic uses.

The catheterization technique, however, was developed primarily
 for the purpose of delivering certain agents, particularly nitrogen
 mustard, more directly to viscera involved by Hodgkin's disease or
 other neoplastic processes. Up to 1 mg./kg. body weight of HN2 has
 been introduced through catheters placed into the hepatic artery, with
 regressions in the size not only of lymphomatous tumors but some
 carcinomas as well. Such decreases in size have been only temporary,
 of course, but can be achieved without damage to the functional
 parenchyma of the liver. Intra-arterial catheterizations have now been
 performed on 23 patients, and one paper on the technique has been
 submitted for approval for publication (9).

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Experimental chemotherapy. The following materials are being evaluated in the treatment of clinical cancer: (1) Nitrogen mustard (methyl bis (beta-chloroethyl)amine hydrochloride); (2) Stilbamidine and pentamidine (4,4'-diamidinostilbens and 4,4'-(pantamethylenedioxy)dibenzamidine); (3) Urethane (ethyl carbamate); (4) Guanazole (amine-triazolo pyrimidine) and benzimidazole; (5) ACTH and cortisone; and (6) Trimethylol melamins and triethyl melamine.

1. Nitrogen mustard. Long-term observations are being made on cases of Hodgkin's disease and lymphosarcoma treated with repeated doses of nitrogen mustard. Particular attention is being paid to a group of 18 cases who have received no other therapy than nitrogen mustard. These patients are being given six monthly doses of 0.3 mg./kg. body weight followed by six additional doses at two-month intervals. The periods are of course lengthened if the hematological status has not recovered from the previous dose.

There is no question that nitrogen mustard produces clinical remissions in these cases but no permanent benefits are apparent on the basis of observations up to 18 months following completion of treatment. The results with this agent, therefore, are in conformity with the results obtained with irradiation, which also ameliorates the disease without effect upon the mean survival of the treated cases.

The number of patients treated with nitrogen mustard but previously treated by other agents, particularly irradiation, now exceeds 150. The results are in entire conformity with those described in the literature, including the summary on the first 67 cases reported from here (1).

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The use of nitrogen mustard by the intra-arterial route has been indicated under section I-D. Recently, a series of combined nitrogen mustard and roentgen therapy has been initiated in collaboration with the Department of Radiology.

2. Stilbamizide and pentamidine. The experience with stilbamizide and pentamidine in multiple myeloma indicated that this drug is of value in reducing or stopping pain in multiple myeloma but that it has no objective effects on the disease. Ten cases of multiple myeloma have been treated with this agent. The effects of stilbamizide on the cardiovascular system, including the production of heart block in mice, have been recorded in two publications (4,6).

3. Urethane. Our experience with urethane has not been satisfactory. Therapy in all cases in our experience, which includes 2 patients with leukemia and 3 with multiple myeloma, had to be interrupted because of nausea and vomiting which the patients could not tolerate. In addition, another limiting factor in the use of this agent is bone marrow depression. In general, and on a limited number of cases, we have found that urethane is of limited use and that these patients can be handled better by other methods.

4. Guanazole and benzimidazole. Two antagonists of amine acid metabolism have been tried on patients with cancer. Experience with guanazole, an antagonist of guanine, is limited to 2 patients who received up to 6 grams per day by the oral route. No effects other than mild diarrhea were obtained in these patients. Recently a parenteral preparation of this guanine inhibitor has been obtained and a small series will be started in the near future.

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Benzimidazole, an adenosine antagonist, has been given to
 patients in intravenous amounts up to 5 grams per day. No noteworthy
 effects have been noted on the growth of neoplasms although one patient
 with acute myelogenous leukemia had a definite drop in the white count
 and the differential count tended to become more normal following this
 therapy. A consistent observation in all patients receiving benzimidazole
 was a marked depression of the basal metabolic rate which persisted for
 prolonged periods after the cessation of administration of the agent.

5. ACTH and cortisone.

ACTH in amounts sufficient to
 treat patients was received from the National Cancer Institute in
 January 1950. Thus far, 3 patients with acute lymphatic leukemia, 1
 adult and 2 children, and 1 adult patient with an acute exacerbation of
 myelogenous leukemia, have been treated with ACTH in daily divided doses
 of 100 mg. Contrary to implications of remarkable results with this
 agent indicated in the press, the clinical benefits of this therapy in
 these 4 patients have been most unimpressive. All 4 patients have
 expired after pursuing the expected course of their disease.
 Cortisone, in daily divided doses of 100 mg. for 10 days,
 50 mg. for 10 days and 25 mg. for a total dose of 1.75 gm. in 30 days,
 has been used in 4 children with lymphatic leukemia. A dramatic response
 was achieved in 2 cases, and the other 2 children are also doing well.
 It is apparent that this agent has little effect on the disease per se.
 in that the bone marrow and white blood counts are not consistently
 affected, but exerts its action by virtue of improving the general
 condition or resistance of the host.

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although in no instance was tumor growth entirely inhibited. There was a
 marked atrophy of the spleen and bone marrow and a drop in the peripheral
 white blood cell count in mice injected with toxic amounts of the agent.
 The pharmacologic effects of this drug closely resembled those of
 nitrogen mustard. Clinical trials of the compound were then initiated.
 Ten patients have now received triethyl melamine in a total dose of
 0.1-0.15 mg. per kg. body weight divided over 3 to 7 daily doses. With
 0.25 mg. per kg. doses there is a marked drop in the white count
 followed by depression of platelets and red blood cells. Definite
 objective clinical responses, in the form of reduction of lymph nodes,
 disappearance of fever and reduction in white blood count were observed
 in one patient with Hodgkin's disease, one patient with lymphoblastoma,
 and two patients with leukemia. Again, the clinical effects resemble
 those of nitrogen mustard but the agent has the advantage of being able
 to be injected intramuscularly without major discomfort at the local
 site and with minimal nausea during the administrations. Further clinical
 trial of this agent, particularly in lymphoma and leukemia, is fully
 warranted and is being continued.

II. Physiology and biochemistry.

A. Fate of normal and leukemic white blood cells. The peripheral
 blood count must be the result of a balance between the rate of delivery
 of cells to the peripheral circulation and the withdrawal from circulation
 or destruction of such cells. Recent data indicate that the life span
 of the white blood cell is extremely short, in man probably being 40 to
 60 hours. Although the classical concept is that in leukemia there is an

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Overproduction of such cellular elements, the high white counts seen in leukemia and related conditions may also be the result of an interference with a removal mechanism of white cells.

During 1948-49 this problem was studied by transfusing non-leukemic cancer patients with blood from leukemic donors. It was found that the white blood cell count could not be raised by this procedure and that the site of removal of these cells was most likely in the lungs. The basis of this conclusion was that when leukemic cells were injected intravenously, all of them could be accounted for in blood samples withdrawn by a catheter placed in the right ventricle; however, these were not recoverable in blood of peripheral arteries and veins after it had passed through the lesser circulation. In addition, leukemic cells introduced into the femoral artery could be accounted for in the femoral vein, indicating that not all capillary beds served to remove such white cells from the circulation (11).

During the past year the studies have been extended to cross transfusions between patients with leukemia and cancer patients without hematological disorders, as well as between patients with myelogenous and lymphogenous leukemia. Up to 150 liters of blood have been exchanged between two partners by means of an artery-to-artery connection. It was found that shortly after the initiation of such a procedure the hematocrit and blood chemistry values (e.g., NPN, uric acid, etc.) quickly equilibrated but that the white cell levels did not. These data also indicate the extremely rapid removal of white blood cells from the circulation.

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Recently additional interest has been aroused in the lymphocyte levels of the thoracic duct in patients with leukemia. In 3 patients with lymphatic leukemia, specimens were obtained from the thoracic duct within two hours after death. Despite very high peripheral blood counts in 2 patients, the lymphocyte count in the thoracic duct fluid was within the normal limits of 5 to 20,000 per cmm. It is now planned to catheterize the thoracic duct in living patients with leukemia in order to observe the effect of diverting this presumed main source of lymphocytes to the blood stream upon the peripheral white blood count and the clinical condition of the patient. The Department of Surgery believes that this procedure is feasible in patients.

B. Cardiovascular dynamics. A systematic attempt is being made to study various physiological changes in patients with cancer with particular emphasis on the cardiovascular and circulatory dynamics. The following information is being gathered on cancer patients before and after the various forms of therapy, as well as in untreated cases as the disease progresses. Normal individuals are used for comparison. It is hoped that through these studies a better understanding may be obtained of some of the physiological changes that occur during progress of neoplastic diseases. It is possible that attempts to reverse some of these changes may lead to better medical management of advanced patients with cancer.

1. Left and right circulation time by the Evans blue oximeter method have been studied in about 200 determinations on 80 patients and normal individuals.

2. Determination of total body water by the antipyrine method has been carried out on 35 patients and 6 normals.

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3. Plasma and total blood volumes have been determined in 33 patients and 3 normals.

4. Cardiac output. The automatic recording of the oximeter changes following the rapid injection of measured amounts of Evans blue appears to have a future as a method of determining the cardiac output. The area displaced by the galvanometer tracing following injection of the dye appears to bear a relationship to cardiac output. Values by this simple procedure and values obtained by repeated Fick determinations on one patient seem to be in conformity. Although much more work remains to be done before the validity for this method for cardiac output can be established, the data are sufficient to indicate that it may be a practical and reliable method of such measurement.

5. In conjunction with the above, biochemical determina-
 tions are made on sodium, potassium, non-protein nitrogen and uric acid on the blood of the patients. Complete blood counts and packed cell volume are determined. The basal metabolic rate and vital capacity, as well as more routine clinical observations, are also carried out at the same time. Correlated studies have been made on 19 patients with cancer and on 4 normal individuals. Statistical analysis is at present being performed to ascertain the fruitful directions of subsequent work.

C. Red blood cell life by sulfhemoglobin method. An investiga-
 tion is being conducted on the use of sulfhemoglobin tagged red cells for a non-radioactive determination of the length of survival of red blood cells. Sulfhemoglobin binds tightly in the red blood cells and disappears

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in approximately the length of time for red blood cell life by the other reliable methods that have been used.

To build up sulfhemoglobin in the blood, an aromatic amine and some source of sulfide ion is necessary. In human beings this is best accomplished by giving 1.2 grams of acetanilid, and 2 grams of flowers of sulfur orally; adequate levels of sulfhemoglobin are reached in 10 to 14 days.

In animals, para-amino-propriophenone given in doses of 60 mg. to a 5 kg. rabbit that has received sulfur in the diet for 5 or 6 days will produce very high sulfhemoglobin levels within 24 hours. One patient, given sulfur for 4 days followed by a single oral dose of 300 mg. aminophenone, developed an adequate level of sulfhemoglobin overnight and had no toxic effects.

The average life cycle of red blood cell as determined by these methods in rabbits is about 40 days; in C3H strain mice, approximately 20 days. C3H mice with mammary tumors showed a decreasing red blood cell life as the tumor progressed, down to 10 days. Much shorter duration of red blood cell life is obtained if drugs are given which markedly disturb the balance in the hemopoietic system. Also, if levels of sulfhemoglobin above 20 per cent are developed, a much shorter red blood cell life results.

The red blood cell life has been determined in a number of patients using acetanilid and sulfur orally. These have varied from 21 days for a case of lymphatic leukemia to 108 days for a case of oral cancer. In three normal human beings, the red blood cell life determined by this method was 65, 66 and 71 days, respectively.

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D. Tests for pheochromocytoma. Sixty-five tests for pheochromocytoma have been carried out in 30 cases of hypertension (7). Benzodioxane, dibenamine, histamine and tetraethylammonium bromide were used. Pheochromocytoma-like reactions were obtained in 3 patients but only one case has come to operation and this patient did not have a pheochromocytoma. The other 2 cases are still under investigation. During the course of these tests 4 toxic reactions, 2 to benzodioxane and 2 each to dibenamine and tetraethylammonium were seen. These consisted of a marked, prolonged hypertension, pulmonary edema and in one case a transient anuria. The observations have been prepared for publication (10).

E. Radiophosphorus partition in blood, urine and tumor tissue.

The radiophosphorus concentration time curve over tumor and non-tumor tissue as determined by surface counting was found to be triphasic in nature: an initial rapid rise of activity, peaking, followed by a rapid decline and a levelling off of activity which then subsequently declined at a very slow rate over a period of days. These changes in activity occurred during the first 60 minutes after intravenous injection of P^{32} .

In 3 of 6 patients, who subsequently showed a good clinical response to the nitrogen mustard therapy, the post-treatment curve of activity in both tumor and non-tumor tissue showed a slower rate of incorporation of radiophosphorus, about one-tenth of the pre-treatment rate. In these same patients the urinary excretion of radiophosphorus after treatment was about doubled. In 3 patients who did not respond clinically to nitrogen mustard therapy, the concentration time course of radioactivity in the tumor and non-tumor tissue after treatment was essentially the same as the pre-treatment curve and the urinary excretion

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of radiophosphorus was the same as during the pre-treatment period. The plasma level of P³² was essentially the same during the pre- and post-treatment periods in all 6 patients.

From the specific activities obtained by fractionation studies of phosphorus-containing compounds in tumor tissue 24 hours after administration of the radiophosphorus, there is strong evidence to indicate that the uptake curves are a measure of the turnover of intracellular inorganic phosphorus and acid soluble phosphorus compounds in tumor tissue.

These studies were carried out in collaboration with Dr. B. V. A.

Low-Beer.

F. Anabolic effects of androgens. In collaboration with Dr. Gilbert S. Gordan, studies are being carried out on the anabolic effect of testosterone with particular reference to comparing the relative anabolic effects of various preparations of testosterone and its analogs. Associated patients with rheumatoid arthritis or with cancer of the breast are maintained on complete balance, with emphasis on nitrogen, potassium, sodium, phosphorus and calcium intake and output. In addition, determinations of 17-ketosteroid and gonadotropin excretion are also carried out. Recently interest has been aroused in methylandrostenediol, which is apparently non-androgenic in the usual doses, but is reported to have considerable anabolic activity. According to communications from Dr. F. Homburger of Tuft College Medical School, the compound produces remissions in cancer of the breast such as those seen with testosterone.

G. Sulfhydryl content of blood. Studies are being conducted on the sulfhydryl content of blood plasma and blood serum from patients with cancer before and after treatment with nitrogen mustard and other agents. It was found the sulfhydryl content of blood is significantly

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have a very short prognosis, only 2 of 14 living as long as 3 months, the remaining expiring within a month after such determinations. The response of patients to intravenous epinephrine also has been studied. In five patients with chronic myelocytic leukemia, this produced a rise in blood histamine. In four cases of acute leukemia, the blood histamine fell after administration of epinephrine.

The histamine determinations are carried out by the classical bio-assay method on guinea pig intestine in vitro. Recently it has been established that the material extracted from the blood of myelocytic leukemia patients has the chemical properties of histamine.

III. Protein Chemistry.

A. Physicochemical characterization of tumor tissue. The program of the past year falls into three main segments, all concerned with the protein or nucleic acid components of malignant tissue:

1. Nucleohistone and nucleic acid of mouse lymphoma.

Purified nucleohistone and a highly polymerized desoxyribose nucleic acid have been isolated from mouse lymphoma. Both nucleohistone and nucleic acid are being studied by a variety of chemical and physico-chemical methods in order to determine their relation to the analogous components of normal tissue.

2. Soluble proteins of mouse mammary tumor. A number of

soluble protein fractions derived from the cytoplasm of the mouse mammary tumor have been examined electrophoretically. These showed definitive and reproducible patterns which will serve as the basis for further

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development of methods for isolation in pure form of certain of the electrophoretic components.

3. Soluble proteins of human malignant tissues.

The phase of this project has mainly involved electrophoretic studies of the soluble cytoplasmic proteins of about a dozen normal and malignant neoplastic human tissues. Two types of preparation have been used: the total solubles prepared by high speed centrifugation, and a fraction derived from these solubles by low temperature alcohol fractionation. Although the work is still in an early stage it is apparent that the protein of each tissue specimen can be characterized by a definitive electrophoretic pattern analogous to those found with such materials as egg white and blood serum.

Using these tumor tissue fractions as antigens, differentiation by immunochemical methods is also being attempted, with particular emphasis on the Schultz-Dale reaction.

B. Radioactive immune globulins. Partially purified (anti-human serum albumin) rabbit globulin has been iodinated with carrier iodine and I^{131} . The iodinated and uniodinated antibody were then serologically tested for changes in immunologic specificity by the quantitative precipitin reaction. It was found that there was no change in immunologic specificity when about 2 iodine atoms were substituted per antibody molecule. The amount of radioactivity in each precipitate in the precipitin reaction was proportional to the amount of antibody nitrogen. Iodination causes a 15 per cent reduction of precipitable antibody in the zone of optimal proportions but there is no shift in the zone (12).

A continuation of these studies is presently being undertaken to determine the in vivo localization of radio-antibody. The same

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Antibody system described above will be studied as well as protein material from tumor material.

Respectfully submitted:

Michael B. Shimkin
Michael B. Shimkin, M.D.
Chief, Laboratory of
Experimental Oncology

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SUMMARY

The objective of the Laboratory is clinical research in cancer. With the cancer patient as the focal point of investigation, the work is oriented along four broad approaches: (1) Experimental therapy, providing clinical material for other studies as well as permitting evaluation of such procedures on neoplastic diseases; (2) Physiology, particularly cardiovascular and respiratory physiology of patients with neoplastic diseases; (3) Biochemistry, including metabolic studies on cancer patients, and investigations of specific biochemical reactions; and (4) The study of protein fractions of cancer and normal tissues of human and animal origin, utilizing physicochemical and immunochemical techniques.

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