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FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
APPLICATION FOR RESEARCH GRANT

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PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH GRANTS
Bethesda 14, Maryland

DATE 25 January 1954

Application is hereby made for a grant in the amount of $ ~~56,977.12~~ 57,003.00 for the period

from September (Month) 1 (Day) 1954 (Year) through August (Month) 31 (Day) 1955 (Year)

Inclusive (Not to Exceed 1 year) for the purpose of conducting a research project on the following subject:

(Give only brief descriptive title)

TITLE OF PROJECT: Clinical Cancer Research with Emphasis on Experimental Therapy and Patho-Physiology

NAME OF PRINCIPAL INVESTIGATOR	TITLE OF PRINCIPAL INVESTIGATOR
David A. Wood, M.D.	Director, Cancer Research Institute and Professor of Pathology (Oncology)

ADDRESS OF PRINCIPAL INVESTIGATOR
University of California School of Medicine, San Francisco 22, California

NAME OF FINANCIAL OFFICER TO WHOM CHECK SHOULD BE MAILED	TITLE OF FINANCIAL OFFICER
Mr. J. H. Corley	Vice- President, Business Affairs

ADDRESS OF FINANCIAL OFFICER
University of California, Berkeley 4, California

AGREEMENT

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 may be revoked in whole or part at any time by the Surgeon General of the Public Health Service, 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 investigators supported by any grant made as a result of this request shall acknowledge such support; (4) that if any patentable discoveries or inventions are madein 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 patenable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

NAME OF INSTITUTION University of California

NAME AND TITLE OF OFFICIAL AUTHORIZED TO SIGN FOR INSTITUTION (Please Type) Robert G. Sproul, President

PERSONAL SIGNATURE

(This agreement must carry the actual signature of the official whose name appears on the line above.)

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These dates to be the same as those given on page 1.

BUDGET PROPOSED FOR THE YEAR 1 September 1954 through 31 August 1955

NOTE: Under column entitled "OTHER" indicate funds presently available or anticipated from other sources including own institution.

	BUDGET REQUESTED FROM P.H.S.	BUDGET OTHER
PERSONNEL (Itemize all positions by indicating type; names of professional personnel, if selected.)		
Dr. David Wood, Director, CRI, and Prof. of Pathology	$	$ *****
Dr. Peter Forsham, Assoc. Prof. of Medicine and Direcotr, Metabolic Unit		*****
Dr. Maurice Galante, Asst. Prof. of Surgery	5,990.00	
Dr. B.V.A. Low-Beer, Professor of Radiology		*****
Snr. Laboratory Technician (Biochemist)	3,750.00	
Laboratory Technician (Cytology) -50%	1,621.00	
State Employees Retirement System Contributions (8.17% plus $5.25 Serv. Ch.)	449.30	
Retirement and Annuities System (9.52% of $5,990.)	570.25	
Research Resident in Medicine (without perquisites)	3,600.00	
PERMANENT EQUIPMENT		
None	- 0 -	
CONSUMABLE SUPPLIES (Itemize)		
Chemical Supplies	2,000.00	
Drugs, hormones, etc.	2,500.00	
Isotopes	1,000.00	
TRAVEL		
None	- 0 -	
OTHER EXPENSE (Itemize) Clinical Research Beds (910 patient days @ $30.00 per diem)	27,300.00	
Special Laboratory Procedures	2,000.00	
X-Rays	2,000.00	
SUBTOTAL	$ 52,780.55	
OVERHEAD	$ [redacted]	
TOTAL FOR THE YEAR	$ 57,003.00	

NOTE: The administrative official signing this application may add an amount for overhead not to exceed 8 percent of the operating costs, i.e. 8 percent of the subtotal.

ESTIMATE OF FUTURE REQUIREMENTS

Estimate of future requirements applies to funds needed from the public Health Service for the years subsequent to the period proposed at the top of this page. The blanks at the right provide space for requesting four additional years support; any amounts entered should include "overhead" if such is to be requested. Do not leave any of these spaces blank - enter one of the following as applicable: The amount needed, "not applicable", "unknown" or "none". FOR FURTHER INFORMATION: See detailed instructions accompanying application forms.

1 $58,500.00
2 $60,000.00
3 _____
4 _____

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PUBLIC HEALTH SERVICE SUPPORT: Show previous and current Public Health Service grants supporting this project:

GRANT NUMBER	TITLE OF PROJECT	AMOUNT	PERIOD OF SUPPORT
PREVIOUS			
CT-493 (C4) (C5)	Cancer Teaching	$4,844.00	(Salary of Dr. M. Galante, 9/1/52 to 8/31/53
CURRENT			
C-2085	Clinical Cancer Research with Emphasis on Experimental Therapy and Patho-Physiology	$70,000.00 Note: $31,682.70 of this sum is allocated to Breast Cancer	9/1/53 - 8/31/54
ALL OTHER SUPPORT:	Excluding Public Health Service, but including that from own institution, list support from other sources for this project. If none, so indicate.		
SOURCE	TITLE OF PROJECT	AMOUNT	PERIOD OF SUPPORT
CURRENT			
American Cancer Society-Inst. Grant 43E	Cancer Research in Action ($4,470. of this grant is allocated toward salary of Dr. Galante)	$75,000.00	9/1/53 - 8/31/54
PENDING			
NONE			

RESEARCH PLAN AND SUPPORTING DATA

On the continuation pages provided give details of the proposed plan and other necessary data in accordance with the outline below. Number each page, the first continuation page being page 4. Additional continuation pages, if needed, may be requested from the Division of Research Grants. See detailed instructions before preparing this portion of the application.

1. RESEARCH PLAN
   A. Specific Aims - Provide a concise statement of the aims of the proposed work.
   B. Method of Procedure - Give details of your plan of attack.
   C. Significance of this Research - Explain why the results of the proposed work may be important.
   D. Facilities Available - Describe the general facilities at your disposal. List the Major items of permanent equipment.

2. PREVIOUS WORK DONE ON THIS PROJECT
   Describe briefly any work you have done to date that is particularly pertinent.

3. PERSONAL PUBLICATIONS
   Cite your most important publications on this or closely related work. List no more than five.

4. RESULTS OBTAINED BY OTHERS
   Summarize pertinent results to date obtained by others on this problem, citing publications deemed pertinent. Select no more than five.

5. BIOGRAPHICAL SKETCHES
   Provide brief sketches for ALL professional personnel selected who are to be actively engaged in this project.

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APPLICATION FOR RESEARCH GRANT (COntinuation Sheet) (LEAVE BLANK)

1. RESEARCH PLAN

The specific aim of this grant renewal request is to provide for continuity during the year 1954-55 of one phase of the clinical cancer research program at the University of California School of Medicine and Hospitals (Support for other phases of the Clinical Cancer Research program will be requested in separate research grant applications). The project proposed in this grant renewal application has to do with the study of hormonal influences in breast cancer. It will entail not only procedures and observations on patients, but such patho-physiological studies as may seem pertinent for purposes of correlation and completeness. Participating in the immediate conduct of the project will be Dr. Maurice Galante (Surgery), Dr. Peter Forsham (Medicine and the Metabolic Unit), Dr. B.V.A. Low-Beer (Radiology)Dr. David A. Wood (Pathology), and a Resident in Research Medicine. The project will encompass close collaboration with other personnel in the Cytology Laboratories of the Cancer Research Institute and in the Departments of Surgery, Medicine, Radiology, and Pathology.

A. Specific Aims - To investigate the effect on the growth and maintenance of various histological patterns of primary and metastatic breast carcinoma produced by:

1) Bilateral oophorectomy and adrenalectomy. (25 patients will be subjected to this procedure requiring an estimated average of 14 days hospitalization each, for a total of 350 hospitalization days)

2) Bilateral oophorectomy, right adrenalectomy, and adreno-splenic shunt by end to end anastomosis of the left adrenal vein and splenic vein. (10 patients, 21 days hospitalization each, total 210 hospitalization days.)

3) Suppression of adrenocortical activity by the continuous daily administration of 50 to 100 mgm. of cortisone acetate. (Primarily, hospitalization in this series will be required for purpose of oophorectomy: 25 patients, 14 days hospitalization each, total 350 hospitalization days)

B. Method of Procedure:

1. Histological proof as to the diagnosis of carcinoma will be required in each case.

2) The dependence of the tumor on estrogen will be evaluated according to the method of Pearson et al., viz.: in the presence of bony metastases and on a calcium-free diet, urinary calcium will be determined during a control period and during the administration of estrogen. A rise of calcium excretion will be taken as an indication of estrogen susceptibility of the tumor. These results will be correlated with the histology of the tumor and clinical course.

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APPLICATION FOR RESEARCH GRANT (Continuation page)

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3) Adrenal function will be evaluated prior to surgery using standardized intravenous ACTH tests and the changes in urinary 17-hydroxycorticoids in an attempt to correlated adrenal cortical activity, adrenal weight, and the course of the neoplastic growth following removal of the adrenal glands and ovaries.

4) The surgical procedures employed will be of the accepted variety except for the adrenosplenic venous shunt. In the latter, the adrenal gland, in addition to being freed from small venous channels, will be covered with omentum. This is designed to prevent the venous return from the adrenal into the systemic rather than the portal circulation.

5) The clinical effects of the various procedures on the growth of the carcinoma will be followed by careful clinical evaluation, x-ray studies, determinations of alkaline phosphatase, electrophoretically determined A/G ratios, and biopsies as indicated.

6) Radioisotope techniques using inorganic and organic tagged compounds will be employed in selected cases for the study of
   a) localization of tumors and their metastases;
   b) the study of the pathway of tagged hormones;
   c) the effect of hormones on the iodine metabolism; and
   d) the study of the rate of incorporation of tagged amino acids into tumor tissue.

7) Vaginal smear patterns will be evaluated. (In pilot observations to date, vaginal smears indicate an abnormally high estrogen effect in some pre-menopausal patients with advanced breast cancer. Residual estrogen effects with apparent fluctuant changes have been noted in patients following oophorectomy without adrenalectomy). These studies will be compared with those on other patients seen in the Advanced Breast Tumor Clinic.

C. Significance of the Research:

By comparing the effects of bilateral oophorectomy and adrenalectomy; bilateral oophorectomy - right adrenalectomy - left adrenosplenic venous shunt; oophorectomy with adrenal suppression by cortisone acetate among each other and contrasting these effects with the natural course of this malignancy, it is hoped an indication will be obtained for evaluation of this type of therapy. Only patients refractory to other established forms of therapy will be used in this study. The physiological data obtained will be of fundamental value, such as:

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a) Correlation of adrenal function with size of the adrenal gland.
b) Determining the fate of adrenal corticoids, estrogens and androgens when shunted into the portal circulation.
c) Ascertaining the effect evoked by the absence of estrogens upon the histological pattern of the tumor, whether produced by removal of ovaries and adrenals or by cortisone suppression.
d) Noting variations, if any, in the concentration of tagged metabolites in tumor tissue before and after the procedures have been carried out.

D. Facilities:

For the period September 1, 1954 to January 1, 1955 two of four clinical beds will be available in the University Hospital. After January 1, 1955 a total of 32 clinical research beds will be available in the new quarters of the Cancer Research Institute on the 12th floor of the about-to-be-completed teaching hospital. Facilities of the Metabolic Unit (Dr. Peter Forsham) will be available for special ketosteroids and other determinations. Facilities of the radiation and radiological laboratories will be utilized insofar as is necessary for such isotope studies as will be undertaken. In addition, facilities of the Cytology laboratories will be available. Patients will be selected from the Advanced Breast Tumor Clinic.

2. PREVIOUS WORK DONE ON THIS PROJECT

Twenty-six cases with advanced breast carcinoma have undergone bilateral oophorectomy and adrenalectomy with twenty-four postoperative survivors. In a nine-months follow-up we have observed either subjective or objective improvement in 45% of patients. Factors evaluated as indicative of possible improvement included: disappearance of pain, diminution in the size of carcinomatous masses, healing of ulcerations, diminution or disappearance of pleural effusions, and re-calcification of bony defects.

Two cases have been subjected to adreno-splenic venous shunt. One patient has shown reutrn of normal adrenocortical function. Postoperatively, no demonstrable estrogens have appeared in the urine. In the other patient, there was no demonstrable evidence of physiological activity of the adrenal gland. Presumably, thrombosis of the venous shunt had occurred.

Daily urinary corticoid excretion has been correlated with adrenal weights and to date we have been unable to establish a direct relationship.

No correlation was found between the histological picture and the effect of bilateral oophorectomy and adrenalectomy on the growth of metastases.

No difference has been noted to date in the adrenal response of controls and patients with metastatic breast carcinoma to ACTH stimulation as determined by 17-hydroxycorticoids urinary excretion (Tables I,II)

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TABLE I

NORMAL ADRENAL RESPONSE TO ACTH STIMULATION

Patient	24-hr.urin. Cpd. F before ACTH	24-hr.urin. Cpd. F after ACTH	% Rise In Cpd.F after ACTH	24-hr. 17-KS	24-hr. 17-KS after ACTH	% Rise in 17-KS
Case I	14	42	200	1	8	700
Case II	9	38	311	7	10	43
Case III	11	53	381	6	10	70

TABLE II

ADRENAL RESPONSE TO ACTH STIMULATION IN PATIENTS SUFFERING FROM CARCINOMA OF THE BREAST

Patient	24-hr. Urin. Cpd. F	24-hr.urin. Cpd. F after ACTH	% Rise in Cpd. F after ACTH	24-hr. 17-KS	24-hr. 17-KS after ACTH	% Rise in 17-KS
Case IV	8	29	263	4	16	300
Case V	12	44	267	5	15	200
Case VI	2.5	8.9	256	1	2	100
Case VII	6	21	250	2	4	100
Case VIII	9	32	255	2	4	100

Laboratory determinations on the patient who had been subjected successfully to an adrenosplenic venous shunt indicate that a) corticoids are not inactivated by the human liver to any appreciable extent (Table III)

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TABLE III

EFFECT OF TRANSHEPATIC SHUNT OF THE LEFT ADRENAL ON URINARY STEROID EXCRETION

Time	17-Hydroxycorticoids mg. Cpd.F/Day		17-ketosteroids mg. Dia/day	
	Control	IV ACTH Test*	Control	IV ACTH Test
Before Surgery	12	41	10	24
After removal of two ovaries and one adrenal	8	21	3	6
108 days after left adreno-splenic shunt	8	18	4	5

*IV ACTH: 25 USP Units of ACTH in 1,000 cc. 5% D/W IV over an 8-hour period during a 24-hour collection

b) That estrogens are inactivated by the human liver since none is eliminated in the urine postoperatively (Table IV)

TABLE IV

ESTROGEN ASSAY IN DAILY URINE SAMPLES BY THE METHOD OF HELLER**
N.B. A rise in rat uterine weight reflects estrogen activity

	Before Surgery	After Oopherectomy and Unilateral Adrenalectomy and 3 days of IV ACTH (25 USP Units for 8 hrs.)	After Adrenesplenic shunt and 3 days of ACTH Gel, 80 Eq. U. per day
Mean percentage rise of uterine weights over controls	250%	40%	0%
Conclusion	Normal estrogen effect	Barely detectable estrogen effect	No estrogen effect

** We are indebted to Dr. Carl Heller of Portland, Oregon, for these determinations.

(The above phenomenon had been observed by other investigators in the experimental animal).

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3. PUBLICATIONS

Two completed manuscripts are being submitted for publication:-

i) The Value of Bilateral Adrenalectomy in Advanced Breast Cancer

ii) The Role of the Liver in the Metabolism of Steroid Hormones in Breast Cancer (determined by performance of adrenosplenic venous shunts).

In addition to the above papers by Drs. Galante, Forsham, and Wood, there are two publications, as follows:

i) Low-Beer, B.V.A., M.D. et al. Clinical and Laboratory Studies on the Uptake of Radioactive Phosphorus by Lesions of the Breast. Surgery 24: 409-415, August 1948.

ii) Low-Beer, B.V.A., M.D. et al. Measurement of Radioactive Phosphorus in the Breast Tumors in Situ; a Possible Diagnostic Procedure. Radiology 47: 493-495; November 1946

4. RESULTS OBTAINED BY OTHERS

a) Huggins has recently reported a series of 53 patients with advanced mammary carcinoma treated by bilateral adrenalectomy with or without bilateral oophorectomy with marked improvement in many cases and with histopathological and chemical correlations (J.A.M.A., April 18, 1953. pp. 1388-1394).

b) Biskind and co-workers have demonstrated the development of ovarian tumors in intrasplenic implants performed in mice. They postulated that estrogens produced by the intrasplenic implants of ovarian tissue were inactivated by the liver. (Bull. Johns Hopkins Hosp. 65: 213, 1939; Endocrinology 32, 97. 1943)

c) Pearson et al. have postulated that the rate of growth of osteolytic metastatic breast tumors can be measured by determining the rate of calcium loss. These studies indicate the possible existence of two types of breast carcinoma in humans which cannot be differentiated by the histological pattern of the tumors, but are distinguishable by their rate of growth as indicated by calcium excretion studies (J. Clin. Inv. June 1953, 6 pp. 594).

5. BIOGRAPHICAL SKETCHES

WOOD, David A., M.D., Professor of Pathology (Oncology) and Director of the Cancer Research Institute.

Forsham, Peter H., M.D. Assoc. Professor of Medicine and Pediatrics. Director of the Metabolic Research Laboratory.

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LOW-BEER, B.V.A., M.D., Professor of Radiology

GALANTE, Maurice, M.D., Instructor in Surgery and Junior Research Surgeon, Cancer Research Institute, recommended for promotion to Assistant Professor of Surgery.

M.D., Ohio State University College of Medicine, 1943. Internship: Morrisania City Hospital, New York City, 1944-45. Residency: University of California Hospital, Surgery: 1945-46 and 1947-52.A.O.A. Graduated "With Honors" from Medical School; Fesca Surgical Award, University of California Hospital, 1950; San Francisco Surgical Society Award, First Prize, 1950. Instructor in Surgery, University of California since 1951.

Author of papers on the Production and Closure of Interventricular Cardiac Septal Defects; Amino Acid Tolerance in Experimental Portocaval Anastomosis; Effects of Continuous Cross-Transfusion on Experimentally Produced Uremia in Dogs; Experimental Study of Thyroid Regeneration following Subtotal Thyroidectomy; Surgical Removal of the Superior Mediastinal Lymphatics for Cancer of the Thyroid Gland; and Breast Cancer (page 9 of this application).

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NOTICE OF RESEARCH PROJECT

Prepared for the Medical Sciences Information Exchange.

Not for Publication or Publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

SUBMITTED TO: Public Health Service, National Institutes of Health, Div. of Research Grants Bethesda 14, Md.

TITLE OF PROJECT:
Clinical Cancer Research with Emphasis on Experimental Therapy and Patho-Physiology

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL, ENGAGED ON THE PROJECT.

Dr. David A. Wood, Director, Cancer Research Institute; Dr. Maurice Galante, Jnr. Research Surgeon; Dr. Peter Forsham, Director, Metabolic Unit; Dr. N.V.A. Low-Beer, Professor of Radiology.

NAME AND ADDRESS OF APPLICANT INSTITUTION:

University of California School of Medicine, San Francisco 22, California.

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

In the Medical Science Information Exchange 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.

Clinical cancer research proposed in this project will be a continuation of studies concerning hormonal influences in human breast cancer. Concurrent with observations on patients, such patho-Physiological studies as may seem pertinent will be carried out.

An attempt will be made to understand more fully the role of steroid hormones in the management of breast cancer. Attention will be focused upon procedures designed to give more knowledge concerning the role of the liver in the metabolism of steroid hormones and the applicability of these procedures in treatment. Primarily, this has to do with the selection of cases suitable for left adreno-splenic venous shunt following adrenalectomy on the right and bilateral oophorectomy. One such pilot procedure has been successful and indicates after nine months follow-up that not only has there been a marked regression of metastases but the estrogens arising in the left adrenal gland have been inactivated by the liver, although the corticoid output remains essentially unimpaired in the systemic circulation. Our present series of bilateral adrenalectomy and oophorectomy cases will be enlarged. A control series with bilateral oophorectomy will be subjected to so-called "medical adrenalectomy" by the administration of cortisone acetate.

SIGNATURE OF PRINCIPAL INVESTIGATOR _____

Itentify the Professional School (medical, dental, public health, graduate, or other) with which this project should be identified:

SCHOOL: _____ of Medicine

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