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CARTON NO. <i>875</i>	
FOLDER NAME <i>W-4-W #1 of 2</i>	
NOTES <i>Chemotherapy - Lung Cancer 2 of 9</i>	
FOUND BY/DATE FOUND <i>Blanchard 1/10/95</i>	

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FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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C-2365

APPLICATION FOR RESEARCH GRANT

P.E.T. (1)

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

Rec. 2-23-54

Date 27 January 1954

June '54 Council

Application is hereby made for a grant in the amount of \$ ~~86,153.51~~ (80) for the period from September 1 1954 through August 31 1955 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 **Chemotherapy and Patho-Physiology in Lung Cancer**

NAME OF PRINCIPAL INVESTIGATOR

David A. Wood, M. D.

H. Glenn Bell, M. D.

Seymour M. Farber, M. D.

ADDRESS OF PRINCIPAL INVESTIGATOR

TITLE OF PRINCIPAL INVESTIGATOR

Director, Cancer Research Institute
Professor and Chairman, Dept. of Surge
Assoc. Cl. Professor of Medicine

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

NAME OF FINANCIAL OFFICER TO WHOM CHECK SHOULD BE MAILED

Mr. J. H. Corley

TITLE OF FINANCIAL OFFICER

Vice-President, Business Affairs

ADDRESS OF FINANCIAL OFFICER

University of California, Berkeley 4, California

Page 3 omitted - no entries (80) 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 investigations supported by any grant made as a result of this request shall acknowledge such support; (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.

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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Form Approved Budget Bureau No. 68-R249.8

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FOUND BY/DATE FOUND	J. Landayuri 4/10/95	

PRIVACY ACT MATERIAL REMOVED

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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.		B U D G E T	
		REQUESTED FROM P.H.S.	OTHER
PERSONNEL (Itemize all positions by indicating type; names of professional personnel, if selected.)			
David A. Wood, M.D., Director, and Prof. Pathology			*****
H. Glenn Bell, M.D., Professor of Surgery			*****
Seymour M. Farber, M.D., Assoc. Cl. Prof. Medicine			*****
Roger H. Wilson, M.D., Instructor in Medicine and Jnr. Research Physician (Pulmonary Physiologist) 75%	\$3,783.00		
Resident in Research Medicine (without perquisites)	3,600.00		
Senior Laboratory Technician (Physiology)	3,750.00		
Senior Laboratory Technician (Cytology)	3,750.00		
PERMANENT EQUIPMENT State Employees Retirement			
Contributions (8.17% plus \$5.25 serv. ch. each)	623.25		
Retirement and Annuities System (9.52% of \$3,783)	360.15		
PERMANENT EQUIPMENT			
Itemized list - see page 2-A	7,910.00		
CONSUMABLE SUPPLIES (Itemize)			
Chemicals, glassware, misc. small items	1,200.00		
Recording paper, spare batteries, etc.	200.00		
TRAVEL (State purpose)			
To attend meetings of National Associations and afford opportunities to confer with other workers in the field	600.00		
OTHER EXPENSE (Itemize)			
5 Clinical Research Beds (1800 patient days at approx. \$30.00 per diem)	54,000.00		
NOTE: The administrative official signing this application may add an amount for overhead in accordance with the instructions.	SUBTOTAL	\$79,776.40	
	OVERHEAD		
TOTAL FOR THE YEAR		\$86,158.40	(80)

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 of 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	\$90,000.00
2	\$100,000.00
3	
4	

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PERMANENT EQUIPMENT
(see page two)

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- | | | |
|-----|--|----------|
| 1. | 5.6 liter Benedict-Roth spirometer adapted for rapid drum movement. (Warren Collins Co.) | \$450.00 |
| 2. | 5 cu. ft. gas prover to specifications with 30 gallons of insulating oil (Amer. Meter Co.) | 575.00 |
| 3. | Kymograph for (2) to specifications (Appl. Biophysics Lab) | 85.00 |
| 4. | Rapid flow valves, residual air valve, to specifications, connectors and tubing | 330.00 |
| 5. | Two Van Slyke manometric gas analyser | 610.00 |
| 6. | Wilson-Givens electrometer complete with constant temperature bath, pH amplifier and polarography electrodes | 725.00 |
| 7. | Glass and calomel electrodes for (6); special vessels for analyses (Braun-Knecht-Heimann) | 120.00 |
| 8. | Scholander microgas analyser (Appl. Biophysics Labs.) | 120.00 |
| 9. | International Clinical centrifuge | 110.00 |
| 10. | Recording system consisting of: | |
| | a) 2-channel recording galvanometer equipped with strain gauge amplifiers | 1,650.00 |
| | b) Single channel recording galvanometer equipped with DC amplifier | 650.00 |
| | c) 2 low pressure and 1 high pressure strain gauges | 825.00 |
| | d) 2 oximeter ear pieces and filter | 260.00 |
| | e) High sensitivity spot galvanometer (Rubicon Co.) | 110.00 |
| | f) Oscilloscope (7") (Waterman Co.) | 275.00 |
| | g) Couplers and adaptors (Appl. Biophysics Labs.) | 110.00 |
| 11. | Interval timers and stop watches | 60.00 |
| 12. | Van Slyke Neill pipettes, special tonometers | 220.00 |
| 13. | Electric sterilizer | 110.00 |
| 14. | Arterial needles, cardiac catheters, etc. | 165.00 |
| 15. | Special gas mixtures, adaptors, reducing valves and demand valve Nos. 11-15 | 350.00 |

TOTAL - PERMANENT EQUIPMENT \$7,910.00

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I. RESEARCH PLAN

The project proposed in this grant application has to do with studies on patho-physiological factors which influence the natural course of lung cancer; the influence of various agents introduced by different routes upon the neoplastic as well as non-neoplastic cellular elements of the lower respiratory tract; and the trial of such chemotherapeutic agents available now and developed in the future. This entails recognition of such problems as dosage, chemical resistance, cell type, etc. It is recognized that in any such program the concept of "total care" is paramount and most desirable. A strong team of interested workers is now available in addition to facilities which make favorable and promising such a study. These include availability of an ample number of patients well studied clinically; a well functioning and productive pulmonary cytology laboratory; a pulmonary physiology unit; and five of thirty-two clinical research beds at the Cancer Research Institute. Such additional beds as may be desirable will also be available at the University Hospital and on the University of California service at the San Francisco Hospital. Participating in the immediate conduct of this project will be Dr. S. M. Farber, Associate Clinical Professor of Medicine, Dr. H. Glenn Bell, Professor of Surgery (and his thoracic surgery personnel, -- Dr. H. Brodie Stephens, Dr. Orville Grimes, and Dr. Benson Roe); Dr. Roger H. Wilson, Clinical Instructor of Medicine (Pulmonary Physiologist); and Dr. David A. Wood, Professor of Pathology. In addition, the proposed project will encompass close collaboration with personnel in other areas of the Cancer Research Institute, as well as in the Department of Medicine (Professor Theo. L. Althausen), Radiology (Professor Robert S. Stone), Pharmacology (Professor H. H. Anderson) and Biochemistry (Professor D. M. Greenberg).

A. Specific Aims

- 1) To evaluate carefully the clinical course of patients with inoperable lung cancer.
- 2) To place emphasis on the energetic evaluation of the effects of chemotherapeutic agents available now and in the future on the clinical course of inoperable lung cancer.
- 3) To establish criteria by which objective results can be gauged. This entails:
 - a) Careful evaluation of histologic patterns
 - b) Ascertaining cell changes by use of cytologic techniques (rigid emphasis being placed on nuclear changes evoked in exfoliated cells by such agents). It is hoped that such a rigid evaluation will be productive of basic information concerning the action of various chemicals.

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4) To evaluate physiologically patients before, during, and after chemical therapy. Complete blood and bronchial air analyses will be employed.

5) To evaluate in appropriate selected patients results obtained by combination of chemical therapy with established surgical and radiation procedures.

B. Method of Procedure

Patients for investigation are selected through the Consultative Tumor Board, the Staff of the University of California School of Medicine, and from non-staff physicians in Northern and Central California. As many patients as possible will be followed on an out-patient basis and will be admitted to the Hospital only for complete initial workup and initiation of therapy except as subsequent events might determine. Autopsies will be energetically sought in the instance of all deaths. Investigative programs on patients are reviewed by and must have prior approval of the Cancer Board of the School of Medicine for their clinical safety. All physicians on the staff of the Cancer Research Institute having to do with the care of patients must hold dual appointments in their respective academic departments of the School of Medicine.

1) Patients with inoperable lung cancer will be evaluated from all clinical and laboratory points of view. This will include histological proof of the diagnosis of carcinoma, and a consideration of epidemiological as well as possible etiologic factors.

2) In addition to the use of chemotherapeutic agents which have been employed with only minor and transient success to date, such as nitrogen mustard and TEM, we propose to study the effects of other agents as they become available in the future. These include such chemicals as the phosphoramides, purine antimetabolites, and the folic acid antagonists. Obviously, this envisions a long range program with coordinated basic laboratory and clinical facilities which lend themselves well toward the conduct of a chemotherapy testing program.

3) Sputum and bronchial secretions will be examined by cytologic techniques to form a "base line" prior to initiation of chemotherapy. Sputum and bronchial secretions will be examined routinely during and after chemotherapy with emphasis on nuclear changes in the exfoliated cells. It is felt that the possibility of a sensitive mechanism for the evaluation of such drugs should be sought by utilization of cytologic techniques.

4) Complete physiological studies will be conducted before, during and after therapy. These will include ventilatory studies, gas analysis of respiratory samples to determine carbon dioxide (CO₂) retention,

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calibration of performance on ventilatory stimulus, studies of alveolar ventilation and respiratory dead space, oxygen (O₂) diffusion in red blood corpuscles (polarographically), gas flow studies by calibrated pressure equipment (pneumotachography), etc.

5) In carefully selected patients, chemotherapy, radiation and surgical procedures in varying combinations will be studied for evaluation of immediate and long-term results.

C. Significance of This Research

The marked trend in the increased incidence of lung cancer during the past several decades clearly indicates that within a few years lung cancer will be the most common form of cancer in man. Less than ten per cent (10%) five-year arrests are now obtained under the most optimum circumstances in the treatment of malignancy. The significance of this proposed research is the expectation that certain chemicals may be found which will be more effective in human pulmonary cancer than those which have been studied to date. The fact that nitrogen mustard promotes effects in certain undifferentiated (oat cell) carcinomas, although only slight and of short duration, keynotes the great desirability of expanding basic and clinical studies in the field of chemotherapy. A careful program of evaluation is essential to any long range consideration. Critical evaluation of cytologic (nuclear) changes may produce criteria by which the efficacy and indication for use of specific chemical compounds can be determined.

The evaluation of pulmonary physiological changes may likewise give information of importance as a possible indication of the action of chemical compounds.

This project will make possible evaluation of combined radiation, surgery and chemotherapy as efficacious in affecting immediate and long term results.

D. Facilities Available

For the period September 1, 1954 to December 31, 1954 two to four clinical beds will be available at the University Hospital. Beds will also be available for certain patients as the needs and circumstances may determine on the University of California service at the San Francisco Hospital. Facilities of the Out-Patient Department will also be available. After January 1, 1955 five of the thirty-two clinical research beds in the new quarters of the Cancer Research Institute on the 12th floor of the about-to-be-completed teaching hospital will be allocated for this project. (These quarters have been made available by a \$1,000,000 construction grant from the Public Health Service). In these new quarters space is available for establishment of a special laboratory for pulmonary physiology and a research pulmonary cytology laboratory. Also situated on this floor will be basic facilities having to do with hematology, biochemistry, isotopes, cell physiology, radio-biology, and pharmacology.

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2. PREVIOUS WORK DONE ON THIS PROJECT

- 1) 1070 autopsy cases of lung cancer have been reviewed from a clinical and pathologic approach.
- 2) Sputum and bronchial secretions of over 2066 patients suspected of lung cancer have been studied and followed to final diagnosis.
- 3) Cellular changes in bronchial secretion as the result of enzymatic therapy have been studied in animals and non-neoplastic diseases of humans.
- 4) Alterations in pulmonary physiology as the result of disease process is now being studied.

3. PUBLICATIONS

"Cytologic Studies of Sputum and Bronchial Secretions in Primary Carcinoma of the Lung", Seymour M. Farber, M.D., F.C.C.P., Mortimer A. Benioff, M.D., John K. Frost, M.D., Milton Rosenthal, M.D., and Gerd Tobias, M.D. Diseases of the Chest, Vol. XIV, No. 5, p. 633, September-October, 1948.

"Cytologic Diagnosis of Lung Cancer", Seymour M. Farber, M.D., Milton Rosenthal, M.D., Edwin F. Alston, M.D., Mortimer A. Benioff, M.D., and Allen K. McGrath, Jr., M.D. Charles C. Thomas, Publisher, Springfield, Illinois, 1950.

"Enzymatic Debridement, with Particular reference to Trypsin and Desoxyribonuclease in the Control of Cough and Sputum associated with Tuberculosis", Seymour M. Farber, M.D., R. Daniel Gorman, M.D., David A. Wood, M.D., Orville F. Grimes, M.D., and Samuel L. Pharr, B.S. The Journal of Thoracic Surgery, p. 45, January 1954

"The Mucolytic and Digestive action of Trypsin in the Preparation of Sputum for Cytologic Study", Seymour M. Farber, M.D., Samuel L. Pharr, B.S., David A. Wood, M.D., and R. Daniel Gorman, M.D., Science, Vol. 117, No. 3051, pp. 687-690, June 19, 1953

4. RESULTS OBTAINED BY OTHERS

Brief remissions induced by nitrogen mustards have been reported by several investigators. Symptomatic relief has been shown to occur, particularly in patients with superior mediastinal obstruction. The cell type

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influences the immediate response; the anaplastic carcinomas being temporarily inhibited with greater frequency.

- a) Boyland, E., Clegg, J. W., Koller, P. C., Rhoden, E., and Warwick, O. H. The Effects of Chloroethylamines on tumors with special reference to bronchogenic carcinoma. Brit. J. Cancer 2: 17-29, 1948.
- b) Gensler, E. A., McKay, D. G., Ware, P. F., and Lynch, J. P. Cytologic Changes in Bronchogenic Carcinoma following Treatment with Nitrogen Mustard. Arch. Path. 46:503-518, 1943.
- c) Karnofsky, D. A., Abelman, W., Carver, L. F., and Burchenal, J. H. The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma with particular reference to Bronchogenic Carcinoma Cancer 1: 634-656, 1948.
- d) Kent, L., and Rett, E. P., Treatment of Bronchogenic Carcinoma with Nitrogen Mustard. Dis. of Chest 17:190-201, 1950.
- e) Skinner, E. F., Carr, D., and Denman, W. E., The Treatment of inoperable Bronchogenic Carcinoma with Methyl Bis. J. Thoracic Surg. 17:429-438, 1948.

5. BIOGRAPHICAL SKETCHES

David A. Wood, M. D., Professor of Pathology (Oncology) and Director of the Cancer Research Institute. M. D. Stanford University 1930. Full time faculty member of Department of Pathology, Stanford Univ. School of Medicine, 1930-1951. At University of California since 1951.

H. Glenn Bell, M. D., Professor and Chairman, Department of Surgery, University of California

S. M. Farber, M. D., Associate Clinical Professor of Medicine, In-Charge University of California Chest Service, San Francisco Hospital

Roger H. Wilson, M. D., Clinical Instructor in Medicine, University of California, since 1953. B.A. Univ. of Cambridge 1941; M. D., Cambridge 1946; M. A. (Pathology), Cambridge, 1950. Member Royal College of Physicians, London, 1948; Institute Disease of the Chest and the Post-Graduate Medical School, London, 1948-50; Medical Research Council, Pneumonokoniosis Unit, Wales 1950-51; Internship (for California State Board Medical licence) Stanford University Hospital, San Francisco, 1951-52; Fellow in Pulmonary Physiology, Stanford University Hospital, 1952-53; Clinical Instructor in Medicine, University of California 1953 to present.

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