8602 074

908

OMB CONTROL NO. 1910-1400

(R)

U.S DEPARTMENT OF ENERGY
UNIVERSITY RESEARCH INSTRUMENTATION PROGRAM

712332

COVER PAGE
(THIS PAGE MUST BE THE FIRST PAGE OF THE APPLICATION)

Name of Institution: University of Southern California

Address: City Los Angeles 3. State CA 4. ZIP 90089-1147

Principal Investigator: Walter Wolf, Ph.D.

Department: Radiopharmacy

Telephone: Area Code (213) Office: 224-7521 Home: [redacted]

Title of Application: Purchase of Biomedical NMR Spectrometer Imaging System

Area of Proposed Research (Select ONE) D *

A. Materials Characterization
B. Catalysis
C. Engineering Science
D. Health & Environmental Effects
E. Other

Research Subcategory (See Section II of DOE/URI FY86 Announcement) Area D not subcategorized

Total DOE Funding for Research in Selected Area, (During the last two fiscal years): $ 1,608,000

Estimated Purchase Price of Equipment: $ 586,000

Amount Requested from DOE: $ 425,000

List all Federal agencies which are currently considering proposals from the institution involving the same or similar equipment.

14. Agency: None Agency Proposal Number:
15. Agency: Agency Proposal Number:

NOTE: The institution is responsible for informing DOE if a proposal involving the same or similar equipment is submitted to a federal agency prior to the announcement of DOE's URI awards.

16. List any federal agency which has provided funds to the institution during the past two years for the same or similar equipment.

Agency: None Amount of Funds:

17. Please check one of the following:

☒ I authorize outside peer review of this proposal.

☐ I do not authorize outside peer review of this proposal. **

Signature of Principal Investigator: Walter Wolf Date: December 4, 1985

Name and Title of Institutional Official (President or Designee)

Cornelius J. Pings

Sr. Vice President for Acadmeic Affairs

University of Southern California

Signature: Cornelius J. Pings

Date: 12/5/85

Name and Title of Financial Officer

William C. Hromadka

Executive Director, Dept. of Contracts and Grants, USC

Signature: William C. Hromadka

Date: 12-05-85

* Note - The application will be evaluated by reviewers in this field.

** Note - May prevent full consideration of this application.

BOX No. B-41-4 Bldg. 2714-H

FOLDER 86020074

REPOSITORY Oak Ridge Operations

COLLECTION Records Holding Area

Document ID 1944-94

1076619

CONTENTS

SUMMARY

This proposal requests funds towards the purchase of a 4.7 T, 150 mm bore biomedical nuclear magnetic resonance (NMR) spectrometer and imaging system. This system will be used for conducting *in vivo* studies using small animals (e.g., rodents such as rats, mice, rabbits) for the purpose of developing new vistas and techniques in the non-invasive study of body chemistry. Towards this end, *in vivo* NMR spectroscopy and innovative imaging or spatial localization techniques will be investigated and integrated to provide chemical and physiological information in conjunction with imaging. In addition to biological and preclinical studies, where our main thrust of research will lie, the requested instrument will greatly enhance the capabilities of the University of Southern California in conducting basic magnetic resonance studies down to the molecular level. Thus, it is imminent that our research will lead to better methods (in terms of sensitivity and quantifiability) of characterizing the biochemical effect of radiation and energy related chemicals on the human body, and it is very probable that the research will provide a better understanding of physiological function at the cellular and molecular level.

Some of the initial research experiments anticipated with the 4.7 T Biomedical NMR system include:

1. Radiopharmacokinetic studies of drugs using ^{19}F (Walter Wolf)
2. Spectroscopic Imaging Studies (Manbir Singh)

3. In vivo NMR Studies of Renal Arginine Synthesis (Luisa Raijman)
4. Sequential Metabolite Pharmacokinetics by In-Vivo NMR Techniques (Kenneth Chan)
5. Fundamental flow studies (E. Philip Muntz and Chih-Ming Ho)
6. NMR Measurements of Lung Water (Steven Lewis)
7. Development and assessment of new paramagnetic contrast agents in animal models (William Boswell)

The following students, who have graduated or are about to graduate from USC's various Ph.D. programs, are among those who have been involved in areas directly related to those research programs whose capability will be greatly expanded by the aquisition of the 4.7 T NMR system:

1. Randy Manaka, Ph.D.
2. David Young, Pharm.D., Ph.D.
3. Ricardo Brechner, M.D., Ph.D.
4. Robert Domenick, Ph.D.
5. Christine Shew, Ph.D.

There are currently a number of students enrolled in our various Ph.D. programs that might directly benefit from the acquisition of this NMR system. They include (list not comprehensive):

1. Rehir bin Dahalan
2. Dan Maneval
3. Rajiv Parti
4. Ahmed El-Tahtawy
5. Chris Horn
6. Janny Leung
7. Anthony Whittemore, M.D., Ph.D. (Radiology Resident)

U.S. DEPARTMENT OF ENERGY
UNIVERSITY RESEARCH INSTRUMENTATION PROGRAM

BUDGET PAGE

ESTIMATED COSTS

Instrumentation	Requested of DOE	Institution's Cost Sharing *(1)*	Other Federal Funds *(2)*	TOTAL
A. Purchase Price *(3)*	425,000	160,750		585,750
Subtotal:	425,000	160,750		585,750
B. Other Allowable Costs				
1. Shipping/Handling	XXXXX	250.		250.
2. Installation	XXXXX	Incl.		
3. Building/Laboratory Renovation	XXXXX	50,000		50,000
Subtotal:		50,250		50,250
C. TOTAL	425,000	211,000(4)		636,000

NOTES:

(1) Non-Federal funds only. (However, may be provided by a third party.)

(2) Estimate funds to be obtained from other Federal agencies for purchasing the instrument, etc.

(3) Only the purchase price of the instrumentation is eligible for DOE funding through this program.

(4) This amount represents allowable cost sharing. (See pages 7 and 8).

A. Purchase Price (List components and unit prices.)

Description	Quantity	Total Estimated Unit Price	Total
Biomedical NMR Spectrometer and Imaging System 4.7 T, 15 cm Horizontal bore	1	550,000	550,000
Tax (6.5%)		35,750	35,750
Subtotal:	1	585,750	585,750

DEPARTMENT OF ENERGY
UNIVERSITY RESEARCH INSTRUMENTATION PROGRAM
GRANT AND CONTRACT SUMMARY FORM

OMB CONTROL NO. 1910-1400

Grant/Contract/Subcontract No.	Principal Investigator	Title	Contract Dates FM MO	FM YR	TO MO	TO YR	Total Award Value	$ AMT Awarded for FY Period 1983 to 1985	DOE Technical Monitor/Location
DE-FG03-84ER60219 (Grant)	W. Wolf	Radiopharmacokinetics Utilization of Nuclear Medicine Techniques in the Non-Invasive Study of Drug Distribution	3	84	2	87	$348,000	$232,000	Dorris Harris/Dr. D. Cole (San Francisco/Washington D.C.)
Grant number unknown	J. Huth	Advance Radiation Detector Development (Mercuric Iodide) Silicon with Internal Gain Hybrid Scintillater/Semiconductor Detector)	12	85	11	86	$260,000	-0-	G. Goldstein/Washington D.C.
Contract No. DE-AS03-76EV72031 (DE-AM03-76SF00034)	J. Huth	Continued Development of Mercuric Iodide and Other New Concepts for the Detection and Spectroscopy of Ionizing Radiations	12	76	11	85	$3,109,240	$1,150,000	G. Goldstein/Washington D.C.
Contract No. DE-AT03-80EV10338 (DE-AM03-76SF00113)	W. Frei	Development of Digital Image Processing for Environmental Assessment	10	79	3	84	$470,000	$226,000	G. Goldstein/Washington D.C.

Only provide information on research projects which are directly related to the selected principal research area.

1076625

RELATED FEDERAL AGENCY GRANTS AND CONTRACTS

Agency	Grant/Contract No.	Title	Grant/Contract Dates FROM MO YR	Grant/Contract Dates TO MO YR	Total Award Value
DHHS-Nat'l Cancer Inst.	2 R01CA28105-06	An Electronically Collimated Gamma Tomography System (P.I.: Singh)	4-01-85	3-31-86	$220,143 (current yr.)
Nat'l Science Foundation	DMB-8412964	The Kinetic Properties of Enzymes in Situ (P.I.: Raijman)	8-01-84	1-31-89	188,126 (current years 1 & 2)
DHHS-Nat'l Cancer Inst.	N01-CM-37600 MAO #2	Assay Development and Preclinical Pharmacology Studies with NSC-338947 Clomesone TASK #15 (P.I.: Chan)	9-30-85	9-29-86	88,955
DHHS-Food & Drug Admin.	223-82-6010	Optimization of Chest Radiography (P.I.: Muntz)	9-30-82	1-15-86	138,776
Air Force Rocket Propulsion Laboratory	F04611-84-K-0026	Liquid Droplet Dynamics (P.I.: Muntz)	7-01-84	6-01-87	217,645
DHHS-Nat'l Heart, Lung, and Blood Institute	5 R01HL30711-03	Multi-Breath, Multi-Gas Studies of the Lung (P.I.: Lewis)	7-01-85	6-30-86	127,488 (current yr.)
Air Force Office of Scientific Research	F49620-85-C-0080	Unsteady Behavior of Turbulent Shear Flows (Three Tasks) (P.I.: Ho)	5-01-85	4-30-88	711,794

Only provide information on research projects which are directly related to the selected principal research area.

RELATED FEDERAL AGENCY GRANTS AND CONTRACTS

Agency	Grant / Contract No.	Title	Grant / Contract Dates FROM MO YR	Grant / Contract Dates TO MO YR	Total Award Value
DHHS-Nat'l Cancer Inst.	5 R01CA31693-03	Pharmacokinetic Studies of Cyclophosphamide Disposition (P.I.: Chan)	6-01-84	3-31-86	$77,863 (current yr.)

6a

Only provide information on research projects which are directly related to the selected principal research area.

1076627

NARRATIVE

TECHNICAL MERIT AND ACCOMPLISHMENTS OF USC'S RESEARCH PROGRAM

The core faculty that is currently in need of and enthusiastic to utilize the biomedical NMR requested, both for spectroscopy and imaging, comes from a varied background and represents a true interdisciplinary team. The key to our interest is that this instrument provides unique capabilities and will contribute significantly to USC's ability of developing methods and procedures for performing truly non-invasive studies of living systems, specially at the mammalian level. Concomitant with the qualifications of the USC faculty, the projects proposed range from the purely physical to the totally biological, and as documented by their research productivity and funding, the faculty is well experienced in the development of new research ideas and methods in these areas. While there are few faculty members at USC who have had, so far, personal 'hands-on' experience in the specific type of equipment requested, the past accomplishments of the faculty at USC and their ongoing programs bode well for the success of the proposed projects, for which the key is the availability, on site, of a biomedical NMR spectrometer. Such availability will greatly enhance the ability of USC Faculty, and of its graduate students (one of the largest graduate student populations in the US) to conduct more advanced research in this area.

As an illustrative example, the PI became interested in 'in vivo' NMR spectroscopy as an extension of his ongoing (DOE funded) program on the development of RADIOPHARMACOKINETICS, a technique which requires non-invasive data on drug biodistribution. Up to the present, such data could only be generated by the use of gamma-labeled drugs and their detection and quantitation using Nuclear Medicine techniques. A key limitation of such an approach is that, while Nuclear Medicine techniques are extraordinarily sensitive to trace quantities, they totally lack any chemical resolution. It became obvious that if Nuclear Medicine detection techniques could be interdigitated and combined with those of NMR (which have the potential of exquisite chemical resolution, but suffer from a very low sensitivity), such a combined study would provide unique new vistas in non-invasive studies of drug biodistribution, metabolism, localization and hopefully, efficacy, in the human body. Prof. Wolf organized an international conference, in 1982, on 'Non-Invasive Studies of Body Chemistry', where these topics were thoroughly reviewed by the leading experts in the field, and then spent his sabbatical working with Prof. George Radda at Oxford University, England. The PI had also organized, some years earlier, a conference sponsored by the Society of Nuclear Medicine which explored the significance of Fluorine as a label, and where he postulated the importance of combined F18/F19 studies. Interestingly, even as recently as 1983, (NIH) study section members questioned whether 'in vivo' F19 studies could ever be carried out. In 1983/84, and not having a biomedical NMR at USC, the PI developed two collaborative programs: one with Dr. John Griffiths, at the St. George's Hospital Medical School, University of London, and one with Drs. Wil-

fried Loeffler and Michael Silver, at Siemens Medical Systems, Iselin, NJ. While these collaborations have allowed the PI the initiation of an active 'in vivo' NMR spectroscopy program, it has also highlighted the need, at USC, of a dedicated instrument to properly develop the methodology and the techniques needed to study and measure (non-invasively) drugs and their metabolites 'in vivo'. Some of the specific studies that the PI and other faculty propose to carry out are described below.

Classical (chemical) NMR, on the other hand, is by now a well established technique and USC has both extensive instrumentation and well qualified faculty in these and directly related areas. Specific research programs of these faculty members include, among others:

1. High Field NMR Studies of $^{13}C-^{13}C$ Coupling Constants, Isotope Effects, C-C Connectivity, HETCOR and Related Studies. George Olah, Ph.D. and G.K. Surya Prakash, Ph.D.
2. Deuterium Isotope Effects on Carbon-13 Chemical Shifts. Kenneth L. Servis, Ph.D.
3. Synthetic Coordination Chemistry. Christopher A. Reed, Ph.D.
4. Synthesis of Spirosiloxanes and Silicon Polymers. William P. Weber, Ph.D.
5. Mechanism of Enzymatic N2 Fixation. Charles E. McKenna, Ph.D.
6. Organophosphorous Chemistry. Charles E. McKenna, Ph.D.
7. NMR Structural Studies. Larry R. Dalton, Ph.D.

Finally, clinical (human) NMR is also of major interest and significance to USC faculty. Several faculty members of the Department of Radiology have been active in clinical Diagnostic Imaging programs, and a contract with a private group (International Imaging) has just resulted

in the siting of a mobile (0.5 T) clinical NMR at the LAC/USC Medical Center. This first, primarily clinical, diagnostic imaging effort is expected to become fully operational in mid 1986, when a dedicated building is completed and an additional 2.0 T NMR system is delivered. The University, for its part, has been developing an agreement with NME (National Medical Enterprises), which will result in the construction of a 250 bed University Hospital. This (private) hospital will make USC the hub of a major medical complex, which will also include the LAC/USC Medical Center, the Kenneth Norris Jr. Cancer Hospital and Research Institute (one of the 19 NCI-designated Cancer Centers), and the Estelle Doheny Eye Hospital. A comprehensive Diagnostic Imaging Center is planned as part of this effort, and the PI has been charged by the University with the development of its Diagnostic Imaging Research effort.

Radiopharmacokinetic Studies of Drugs Using ^{19}F (Walter Wolf, Ph.D.)

There are two key questions that need to be addressed, whenever a new technique is developed:

1. what information can this new methodology provide that is qualitatively different from currently available methods? and
2. what information, currently available, can this new technique provide in a better and more efficient manner than previous technology?

NMR spectroscopy is a powerful new tool that allows the non-invasive analysis of the chemical composition of selected organs and tissues in the human body. Such analyses can be carried out on two types of products:

1. physiological compounds, to determine changes in the location and the kinetics of metabolic activity of naturally occuring biochemicals
2. pharmacological agents, to measure individual variations in the nature and the kinetics of both the biodistribution as well as the biotransformation of drugs

While the hydrogen atom is the one atom with the highest sensitivity of detection by NMR techniques, it is both the most pervasive and one where differences in chemical shifts are relatively small. The next atom with the highest sensitivity (84% that of the proton) is F-19, which has the added advantage that there are few, if any, naturally occuring fluorinated compounds in the human body. In addition, chemical shifts of fluorinated compounds are large, allowing for the detection of chemical changes in the nature of the products measured even at low signal-to-noise ratios. All these features make F-19 a natural nuclide for NMR studies of drugs. The work that the PI has been developing over the last several years is aimed at elucidating whether information on individual variations of drug biodistribution and biotransformation bear a direct relationship with the drug's efficacy in that individual, and whether it is possible to optimize drug dosage by a knowledge of the organ pharmacokinetics of the drug, as opposed to the currently available blood pharmacokinetics.

There is one further and added dimension: while the presence of the fluorine atom will, in many instances, confer new and different properties to a compound, it may also, under the proper circumstances, be placed in a molecule <u>without</u> any modifications of that molecule's prop-

erties. Hence, and given that hydrogen does not have a radioisotope that is a gamma emitter, F-18 has been proposed as a possible tracer for organic molecules, if and when a fluorine can be introduced into that molecule at an 'innocuous' position.

Thus, fluorine offers a unique combination: F-19 is an ideal element for NMR studies, while F-18 (a positron emitter with a half-life of 2 hours) is an excellent radionuclide for nuclear medicine studies. What is more, the simultaneous and combined use of both techniques offers more than a sum: it potentiates and expands the level of information that can be gleaned from either methodology. The specific work proposed with 5-fluorouracil has a dual purpose: to provide information useful to the handling and properties of that drug itself, and to document, with a specific example, the potential and the scope of NMR spectroscopy in animal and human studies.

Prior work in animals (1), and subsequently, in humans (2,3), had suggested that an analysis of the biodistribution of 5-Fluorouracil might be helpful in predicting, both the possible value of the use of that drug in an individual patient, as well as the level of drug needed for optimization of chemotherapy. However, while a radiopharmacokinetic analysis of a radiolabeled drug has proven succesful in drugs that can be analyzed by a 'mere' 7-10 compartment model (e.g., cisplatin; see ref. 4 and 5), it has proven unsuccesful in the case of 5-FU, where even simplified radiopharmacokinetic models have more than 12 compartments (6). More information is needed. And while a study of the kinetics of the biodistribution of F-18-labeled 5-FU provides uniquely sensitive data, it lacks one key component: the information provides the total

fluorine concentration, whereas what is needed is some indication of the nature of the compounds present. Recent work by Griffiths et al. (7), and, more recently, in collaboration with the PI (8), has documented that the nature and the kinetics of the biodistribution of 5-FU can be studied in mice by the use of NMR spectroscopic techniques. Griffiths (9) has extended this work to other fluorinated drugs, and observed kinetic differences. What we wish to do is to analyze the role and significance of various pathophysiologies: how does the presence of a tumor, and its degree of responsiveness to drug treatment, affect the drug's biodistribution and biotransformation? Above all, can relevant differences be measured non-invasively, specially differences that would guide us in how best to use this drug in patient care? As a first step, we wish to measure the kinetics of drug biodistribution and biotransformation in the liver and the tumors of mice, rats and rabbits, and compare such data with those obtained from both F-18 and blood pharmacokinetic analyses. Finally, recent work by Alice Wyrwicz (10), presented in August 1985 at the Fourth Annual Meeting of the Society of Magnetic Resonance in Medicine, has dispelled one further notion: that F-19, present in pharmacological doses, could never be imaged. Images of F-19, following administration of halothane, were obtained by NMR.

REFEREENCES

1. Shani, J. and Wolf, W.: Canc. Res. 37, 2306-2308 (1977).
2. Shani, J., Young, D., Siemsen, J.K., Chlebowski, R.T., Bateman, J.R., Schlesinger, T. and Wolf, W.: Int. J. Nucl. Med. Biol. 9, 25-35 (1982).

3. Young, D., Vine, E., Ghanbarpour, A., Shani, J., Siemsen, J.K. and Wolf, W.: Nuklear Medizin 21, 1-7 (1982).

4. Brechner, R., Wolf, W., Dahalan, R., D'Argenio, D.Z., Butler, T.A. and Knapp, F.F.: Proc. 2nd. Int. Conf. Radiopharmaceuticals, p. 451-460, IAEA, 1985.

5. Manaka, R.C and Wolf, W.: In "Cisplatin - Current Status", S. Carter, S. Crooke and A. Prestayko, Eds, Academic Press, New York, 1984

6. Young, D. "Radiopharmacokinetic Model Development and Structural Identification". Dissertation, USC, 1982.

7. Stevens, A.N., Morris, P.G., Iles, R.A., Sheldon, P.W. and Griffiths, J.R.: Br. J. Cancer, 50, 113-117 (1984).

8. Wolf, W., Griffiths, J.R., Silver, M. and Bruckner, H.: Abstract, SNM Symposia on NMR and Nuclear Medicine, March 1986

9. Prior, M.J.W., Maxwell, R.J., Prysor-Jones, R.A., Stevens, A.N. and Griffiths, J.R. Proc., 4th. Ann. Mtg. Soc. Mag. Resonance Medicine, p. 740, London, August 1985.

10. Conboy, C.W. and Wyrwicz, A.M. Proc., 4th. Ann. Mtg. Soc. Mag. Resonance Medicine, p. 775, London, August 1985.

Spectroscopic Imaging (Manbir Singh, Ph.D.)

In general, spectroscopic imaging refers to techniques which combine NMR spectroscopy with in-vivo imaging to provide a spatial distribution of chemically shifted components within a species. For example, aqueous and lipid components of hydrogen in the body show a chemical shift of about 3.4 ppm. Techniques for producing separate images of the aqueous

and lipid components (also called chemical-shift imaging) fall under the general category of spectroscopic imaging. In addition, spatially localized spectroscopy, which involves measurements of the chemical shift spectrum from a well defined region, is included in the category of spectroscopic imaging when the sensitive region is spatially scanned within the body.

In addition to hydrogen, phosphorus and carbon naturally occuring in the body are also amenable to spectroscopic imaging within constraints imposed by the signal to noise ratio of the detected signal. Phosphorus, for example, is present over a range of about 25 ppm in several compounds which are important in cell metabolism. By imaging or spatially mapping the relative amounts of phosphocreatine, adenosine triphosphate and inorganic phosphate, it would be possible to quantify specific aspects of metabolic function within an organ or a desired region of interest. Similarly, using F-19 labelled drugs or compounds, it would be possible to quantify a variety of biochemical processes which would be invaluable in, for example, monitoring 5-fluorouracil chemotherapy as mentioned earlier.

Since the relative sensitivities at constant field for imaging natural phosphorus and carbon are about $6X10^{-4}$ and $1X10^{-4}$ respectively compared to hydrogen, and since the amount of F-19 that can be introduced safely in the body is also about 10^{-3}-10^{-4} the concentration of hydrogen, it is imperative to optimize the sensitivity of spectroscopic imaging techniques for nuclei other than protons. One of our key research tasks with the requested spectrometer will be to seek for new techniques as well as to optimize existing techniques with the aim of improving the

sensitivity of spectroscopic imaging. A brief description of existing spectroscopic imaging techniques and our proposed research is given below.

Spectroscopic imaging without surface coils.

Because of the relatively large abundance of hydrogen, spectroscopic imaging of protons can be performed without surface coils. A simple way to make an image of a desired chemical component is to eliminate signals from all other components. For example, by saturating the aqueous protons with a precisely tuned r.f. pulse, it is possible to obtain signals only from lipid protons. A conventional phase encoding method (spin-warp imaging) would subsequently produce an image of lipid protons. This method requires a very homogeneous static magnetic field, but is as fast as the conventional phase encoding method. Another approach to hydrogen chemical shift imaging is to phase encode the shifts. Protons with different chemical shifts precess at different rates. Thus, a phase difference develops between different chemical components. By using a variable spin-echo time, it thereby becomes possible to obtain signals from different phase combinations of the chemical components. For example, with aqueous and lipid components, it is possible to adjust the spin-echo timing to produce signals when the lipid and aqueous components are in phase as well as when they are exactly out of phase (1). With these two signals, it is straightforward to produce the separated lipid and aqueous component images. The method can be extended to more than two chemical components by changing the time interval between the 90° and 180° pulses in steps, thereby acquiring signals from several linear combinations of phases (2). In general, to image n chemical com-

ponents, n independent linear combinations of phases among the chemical components would be required. We propose to investigate the applicability of this method to F-19 chemical shift imaging where two or three chemical components predominate.

When the number of chemical shift components becomes large, it is more efficient to phase encode both spatial directions (for a selected plane) or all three directions (for 3-D imaging), and record the FID in the absence of any gradient. A 3-D FFT (for planar imaging) or a 4-D FFT (for 3-D imaging) subsequently yields the chemical shift spectrum as a function of spatial coordinates. Obviously this method is slow because the FID represents only one point in Fourier frequency space, and a large roster of points must be determined to reconstruct an object. To increase speed, either the object region to be imaged is made small, or the spatial resolution is made coarse. Nevertheless, even with coarse spatial resolution (e.g. 1-2 cm pixel size instead of the conventional 1-2 mm pixels) spectroscopic imaging would be invaluable and we propose to investigate the various trade-offs in this approach.

Spectroscopic imaging with surface coils.

Because of their high sensitivity and high signal to noise ratio, surface coils are preferred in spectroscopic studies of nuclei other than hydrogen. Unlike the saddle shaped body coils used in conventional imaging, surface coils produce non-uniform field distributions. The greatest sensitivity of surface coils is at the surface and it diminishes with depth. The problems with surface coils therefore involve optimization of sensitivity profiles and delineation of the sensitive region so that the components giving rise to the NMR signal can be spatially

identified and quantified as accurately as possible. Various approaches to this problem are summarized below.

Surface coil based techniques fall into two broad categories -- a single point measurement scheme which detects the signal from a specified region only, and a spatial encoding technique which requires multiple measurements to obtain a sampling of the Fourier frequency domain of the object.

The simplest approach is to restrict the sensitive volume. By varying the duration or strength of the transmitted r.f. pulses, different spatial regions can be emphasized. Multiple pulse sequences known as "depth pulses" have been studied in this context (3). The objective of these depth pulses is to maximize the signal from the region localized by a selective 90° pulse and minimize contributions from the 270° and 450° regions. Several variations are possible and one of our graduate students (Chris Horne) is studying novel pulse sequences and the resulting signal to noise ratio, with the objective of improving the sensitivity of these measurements.

Other approaches use magnetic field gradients to define a sensitive "point" region. The simplest way is the Topical Magnetic Resonance (TMR) technique (4) where the static gradients are designed to vary rapidly at all points except a null region. A simple filtering of the FID can isolate the NMR signal originating from this null region. A surface coil placed near the sensitive volume assures good sensitivity. By manipulating the gradients, it is possible to scan the sensitive point across the object. Thus, a synchronous step-wise scan of the surface coil and the sensitive region would generate a coarse spectroscopic image.

An alternative technique for eliminating surface tissue contributions is called Depth-resolved surface coil spectroscopy (DRESS) (5). In this approach, a conventional rf coil or a large surface coil is used to uniformly excite a desired volume of the object and a smaller diameter surface coil is used to detect the NMR signal. A selective excitation pulse is applied in the presence of a magnetic field gradient pulse whose direction is coaxial with the surface coil. The combination of the narrow-band selective excitation pulse and the gradient results in excitation of a plane perpendicular to the axis of the surface coil. The lateral extent of this plane is determined by the sensitivity profile of the detection surface coil (which is small). Thus, signals from a narrow, well-defined plane are collected, resulting in good spatial localization. The method, however, suffers from the drawback inherent in all single point scanning approaches in that it is slow, especially since the repetition time between excitation pulses must be several times the relaxation time to minimize saturation.

The speed of DRESS can be increased by interrogating other planes during the time between measurements on a selected plane (6). To minimize saturation, non-contiguous planes are excited sequentially. With this innovation, several spatially localized spectra can be obtained in the same time normally required to collect a single spectrum. As sensitivity is the critical factor in imaging nuclei other than hydrogen, we will investigate these variations of DRESS as well as other techniques that could result in an overall increased sensitivity.

REFERENCES

1. Dixon, W.T. : Radiology 153, 189 (1984).

2. Sepponen, R.E. et al.: J. Comp. Ass. Tomography, 8, 585 (1984).

3. Bendall, M.R. and Gordon, R.E. : J. Mag. Res. 53, 365 (1983).

4. Gordon, R.E. et al. Nature (London) 287, 736 (1980).

5. Bottomley, P.A. et al.: J. Mag. Reson. 59, 338 (1984).

6. Bottomley, P.A. et al.: J. Mag. Reson. 64, 347 (1985).

In Vivo NMR Studies of Renal Arginine Synthesis (Luisa Raijman, Ph.D.)

Sequential Metabolite Pharmacokinetics by In Vivo NMR Techniques (Kenneth Chan, Ph.D.)

Several of the research projects of Kenneth K. Chan, Ph.D., have been based on the use of NMR techniques. The following are the common major objectives of these projects:

1. To probe into molecular dynamics of medium size organic chemicals (drugs or biological active organic molecules with MWT approximately at the range of 200-800) of medicinal and pharmacologic interests under physiologic conditions using proton and carbon-13 NMR.
2. To detect and elucidate structures of reactive intermediates of these organic chemicals that are generated in biological system by enzymatic and/or chemical transformation (labile metabolites and metabolic intermediates) using specific stable isotope labeling (C-13 and deuterium, etc.) and high field NMR technique.
3. To assess the kinetics of the transformation processes of these chemicals to unstable intermediates and stable products in situ in a biological system using organ perfusion and non-invasive in vivo NMR techniques.

Rationale. While structures of biologically active organic compounds are well known, their preferred conformation especially under physiologic conditions and in the presence of macromolecules are poorly understood. The latter may be the major determinant for their biological activity. This aspect can now be readily investigated using FT NMR by examination of the resonance characteristics of the appropriate nuclei in physiologic media with the aid of model compounds and various spectroscopic techniques.

The biologic activity of these compounds (pharmacologic and toxicologic) may often be related to the biotransformed products in vivo. While the stable biotransformed products (metabolites) can be isolated and identified by conventional chromatographic, spectroscopic, and spectrometric methodologies, the reactive (thus labile) metabolic intermediates often escape detection and identification, though their existence can be inferred by appropriate entrappment and by the detection of the end products. The detection and identification of these intermediates can now be facilitated by high field NMR using appropriate stable isotope labelling at the strategic positions.

The time course of the movement of the parent organic molecules and the biotransformed products and their kinetic relationship within the biologic system may also be extremely important in determining their overall biologic activities and their duration of action. While such investigation has been actively pursued by a well founded discipline of pharmacokinetics, the traditional method has been accomplished by invasive, discontinued (or discret time points), and relative slow sampling techniques. These techniques are coupled to conventional analytic methodologies. Often, artefactual information cannot be avoided. Additionally, these techniques cannot be used to monitor relative rapid kinetic process uninterruptedly. Using organ perfusion technique and non-invasive in vivo NMR technique coupled to specific isotope label, if appropriate, the in situ pharmacokinetic of the parent pharmacologic agents as well as the reactive intermediates and the metabolities may be followed and their kinetic relationship defined.

Significance. The above studies will likely generate detailed understanding of the role of molecular dynamics of substrates in biologic activity and to give insight into relationship between energetics of molecules and biologic activity. Secondly, by detecting and identifiying the reactive intermediates of organic molecules, it will provide information on the fundamental mechanism of biotransformation process of organic molecules in a biologic system. Finally, the in situ pharmacokinetic assessment by organ perfusion and non-invasive NMR techniques will likely generate new and useful pharmacokinetic principles particularly in defining the sequential pre-cursor and successor relationship.

Ongoing Activities. Using FT NMR to monitor natural and enriched C-13 organic compounds, we have selected the investigation of the structures of warfarin, an anticoagulant in solution and when bound to macromolecules. We also employed off-lined coupling of HPLC to NMR, investigated the stability of an antitumor agent and potent mutagen, 5-azacytidine and the chemistry of the ring opening in relationship to its biotransformation. Similarly, we investigated the chemistry of interconversion between 4-hydroxycyclophosphamide and aldophosphamide, the first microsomal metabolite of an important alkylating antitumor agent and immunosuppressant cyclophosphamide using proton NMR. Recently, using phosphorus NMR, we investigated the mechanism of alkylation and stability of phosphormaide mustard, the ultimate active alkylating metabolite of cyclophosphamide. In another study with molecular dynamics, we have investigated the most stable coinformation of dihydro-5-fluorouracil in solution, using proton and fluorine NMR. These preliminary research has formed the basis and background information in

a number of potential agents to be examined under objectives 2 and 3, which constitute the major objectives of this proposal involving this project. Presently, we do not have the instrument required for the continuation of this project. The results of the ongoing studies are summarized in the following selected biography.

1. Giannini, DD, Chan, KK, and Roberts, JD. Carbon-13 nuclear magnetic resonance spectroscopy: Structure of the anticoagulant warfarin and related compounds in solution. Proc. Natl. Acad. Sci. 71 :4221-4223, 1974.
2. Chan, KK, Giannini, DD, Cain, AH, Roberts, JD, Porter, W, and Trager, WF. Carbon-13 nuclear magnetic resonance studies of coumarin and related compounds. Tetrahedron 33 :899-906, 1977.
3. Chan, KK, Staroscik, J, Giannini, DD, and Sadee, W. High pressure liquid chromatographic and C-13 nuclear magnetic resonance analysis of 5-azacytidine and its kinetics of hydrolysis. J. Pharm. Sci. 68 :807-812, 1979.
4. Valente, EJ, Chan, KK, and Servis, KL. Proton magnetic resonance studies of the in vitro decomposition of

Fundamental Flow Studies (E. Philip Muntz, Ph.D. and Chih-Ming Ho, Ph.D.)

It is now well established (1) that magnetic resonance images are highly sensitive to the interaction of fluid flows with the pulse sequences of the imaging process. Conventionally, this is described as a fairly straightforward convective relaxation phenomena. However, flows of real fluids in compliant structures such as blood in arteries, specially near obstructions, is a complicated unsteady phenomena. Flow turbulence, which is distinct from the unsteady nature of arterial blood flow, is also important. Both the unsteadiness and the presence of turbulence make the simple convective relaxation picture incorrect detail. While this view may be satisfactory for the initial interpretation of magnetic resonance images, it seems that an understanding of the actual situation may provide a greater degree of diagnostic information. This is particularly true for the highest resolution images. There is a rather interesting fundamental issue of how to describe the interaction of the imaging process with the vortical nature of fluid flow, which will tend to induce changes of the spin vectors relative to the field direction.

One of the principal investigators of this specific task (E.P. Muntz) has extensive experience in modelling radiographic images as well as in fluid flows involving relaxation phenomena. The other principal investigator of this task (C.M.H.) is experienced in unsteady turbulent fluid flow of all kinds. Specifically, we propose to study in detail the response of the magnetic imaging system to well characterized fluid flows. The flow characterization will be done with laser doppler velocimetry, bubble and laser induced fluorescence, and with tracer techniques. The

resulting magnetic resonance images will be compared to predictions based on an empirical knowledge of the flow field details and hypotheses concerning the physics at the molecular level of the field-spin vector interactions, as they are affected by the fluid motion.

The proposed effort represents a collaboration between the Departments of Radiology and Aerospace Engineering at the University. This is particularly significant since the Aerospace Engineering Department is one of the major fluid mechanics group in the country, thus offering the possibility of bringing an expertise to magnetic resonance flow imaging that has not been available before.

1. V.W. Welden et. al: Science, 230, 946 (1985).

NMR Measurement of lung water (Steven Lewis, Ph.D.)

Measurement of lung water is an important clinical index of the condition on patients with a wide variety of pulmonary injuries. It is currently believed that the onset of pulmonary edema is a two stage process: first, relatively small changes occur in the total lung water as the balance of filtration across the alveolar membrane is disrupted. This is followed after some interval by alveolar flooding as reduction in surfactant forces and alveolar diameter lead to a positive feedback cycle (4). The presence of massive alveolar flooding is readily observed on chest radiographs and is correlated with severe pulmonary edema. It is desirable to measure the early changes in lung water which preceed the development of florid pulmonary edema in order to anticipate and correct a significant clinical problem.

A variety of techniques are available for the assessment of lung water, none of which is very satisfactory in the cases of interest (5). Three non-invasive approaches are used: first, the uptake of one or two soluble tracer gases during a rebreathing maneuver may be partitioned into components related to the exchangeable lung water and the cardiac output. The measurement of lung water is extremely variable and in patients with significant lung function disorders may have a variance far exceeding the changes of interest (6). A second approach involves measurement of chest impedance. Because pulmonary water constitutes approximately 10% of total chest water, changes in impedance are small. The measurement is difficult to calibrate in terms of absolute lung water, although it has some uses in measuring rapid changes (7). Third lung water may be measured radiographically. In the absence of florid edema, conventional radiographic approaches suffer from much the same problems seen with the impedance measurement. Tomographic measurement allows somewhat better resolution and may be more promising in the future (8).

Invasive measurement represents the best approach currently available. These tests involve measurement of the clearance kinetics of a tracer bolus of a diffusable indicator such as cold, tritiated water or antipyrene. These studies are technically difficult and require both ventral venous and arterial cannulation. Because of the technical difficulties, these have been largely confined to research settings (3).

There are significant problems with the measurement of lung water using NMR. The proton density of lung tissue is 10-30% of that seen in body tissues with the lowest densities occurring at the largest lung volumes (2). Periodic breathing movements are a significant problem. The

easiest method of reducing movement is to scan at high lung volume while breathholding, further reducing the available water density. Despite these difficulties, the non-invasive nature of NMR imaging makes this approach attractive in the measurement of lung water.

Increased lung water has been shown to correlate linearly with changes in T1 and T2 (1) although these changes are measured during florid edema. The lengthened relaxation times in edematous fluid offers the hope that careful study of the components of the NMR signal may offer information beyond total water content.

The proposed studies will procede in three phases. First we will use the Biomedical NMR to measure total water and T1 and T2 weighted images in the lungs of freshly exsanguinated rabbits. These measurements will be compared with the wet/dry ratios of the lung tissue after removal from the chest. A second series of animals will be treated with alloxan injection prior to sacrifice to increase capillary permeability and thus lung water. Both of the above series will be performed post mortum with the lungs inflated to cm water. This will eliminate problems with breathing artifacts.

The next series will involve studies in living paralyzed animals. The animals will be ventilated and periods of imaging during breathold will be interspersed with periods of mechanical ventilation. During this series the sensitivity of the measurements to changes in lung volume will be assessed as well as the advantages of using feedback from non-metallic thoracic circumference detectors. Again animals with and without elevated capillary permeability will be assessed.

REFERENCES

1. Skalina S., Kundel H.L., Wolf G. and Marshell B., The Effect of Pulmonary Edema on Proton Nuclear Magnetic Resonance Times, Invest Radiology 19:7-9,1984.

2. Hayes C.E., Case T.A., Ailon D.C. et.al., Lung Water Quantitation by Nuclear Magnetic Resonance Imaging, Science 216:1313-15,1982.

3. Effros R.M., Lung Water Measurement with mean transit time approach. J. Appl. Physiol. 59:673-683,1985.

4. Bengard F.S. M. Matthay, Mackersie R.C., F.R. Lewis, Morphological and Physiological Correlates of Increased Lung Water, Surgery 96:395-403,1984.

5. Cassuburi R, K Wasserman and R. M. Effros, Detection and Measurement of Pulmonary Edema, IN Staub N Lung Water and Solute Exchange, Dekker N.Y. 1978.

6. M.A. Sackner, D. Greeneltch, M.S. Neiman, et.al. Diffusing Capacity, membrane diffusing capacity, Capillary blood Volume, Pulmonary Tissue Volume and Cardiac Output measured by Rebreathing Technique, Am. Rev. Resp. Dis. 111:157-165,1975.

7. Pomarantz M. R Baumgartner, J. Lauridson and B. Eisman, Transthoracic electrical impedance for early detection of pulmonary edema. Surgery 66:260-268,1969.

8. Hedlund L.W. P. Vock, E.L. Effman, M.M. Lischko and C.E.Putman, Hydrostatic Pulmonary Edema An Analysis of Lung Density Changes by Computed Tomography, Invest. Radiology 19:254-262 1984.

Development and Assessment of New Paramagnetic Contrast Agents in Animal Models. (William Boswell, M.D.)

While the sensitivity of NMR in detecting abnormalities within the human body is now well established, the specificity of these clinical experiments remains below the anticipated levels. Within the brain, NMR examinations detect 33% more abnormalities than conventional CT scanning. Paramagnetic contrast agents, such as chelates of Gd, have shown some promise in increasing the specificity of NMR studies in both the animal and human model. The development of new paramagnetic contrast agents that may be organ or disease specific will lead to improved sensitivity and specificity of NMR examinations. These new agents must be tested in an animal model before any assessment of potential use in the human body can be tested. The small bore, high field biomedical NMR system is the ideal environment for development and preclinical testing.

Much work has been directed at the detection of disease states with the newer imaging modalities of CT, ultrasound and NMR. What is now required is a method for detecting subtle changes in disease states with treatment. As in the cancer patient where many chemotherapeutic agents are quite toxic, it is necessary to identify changes of progression or regression of the disease process as early as possible before the toxic side effects of the drugs adversely effect the patient. Both NMR imaging with analysis of T1 and T2 changes and NMR spectroscopy hold promise in the earlier and more accurate evaluation of these patients. This hypothesis must be tested in the preclinical animal model using a small bore, high field strength NMR system before it can be applied to the clinical cancer patient population.

QUALIFICATIONS OF FACULTY ASSOCIATED WITH NON-INVASIVE RESEARCH

The University of Southern California has over 1200 full-time faculty members, and the current proposal for a Biomedical NMR Spectroscopy and Imaging system proposes projects submitted by those 6 faculty members who currently have the most direct interest to the use of such an instrument. All of us have direct experience in the use of NMR techniques with the instruments currently available, and some of us have been able to acquire some 'hands-on' experience with the few prototypes of the new biomedical NMR systems (human and animal) that have become available. Above and beyond these faculty members, we know of other faculty that have projects, not yet fully formulated, that will make use of this equipment. As an example, and as discussed elsewhere, Dr. William Boswell and his colleages are interested in testing and assaying a variety of NMR contrast agents as part of pre-clinical evaluation; Dr. William Engel, Professor of Neurology, is currently studying the changes in muscle metabolism of phosphorous compounds in relation to a number of neurological disorders. While his current work is focused on 'in vitro' analysis, he has expressed great interest in extending this program to 'in vivo' work.

What is also significant is the support that can be provided by high level collaborators in related disciplines. One of the unique characteristics of work at USC is the tradition of interdisciplinary team work, where several faculty come together and actively collaborate on a project. As an example, both. Profs. Kenneth D. Servis and George Olah (Department of Chemistry) have agreed to continue collaborating actively in NMR studies, and provide their advise and expertise to the PI and his

coworkers. Dr. Hans Bozler (Department of Physics) is a world specialist in ultra-low temperature and magnetic conductivity, and he has expressed a desire to become significantly involved in the development of our NMR program. Dr. David D'Argenio (Department of Biomedical Engineering) a specialist in pharmacokinetic modelling, and who is already an active coworker of the PI in several programs, has placed the resources of his recently funded Biomedical Resource Grant to the disposal of the NMR program, as a logical and desirable extension. While this list could be greatly extended, it documents the atmosphere of collaborative research prevailing at USC. The availability of the Biomedical NMR Spectroscopy and Imaging system will thus be of significance, not only to the faculty members directly involved and to their students, but to a number of other faculty members, and to the University as a whole.

COST SHARING PLANS

The University of Southern California has made a commitment to the development of a diagnostic imaging research effort, whose initial emphasis will be focused on NMR and on PET. The clinical instrumentation required for this effort is being obtained through cooperative programs with major medical organizations (International Imaging and National Medical Enterprises (NME)). The present proposal is part of a comprehensive plan to complement the facilities and resources available in the basic and clinical sciences.

The University will provide from its own resources and from funds it has and/or will raise from non federal sources the costs above and beyond the amount requested from DOE for the purchase of the Biomedical

NMR Spectrometer and Imaging system, as well as the full costs of renovation/modification of laboratories for the proper installation of this instrument.

The University will also operate and maintain the above instrument. Operational costs of the instrument will be borne primarily by grants to the participating investigators, all of whom have a succesful track-record of funding. In addition, funds will be allocated and/or raised, specifically, for the operation of the Diagnostic Imaging Research effort as a University-wide resource.

USC'S EXPERIENCE IN USING MAJOR RESEARCH EQUIPMENT

The University of Southern California has currently over 111 million dollars in research grants and contracts in fiscal 1984. It owns and operates a large number of major research equipment. Of particular relevance to the proposed purchase of the Biomedical NMR Spectrometer and Imaging System are the chemical NMR spectrometers currently available at USC. They include:

1. A Hitachi-Perkin Elmer 60 MHz CW NMR Spectrometer (Biomedicinal Chemistry).
2. A JEOL 90 MHz FT NMR Spectrometer (Department of Chemistry)
3. A Varian 200 MHz FT NMR Spectrometer (Hydrocarbon Research Institute)
4. A Brucker 270 MHz FT NMR Spectrometer (Department of Chemistry)

The University of Southern California also is an active participant in the use of the 500 MHz NMR Spectrometer, located at the California Institute of Technology as a regional resource. Finally, the Department

of Chemistry has recently submitted a proposal to the National Science Foundation for the purchase of a Varian XL-400, 9.4 T, 54 mm bore NMR system. This latter instrument, specifically intended for chemical and laboratory science work, will significantly complement, but in no way duplicate, this current proposal.

The PI and the other key investigators in this proposal have extensive experience in the operation and the development of instrumentation. The PI has a Varian E3 ESR Spectrometer, purchased in 1969, and Dr. Manbir Singh has built, developed and modified several gamma cameras and imaging systems, as part of both the PI's DOE program and of his own, NIH-funded, research effort in medical imaging.

CURRICULUM VITAE

Name: Walter Wolf

Place and date of birth: [redacted] Germany, [redacted]

EDUCATION: [redacted]

PROFESSIONAL EXPERIENCE:

Professor and Director, Radiopharmacy Program, USC, 1970-present
Director, Radiopharmacy Service, LAC/USC Medical Center, 1970-present
Chairman, Dept. Biomedicinal Chemistry, USC, 1969-1973
Associate Professor of Biomedicinal Chemistry, USC, 1965-1970
Assistant Professor of Pharmaceutical Chemistry, USC, 1962-1965
Visiting Assistant Professor of Chemistry, USC, 1961-1962
Research Associate, USC and Amherst College, 1958-1961
Associate Professor of Organic and Biological Chemistry, Univ. Concepcion, Chile, 1956-1958
Stagiaire, then Attache de Recherches, CNRS, Paris, 1955-1956

PROFESSIONAL SOCIETIES AND HONOURS:

Intl. Member, Academie de Pharmacie, Paris, France; Fellow, Academy of Pharmaceutical Sciences, USA; President, Education and Research Foundation, Society of Nuclear Medicine; Chairman, Scientific Advisory Board, Syncor Intl.; Chairman, Science Council, Intra-Science Research Foundation.

Most Recent Publications (out of 132):

The Radiopharmacokinetic Technique for the Non-Invasive Study of Drug Biodistribution. W. Wolf. Radiopharmacy and Radiopharmacology Yearbook, (P. Cox, ed.) Gordon and Breach, London 1985.

Noninvasive Estimation of Bound and Mobile Platinum Compounds in the Kidneys. R. Brechner, W. Wolf, R. Dahalan, D.Z. D'Argenio, T.A. Butler and F.F. Knapp. Proceedings of the 2nd Conference on Radiopharmaceuticals and Labelled Compounds, Tokyo, Japan. IAEA Publications, p. 451-460, 1985.

Kinetic Studies with Radiopharmaceuticals, Wolf, W., Brechner, R., Young, D., Dahalan, R., and Singh, M. Proceedings of the 2nd International Conference on Radiopharmaceuticals and Labelled Compounds, Tokyo, Japan. IAEA Publications, p.423-433, 1985.

Assay and Time Course of 5-Fluorouracil Incorporation into RNA of L1210/0 Ascites Cells in Vivo. C.P. Spears, J. Shani, A.H. Shahinian, W. Wolf, C. Heidelberger and P. Danenberg. Molecular Pharmacology, 27, 302-307, 1985.

Comparative Radiopharmacokinetics of F-18-5-Fluorouracil Administered IV to Rats Bearing a Mammary Tumor. J. Shani, R.C. Manaka, D. Young J.L. Cohen and W. Wolf, Intl. J. Nucl. Med. Biol., 12, 9-12, 1985.

CURRICULUM VITAE

NAME: Manbir Singh

DATE OF BIRTH: [redacted]

EDUCATION:
[redacted]

PROFESSIONAL EXPERIENCE:

Associate Prof. of Research Radiology, Dept. of Radiology, USC	1983 -
Assistant Clinical Prof, Dept. of Radiology, USC	1978-1983
Physicist, Medical Imaging Science Group, Dept. of Radiology, USC	1977-1978
Visiting Scientist, Biophysical Sciences Unit, Mayo Clinic, Rochester	1976-1977
Post-Doctoral Scholar, Laboratory of Nuclear Medicine and Radiation Biology, Univ. of California, Los Angeles	1973-1976

HONORS:
Elected national representative for nuclear medical sciences administrative committee, IEEE Nuclear and Plasma Sciences Soc, 1986-1989.
Member, Nuclear Medical Sciences Technical Committee, IEEE.
Visiting Scientist Award, American Heart Association.
Kamani Gold Medal, R.K. Birla Gold Medal, Zaver Morar Lavangia Prize.
National Scholarship for Post-Matriculation Studies.

SELECTED PUBLICATIONS:

1. Singh, M. and Doria D., Single Photon Imaging with Electronic Collimatio Invited Paper, IEEE Trans. Nucl. Sc. NS-32 (1), 843, 1985.

2. Singh M., Doria D., Henderson V.W., Huth G.C. and Beatty J., Reconstuction of Images from Neuromagnetic Fields, IEEE Trans. Nucl. Sc. NS-31(1), 585, 1984.

3. Singh, M., An Electronically Collimated Gamma Camera for Single Photon Emission Computed Tomography, Part I, Medical Physics 10(4), 421, 1983.

4. Singh, M. and Doria D., An Electronically Collimated Gamma Camera for Single Photon Emission Computed Tomography, Part II, Medical Physics 10(4), 428, 1983.

5. Singh M., Berggren M.J., Gustafson, D.E., Dewanjee, M.K., Bahn R.C. and Ritman E.L., Emission Computed Tomography and its Application to Acute Myocardial Infarct Imaging in Intact Dogs using Tc-99m Pyrophosphate, J. Nucl. Med. 20(1), 50, 1979.

6. Singh, M., Sunier, J.W., DeVries, R.M., and Thompson, G.E., Decay of th Light Antimony Isotopes 110,111,112,113,114 Sb Following the 112,114 Sn(p,xn) Reactions, Nucl. Phys. A193, 449, 1972.

7. Cho, Z.H., Singh, M., and Chan, J., Three-Dimensional Radionuclide Tomography with Circular Ring Positron Camera, Optical Engineering 61 (1), 11, 1977.

8. Singh, M., Melvin, J., and Cho, Z.H., Design Study of a 200 keV Scannin Proton Microprobe Using a Field Ionization Source, IEEE Trans. Nucl. Science NS-23, 657, 1976.

CURRICULUM VITAE

NAME: E. Phillip Muntz

Date of Birth: [redacted]

[redacted]

ACADEMIC POSITIONS:

Associate Professor, Department of Aerospace Engineering, University of Southern California.	1969-1971
Professor, Department of Aerospace Engineering, University of Southern California	1971-1974
Professor, Departments of Aerospace Engineering and Radiology, University of Southern California	1974 -

INDUSTRIAL POSITIONS:

Group Leader, Molecular Gas Dynamics, Generalf Electric Missle and Space Division, Space Sciences Laboratory Valley Forge, Pennsylvania	1961-1969
Director, Division of Medical Sciences, Xonics, Inc. Van Nuys, CA	1973-1974

MONOGRAPHS AND BOOKS:

Reduced Dose Mammography, co-editor, Masson, New York, 1979	1978

COMMITTEE AND PROFESSIONAL RESPONSIBILITIES:

Organizer of the 1979 Meeting, Bureau of Radiological Health, Buffalo, N.Y.: "Reduced Dose Mammography"

1979-1982	Member, American College of Radiology Committee on Pneumooniosis
1981-1984	Member, American Assoc. Physicists in Medicine Committee on Diagnostic Radiology.
1983-	Member, NAS/NRC Committe on the Review of Physics, Plasma & Fluids

PATENTS:

"Radiographic System with Xerographic Printing", with A. Proudian and P.B. Scott, U.S. Patent 3,774,029, 1973

"Electron Radiographic System with Liquid Absorber", with F. Allan, J. Lewis, K. Lewis, A.L. Mosell, P.B. Scott and M.S. Welskowsky, U.S. Patent No. xyz, 1976.

PUBLICATIONS:

Focal Spot Size and Scatter Suppression in Magnification Mammography, with Logan, W., American Journal of Roentgenology, 133, p. 453, 1979.

D.Q.E. Analysis of Electrostatic Imaging and Screen-Film Imaging in Mammography", with Wagner, R., SPIE Medicine VII Proceedings, 1979.

An Analysis of the Role of Scatter in Reduced Dose Mammography Including Scatter Suppression, Magnification Effects, Focal Spot and Detector Blurring, Medical Physics, 6. (2), 110, 1979.

Dose Efficiency of Fluoroscopic Examination, with Bernstein, H., Medical Physics, March/April 1981.

On the Significance of Very Small Angle Scattered Radiation to Radiographic Imaging at Low Energies, with Fewell, Jennings and Bernstein, Med. Phys., 10(6), 819, 1983.

A Summary of the Results of a Self-Consistent Multiparameter Optimization of Mammography Using Current Technology, Medical Physics, Jan/Feb 1985.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Chan, Kenneth K.	Associate Professor of Pharmacy	[redacted]

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[redacted]	[redacted]	[redacted]	[redacted]

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

Positions: 1964-65, Research Biochemist, VA Hospital, Palo Alto, Calif.
1965-67, Teaching Assistant and Research Assistant, Univ. of Calif.,Davis
1968-72, Teaching Assistant, Univ. of Calif.San Francisco, Calif.
1972-73, Research Assocaite, Univ. of So. Calif., Los Angeles, Calif.
1973-74, Assistant Clin. Professor of Pharmaceutical Chem., USC, Los Angeles
1973-79, Head, Pharmacokinetic Laboratory, John Wesley County Hospital, L.A.
1974-79, Assistant Professor of Pharmacy, Univ. of So. Calif., Los Angeles
1979-present, Director, Pharmacoanalytic Laboratory, LAC/USC Com.Cancer Center
1979-present, Associate Professor of Pharmacy, Univ. of So. Calif., L.A.

Honors: Departmental honored graduate, Calif. State Univ., San Jose, Calif. 1964

Societies: American Chemical Society, American Association for Cancer Research, Academy of American Pharmaceutical Association, Cancer Associates (USC)

Advisory: Ad hoc member of the National Cancer Institute Cancer Program Project Review Subcommittee (site visit team): March 1979, June 1979, Nov. 1981; US Food & Drug Administration Science Advisor, Los Angeles District, 1982-present

Publication:

32 other publications are not listed here.

Giannini, DD, Chan, KK, and Roberts, JD. Carbon-13 nuclear magnetic resonance spectroscopy: structure of the anticoagulant warfarin and related compounds in solution. Proc. Natl. Acad. Sci. 71, 4221-4223(1974).

Chan, KK, Giannini, DD, Cain, AH, Roberts, JD, Porter, W, and Trager, WF. C-13 nuclear magnetic resonance studies of coumarin and related compounds. Tetrahedron 33, 899-906(1977).

Chan, KK, Staroscik, J, Giannini, DD, and Sadee, W. High pressure liquid chromatographic and C-13 nuclear magnetic resonance analysis of 5-azacytidine and its kinetics of hydrolysis. J. Pharm. Sci. 68, 807-812(1979).

Valente, EJ, Chan, KK, and Servis, KL. Proton magnetic resonance studies of the decomposition of 4-hydroxycyclophosphamide, a microsomal metabolite of cyclophosphamide. Pharm. Res. 2,89-92(1984).

Watson, E, Dea, P, and Chan, KK. Kinetics of phosphoramide mustard hydrolysis in aqueous solution. J. Pharm. Sci. (In press)

Chan, KK, Hong, SC, Watson, E, and Deng, SK. Identification of new metabolites of phosphoramide and nor-nitrogen mustards and cyclophosphamide in rat urin using ion cluster techniques. Biomed. mass Spectrom. (In press)

Chan, KK, Bolger, MB, and Pang, KS. Statistical moment theory in chemical kinetics. Anal. Chem. 57, 2145-2151(1985)

Chan, KK, Watson, E, and Hong SC. The application of stable isotopes in antineoplastic drug research. In Current Topics in Pharmaceutical Sciences, ed. Breimer, Elsevier, The Netherlands, 1986 (In press).

CURRICULUM VITAE

NAME: William D. Boswell, Jr.

Place and Date of Birth: [redacted], PA. [redacted]

EDUCATION:

[redacted]

ACADEMIC POSITIONS:

Supervisor of Residents, Clinical Instructor of Radiology, USC School of Medicine	1976-19
Assistant Professor of Radiology, USC School of Medicine	1977-19
Associate Professor of Clinical Radiology, USC School of Medicine	1984
Vice Chairman, Department of Radiology, USC School of Medicine	1982-pres
Chief of Diagnostic Radiology, LAC/USC Medical Center	1979-pres

RECENT PUBLICATIONS (out of over 30)

Ralls, P.W., Quinn MF, Juttner HU, Halls JM, Boswell WD: Ultrasonographic evaluation of gallbaldder wall thickening: patients without intrinsic gallbladder disease. AJR 1981;137-65-68.

Quinn MF, Ralls PW, Boswell WD, Halls JM: The value of sonographic data in the differentiation of common bile duct obstruction Invest Radiol 1981;16:382.

Ralls, PW, Halls, JM, Lapin, SA, Quinn MF, Morris UL, Boswell WD: Prospectiv evaluation of the sonographic Murphy sign in suspected acute cholecystiti J. Clin Ultrasound 1982; 10:113-115.

Quinn MF, Ralls, PW, Boswell WD, Lapin SA, Morris UL, Halls JM: Predicting the cause of common bile duct obstruction with sonographic data: analysis of binary variables. Invest Radiol 1982;17:316-323.

Ralls PW, Quinn MF< Boswell WD, Colletti PM, et al: Patterns of resolution successfully treated hepatic amebic abscess: sonographic evaluation. Radiology 1983;149:541-543.

Radin DR, Rosenstein H, Boswell WD, et al: Burkitt lymphoma in acquired immune deficiency syndrome. JCAT 1984;8:173-174.

Gill PS, Levine AM, Meyer PR, Boswell WD, et al: Primary central nervous system lymphoma in homosexual men: clinical, immunologic and pathologic features. Am J Med 1985;78:742-748.

Ho, Chih-Ming

EDUCATION

[redacted]

ACADEMIC POSITIONS

1985- : Professor, Department of Aerospace Engineering, Univeristy of Southern California

1981-85 : Associate Professor, Department of Aerospace Engineering, University of Southern California

1976-81: Assistant Professor, Department of Aerospace Engineering, University of Southern California

EDITORIAL BOARD OF PROFESSIONAL JOURNAL

Associate Editor 1985-87: Journal of American Institute of Aeronautics and Astronautics

NATIONAL ADVISORY COMMITTEE

1980-84: Technical Committee of Aeroacoustics
American Institute of Aeronautics and Astronautics

PUBLICATIONS

80 papers were published, several key publications are listed below:

"Acoustics Shadowgraph," with Kovasznay, L.S.G., Physics of Fluids, Vol. 9, p. 1118-1123, 1976.

"Dynamics of an Impinging Jet: Part 1.; The Feedback Mechanism," with Nosseir, N.S.M., Journal of Fluid Mechanics, Vol. 105, p. 119-142, 1981.

"Unsteady Kutta Condition of a Plunging Airfoil," with Chen, S.H. Unsteady Turbulent Shear Flows, p. 197-206, Springer/Berlin, 1981.

"Subharmonics and Vortex Merging in Mixing Layers," with Huang, L.S., Journal of Fluid Mechanics, Vol. 119, p. 443-473, 1982.

"Perturbed Free Shear Layer," with Huerre, P., Ann. Rev. of Fluid Mech., Vol. 16, p. 365-424, 1984.

"Unsteady Separation in a Boundary Layer Produced by an Impinging Jet", with Didden, N., Journal of Fluid Mechanics, Vol. 160, p. 235-256, 1985.

"Vortex Induction and Mass Entrainment in a Small Aspect Ratio Elliptic Jet" with Gutmark, E., submitted to Journal of Fluid Mechanics, 1985.

CURRICULUM VITAE

NAME: Steven Mark Lewis

EDUCATION:

[redacted]

EDITORIAL POSITIONS:
Editor BMES Bulletin
Editorial Board - Journal of FORTH Application and Research

POSITIONS HELD:

Associate Professor, Department of Biomedical Engineering, USC	1982-preser
Assistant Professor, Department of Biomedical Engineering, USC	1976-1982
Associate Research Scientist, City of Hope Med Ctr, Duarte, CA	1978-preser
Postdoctoral Fellow, Department of Medicine, University of California, San Diego, CA	1975-1976
Postdoctoral Fellow, Virginia Mason Research Center, Seattle	1974-1975

RECENT PUBLICATIONS:

Characteristics of the washout dead space. S.M. Lewis and C.J. Martin, Respiration Physiology, 36:51-63, 1979.

Effect of plasma carbonic anhydrase (CA) on ventilation in exercising dogs, S.M. Lewis and E.P. Hill, J. Appl. Physiol, 49:708-714, 1980.

Competitive inhibition of CO Transport: Evidence Against a Carrier, D.Z. Rubin, KD. Fujino, C. Mittman and S.M. Lewis, J. Appl. Physiol, 50:1061-1064, 1981.

Distribution of Ventilation and Diffusing Capacity in the Normal and Diseased Lung, S.M. Lewis, D.Z. Rubin and C. Mittman, J. Appl. Physiol, 51:1463-1470, 1981.

Distribution of Specific Ventilation in Cystic Fibrosis, A.A. Jalowayski, S.M. Lewis, I. Young, N. Olmsted and I.R. Harwood, Respiration, 43:249-257, 1982.

Optimal Inputs for Parameter Determination of Inert Gas Washout from the Lung, S.M. Lewis, D.Z. D'Argenio, D.Z. Rubin and G.A. Bekey, Resp. Physiol, 50:111-127, 1982.

Models of the expired CO waveform based on multiple tracer, multiple breath studies, D.Z. Rubin, S.M. Lewis and C. Mittman, J. Appl. Physiol. 708-715, 1984.

U.S. DEPARTMENT OF ENERGY

ASSURANCE OF COMPLIANCE

Nondiscrimination in Federally Assisted Programs

(Hereinafter called the "Applicant")

(Name of Applicant)

HEREBY AGREES to comply with Title VI of the Civil Rights Act of 1964 (Pub. L. 88-352), Section 16 of the Federal Energy Adminstration Act of 1974 (Pub. L. 93-275), Section 401 of the Energy Reorganization Act of 1974 (Pub. L. 93-438), Title IX of the Education Amendments of 1972, as amended, (Pub. L. 92-318, Pub. L. 93-568, and Pub. L. 94-482), Section 504 of the Rehabilitation Act of 1973 (Pub. L. 93-112), the Age Discrimination Act of 1975 (Pub. L. 94-135), Title VIII of the Civil Rights Act of 1968 (Pub. L. 90-284), the Department of Energy Organization Act of 1977 (Pub. L. 95-91), and the Energy Conservation and Production Act of 1976, as amended, (Pub. L. 94-385). In accordance with the above laws and regulations issued pursuant thereto, the Applicant agrees to assure that no person in the United States shall, on the ground of race, color, national origin, sex, age, or handicap, be excluded from participation in, be denied the benefits of, or be otherwise subjected to discrimination under any program or activity in which the Applicant receives Federal assistance from the Department of Energy.

Applicability and Period of Obligation

In the case of any service, financial aid, covered employment, equipment, property, or structure provided, leased, or improved with Federal assistance extended to the Applicant by the Department of Energy, this assurance obligates the Applicant for the period during which Federal assistance is extended. In the case of any transfer of such service, financial aid, equipment, property, or structure, this assurance obligates the transferee for the period during which Federal assistance is extended. If any personal property is so provided, this assurance obligates the Applicant for the period during which it retains ownership or possession of the property. In all other cases, this assurance obligates the Applicant for the period during which the Federal assistance is extended to the Applicant by the Department of Energy.

Employment Practices

Where a primary objective of the Federal assistance is to provide employment or where the Applicant's employment practices affect the delivery of services in programs or activities resulting from Federal assistance extended by the Department, the Applicant agrees not to discriminate on the ground of race, color, national origin, sex, age, or handicap, in its employment practices. Such employment practices may include, but are not limited to, recruitment, recruitment advertising, hiring, layoff or termination, promotion, demotion, transfer, rates of pay, training and participation in upward mobility programs, or other forms of compensation and use of facilities.

Subrecipient Assurance

The Applicant shall require any individual, organization, or other entity with whom it subcontracts, subgrants, or subleases for the purpose of providing any service, financial aid, equipment, property, or structure to comply with laws cited above. To this end, the subrecipient shall be required to sign a written assurance form, however, the obligation of both recipient and subrecipient to ensure compliance is not relieved by the collection or submission of written assurance forms.

Data Collection and Access to Records

The Applicant agrees to compile and maintain information pertaining to programs or activities developed as a result of the Applicant's receipt of Federal assistance from the Department of Energy. Such information shall include, but is not limited to, the following: (1) the manner in which services are or will be provided and related data necessary for determining whether any persons are or will be denied such services on the basis of prohibited discrimination; (2) the population eligible to be served by race, color, national origin, sex, age and handicap; (3) data regarding covered employment including use or planned use of bilingual public contact employees serving beneficiaries of the program where necessary to permit effective participation by beneficiaries unable to speak or understand English; (4) the location of existing or proposed facilities connected with the program and related information adequate for determining whether the location has or will have the effect of unnecessarily denying access to any person on the basis of prohibited discrimination; (5) the present or proposed membership by race, color, national origin, sex, age and handicap, in any planning or advisory body which is an integral part of the program; and (6) any additional written data determined by the Department of Energy to be relevant to its obligation to assure compliance by recipients with laws cited in the first paragraph of this assurance.

The Applicant agrees to submit requested data to the Department of Energy regarding programs and activities developed by the Applicant from the use of Federal assistance funds extended by the Department of Energy. Facilities of the Applicant (including the physical plants, buildings, or other structures) and all records, books, accounts, and other sources of information pertinent to the Applicant's compliance with the civil rights laws shall be made available for inspection during normal business hours on request of an officer or employee of the Department of Energy specifically authorized to make such inspections. Instructions in this regard will be provided by the Director, Federally Assisted Programs Division, Office of Equal Opportunity, U.S. Department of Energy.

This assurance is given in consideration of and for the purpose of obtaining any and all Federal grants, loans, contracts (excluding procurement contracts), property, discounts or other Federal assistance extended after the date hereto, to the Applicant by the Department of Energy, including installment payments on account after such date of application for Federal assistance which are approved before such date. The Applicant recognizes and agrees that such Federal assistance will be extended in reliance upon the representations and agreements made in this assurance and that the United States shall have the right to seek judicial enforcement of this assurance. This assurance is binding on the Applicant, its successors, transferees, and assignees, as well as the person whose signature appears below and who is authorized to sign this assurance on behalf of the Applicant.

12/5/85
(Date)

Cornelius J. Pings

University of Southern California
(Name of Applicant)

University Park
Los Angeles, CA 90089-1147
(Address)

Cornelius J. Pings, Senior Vice President for Academic Affairs
(Authorized Official)

(213) 224-7033
(Applicant's Telephone Number)

*U.S. GOVERNMENT PRINTING OFFICE: 1985-461-208:20131

UNIVERSITY OF SOUTHERN CALIFORNIA
HEALTH SCIENCES CAMPUS
2025 ZONAL AVENUE
LOS ANGELES 90033

DEPARTMENT OF CONTRACTS AND GRANTS

TELEPHONE: (213) 224-7033
TELEX: 674-803
UNIVSOCAL LSA

December 5, 1985

IN REPLY REFER TO: 008125

DOE University Research Instrumentation Program
Energy Programs and Support Division
U.S. Department of Energy
Oak Ridge Operations Office
200 Administration Road
Oak Ridge, Tennessee 37830

8602 074

SUBJECT PROPOSAL: Purchase of Biomedical NMR Spectrometer Imaging System

Principal Investigator:	Walter Wolf, Ph.D.
Amount Requested:	$425,000
Period of Performance:	6-01-85 through 5-31-86
Number of Copies:	Three (Original + 2)

Ladies and Gentlemen:

We are pleased to forward the subject proposal for your consideration and approval. This proposal has been approved by the administration of the University and signed by Cornelius J. Pings, Senior Vice President for Academic Affairs.

Should you have any questions of a technical nature regarding this proposal, please contact the Principal Investigator. Information of a business or administrative nature should be directed to the attention of Mrs. Sarah J. Cusimano, Senior Contract and Grant Administrator at the above address.

Very truly yours,

William C. Hromadka

William C. Hromadka
Executive Director

Enclosure

cc: Dr. W. Wolf

35DEC 6 P2:01

1076666