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Federal Security Agency
Public Health Service
National Institutes of Health

APPLICATION FOR RESEARCH GRANT

April 16, 1956

Public Health Service
National Institutes of Health
Division of Research Grants
Bethesda 14, Maryland

Application is hereby made for a grant in the amount of $ 19,135.46 for the period from January 1, 1957 through December 31, 1957 inclusive (not to exceed 1 year) for the purpose of conducting a research project on the following subject:

Title of Project	Blood volume in relation to height, weight, sex, age and physical training, and in pathologic states including obesity.
Name of principal investigator Ellen Brown, M.D. James Hopper, Jr., M.D. Kenneth G. Scott, Ph. D.	Title of principal investigator Associate Professor of Medicine Assistant Professor of Medicine Associate Professor of Experimental Radiology
Address of Principal Investigator University of California Medical Center San Francisco 22, California	
Name of financial officer to whom check should be mailed Stanley C. Bateman Make checks payable to: The Regents of the University of California	Title of financial officer Business Manager
Address of financial officer University of California Medical Center San Francisco 22, California	

BEST COPY AVAILABLE

Name of Institution University of California

Name and title of official authorized to sign for institution Robert G. Sproul, President

Personal signature _____
Robert G. Sproul

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Proposed Budget, for the period shown on page 1 - January 1, 1957 through December 31, 1957

	BUDGET Requested from P.H.S.	Other
Personnel		
Principal Laboratory Technician This includes $5232.00 salary plus plus 8.74% ($457.28) for matching contrib. to State Employee's Retirement System, plus $5.25 service charge	$ 5694.53	
General Assistance		
(Part-time laboratory assistant and vacation and sickness relief)	1000.00	
Research Associate		
(49% of full-time) Reidar Wennesland, M.D.	3975.00	
Permanent Equipment		
Scintillation counter with pulse height discriminator (non-recurrent item)	3000.00	
Consumable Supplies		
Radiochromium $75.00/month	900.00	
Glassware and chemicals	450.00	
Travel		
Expenses for one investigator to East coast	420.00	
Local travel to institutions where subjects are obtained	200.00	
Other Expense		
Payments to volunteer subjects @ $10.00 per experiment	1000.00	
SUBTOTAL	$ 16,639.53	
Plus 15% overhead — PHS Participation in Indirect Costs	2,495.93	
TOTAL FOR THE YEAR	$ 19,135.46	

Estimate of Future Requirements

	Direct Costs	Indirect Costs
1.	$ 13,639.53	$ 2,045.93
2.	13,639.53	2,045.93
3.	13,639.53	2,045.93
4.	None	None

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Public Health Service Support

Grant Number	Title of Project	Amount	Period of Support
Previous			
H 1271 H 1271 (C) H 1271 (C2)	Blood volume in relation to height, weight, sex, age and physical training, and in pathologic states including obesity.	$ 7,982	Jan. 1 - Dec. 31 1953 1954 1955
Current			
H 1271 (C3)	Blood volume in relation to height, weight, sex, age and physical training, and in pathologic states including obesity.	$ 8,499	Jan. 1 - Dec. 31 1956

All Other Support

Source	Title of Project	Amount	Period of Support
Current			
San Francisco Heart Association	Studies on the Blood Volume of Normal Man	$ 2,500	March 1955 —
Univ. of Calif. Research Committee	Blood Volume Studies	$ 700	July 1, 1955 - June 30, 1956

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Personnel:

Funds for partial salary support for Dr. Reidar Wennesland are requested as part of this grant. Dr. Wennesland has been associated with Project H-1271 for over three years and has been responsible for a great deal of the planning and execution of the work. He has devoted full time to the activity and has received financial support through fellowships from the American Heart Association and from Monterey and San Francisco County Heart Associations. Dr. Wennesland is expected to receive his final papers for U.S. citizenship during 1957. Review of Dr. Wennesland's biography and publications will explain that he is an experienced and versatile experimental biologist and he is peculiarly equipped to contribute to the work of this project. He is a fastidious worker and a resourceful planner of research and he is anxious to devote at least half his time to this project. If we cannot find means for the support of this scientist, he will resort to the private practice of medicine for income. Not only is it important to us to have Dr. Wennesland continue with the project, but we feel that this represents an illustration of the pressing need to utilize and encourage qualified scientists in the United States.

Permanent Equipment:

Funds are requested in the 1957 grant for the purchase of radioactivity counting equipment to be used in the blood volume studies with radiochromium. During the past three and one-half years we have shared the use of counting equipment at the Radioactivity Center with other research and training groups on the Campus. With the opening of the thirteenth floor of Moffitt Hospital as a cardiovascular research area, we will be able to centralize our activity and will have a place in which to locate counting equipment which we can utilize primarily for our own needs. This will obviate losses of time which have been experienced in the past because of scheduling difficulties for the use of the shared equipment, and geographic separation between our technician's home base and the location of the Radioactivity Center. The equipment for which funds are being requested will provide better sensitivity than the instruments which we now use and thus permit counting lower amounts of radioactivity with suitable accuracy.

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RESEARCH PLAN AND SUPPORTING DATA

1. RESEARCH PLAN

A. Specific Aims

The overall aim of this research is to study the basic factors regulating the volume of red cells and plasma within the circulation. This work will be continued along the following lines: -

i. By extending our knowledge of the normal values and variations of red cell (blood) volume in humans especially with regard to

Females
Age
Obesity and Leanness
Physical Training

ii. To continue observations concerning adjustments of blood volume in selected pathologic states such as

Cardiac Insufficiency
Polycythemia
Anemia
Hypo- and Hyper-proteinemic States
"High Output" States

B. Method of Procedure

Red cell volume will be measured by a modification of the Cr^{51} method of Sterling and Gray as employed by our group over the past four years. Whole blood and plasma volumes will be calculated from the hematocrit. In some experiments, plasma volume will be determined directly with T-1824.

Basal oxygen consumption will be determined by direct spirometry.

Volunteer healthy subjects will be recruited from among the personnel of the Medical Center, from industrial health screening services, and from suitable sources where athletic training is conducted.

These subjects will be screened for general health by means of history taking, physical examination, chest film, and suitable laboratory tests.

Individuals undertaking athletic training programs will be compared with the normal series for the same sex and body measurements before, and in the course of training.

Clinical material will be chosen from the Wards and Outpatient Departments of the University Medical Center.

Observed red blood cell and blood volumes will be related to the body measurements of the subjects, height and weight being considered together. Results in the various groups of subjects will be compared mathematically with similarly derived results from our large series of healthy males in the age groups 20 to 40 (see Section 2).

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The degree of correlation between red cell and blood volumes and the basal oxygen consumption will be tested.

An attempt will be made to follow changes in blood volume concurrently with therapeutic programs in the Obesity Clinic.

Attention will be given to the possible influences of factors such as blood donations, seasonal changes, menstrual cycle and exercise habits on the blood volume of healthy individuals.

C. Significance of this Research

i. Progress in the study of mechanisms regulating the circulating red cell mass and plasma volume has been slow and the results relatively nonconclusive because of inadequacy and controversy about methods of measurement, and because of the lack of reference standards derived from sufficiently large numbers of normal individuals of either sex.

ii. The introduction of methods for tagging red cells with radioactive materials reopened this field to active work. Our group has studied extensively the factors influencing the accuracy of the Cr^{51} method for determining circulating red cell mass and has prepared standards for predicting red blood cell and whole blood volume based on study of a large group of healthy males (250 prison inmates aged 20 to 40).

iii. Reference standards which are to be useful in application of blood volume work to physiologic and clinical problems must be based on broader material than that which we have studied so far and that which is described in the literature. It is, therefore, important to collect sufficient data to permit prediction of blood volume for all age groups and the female sex, and to consider body build and physical training in the development of standards.

iv. Only after suitable standards of prediction of the normal blood volume have been prepared will it be possible to evaluate observations made in disease states and under physiologic stress. The latter will be important sources of knowledge concerning the regulating mechanisms for red cell and plasma volume, which are now poorly understood.

2. PREVIOUS WORK DONE ON THIS PROJECT

Members of this group have developed and studied applications of several blood volume techniques (see references 1, 2 and 3).

Over the past three years a project has been carried out involved primarily with collection of values for circulating red cell volume in healthy males and relating these to height and weight (see reference 4 and Progress Report for Project M-1271). The influences of somatotype and habits of physical activity on the blood volume have been studied in this material and extensive mathematical analysis of the variance of the data carried out by Professor Hodges of our Department of Mathematical Statistics. As part of the Project, extensive tests of the method have been carried out, including animal studies in which the relative concentrations of Cr^{51} and carbon monoxide have been analyzed in various organs (see reference 5).

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Data regarding the blood volume in pathologic states have been collected for a number of years using the carbon monoxide and dye methods, as well as Cr^{51}. These conditions have included: - heart disease, hypo- and hyper-proteinemic states, polycythemia, and anemia, patent ductus arteriosus and other vascular shunts; normal and pathologic pregnancy.

3. REFERENCES TO PREVIOUS WORK OF THIS GROUP

i. Nemof, N., Hopper, J. Jr., Brown, E., Scott, K., and Wennesland, R., Simultaneous Determinations of the Total Volume of Red Blood Cells with CO and Cr^{51} in Healthy and Diseased Human Subjects, J. Clin. Invest., 33:1382, October 1954.

ii. Brown, E., Hopper, J. Jr., Sampson, J.J., and Mudrick, C., Venous Congestion of the Extremities in Relation to Blood Volume Determinations and to Mixing Curves of Carbon Monoxide and T-1824 in Normal Human Subjects, J. Clin. Invest., 30:1441, 1951.

iii. Hopper, J., Jr., Tabor, and Winkler, Simultaneous Measurements of Blood Volume in Man and Dog by Means of Evans Blue Dye, T-1824, and by Means of Carbon Monoxide. I. Normal Subjects, J. Clin. Invest., 23:628, 1944.

iv. Hopper, J., Jr., Brown, E., Wennesland, R., Scott, K., Bradley, B., Hodges, J.L., Jr., and Guttentag, C., Relation of Whole Blood and Red Cell Volumes as Estimated with Radiochromium to Body Measurements in Healthy Males, Fed. Proc., 14:76, March 1955, (Abstract).

v. Wennesland, R., Nemof, N., Hopper, J., Jr., and Bradley, B., Intravascular and Extravascular Distribution of Carbon Monoxide and Radioactive Chromium in Blood Volume Determinations, Fed. Proc., 14:162, March 1955 (Abstract).

See also the Progress Report on Project H-1271

4. RESULTS OBTAINED BY OTHERS

Whereas a moderate amount of information concerning the influence of obesity and sex differences on red cell and blood volume had been collected using plasma tags (see reference 1) and carbon monoxide (see reference 2), reported experience using radioactively tagged cells is meager (see references 3 and 4).

Extensive studies of the influence of physical exercise on blood volume have been reported, but the reliability of the carbon monoxide method used by Sjostrand is open to question (see reference 5). Since this method measures a space slightly larger than the blood volume, presumably including muscle pigments, it is particularly unsuitable for study of the effects of physical training on the blood volume.

References to Results Obtained by Others:

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3. Berlin, N.I., Hede, O.M., Parsons, R.J., and Lawrence, J.H., The Blood Volume in Various Medical and Surgical Conditions, New Eng. J. Med., 247:675-684, 1952.

4. Huff, Rex L., and Feller, D.D., Relation of Circulating Red Cell Volume to Body Density and Obesity, J. Clin. Invest., 35:1, 1956.

5. Kjellberg, S.R., Rudhe, U., and Sjostrand, T., Increase of the Amount of Hemoglobin and Blood Volume in Connection with Physical Training, Acta Physiol. Scand., 19:146-151, 1949.

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BIOGRAPHY

Allen Brown, M.D.

Born:

Parents: and

Education: B.A. University of California 1934
M.D. University of California 1939

Clinical Training, Fellowships and Academic Appointments:

1938-1939 Internship, San Francisco Hospital

1939-1940 Assistant Resident in Medicine, University of California, San Francisco

1940-1941 Assistant Physician, Student Health Service, University of California, Berkeley

1941-1942 Research Assistant, Institute for Child Welfare, Berkeley

1942-1943 Resident in Medicine, University of California, San Francisco

1943-1944 Clinical Instructor in Medicine, University of California Medical School, San Francisco

1943-1944 Assistant to Dr. William J. Kerr, University of California Medical School, San Francisco

1944-1946 Research Fellow in Physiology (Commonwealth Fund), Harvard Medical School

1946-1947 Instructor in Medicine, University of California Medical School, San Francisco

1947-1953 Assistant Professor of Medicine, University of California School of Medicine, San Francisco

1953- Associate Professor of Medicine, University of California School of Medicine, San Francisco

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Allen Brown, M.D.

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Phi Beta Kappa
Sigma Xi Associate
Iota Sigma Pi
Alpha Omega Alpha

Professional Societies

San Francisco County Medical Association
American Medical Association
California Medical Association

Scientific Societies

American Federation for Clinical Research
Western Society for Clinical Research
Society for Experimental Biology and Medicine
American Heart Association, California Heart Association,
San Francisco Heart Association
Scientific Council and
Section on Circulation, American Heart Association
International Society of Angiology
American Physiological Society
Honorary Member, La Agrupacion Medica Femenina de Chile
Corresponding Member, Sociedad Medica de Santiago

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Bibliography - Ellen Brown, M.D.

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2) The Effect of Cold on Capillary Permeability and Fluid Movement in the Frog, with Landis, E.M., Biol. Bulletin, 1946, 91:236 (Abstract).

3) Circulatory Changes Resulting From Obstetric Labor, with Sampson, J. J., and Hopper, J.J., Jr., Amer. Heart J., 1947, 33:703 (Abstract).

4) Effect of Local Cooling on Fluid Movement, Effective Osmotic Pressure and Capillary Permeability in the Frog's Mesentery, with Landis, E.M., Amer. J. Physiology, 1947, 149:302-315.

5) Physiologic Changes in the Circulation During and After Obstetric Labor, with Sampson, J.J., Wheeler, D.G., Gundelfinger, D.F., and Gianciracusa, J., Amer. Heart J., 1947, 34:311-333.

6) The Effect of Local Cooling on the Filtration and Absorption of Fluid in the Human Forearm, with Wise, C.S., and Wheeler, D.G., J. Clin. Invest., 1947, 26:1031-1042.

7) Recent Advances in the Treatment of Heart Disease, with Atkinson, D., J. Amer. Med. Women's Assoc., 1947, 2:494.

8) Effects of Local Venous Congestion on Carbon Monoxide-Available Volume and on Mixing Curves of Carbon Monoxide and T-1824 in Venous Blood, with Hopper, J.J., Jr., Mudrick, C., and Sampson, J.J., Amer. J. Med., 1948, 4:619 (Abstract).

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10) Some Practical Considerations of the Blood Volume, with Hopper, J. J., Jr., Amer. Practitioner, 1949, 4:191.

11) Effect of Exercise on Venous Pressure of Patients with Heart Disease in the Absence of Increased Blood Volume, with Lange, J.D., Thorr, B., and Hopper, J.J., Jr., Am. J. Med., 1950, 8:529 (Abstract).

12) Studies of Skin Temperature and of Indirect Vasodilatation in Amputation Stumps, with Foreman, Nadine, Am. J. Med., 1951, 10:112 (Abstract).

13) Venous Congestion of the Extremities in Relation to Blood Volume Determinations and to Mixing Curves of Carbon Monoxide and T-1824 in Normal Human Subjects, with Hopper J.J., Jr., Sampson, J.J., and Mudrick, C., J. Clin. Invest., 1951, 30:1441.

14) Effects of Exercise on Peripheral Venous Pressure, Studied in Relation to Blood Volume, Cardiac Competence, and Pulmonary Arterial Pressure, in Selected Cases of Heart Disease, with Daniels, D.D.,

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15) Observations on Pulmonary Circulatory Dynamics During Cortisone Treatment of Chronic Pulmonary Disease, with Daniels, D.D., Giansiracusa, J.E., Hopper, J., Jr., Leede, S.E., and Rapaport, E., Proceedings, Western Society for Clin. Research, Feb. 1952 (Abstract).

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18) Chapter on Vascular Studies, in Progress Report entitled "Studies Relating to Pain in the Amputee," Advisory Committee on Artificial Limbs, National Research Council—Prosthetic Devices Research Project, Univ. of Calif. Institute of Engineering Research, Series 11, issue 23, June 1952.

19) Studies of Peripheral Venous Pressure in Relation to Exercise, Blood Volume, Cardiac Competence and Pulmonary Pressure, I. In Normal, Hypervolemic, and Hypovolemic Subjects, with Hopper, J., Jr. and Lange, J., Proceedings 4th Interamerican Cardiological Congress, Buenos Aires, Sept. 1952 (Abstract).

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21) Chapter on Raynaud's Syndrome, in Current Therapy, 1953, R.F. Conn. Ed., Saunders, 1953.

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23) Mechanism of Action of Sympathetic Blocks in Relief of Pain, Am. J. Med., 15:411, Sept. 1953 (Abstract).

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25) Relationships Between Cardiac Output, Blood Volume, and Pressures Within the Cardiovascular System in Constrictive Pericarditis Before and After Surgery, with Patel, D., Nomof, N. and Hopper, J., Clin. Research Proceedings, 1954, 2:139 (Abstract).

26) Blood Volume in Congestive Heart Failure Studied by Cr^{51}, CO, and T-1824 Methods, with Hopper, J., Nomof, N., Wennesland, R. and

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32) Intra- and Extra-vascular Distribution of Carbon Monoxide (CO) and Radioactive Chromium (Cr51) in Blood Volume Determinations, with Wennesland, R., Romof, M., and Hopper, J., Am. J. Med., 19:287, August 1955 (Abstract).

33) Study of Variation in Blood Volume of Healthy Males, Using Radiochromium, with Wennesland, R., Hopper, J., Hodges, J.L., Guttentag, O., Tucker, L.M., and Bradley, B., Circulation, Vol. XII, No. 4, October 1955 (Abstract).

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BIOGRAPHY

James J. Hopper, Jr., M.D.

Born: February 22, 1910, Paris, France - Derrivative Citizenship U.S. 1917

Education: B.A. University of California - 1933
Attended McGill School of Medicine 1933-34
M.A. University of California - 1936
M.D. University of California - 1939

Clinical Training, Fellowships and Academic Appointments:

1939-1940 Internship, University of California Hospital

1940-1941 Assistant Resident in Medicine, University of California Hospital

1941-1942 Fellow Yale University School of Medicine, Division Metabolic Medicine (Alexander Brown Cone Memorial Fellow)

1942-1943 Fellow Yale University School of Medicine, Division Metabolic Medicine (American College of Physicians Fellow)

1943-1949 Clinical Instructor in Medicine and Director of Clinical Laboratories

1949-1954 Assistant Professor of Medicine & Director of Clinical Laboratories

1954- Assistant Professor of Medicine and Assistant Director of Clinical Laboratories

Societies:

Sigma Xi
American Federation for Clinical Research
Western Society for Clinical Research
American Federation for Clinical Research - San Francisco Branch

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Bibliography - James Hopper, Jr., M.D.

Published writings:

1) Water Metabolism in Relation to the Pituitary Body, Proc. Soc. Exp. Biol. and Med., 34:14-17, 1936.

2) Simultaneous Measurements of the Blood Volume in Man and Dog by Means of Evans Blue Dye, T 1824, and by Means of Carbon Monoxide I. Normal Subjects, J. Clin. Invest., Vol. XXIII, No. 5, pp. 628-635, Sept. 1944.

3) Simultaneous Measurements of the Blood Volume in Man and Dog by Means of Evans Blue Dye, T 1824, and by Means of Carbon Monoxide. II. Under Abnormal Conditions, Including Secondary Shock, J. Clin. Invest., Vol. XXIII, No. 5, pp. 636-648, Sept. 1944.

4) Plasma Volume of Dogs in Dehydration, With or Without Salt Loss, J. Clin. Invest., Vol. XXIII, No. 1, pp. 111-117, January 1944.

5) Experimental Hypertonicity: Alterations in the Distribution of Body Water, and the Cause of Death, J. Clin. Invest., Vol. XXIII, No. 1, pp. 103-109, January 1944.

6) A Simple Method of Determining the Specific Gravity of Small Samples of Urine, J. Laboratory and Clinical Medicine, Vol. 31, No. 3, pp. 934-935, August 1946.

7) Creatinine Clearance: A Simple Way of Measuring Kidney Function (A Statistical Study of 102 Normals), The Bulletin of the University of California Medical Center, Vol. II, No. 3:315, Dec. - Jan., 1950-1951.

8) A Comparison of the Bromsulfalein and Rose Bengal Tests, J. Laboratory and Clinical Medicine, Vol. 34, No. 2, pp. 246-249, February 1949.

9) Effects of Potassium and Lanatoside-C on the Failing Heart-Lung Preparations, Fed. Proc., Vol. 8, No. 1, March 1949.

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2) Effects of Local Venous Congestion on Carbon Monoxide-Available Volume and on Mixing Curves of Carbon Monoxide and T 1824 in Venous Blood. Abstract of paper submitted for presentation at Annual Meeting of the Western Society for Clinical Research, Nov. 7-8, 1947.

3) Effect of Exercise on Venous Pressure of Patients with Heart Disease in the Absence of Increased Blood Volume. Abstracted for presentation at the American Federation for Clinical Research, Atlantic City, New Jersey, January 4, 1948.

4) Studies of Peripheral Venous Pressure in Relation to Exercise. Blood volume, cardiac competence and pulmonary pressure. I. In normal hypervolemic and hypovolemic subjects (1). J. Hopper, Jr., H. Lange

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5) Studies of Peripheral Venous Pressure in Relation to Exercise. Blood Volume, Cardiac Competence and Pulmonary Pressure. II. In Selected Patients with Heart Disease. Presented at Inter- American Congress on Cardiology, Buenos Aires, South America, Sept. 1952. E. Brown, H. Lange & J. Hopper, Jr.

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Kenneth Gordon Scott, Ph.D.

Born:

Education: A.B. Physiology, University of California 1934
Ph.D. Physiology, University of California 1948

1942-194[illegible] Radiation Laboratory, Manhattan Project

1948-19[illegible] Assistant Professor of Radiology, University of California Medical Center, San Francisco

1948-19[illegible] Research Associate [illegible] Laboratory, University of California, Berkeley

1948- Consulting Biophysicist, [illegible] Veterans' Administration Hospital

1951- Director of Radioactivity Center, University of California Medical Center, San Francisco

1951- Associate Professor of Experimental Radiology, University of California Medical Center, School Of Medicine, San Francisco

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1) The Metabolism of Americium in the Rat, Jour. Biol. Chem., with Copp, D.H., Axelrod, D.J., and Hamilton, J.G., 175:2; 1948.

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BIOGRAPHY

Reidar Rennesland, M.D.

Born:

Norwegian citizen. American visa 4(d) No. 628. Reg. No. A 6623501.
First papers - March 11, 1952
California Physician's and Surgeon's License No. A-15525

Education: B.A. University of Oslo, 1929
M.D. University of Oslo, 1936

Training, Fellowships, Academic appointments:

1931-1934 Student instructor, Department of Anatomy, Oslo University

1937-1946 Assistant Professor of Anatomy, Medical School, Oslo University

1946 Norwegian Government Fellowship

1947-1948 Research Associate, Biology Department, Swarthmore College, Pennsylvania

1949-1950 Research Associate, Physiology Department, Stanford University, California

1951-1952 Rotating Internship, Permanente Hospital, Oakland, California

1952 Assistant Resident in Medicine, Central Laboratory, School of Medicine, University of California Hospital, San Francisco, Calif.

1953-1954 Research Fellow in Medicine, School of Medicine, University of California Hospital, San Francisco, California

1954- Research Fellow in Medicine and Clinical Instructor in Medicine, School of Medicine, University of California Hospital, San Francisco, California

Training, experience and research:

Broad experience in teaching of human gross anatomy, histology and microscopic anatomy, embryology and neuroanatomy for medical students, dental students, psychology students at Oslo University. Teacher, anatomy and physiology in Norwegian schools of nursing.

Experience in general practice, medical administrative and organizational work as Chief Physician of Norwegian Military Police and Norwegian Government Repatriation Service during the war.

Research in carbon monoxide poisoning, and development of methods for determination of CO and CO_2 in blood, other biologic fluids and tissues (see list of publications 1 - 6).

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Reidar Wennesland, M.D.

As research associate at Swarthmore College Biology Department studies of the methods developed there for gas analysis and metabolic research.

As research associate at Stanford University Physiology Department studies of tissue respiration and development of microrespirometric apparatus (publications 7 - 8).

Experience in the use of radioisotopes from a six months stay at The Donner Laboratory of the University of California, Berkeley, 1949.

Medical training and research in cardiovascular and renal disease as research fellow and clinical instructor at the University of California hospital, School of Medicine, Department of Medicine (publications 10 - 13).

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12. Wennesland, R., Nomof, N., Hopper, J. Jr., and Bradley, B., Intravascular and Extravascular Distribution of Carbon Monoxide and Radioactive Chromium in Blood Volume Determinations, Federation Proceedings, 14:182, March 1955. (Abstract)

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