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James W. Crisell
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Studies of the Metabolism of Certain Fission Products and Plutonium

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By

Bergene Kawin

B.S. (University of California) 1940

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Physiology

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

Approved:

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Committee in Charge.

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CARDIOVASCULAR FLOW AND METABOLISM

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I. INTRODUCTION TO THE PROGRAM PROJECT

The major underlying theme of this program project is the perfection of methods for the detection and characterization of atherosclerosis and the evaluation of ischemia, particularly in the heart, but also in the brain. The biological and medical issues which we have been addressing over the past few years are:

1) early detection of coronary artery disease by noninvasive methods,
2) noninvasive sizing of the volume of infarcted and ischemic tissue,
3) evaluation of the metabolism of the compromised and normal myocardium,
4) early detection of hypertension,
5) evaluation of glucose, fatty acid, and protein synthesis in the myocardium,
6) noninvasive methods for determining the composition of atheromata,
7) evaluation of the biological properties of the arterial wall in the normal and diseased states using tracer methods, and,
8) investigation of the glycogen and lipid composition of skeletal muscle in patient groups with various lipoprotein patterns.

The methods used include noninvasive techniques of determining body metabolism as well as quantitatively imaging flow in three dimensions using positron emission tomography, nuclear magnetic resonance, dynamic spectrometry of exhaled metabolites, and HPLC analyses of metabolites of the injected tracer in plasma samples. In addition to and in support of the biological and medical projects, this program includes development of new instrumentation and cyclotron based radiochemical syntheses.

The previous program was based on the Donner 280-crystal positron emission tomograph. Initially this instrument was designed to image the spatial distribution of rubidium-82 in the heart as a method for the evaluation of infarct size and relative perfusion. Rb-82 (a potassium analog) is a positron emitter available from a table-top generator. Because this cation has a 76 sec half-life, myocardial perfusion imaging can be performed repeatedly over short time intervals. This system's design and construction was conceived at approximately the same time as the PET systems built at Washington University by Drs. Ter-Pogossian, Phelps, Hoffman, Mullani and others; however, because our plans required the ability to use rubidium-82 for sequential studies of the myocardium in transverse section, the design required a stationary system capable of rapid data acquisition, with special crystal and mechanical properties that had to be developed (1). The system was developed under NIH as well as DOE funding.

II. HISTORICAL BACKGROUND AND EVOLUTION OF COLLABORATIONS

Our efforts in remote imaging and measurement of flow have continued for more than ten years. The specific emphasis on the human heart commenced twelve years ago (2) when Program Director Thomas F. Budinger and chemist Yukio Yano undertook studies with radionuclides that accumulate in the heart. Our studies were directed toward finding a suitable imaging agent for the heart with the objectives of diagnosis of coronary artery disease and quantification of the myocardial region at risk. We studied the properties of eight radionuclides (Cs-129, Rb-79, Rb-81, Rb-82, K-43, Tl-201, $^{13}NH_4$, and ^{11}CN) and different imaging methods over eight years in 80 patients. After each study we analyzed the limitations and moved along the path to a solution. Because these former techniques, widely used today in practical clinical studies, told us little about the mechanism of the disease, in 1972 we investigated dynamic first pass functional gated blood pool imaging (3). We

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turned to tomographic methods for evaluating perfusion, including the first multiple pinhole imaging of the human heart in 1973 (4), the first gated human heart imaging of Tl-201 in transverse section in 1975(5,6), and finally, the first human heart imaging in transverse section before and after exercise in 1979 (7), with ^{82}Rb.

Development of statistical aspects and mathematical algorithms (8,9) applicable to emission-tomography was also a major basic element of our cardiovascular research objectives (10).

Positron Emission Tomography

Until recently, as each milestone was reached, we could see the realization of our objectives required substantial changes in approach. Now that we can image infarcts less than 1 cc in volume and understand the behavior of rubidium uptake, our medical and biological objectives of the past years can be pursued. This is not to say we are satisfied with our present instrumentation. Indeed, though the Donner 280-crystal dynamic positron emission tomograph is able to perform the human and animal experiments proposed in this program, there are important limitations in the present single section design. The basic improvement we seek is the ability to simultaneously acquire seven transverse sections of the heart. To implement such a large improvement in our present system, research is required in key components such as scintillators and their coupling to phototubes or other detector elements.

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The construction of a multilayer system would involve over $2 million and the devotion of researchers to an engineering effort which would exclude them from embarking on new research initiatives and from applications of the presently available instruments to cardiovascular research. Thus we have transferred many aspects of our technology to industry and have been successful in that The Cyclotron Corporation is producing a three-level (two ring) PET for imaging the thorax. This device will be purchased by Case Western Reserve University and we will use it to complete our protocols before transfer of the instrument to Cleveland.

A third PET device for very high resolution imaging is now under construction by our group. This device was designed for imaging biological properties of atheromata in the carotids of man, aortas of monkeys and dogs, and hearts of dogs. This single layer research device of 600 crystals will provide an in-plane resolution of 2 to 3 mm full width at half maximum (FWHM).

In Vivo Quantitation of Physiological Processes

The two basic methodological problems addressed by this program project are first, separation of the region of interest from the background, and second, derivation of physiological rate constants from the accumulation data kinetics. The first problem is in good part solved by emission computed tomography. However, success in the ability to image dynamically the uptake and washout of radionuclides in any portion of the body is not the complete solution to the stated problem. Within each volume element being studied there is another superposition problem: the vascular compartment, interstitial fluid space, and intracellular compartment are all present, thus constituting functional as well as spatial superposition.

To obtain physiological rate constants, we must use kinetic models, including some independent measure of blood flow or a reference tracer. No single method exists at present for the determination of the contribution of flow, metabolism and the input function to the amount of material which accumulates in or passes through some portion of the cardiovascular system or target organ.

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What we measure with injected radionuclides can generally be described by the mathematical statement:

$$Q(T) = F \cdot E \cdot \int_0^T A(t)d(t) \quad . \qquad (1)$$

This equation, which is derived from a basic statement of the conservation of mass, states that the amount accumulated up to time T equals flow times extraction times amount delivered in that time interval. We have learned that this simple model is too restrictive, perhaps even for a cation such as Rb^+.

The basic problem in the past was the need to determine both flow and metabolism from the amount of an inert or metabolizable substance which accumulates in some organ. The statement of Eq. (1) is naturally modified by other terms to include the amount which disappears through radioactive decay and metabolism. That is, the change in the amount of a substance which accumulates in an organ with time is equal to the flow times the concentration in minus the concentration out, minus the amount that disappears due to radioactive decay and metabolism. Even with this more complete model it is not a simple matter to deduce flow, metabolism or extraction from analysis of the uptake-washout curves in some organ. Another term missing from Eq. (1) is the tissue blood pool contribution, and of great importance in understanding the meaning of our data is a knowledge of the chemical fate of the label immediately after injection. For these reasons, more complex models are to be examined and HPLC analyses and autoradiographic procedures are being incorporated into the PPG.

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NMR

An initiative which commenced five years ago with Professor Jerome Singer on NMR imaging of flow was not supported during the past two years in this program project and no work on flow imaging using NMR was pursued by the P.I. However, we have focused on the health hazards of NMR (11) and the use of NMR proton imaging as a potential tool for the detection and characterization of ischemic heart disease and on high resolution submillimeter imaging of arterial wall composition in an effort to understand the natural history of atherosclerosis. In addition, we now believe we can evaluate noninvasively the relative abundance of various lipid classes and glycogen in human skeletal muscle using carbon-13 NMR. In order to pursue these objectives we are acquiring a 30 cm, 1.9 T imaging system from Bruker Instruments (West Germany) with funds made available outside the program project budget. In addition, three other imaging systems for the whole body will be available to this program project without a significant financial burden.

III. NEW COLLABORATORS

Common interests among University of California, San Francisco (UCSF) groups, others involved in noninvasive imaging, and our team at Donner Laboratory are being amalgamated in the following areas:

1. Comparison of NMR to PET for study of ischemic heart disease. Dr. Lipton, Dr. Herfkens, Dr. Schiller, Dr. Botvinick, Dr. Margulis, Dr. Kaufman, Dr. Crooks (all UCSF); Dr. R. Alfidi (Case Western Reserve University), Dr. William McIntyre (Cleveland Clinic).

2. New photon detector systems. Dr. Peschman and Dr. Boyd (UCSF).

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3. Carbon-13 topical NMR studies. R. Nunlist (UC Berkeley), Dr. Nunnally (University of Texas Health Science Center, Dallas), Dr. Matwiyoff, Dr. London (Los Alamos Scientific Laboratory), Dr. Willcott (Baylor University).

4. Flow and metabolism in the myocardium. Dr. Renkin (UC Davis), Dr. Schelbert (UCLA).

5. Composition of the arterial wall and the relationships between muscle lipid patterns and lipoproteins. Dr. Krauss, Dr. Nichols (Companion Program Project at Donner Laboratory).

6. Biological properties of the arterial wall measured by tracer techniques. Dr. Price (UCSF), Dr. Krauss (UC Berkeley).

IV. SUMMARY OF PROJECTS AND CORES

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Project 1 The basic myocardial flow and metabolism imaging objectives of this PPG comprise Project 1. We will employ noninvasive flow methods using Rb-82 and glucose metabolism models using F-18 deoxyglucose in dogs and man. A combination of these methods is proposed as a new tool for evaluation of myocardial ischemia. Amino acid studies include evaluation of methionine and taurine kinetics in the myocardium with PET and with high resolution autoradiographic methods for assessment of the cellular localization of taurine.

Project 2 The major objective of Project 2 is to develop a method for the measurement of platelet dynamics at arterial sites and for noninvasive measurement of platelet distribution in man using ^{68}Ga-labeled platelets and a new, high resolution PET device. Animal studies will be followed by studies of patients with transient ischemic attacks and patients undergoing vascular surgery.

Project 3 Investigations of the efficacy of hyperbaric oxygen and of fluorocarbons in the treatment of ischemic brain disease will be conducted in the cat using a middle cerebral artery occlusion model. Flow and metabolism will be measured using autoradiographic methods in the cat to evaluate the effects of these interventions. The high resolution PET system will be used primarily to develop for man, a new radiopharmaceutical, ^{122}I-dimethoxy-phenylalkyl amine for measurement of cerebral blood flow. This system will be applied to the evaluation of cerebral vascular disease and methods of treatment.

Project 4 Four aspects of nuclear magnetic resonance (NMR) application to cardiovascular research will be studied: 1) a comparison of the relative sensitivity of PET and NMR for the detection of ischemia in the dog and human myocardium; 2) development and use of a submillimeter imaging device for detection and characterization of atherosclerotic lesions in animals and man; 3) evaluation of the possible hazards from induced electric currents from rapidly changing magnetic fields; and 4) investigation of the C-13 spectra of skeletal muscle glycogen and lipids before and after exercise in populations with specific lipoprotein patterns, using topical magnetic resonance techniques in man.

Project 5 This project focuses on new instrumentatian developments for positron emission tomography. A 2-3 mm resolution PET device is to be completed in the first year, and during subsequent years a new scintillator-detector system applicable to high resolution PET and single photon tomography will be perfected. This new detector assembly will be used to build a two ring (three level) system for patient and animal studies of Projects 1, 2, 3, 4 and as a prototype for transfer to commercial developers.

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Project 6 The computer science and digital electronics aspects of positron emission tomography and NMR comprise this project. New high speed electronics configurations and development of advanced algorithms and compartment models contribute to Projects 1, 2, 3, 4, and 5 as well as to computational sciences of noninvasive imaging.

Core A is a radiopharmaceutical development core which serves Projects 1, 2, and 3. Various radiopharmaceuticals have been and are in process of being developed, including a new synthesis of carbon-11 taurine and already published syntheses of carbon-11 valine, carbon-11 palmitic acid, fluorine-18 deoxyglucose, etc. The core includes the continuing development of a rubidium-82 generator for use in Projects 1, 2, and 4.

Core B is an administrative core.

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V. INSTITUTIONAL ENVIRONMENT AND RESOURCES

Donner Laboratory is located on the Berkeley campus adjacent to the Lawrence Berkeley Laboratory. Donner Laboratory is directed by Professor Edward Alpen who is also Associate Director of the Lawrence Berkeley Laboratory, a national laboratory of about 3,000 employees. The work to be done will be accomplished through the use of resources in the Biology and Medicine Division of the Lawrence Berkeley Laboratory. This division is generally known as Donner Laboratory.

The major institutional advantages at Donner Laboratory and the Lawrence Berkeley Laboratory are: the presence of the 280-crystal Donner ring; a new 2 to 3 mm resolution PET under construction; an NMR imaging system for animals and arms and legs of patients; the Rb-82 generator; the availability of a cyclotron for preparation of radionuclides; an animal colony with appropriate surgical facilities; computer facilities for sophisticated kinetic analysis; microsphere counting laboratory; Harmon Gymnasium exercise physiology program; and a convenient clinical setting for referral patients. Figure 1 is a schematic which shows the general location of the facilities available.

VI. ORGANIZATIONAL AND ADMINISTRATIVE STRUCTURE OF THE PROGRAM PROJECT

The organizational structure for the most part follows naturally from the organization of the Research Medicine Group at Donner Laboratory. The Program Director has appointments at the Lawrence Berkeley Laboratory and the Department of Electrical Engineering and Computer Sciences, University of California, Berkeley. In addition, he is the head of the Donner Medical Group, which is a patient care group, and is head of the Donner Research Medicine Group. He reports to the Director of the Donner Laboratory, Professor Edward Alpen, for Lawrence Berkeley Laboratory responsibilities and to Professor George Turin for academic responsibilities. The investigators of Projects 2, 5, and 6 report directly to the Program Director. Professor Philip Weinstein reports to Professor Charles Wilson of UCSF and is a guest scientist in the Research Medicine Group at Donner Laboratory. Professor George Brooks has become an associate member of the Donner Research Medicine Group and participates in scientific studies on lactate metabolism.

Advisory Groups

The Executive Committee is comprised of Project Leaders of the six projects as well as Dr. Thornton Sargent. The Executive Committee will meet formally monthly to review scientific progress, budget status, and advise on personnel and program changes.

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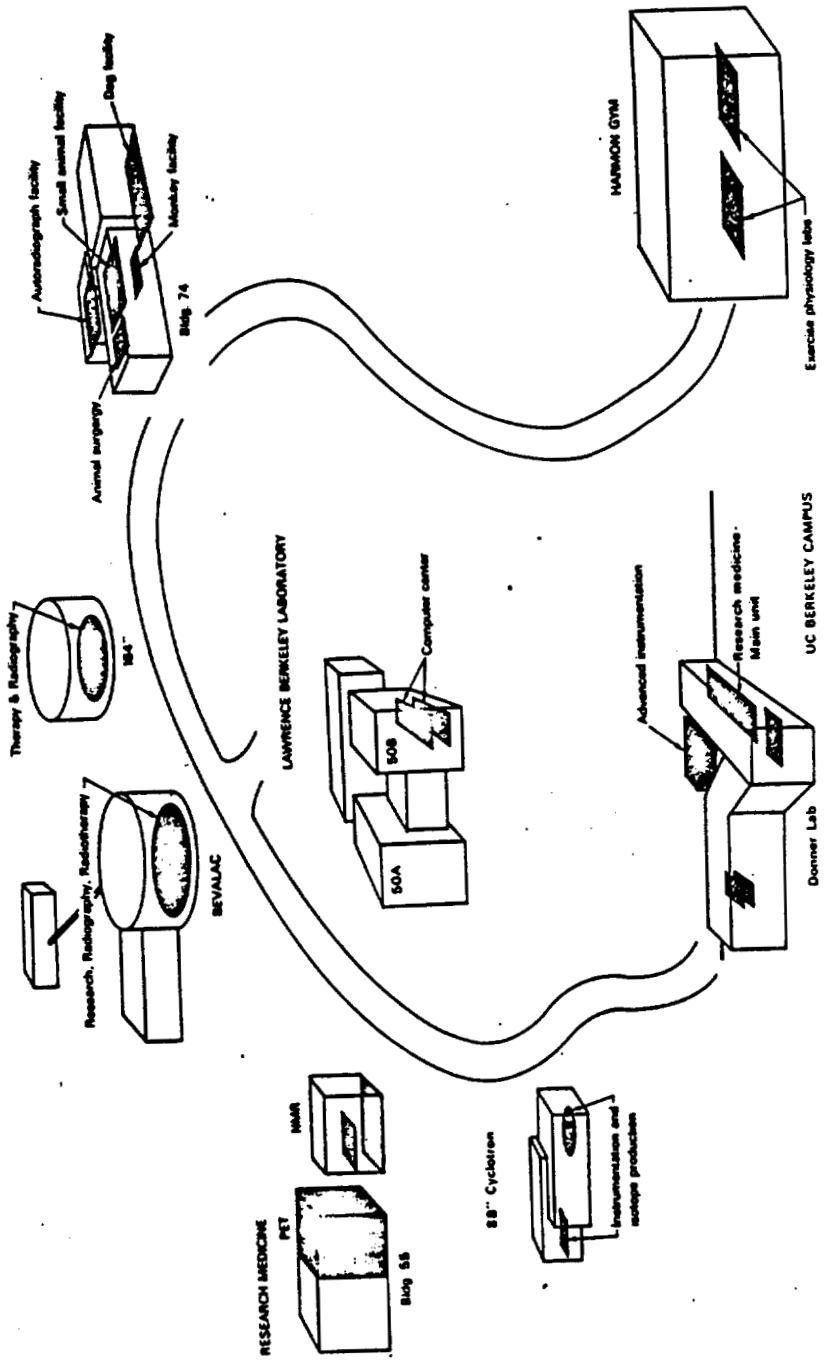

Figure 1.

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Outside Advisory Groups

We propose an annual review of the program with advisors from other institutions, including other parts of the University of California. Proposed advisors are:

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1) Professor Julian Hoffman, University of California, San Francisco
2) Professor Gene Renkin, University of California, Davis
3) Professor M. Paul Capp, University of Arizona
4) Professor Dominique Comar, Hopital D'Orsay, France
5) Dr. Hal O'Brien, Los Alamos Scientific Laboratory
6) Dr. William Brody, Stanford University
7) Professor Al Macovski, Stanford University
8) Professor Heinrich Schelbert, UCLA
9) Dr. Nicolas Matwiyoff, Los Alamos Scientific Laboratory

Managerial Responsibilities

The day to day administrative details will be monitored by Ms. Linda Lutgens, who is the Research Medicine Group administrative assistant. She will consult when appropriate with Mr. Baird Whaley, who is the Donner Laboratory Personnel and Financial Officer, and the Donner Laboratory Fiscal Officer for NIH affairs, Mr. Wendell Hom.

Relation to Other Research Programs

This program project (now in its third year) involved a consolidation of efforts previously supported by the National Institutes of Health (NIH), the Department of Energy (DOE), and the National Science Foundation (NSF). The DOE support of aspects of the nuclear chemistry and nuclear physics and mathematics is vital to our overall program. There exists a strong collaboration between our group and other DOE laboratories in the areas of new detector development. For example, the Stable Isotopes program at Los Alamos Scientific Laboratory is essential to a ^{13}C NMR program.

We anticipate many of our facilities and some personnel talents will be shared with another program project extant at Donner Laboratory: "Lipoprotein Methodology and Biomedical Applications", F. Lindgren, Principal Investigator. At present we share clinic space and the Gilford autoanalyzer. In addition, we perform blood chemistry analyses for this program project. The 2000-patient lipoprotein survey by that program project was set up initially in collaboration with Dr. Budinger. The patient activities of both programs are formally under the Donner Medical Group.

Designation of Replacement for Program Director

Should it become necessary to appoint a replacement for the Program Director, Professor Edward Alpen, Director of Donner Laboratory, in consultation with the Executive Committee and the Advisory Committee will select the Program Director. There are a number of senior staff at Donner Laboratory who are cognizant of the overall theme and competent in both clinical and physiological aspects of the approach of this program. Dr. Stephen Derenzo will lead the instrumentation aspects of the program and one of the following individuals will guide the medical aspects: Dr. Shirley Ebbe, Dr. Ronald Krauss, Dr. Jack Fabrikant.

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following intravenous injection has been studied by Jones and Copp (49). Immediate uptake of strontium in the bones of the young normal and rachitic animals was greater than in the adult animals. The greatly increased renal clearances of strontium in the rachitic group suggested an effect of rickets upon tubular reabsorption of the element. On the basis of this work, Jones has suggested a hypothetical mechanism for bone calcification. He has postulated an initial labile combination of the strontium in bone, followed by fixation as bone salt in normal animals.

The localization of strontium in the areas of active bone formation has suggested its use for the radiation treatment of osteogenic sarcomata (50,51). However, such use of radiostrontium in therapy is restricted by the diffuse distribution and retention of this element in bone, with the danger of bone marrow depression and production of new bone tumors (1,39,44).

JHL. Am J. Roentgenol. Rad. Therapy 45, 283 (1942)

Treadwell, A, et al Am J Med Sci 204, 823 (1942)

2. Other Fission Products (Cerium, Columbium, Yttrium, and Zirconium) and Plutonium

The elements cerium, columbium, plutonium, yttrium, and zirconium are also deposited in bone. When internally administered, they are distributed in a pattern differing from the alkaline earths, radium and strontium. The latter localize in bone salt, with only traces in the soft tissues; on the other hand, cerium, columbium, plutonium, yttrium, and zirconium are also found in liver, spleen, and other soft tissues. They are all characterized by a high degree of deposition and retention in the skeletal tissues of animals. As much as sixty five percent of an administered dose of these elements is deposited in bone (37). With the exception of columbium, which has a skeletal half-time of 30 days, these elements have biological half-times ranging from one to three years (37,46). The slow rate of elimination and the long half-lives present a potential health hazard from chronic irradia-

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We have also become encouraged about the investigations on the nature of the fundamental abnormality in atherosclerosis resulting from the ultracentrifugal study of blood serum and the studies with radioactive cholesterol, and feel that perhaps there will be, in the near future, striking advances in the prevention of this disease.

Respectfully submitted,

John H. Lawrence, M. D.

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