



Lawrence Livermore National Laboratory

702623

March 18, 1987

Dr. Susan Rose
Human Health & Assessments Division, ER-73
Office of Health & Environmental Research
Office of Energy Research
U.S. Department of Energy
Washington, D.C. 20545

Dear Dr. Rose:

Attached is information on some projects for which you already have HHS-596 and consent forms, as well as information on several current projects that we have approved and finally assembled data on. The projects and P.I. for each are listed below:

<u>P.I.</u>	<u>Project Title</u>
Paul T. Williams	Lipoprotein Subfractions and Heart Disease Mortality
Tore Straume	Chromosome Aberration Frequencies in Patients Undergoing Radiation Therapy with X-rays or Fast Neutrons
Paul Meyer	Human Subjects Experiments (Divers) with Air Tagged with Radioisotopes ¹³ N and ⁴¹ Ar
S. Fry/D.H. Moore	DOE 5-Rem Study/Health and Mortality Study of DOE Workers
Arthur H. Bierman	Transfer of Particulates to Hands
Dr. David Discher	Workplace Investigation for Melanoma Risk Factors

Sincerely,

Frederick T. Hatch, M.D., Ph.D.
Assistant Associate Director
Biomedical and Environmental
Research Program

REPOSITORY DOE - OAK
COLLECTION Environment & Safety Support Div.
BOX No. Central Files
FOLDER 1300.3.B Human Subject testing 1986-1987

00211331

FTH:gw

Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PROTECTION OF HUMAN SUBJECTS
ASSURANCE/CERTIFICATION/DECLARATION

ORIGINAL FOLLOWUP EXEMPTION
(previously undesignated)

GRANT CONTRACT FELLOW OTHER
 New Competing continuation Noncompeting continuation Supplemental

APPLICATION IDENTIFICATION NO. (if known)

American Heart Association

POLICY: A research activity involving human subjects that is not exempt from HHS regulations may not be funded unless an Institutional Review Board (IRB) has reviewed and approved the activity in accordance with Section 474 of the Public Health Service Act implemented by Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46—as revised). The applicant institution must submit certification of IRB approval to HHS unless the applicant institution has designated a specific exemption under Section 46.101(b) which applies to the proposed research activity. Institutions with an assurance of compliance on file with HHS which covers the proposed activity should submit certification of IRB review and approval with each application. (In exceptional cases, certification may be accepted up to 60 days after the receipt date for which the application is submitted.) In the case of institutions which do not have an assurance of compliance on file with HHS covering the proposed activity, certification of IRB review and approval must be submitted within 30 days of the receipt of a written request from HHS for certification.

1. TITLE OF APPLICATION OR ACTIVITY

Lipoprotein Subfractions and Heart Disease Mortality

2. PRINCIPAL INVESTIGATOR, PROGRAM DIRECTOR, OR FELLOW

Paul T. Williams

3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION (see reverse side)

4. HHS ASSURANCE STATUS

This institution has an approved assurance of compliance on file with HHS which covers this activity.

M-1415

Assurance identification number

OIXB

IRB identification number

No assurance of compliance which applies to this activity has been established with HHS, but the applicant institution will provide written assurance compliance and certification of IRB review and approval in accordance with 45 CFR 46 upon request.

5. CERTIFICATION OF IRB REVIEW OR DECLARATION OF EXEMPTION

This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts. This certification fulfills, when applicable, requirements for certifying FDA status for each investigational new drug or device. (See reverse side of this form.)

11/25/86

(month/day/year)

Date of IRB review and approval. (If approval is pending, write "pending." Followup certification is required.)

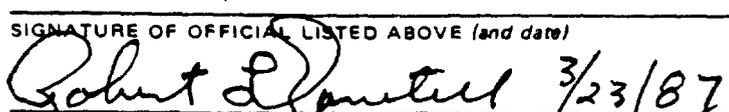
Full Board Review

Expedited Review

This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered 45 CFR 46 will be reviewed and approved before they are initiated and that appropriate further certification (Form HHS 596) will be submitted.

Human subjects are involved, but this activity qualifies for exemption under 46.101(b) in accordance with paragraph _____ (insert paragraph number of exemption in 46.101(b), 1 through 5), but the institution did not designate that exemption on the application.

6. Each official signing below certifies that the information provided on this form is correct and that each institution assumes responsibility for assuring required future reviews, approvals, and submissions of certification.

APPLICANT INSTITUTION	COOPERATING INSTITUTION
NAME, ADDRESS, AND TELEPHONE NO. Lawrence Livermore National Laboratory P.O. Box 808 Livermore, CA 94550 (415) 422-9136	NAME, ADDRESS, AND TELEPHONE NO.
NAME AND TITLE OF OFFICIAL (print or type) Robert L. Zanetell, Finance Manager	NAME AND TITLE OF OFFICIAL (print or type)
SIGNATURE OF OFFICIAL LISTED ABOVE (and date)  3/23/87	SIGNATURE OF OFFICIAL LISTED ABOVE (and date)

Purpose:	Follow-up of fatal coronary heart disease and stroke in 1961 men and fatal and nonfatal heart disease in 423 women. <u>No validation</u>	Follow-up of fatal and nonfatal coronary heart disease and stroke in 2880 men and women. <u>Validation of all events</u> from hospital record, medical records at LLNL, and contact with physician.
Period:	Sept 1, 1986-June 30, 1987, expected to be continued through June 30, 1988.	July 1, 1987-June 30, 1991 (if funded).
Human use approval:	Protocol approved as part of the Lipoprotein Program Project at February 1986 Human Subjects Meetings (CPHS # 85-9-36). LBL Human Use Committee, and U.C. Berkeley Committee for the Protection of Human Subjects.	Approved, 2/21/86 by full board review by the Committee for Protection of Human Subjects, University of California, Assurance identification number M1349
Lipoprotein data:	Data was collected by Dr. John Gofman, 1954-1957 and currently exists on secured computer files at the Donner Laboratory of Medical Physics.	
Additional medical data: (from LLNL)	<u>The following information is useful, but not essential for this study:</u> Heart rate at rest, family history of heart disease and stroke, menstrual history, oral contraceptive use, smoking history, coffee consumption recorded incident of stroke or heart disease.	<u>Permission is requested to examine all medical records for history of nonfatal coronary heart disease or stroke.</u> Heart rate at rest, family history of heart disease and stroke, menstrual history, oral contraceptive use, smoking history, coffee consumption, recorded incident of stroke or heart disease, twelve lead electrocardiograms.
Data for follow-up of LLNL cohort:	When the vital status of an individual cannot be determined from other sources, we will want to obtain from LLNL medical records: date of birth, address, telephone number, name of spouse and personal physician, number of children, employment history, and medical plan number. Additional information on social security number, retirement status, date of birth, name of supervisor will be requested.	
Other follow-up data:	Motor vehicle department records, California death certificates, Social Security records, Telephone directories, contact with previous coworkers and supervisors, neighbor, public school records, other records in the public domain.	
Contact with participants.	Men will be contacted only if their vital status cannot be determined from other sources. Personal contact will be preceded by a letter describing the purpose of the study and a questionnaire which can be returned. If the questionnaire is not received within three weeks, the subject will receive a telephone interview to determine vital status and history of nonfatal heart disease and stroke. All women will be interviewed.	All members of the cohort will be contacted by telephone to obtain information history of nonfatal heart disease and stroke. A letter of introduction will precede any telephone contact with the cohort.

21. Abstract of Research Plan

State the objectives and specific aims and describe concisely the methodology for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. DO NOT EXCEED THE SPACE PROVIDED.

We propose to investigate the relationship of coronary heart disease and stroke to lipoprotein subfraction mass concentrations (i.e., two high-density lipoprotein subfractions: HDL₂ and HDL₃; low-, intermediate-, and very-low density lipoprotein subfractions) and other established risk factors in a group of men and women who received medical examinations and other detailed lipoprotein measurements prior to 1958. The incidence of heart disease and stroke in the men was studied initially by Dr. John Gofman in 1966 (8 years after the measurement of their risk factors [1]). With the exception of Gofman's preliminary study, there are no prospective epidemiologic studies on the relationship of fatal coronary heart disease to lipoprotein subfractions. Our study will extend this earlier investigation to 22 years of follow-up.

Computer files to be used in this study were created in 1958 by Dr. Gofman at the Donner Laboratory, for epidemiologic studies of lipoprotein subfractions. These files include name, age and gender, and the following medical information: cholesterol, lipoprotein subfraction concentrations, blood pressure, weight, smoking history, hemoglobin, red and white blood cell counts, and blood proteins. To establish the relationship between these variables and coronary heart disease and stroke, we will attempt to determine the vital status (i.e., alive or dead, primary cause and age of death) for all individuals in the cohort from information available through the public domain (i.e., California and national death certificates, Motor Vehicle Department, Social Security Records) and, where possible, records from the personnel and retirement organizations at the Lawrence Livermore Laboratory.

Survival analysis will be used to study the relationship of the lipoprotein subfractions and other variables to fatal coronary heart disease. Each individual in the cohort will be recorded as a coronary heart disease death or as a censored observation (i.e., alive at the end of the trial or death or loss to follow-up) and the time of death or censoring. The analyses will include both univariate and multivariate analysis of relative risk.

At a later date, this cohort of men and women may be considered for more extensive investigations into the relationship of lipoprotein subfractions to carotid atherosclerosis and nonfatal heart disease and stroke in men.

22. If you consider yourself to be an established investigator, either in terms of time since your degree, academic rank, grant support, or publications, please use this space to justify support of your application.

AMERICAN HEART ASSOCIATION, CALIFORNIA AFFILIATE GRANT-IN-AID AWARD APPLICATION

see correspondence attached

19 a. The undersigned accept the obligation to comply with the Grant-in-Aid policies of the supporting Heart Association in effect at the time of the award which are hereby specifically made a part of this application. They further agree that applications for patents related to discoveries or inventions resulting from research supported with Grant funds from the Heart Association will be subject to the patent policies of the supporting Heart Association in effect at the time the patent application is submitted.

b. The Principal Investigator and the Institution affirm:

That the investigations involving human subjects proposed and subsequently carried out in the application have been endorsed by the committee on clinical investigation, or other clearly designated appropriate body of the sponsoring institution; and

that any research involving human subjects will conform ethically with the guidelines prescribed by the National Institutes of Health (NIH) including the provision of suitable explanation to human subjects or their guardians concerning the experimental design and all significant hazards, so that they may be in a position to provide appropriate informed consent prior to the investigations; and

that research involving animals will conform with the "Guiding Principles in the Care and Use of Animals" approved by the Council of the American Physiological Society, and with federal laws and regulations; and

that whatever applicable, the research protocol will be reviewed and approved by the institution's biohazards committee, as well as conforming to NIH guidelines.

Name of university, school, hospital or institution which assumes professional responsibility <u>Lawrence Berkeley Laboratory</u>	Signature of Principal Investigator <u>Paul T. Williams</u>	Date <u>Dec 2, 1985</u>
Name of Department Head (please type) <u>Edward L. Alpen</u>	Name of institution which assumes fiscal responsibility <u>Lawrence Berkeley Laboratory</u>	
Signature of Department Head <u>Edward L. Alpen</u>	Name, title, institution and address of fiscal officer to whom checks should be mailed please include phone number. <u>Barbara F. Perry (415) 486-5882</u> <u>Bldg. 90, Rm 1114</u> <u>Lawrence Berkeley Laboratory</u> <u>University of California, Berkeley 94720</u>	
Name of Dean or Director (please type) <u>Edward L. Alpen</u>		
Signature of Dean or Director <u>Edward L. Alpen</u>		
Signature of other Institutional Official (optional)	Signature of Fiscal Officer <u>[Signature]</u>	Date <u>12/2/85</u>

Contact person, address, and phone number if different from the Fiscal Officer

20. List name, degree and position of each professional person associated with indication of capacity (e.g., Principal Investigator, Collaborating investigator, Research Associate, Consultant, etc.)

NAME	DEGREE	% OF TIME ON PROJECT	CAPACITY
Paul T. Williams	M.S. (Ph.D.)	20% (no salary) expected 3/86)	Principal Investigator
Karen Vranizan	M.S.	10% (Yr. 2 only)	Statistical Programmer

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

*School of Medicine and University Hospital
Department of Radiation Oncology*

*Divisions
CLINICAL RADIATION ONCOLOGY
MEDICAL RADIATION PHYSICS
EXPERIMENTAL BIOLOGY*

August 7, 1985

Tore Straume, Ph.D.
Neutron Hazard Research Program
Biomedical and Environmental Sciences Division
Lawrence Livermore National Laboratory
PO Box 5507
Livermore, CA 945510

Dear Tore:

Our joint project to quantitate the chromosomal aberration frequencies in patients treated with neutron irradiation has been approved for our Human Subjects. Enclosed is a copy of the approval for your institution. We can begin the project at your convenience.

Yours truly,



George E. Laramore, Ph.D., M.D.
Professor of Radiation Oncology
Clinical Director, University of Washington
Fast Neutron Radiotherapy Project

GEL:jt

encl.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PROTECTION OF HUMAN SUBJECTS
 ASSURANCE/CERTIFICATION/DECLARATION

GRANT CONTRACT FELLOW OTHER
 New Competing continuation Noncompeting continuation Supplement

ORIGINAL FOLLOWUP EXEMPTION
 (previously undesignated)

APPLICATION IDENTIFICATION NO. (if known)
 12260

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1. TITLE OF APPLICATION OR ACTIVITY
 Radiation Therapy Oncology Group
 Project Title: Protocol to Measure the Chromosomal Aberration Frequencies in Patients Undergoing Radiation Therapy with X-rays or Fast Neutrons

2. PRINCIPAL INVESTIGATOR, PROGRAM DIRECTOR OR FELLOW
 Dr. George E. Laramore

3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION (see reverse side)

4. HHS ASSURANCE STATUS

This institution has an approved assurance of compliance on file with HHS which covers this activity.
 M1183 Assurance identification number 01XB IRB identification number

No assurance of compliance which applies to this activity has been established with HHS but the applicant institution will provide written assurance of compliance and certification of IRB review and approval in accordance with 45 CFR 46 upon request.

5. CERTIFICATION OF IRB REVIEW OR DECLARATION OF EXEMPTION

This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts. This certification fulfills, when applicable, requirements for certifying FOA status for each investigational new drug or device (see reverse side of this form).

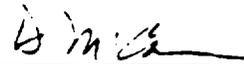
8-5-85 Date of IRB review and approval. (If approval is pending, write "pending". Followup certification is required.)
 (month/day/year)

Full Board Review Expedited Review

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Human subjects are involved but this activity qualifies for exemption under 46.101(b) in accordance with paragraph _____ (insert paragraph number of exemption in 46.101(b), 1 through 5), but the institution did not designate that exemption on the application.

6. Each official signing below certifies that the information provided on this form is correct and that each institution assumes responsibility for assuring required future reviews, approvals, and submissions of certification.

APPLICANT INSTITUTION	COOPERATING INSTITUTION
NAME, ADDRESS, AND TELEPHONE NO. University of Washington Seattle, Washington 98195 (206) 543-0098	NAME, ADDRESS, AND TELEPHONE NO.
NAME AND TITLE OF OFFICIAL (print or type) Ms. Diana McCann, Director Human Subjects Office	NAME AND TITLE OF OFFICIAL (print or type)
SIGNATURE OF OFFICIAL LISTED ABOVE (and date)  8-5-85	SIGNATURE OF OFFICIAL LISTED ABOVE (and date)

0021139

UNIVERSITY OF WASHINGTON
DEPARTMENT OF RADIATION ONCOLOGY

CONSENT FORM
PROTOCOL TO MEASURE THE CHROMOSOMAL ABERRATION FREQUENCIES IN PATIENTS
UNDERGOING RADIATION THERAPY WITH X-RAYS OR FAST NEUTRONS

G.E. Laramore, Ph.D., M.D., Principal Investigator	548-4100
T.W. Griffin, M.D., Professor	548-4100
K.H. Luk, M.D., Associate Professor	548-4100
A.H. Russell, M.D., Assistant Professor	548-4100
R.S. Scott, Ph.D, M.D., Acting Assistant Professor	548-4100
B.R. Griffin, M.D., Acting Assistant Professor	548-4100
J.G. Pelton, M.D., Acting Assistant Professor	548-4100

DEPARTMENT OF RADIATION ONCOLOGY

Emergency Day phone 8:00 a.m. to 5:00 p.m. 548-4100
(state name, nature of call, attending physician)

Emergency phone nights/weekends 548-3300
(ask for radiation oncologist on call)

INVESTIGATORS' STATEMENT

PURPOSE AND BENEFITS

The purpose of this study is to quantify the nature of radiation-induced changes for both neutrons and x-rays in a population that is already undergoing planned radiotherapy for various malignancies; and to determine the effects of reproducing white blood cells (chromosomal changes) due to neutron radiation. These changes will be followed for a period of time and compared with similar changes induced by x-ray. There will be no additional health hazard to subjects in this study. Chromosomal changes are an indicator of both short and long term radiation exposure. The information obtained in this study will be important in analyzing the risk factors of carcinogenesis (cancer causing substance) and mutagenesis (radioactive substance) in the Hiroshima and Nagasaki atomic bomb survivors, in critical accident victims, and for personnel working in the radiation field.

0021140

PROCEDURES

10 PATIENTS RECEIVING PELVIC RADIATION WITH NEUTRONS
10 PATIENTS RECEIVING PELVIC RADIATION WITH PHOTONS
10 PATIENTS RECEIVING NO RADIATION

All subjects must not have received any prior or planned chemotherapy. The 10 patients having received no radiation, must not have had or planned radiation in the immediate future.

If you decided to participate in this study you will have 10cc (approximately 2 teaspoonsful) of blood drawn from your vein in your arm. The blood sample will be placed into a tube that contains 0.1cc of EDTA (prevent clotting). Standard sterile techniques for blood drawing will be used. If you are receiving or have received radiotherapy, this blood sample will be coordinated with any other planned blood test to minimize the discomfort or inconvenience.

The first sample will be obtained prior to radiotherapy to measure the changes that might occur. If you are receiving radiotherapy you will have your blood drawn every month for the first 6 months, and again at 9 months, 1 year, 18 months, 2 years, 2 1/2 years, and 3 years.

If you are not receiving radiotherapy, you will have your blood drawn at the beginning of the study and again at 12 months, 2 years, and three years.

The blood samples will then be packed in standard shipping container and sent via an "overnight" delivery service to the Lawrence Livermore Laboratory where the actual blood tests will be performed.

RISKS, STRESS, OR DISCOMFORTS

The insertion of the needle to draw blood may cause temporary discomfort or pain and a bruise may form where the needle enters the vein.

OTHER INFORMATION

Your identity will remain confidential with the following exception: Livermore Laboratory will receive your name and has the right to review study data which may contain identifying information. Study data will be retained by the investigator indefinitely. Controls over access to the information have been approved by the National Cancer Institute.

You will be informed of any significant new findings based on this research which may affect your willingness to continue participation. Your physician will answer any future questions you may have about the research.

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SEARCHED
SERIALIZED
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FILED

There will be no charge for the blood drawing procedure and you will be paid \$10.00 for each blood sample. In the event of complications, you will be managed by your physician or, if appropriate, you will be referred to another physician specialist. You or your insurance company will be responsible for these costs.

Signature of Investigator Date

SUBJECT'S STATEMENT

I have read and understand the above document. I have had the opportunity to ask questions, and all of my questions have been answered to my satisfaction. I voluntarily agree to participate in this research, and understand that I am free to refuse to participate and to withdraw from the study at any time without penalty or loss of benefits to which I am otherwise entitled. I understand that future questions I may have about the research or about subjects' rights will be answered by one of the investigators listed above.

Signature of Subject Date

00211421

UNFILED FORM

October 8, 1984

To: IRB File on P. Meyer Project
From: Fred Hatch, Chair, IRB
Subject: Update on review of project

F. T. Hatch, M.D.

Our concern about this project, specifically the elective administration of somewhat less than 0.5 rem of radiation, has been discussed extensively with IRB members George Lawton and Sam Cole, Legal Office attorney Max Creamer, and with CDR L. Yaffee, Chair of the IRB at the NMRI. In addition a state-of-the-art risk estimate for lung cancer has been made by Lynn Anspaugh of ENV Division. This risk estimate lies between 1 per 10E5 and 1 per 10E4. The risk is not negligible by some people's interpretation; and Dr. Anspaugh (also Art Toy of H.C.) question whether LLNL should go through with this experiment.

On the basis of the above discussions, I have drawn the following conclusions. 1) NIH guidelines will be complied with provided the consent form (revision attached) sets forth the risk clearly; 2) The ethical concern is largely removed by following NIH guidelines, by having in hand the approval by the IRB at NMRI, and by assuring ample discussion of the procedures and attendant risk at a briefing session before the experiments take place; 3) The institutional risk to LLNL and the University cannot be mitigated, but is considered acceptable to the Legal Office provided a very thorough file on the experiments, including all dosimetric data, is maintained in the IRB Office (in a form that will be usable many years hence when any consequent litigation may occur).

Based on discussions and literature provided by P. Meyer, I can state that there is significant potential benefit from this project to the diving profession, both in the military and in civilian activities. The results obtained in previous work on this project have been published in scientific journals and presented at various meetings, so they are made freely available to the public.

The draft approval memorandum from V. Shepherd to P. Meyer dated 27 Aug., 1984 will be revised to include the above admonition regarding complete file preparation and submission to the IRB, use of both NMRI and LLNL (revised) consent forms, and brought to current date.

Paragraph 3 of the LLNL consent form shall be revised to read as follows:

"I understand that the following risks and discomfort may result from the procedures:

a. discomfort from breathing through a mouthpiece for up to 2 hours.

b. Any exposure to ionizing radiation carries a small risk of causing cancer--in this case potentially of the lung or trachea where most of the dose is delivered. The best estimate of the risk of this procedure lies between 1 chance in 100,000 and 1 chance in 10,000. The radiation exposure in this procedure will be less than 0.4 rem. This amount is slightly below the Federal exposure limit for annual exposure of the general

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population; is one-tenth of the permissible annual exposure of radiation workers; and is approximately twice the natural background radiation received in most geographical areas of the United States."

Paragraph 6 of the LLNL consent form shall have the following sentence added at the end.

"The findings will be of significant benefit to the diving profession in the future, and will be made available as soon as the studies are completed."

0021144

Nitrogen gas exchange in the human knee

P. K. WEATHERSBY, P. MEYER, E. T. FLYNN,
L. D. HOMER, and S. SURVANSI

Hyperbaric Medicine Program Center, Naval Medical Research Institute, Bethesda, Maryland 20814-5055; and Lawrence Livermore National Laboratory, Livermore, California 94550

WEATHERSBY, P. K., P. MEYER, E. T. FLYNN, L. D. HOMER, AND S. SURVANSI. *Nitrogen gas exchange in the human knee.* *J. Appl. Physiol.* 61(4): 1534-1545, 1986.—Human decompression sickness is presumed to result from excess inert gas in the body when ambient pressure is reduced. Although the most common symptom is pain in the skeletal joints, no direct study of nitrogen exchange in this region has been undertaken. For this study, nitrogen tagged with radioactive ^{13}N was prepared in a linear accelerator. Nine human subjects rebreathed this gas from a closed circuit for 30 min, then completed a 40- to 100-min washout period breathing room air. The isotope ^{13}N was monitored continuously in the subject's knee during the entire period using positron detectors. After correction for isotope decay (half-life = 9.96 min), the concentration in most knees continued to rise for at least 30 min into the washout period. Various causes of this unexpected result are discussed, the most likely of which is an extensive redistribution of gas within avascular knee tissues.

inert gas kinetics; tracer; decompression sickness; nitrogen isotope; positron emission

HUMAN DECOMPRESSION SICKNESS (DCS) is presumed to follow a supersaturation of inert gas and formation of bubbles that occurs when the rate of pressure reduction is too fast compared with the rate of gas elimination. Experimentally derived gas kinetics have not been available. Symptoms of DCS can occur in many organ systems, but the most common presentation is pain in the skeletal joints. The knee is the primary focus of pain in approximately 30% of deep-sea divers presenting symptoms of DCS. Indirect evidence from numerous studies in decompressed aviators supports a local source for this pain (20). This suggests that the knee may be peculiar in its gas exchange.

Nitrogen gas exchange in organs was studied directly by Campbell and Hill (5) in the early part of this century and more recently by Thomas et al. (28). Most studies since then have concerned centrally sampled gas (venous blood or expired air), which cannot be used to infer kinetic behavior of any specific organ (1). Insight into partially localized gas exchange may be achieved using inhaled radioisotopes and external detection. Several animal studies performed with ^{133}Xe were directed toward the entire animal or the joints in particular. The ^{133}Xe isotope was also used in many human studies of local blood flow, especially within the brain and skeletal muscle. Our survey in dogs with a large-field gamma detector showed an unusually slow exchange of ^{133}Xe in

the shoulder joints and knees (31). Others (27) have shown skeletal retention of xenon for several days. When radioactive argon is formed in bone mineral by activation of calcium, the excretion rate is very prolonged (2). Direct injection of xenon into the knee is followed by redistribution of the isotope through several nearby tissues (24) and an overall slow rate of excretion (26). Inert gases exchange slowly in human knees.

Isotopes of the inert gases normally used for diving, nitrogen and helium, are not commonly available. There is no usable isotope of helium and all radioisotopes of nitrogen are short lived. The most promising, positron-emitting ^{13}N , must be studied at the site of production because it decays at a half-life of 9.96 min. Apparently, this isotope has not been used to study nonpulmonary tissues, but its use in decompression studies was suggested by West (33).

This work was designed to obtain quantitative measures of nitrogen exchange rates in human knees using a radiotagged nitrogen tracer. Data would be used to evaluate physiological models of gas exchange and provide a data base for decompression calculations. The results, however, were unexpected, indicating a rise in knee nitrogen concentration for more than 1 h after a change in inspired gas gradient. The best explanation is a significant flux of gas into a local sink that coincides with the most sensitive area for detection with the specific instrumentation employed.

METHODS

Experimental. Each subject inspired a normoxic gas with radioactive $^{13}\text{N}_2$ for 30 min and room air for a 1.5-h washout period thereafter. Isotope activity was monitored by two detectors: one of 13 cm diam and the other a 40-cm-diam positron camera. In *experiments 1-7* the small detector was aligned over the left knee and the camera over the upper extremities. In *experiments 8 and 9*, the camera was over the knee and the small detector on an inspiratory section of the rebreathing circuit. Details of isotope production and detection are in APPENDIX 1.

The breathing circuit is shown in Fig. 1. After production, the $^{13}\text{N}_2$ was analyzed for ozone (< 0.1 ppm) and NO_2 (< 2 ppm). Then about 50 liters of the $^{13}\text{N}_2$ were mixed with pure O_2 to reach a final concentration of $20.8 \pm 0.2\%$ O_2 . The $\text{N}_2\text{-O}_2$ mixture was kept in a 100-liter gas bag behind a 1-cm lead shield to minimize personnel exposure and camera overload. The bag was connected



DEPARTMENT OF THE NAVY
NAVAL MEDICAL RESEARCH INSTITUTE
NAVAL MEDICAL COMMAND NATIONAL CAPITAL REGION
BETHESDA MD 20814

IN REPLY REFER TO

PROJECT TITLE: Scientifically Based Decompression Tables for Air Diving

SUBTITLE: Tracer Gas Kinetic Studies for Decompression Table Design

PRINCIPAL INVESTIGATOR: M.E. BRADLEY CAPT MC USN

REQUIREMENTS FOR REVIEW BY THE
COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS

a. What are the risks that may or may not be encountered by the subjects?

The only risks inherent in the procedure are those arising from the special gas breathed. Chemical risks arise from the possibility of creating noxious gases in the radioactive nitrogen preparation. These could include ozone and nitrogen dioxide. The major risk is radiological, that is, the unavoidable exposure of subjects to ionizing radiation. The total dose of radiation from the studies is estimated to not exceed 0.5 rad to the lungs and trachea and 0.01 rad to the body (1). This dose can be compared to the 0.18 rad/year of natural background exposure of the total population; 0.026 rad for a single chest x-ray; 5.0 rad/year, the current federal statutory limit for occupational exposure; and 4,000 rad in clinical radiation therapy (2).

b. What are the safeguards against these risks:

The procedure to be used will attempt to minimize the chance of any chemical risks and to prevent any radiation exposure above the amount stated previously. The radioactive nitrogen and argon will be prepared using techniques developed by P. Meyer. Only very pure gases will be exposed to the gamma-ray source (LINAC electron beam with heavy metal target). After activation, samples of the gas will be taken and analyzed immediately for ozone and nitrogen dioxide. Only when these analyses are completed will the mixture be added to oxygen and breathed by the subject. Expired gases will be directly vented outside the lab building to prevent any other exposure. Subject doses will be calculated by standard methods (1) as the major exposure is too localized and transient to be measured directly.

Procedures will follow those established earlier in work unit M0099PN.01A.0001. In those experiments, the measured ozone and nitrogen dioxide were well below specification in every case. External dosimetry of test subjects showed no detectable radiation dose (less than 0.01 rad). Final internal dosimetry calculations showed lung doses in the subjects of 0.30 to 0.45 rad, compared to the chosen limits of 0.50 rad.

c. What benefit will science or the subject potentially realize?

No direct benefits will be realized by the subjects. Indirect benefits may be realized by U.S. Navy divers, a group that is expected to provide the majority of subjects. The project is designed to provide data on the rate of

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nitrogen uptake and elimination in the human body. Decompression sickness among divers is thought to be caused by an inability to remove the excess nitrogen from a diver's body after breathing high-pressure air. Prevention of decompression sickness is approached by adherence to decompression tables that are calculated to match the rate of nitrogen removal with the rate of diver return to normal pressure. The proposed study will attempt to provide the data necessary for NMRI to provide the safer decompression tables required by the Navy.

d. Have the required elements of informed consent been satisfied? Discuss how the consent will be obtained and attach a copy of the consent form.

Consent forms for both NMRI and the Lawrence Livermore Laboratory are attached. Potential subjects will be briefed at both sites on the procedures, risks, and results to date. In previous experiments, the briefing questions and discussion have required 1-3 hr for each experimental subject.

e. Are the procedures established and accepted nationally and locally and are they for the patient's benefit?

The isotope preparation and detection, and the radiation dosimetry are established and accepted at the Livermore Laboratory. The procedures are specialized and use unusual facilities, so no national standard is possible. The breathing equipment is assembled with components common to pulmonary physiology laboratories. The subjects are healthy and the procedures are not for their individual benefit.

REFERENCES

1. Ozaki, C.B. (memorandum from the Lawrence Livermore Laboratory to Paul Meyer). Estimation of total absorbed doses from inhalation of $^{13}\text{-N}$, $^{15}\text{-O}$, $^{37}\text{-Ar}$, and $^{85}\text{-Kr}$. May 23, 1980.
2. The effects on population of exposure to low levels of ionizing radiation. National Academy of Science, National Research Council, Washington, D.C.

SECRET

LAWRENCE LIVERMORE NATIONAL LABORATORY
EMPLOYEES INCLUDED IN HEALTH STUDIES

Present and former Lawrence Livermore National Laboratory (LLNL) employees and others at some 75 active and disbanded Department of Energy (DOE) and its predecessors' contractor sites nationwide are included in an important epidemiologic study--the Health and Mortality Study of DOE Workers. In this study, sponsored by DOE's Office of Health and Environmental Research, epidemiologists at Oak Ridge Associated Universities (ORAU), Oak Ridge, Tennessee; Los Alamos National Laboratory (LANL), Los Alamos, New Mexico; and Hanford Environmental Health Foundation (HEHF) with Battelle's Pacific Northwest Laboratory, Richland, Washington, are examining relationships between illness (morbidity) and death rates (mortality) among workers at the various sites and their earlier occupational exposure to radiation and other physical and chemical agents in the work place.

In addition to ongoing studies of the workforces of individual plants at Savannah River, Oak Ridge, Paducah, Portsmouth, Fernald, and from several inactive Manhattan Engineer District sites around the country, the researchers at ORAU and their collaborators at the University of North Carolina, Chapel Hill, also are conducting a study of all contractor employees since 1947 who ever equalled or exceeded the current annual occupational external radiation exposure limit of 5 rem. The researchers surveyed 76 present and former DOE sites and identified approximately 3,100 active and former employees at 40 sites who met these criteria--this group or cohort represents 0.5 percent of the entire DOE work force since 1943 and includes a total of 18 LLNL employees (15 at LLNL and 3 at LLNL-NTS).

The "5 Rem Study" has three phases. In Phase I the mortality among the radiation workers is being compared with that of the U.S. population. Preliminary findings for white males followed through 1979 are of fewer than expected number of deaths--26 percent fewer deaths overall and 23 percent fewer deaths from all types of malignant diseases. Among the approximately 55 causes of death examined, only the number of deaths due to cancer of the digestive organs and peritoneum was higher but not statistically different from what was

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expected for white males of similar ages in the general population (19 deaths observed, 17 expected). Of the digestive cancer deaths, 6 were due to cancer of the rectum where 2 were expected; this as yet unexplained increase was statistically significant.

Overall the fewer than the expected number of deaths in this population of workers probably is a reflection of a "healthy worker effect," which can result when workers are compared with the general population, because only persons healthy enough to work are hired and others are excluded for medical reasons.

To overcome the effect of the healthy worker, Phase II of the study, which is in progress, will compare the mortality of workers exposed to 5 or more rem of radiation with that of workers, employed at the same time at the same plants, who never received an annual dose of 5 or more rem. Phase III of the study, also in progress, is to be a comparison of the subsequent health of workers who received 5 or more rem with those who did not.

The comparison group for these phases of the study is being identified by matching up each employee with 5 or more rem in a year with four current or former employees who worked at the same plant and who have similar characteristics except they never had 5 rem or more in a year; thus Phases II and III of the study will include a maximum of 75 LLNL and 15 LLNL-NTS employees.

Present and former LLNL employees included in the 5 Rem Study will receive a letter inviting them to participate in the follow-up interview phase (III) of the study; they can indicate their willingness or not to participate by returning a pre-stamped and addressed card to the researchers in Oak Ridge. Persons willing to participate then will be interviewed by telephone to determine whether they have experienced or are experiencing any health problems. The interviewers will not know whether the person they interview is one of the 5 rem group or a member of the comparison group. During the 20- to 30-minute interview, the study participants are asked a series of questions about their current health, health problems in the past, and other factors that could influence health, such as smoking habits, and the types of work they have done, and the years spent at each type of work.

The ORAU researchers expect to complete and report the results of Phases II and III of the 5 Rem Study during fiscal year '88. In the meantime,

they have begun work on a collaborative study with LLNL epidemiologist, Dr. Dan Moore, to evaluate the causes of death among persons employed at LLNL anytime from the start of operations in 1952 to the present. This study will be an expansion of Dr. Moore's 1979 study of mortality among workers employed at LLNL between 1964 and 1979. It will be conducted as part of the overall Health and Mortality Study using plant and employee records maintained by LLNL since 1952.

If you have any questions about these studies, contact Dr. Dan Moore at the Biomedical Sciences Division, LLNL (phone: 422-5631) or Dr. Shirley Fry, Program Director, Center for Epidemiologic Research, Oak Ridge Associated Universities (FTS 626-3480; commercial (615) 576-3480).

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Interdepartmental letterhead

Mail Station 280

Ext: 2-9678

July 5, 1984

TO: Frederick T. Hatch, Chairman Human Subjects Committee
FROM: Paul Meyer
SUBJECT: Renewal of Human Subjects Approval 80P-109-02

The purpose of the work proposed is to measure the rate of uptake and elimination of nitrogen and argon in the body of normal, healthy humans. Experiments will involve breathing of ^{13}N and ^{41}Ar labelled air for up to two hours at an initial specific activity of up to $\sim 1 \mu\text{Ci}$ per liter of ^{13}N and $24 \mu\text{Ci}$ per liter of ^{41}Ar . P. K. Weathersby, CDR, MSC, USN, is the principal investigator and E. T. Flynn, Jr., Capt., MC, USN and myself are associate investigators. All test subjects will be Navy personnel volunteers. The protocol for the proposed experiments is identical to that followed in 1982 and an Operating Safety Procedure renewal is presently being processed by Hazards Control. Calculated radiation exposures are as indicated in an enclosed clinical record of a 1982 test subject. Experiments are scheduled for September 1984 and funding is provided by the Naval Medical Research Institute in Bethesda, MD. I would appreciate your written approval before September of this year.

PM/pld 0595m/0038m

Encl.: Background material: Navy Publication
OSP No. 194.27, expired 4/20/83
clinical record of 1982 test subject

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University of California

LAWRENCE LIVERMORE LABORATORY



Lawrence Livermore National Laboratory

UNIVERSITY OF CALIFORNIA
LAWRENCE LIVERMORE NATIONAL LABORATORY

Consent to Act as a Human Subject

LLNL Human Subjects Committee
Approval Number: 87R-101
Approval Date: November 25, 1986

Transfer of Particulates to Hands

Subjects Name: _____

Date: _____

1. I hereby agree to participate in the Particle Transfer tests being conducted by the Hazards Control Department of Lawrence Livermore National Laboratory.
2. I understand that the procedures for conducting these tests are as follows:

Volunteer participants will press their hand on a metal plate which has been coated with fine particles. Immediately after, they will wash any collected particles off their hand. A single test will last approximately 1.5 minutes.
3. I understand that the possible risks and discomfort from participation in this experiment would be associated with individual allergic responses to the chemical composition of the fine particles.
4. At the conclusion of this procedure it is expected that I will be able to function normally immediately.
5. I understand that the purpose of performing these procedures is to determine the parameters governing the amount of fine particles which may be transferred from metallic surfaces to hands by physical contact.
6. I further understand that this study may result in no direct benefit to me but it may benefit some individuals in the future.
7. I understand that Arthur H. Biermann, the Principal Investigator, and/or such assistants as may be selected will answer any inquiries I may have at any time concerning the procedures and/or investigation.

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Subjects Initials
Page 1 of 2

LLNL Human Subjects Committee
Approval Number: 87R-101
Approval Date: November 25, 1986

8. Any publication arising from this study will be made without specific reference to my name.
9. I recognize that my participation in this experiment is entirely voluntary and I may refuse to participate or may withdraw at any time without jeopardy. Owing to the scientific nature of the study, the investigator may in his absolute discretion terminate the procedures and/or investigations at any time.
10. Arthur H. Biermann, an employee of the University of California, Lawrence Livermore National Laboratory, is responsible for the conduct of the research in which I am to participate. This research is sponsored by the Hazards Control Department of Lawrence Livermore National Laboratory which is operated by the University of California under contract with the United States Department of Energy, and the United States Department of the Army.
11. I understand that I am entitled to a copy of this consent form and the Lawrence Livermore National Laboratory Experimental Subject's Bill of Rights.
12. I understand that I am participating in this experiment as an employee of the University of California, Lawrence Livermore National Laboratory as a part of the work performed under Contract W7405-ENG-48 between the University of California and Department of Energy.
13. I understand that if I have any complaints or concerns about the procedures, I may address them to Vivian L. Shepherd, Secretary of the Human Subjects Committee, in person, by telephone, or in writing. Ms. Shepherd can be reached at (415) 423-2887, L-319, Lawrence Livermore National Laboratory, P.O. Box 808, Livermore, CA. 94550.

Subject's Signature _____

Witness _____

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Lawrence Livermore National Laboratory

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The management and staff of the University of California, Lawrence Livermore National Laboratory, wish you to know:

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment, if applicable.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment, if complications should arise.
7. Be given the opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of the signed and dated written consent form.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

If at any time you have any questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may also seek assistance from the Human Subjects Committee which was established for the protection of volunteers in research projects. The Secretary of that Committee, Vivian L. Shepherd, may be reached by calling, (415) 423-2887, from 8:00 a.m. until 5:00 p.m., Monday through Friday, or writing to the Human Subjects Committee, L-319, Lawrence Livermore National Laboratory, P.O. Box 808, Livermore, CA 94550.

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Interdepartmental letterhead

Mail Station 386

Ext 2-8017

November 4, 1986

TO: The LLNL Human Subjects Committee
Attn: Vivian Shepherd

FROM: A. H. Biermann

SUBJECT: Request for Permission to Investigate the Transfer of
Particulates to Hands Using Human Subjects

The Safety Science Group in Hazards Control has been investigating the adhesion of particles to surfaces and their subsequent removal. We have reached a point in our studies where we would like to obtain actual experimental data on the numbers of particles transferred from surfaces to hands. We want to be able to predict the amount of particles that a hand might pick up from a surface coated with small particles. Because of the initial low funding level at this time, only one participant will be included in our experiments. However, we may want to expand this number to 8 or 10 participants in the event of increased or renewed funding. All participants would be current full-time employees at the Laboratory.

We are interested in the removal of particles from unpainted and painted metallic surfaces. Several types of particles are of interest in the size ranges from 1 to 200 microns in diameter. These include small solid glass spheres, starch, myosin, carmine sulfate, sodium fluorescein, zinc sulfide, and sugar. These specific materials are not mandated; other materials could be used as possible substitutes if these are found to be toxic or irritable to the skin.

To determine the amount of particle transfer from a surface to a hand, we envision the following experimental protocol. Prior to the actual experiment, the surface will be dusted with particles of a certain type and size range in a closed chamber. The desired surface concentrations will be far less than a complete monolayer coverage. The participant's hand will be washed in a prescribed manner, probably with either water, isopropanol, or both. At least 2, and perhaps 3, washings will be done so that complete removal of the particles can be verified. The contact force may vary up to 90 gm/cm² and will be monitored with a scale. Actual contact of the hand on the surface will be short, only 10 to 30 seconds. After contact, the hand will again be washed to quantitatively recover the particles that were transferred from the surface to the hand. Environmental conditions will be regulated at a temperature of approximately 20°C and a relative humidity of 30%. As you can see, the procedure itself is fairly simple.

University of California

 Lawrence Livermore
National Laboratory

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5. Total contact time of the subject's hand with the particles will be short, less than 90 seconds.
6. The quantity expected to be transferred to a hand will be minimal. Assuming a 100% transfer of particles to the hand over the total hand area (including areas which will not actually touch the surface), we estimate no more than 100 mg would be transferred to a hand. In many experiments involving a sensitive detection method such as the case of fluorescein, lesser amounts could be used.

If we receive more information on the toxicology consequences of these compounds, we will pass this along to you. Meanwhile, we would appreciate a committee review as soon as possible so that we can begin our experiments. A separate operation safety procedure (OSP) is not planned for this experiment because the hazards are covered under the Building 253 OSP. If you have questions or require additional information, please let me know.



Arthur H. Biermann
Special Projects Division
Hazards Control Department

AHB:beb

Encls:

cc: J. S. Johnson, LLNL
Harvey Lee, SAN
Fred Hatch, LLNL ✓

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PROTECTION OF HUMAN SUBJECTS
 ASSURANCE/CERTIFICATION/DECLARATION

GRANT CONTRACT FELLOW OTHER
 New Competing continuation Noncompeting continuation Supplemental

ORIGINAL FOLLOWUP EXEMPTION
 (previously undesignated)

APPLICATION IDENTIFICATION NO. (if known)

POLICY: A research activity involving human subjects that is not exempt from HHS regulations may not be funded unless an Institutional Review Board (IRB) has reviewed and approved the activity in accordance with Section 474 of the Public Health Service Act implemented by Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46—as revised). The applicant institution must submit certification of IRB approval to HHS unless the applicant institution has designated a specific exemption under Section 46.101(b) which applies to the proposed research activity. Institutions with an assurance of compliance on file with HHS which covers the proposed activity should submit certification of IRB review and approval with each application. (In exceptional cases, certification may be accepted up to 60 days after the receipt date for which the application is submitted.) In the case of institutions which do not have assurance of compliance on file with HHS covering the proposed activity, certification of IRB review and approval must be submitted within 30 days of the receipt of a written request from HHS for certification.

1. TITLE OF APPLICATION OR ACTIVITY

Workplace Investigation for Melanoma Risk Factors

2. PRINCIPAL INVESTIGATOR, PROGRAM DIRECTOR, OR FELLOW

Dr. David Discher

3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION (see reverse side)

4. HHS ASSURANCE STATUS

This institution has an approved assurance of compliance on file with HHS which covers this activity.

M-1415 Assurance identification number 01XB IRB identification number

No assurance of compliance which applies to this activity has been established with HHS, but the applicant institution will provide written assurance of compliance and certification of IRB review and approval in accordance with 45 CFR 46 upon request.

5. CERTIFICATION OF IRB REVIEW OR DECLARATION OF EXEMPTION

This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts. This certification fulfills, when applicable, requirements for certifying FDA status for each investigational new drug or device. (See reverse side of this form.)

11/25/86 Date of IRB review and approval. (If approval is pending, write "pending." Followup certification is required.)
 (month/day/year)

Full Board Review Expedited Review

This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by 45 CFR 46 will be reviewed and approved before they are initiated and that appropriate further certification (Form HHS 596) will be submitted.

Human subjects are involved, but this activity qualifies for exemption under 46.101(b) in accordance with paragraph _____ (insert paragraph number of exemption in 46.101(b), 1 through 5), but the institution did not designate that exemption on the application.

6. Each official signing below certifies that the information provided on this form is correct and that each institution assumes responsibility for assuring required future reviews, approvals, and submissions of certification.

APPLICANT INSTITUTION	COOPERATING INSTITUTION
NAME, ADDRESS, AND TELEPHONE NO. Lawrence Livermore National Laboratory P.O. Box 808 Livermore, CA 94550 (415) 422-9136	NAME, ADDRESS, AND TELEPHONE NO.
NAME AND TITLE OF OFFICIAL (print or type) Robert L. Zanetell, Finance Manager	NAME AND TITLE OF OFFICIAL (print or type)
SIGNATURE OF OFFICIAL LISTED ABOVE (and date) <i>Robert L. Zanetell</i> 3/23/87	SIGNATURE OF OFFICIAL LISTED ABOVE (and date)

Report on comparison of LLNL cases with South Bay pathology laboratory cases submitted to Cancer

An important question concerning the melanoma cases at LLNL has been whether their lesions were identified and removed at an earlier stage than is generally true in the community, presumably because of increased awareness at LLNL. Dan Moore and Jeff Schneider extracted extensive records from a busy dermatologic pathology laboratory in Los Gatos covering a period of several years. The findings were that LLNL lesions were generally thinner than those in the laboratory collection. They have submitted an article for publication in *Cancer* (preprint UCRL-95484).

E. Epidemiologic study of the unrecorded incidence of cutaneous malignant melanoma

The MITG is currently seeking a contractor to perform a study which would attempt to ascertain the frequency and histopathologic and demographic characteristics of CMM that are diagnosed in residents of Alameda and Contra Costa counties at locations not normally accessed by the field staff of the California Tumor Registry, resulting in identification of cases of CMM that are unrecorded in the Registry. This study will involve extensive field interactions with pathologists, dermatologists, and other clinicians for case-finding and recording of pathologic and demographic information on melanoma patients. Data will be gathered and converted to computer-readable form; pathologic reports and specimens (slides) will be obtained for a sample of the unrecorded cases. Interactions will then occur with the CTR and with a panel of three expert dermatopathologists. An oversight committee composed of members of the MITG and Drs. Austin and Reynolds of the California Tumor Registry will provide general guidance, oversee the work of the contractor, direct details of the workscope as the study evolves, and receive and approve the reports produced by the contractor. A preliminary phase of the study should begin in April 1987, with completion of the full study in about one year.



F. Workplace Investigation Plan

In 1984 the University of California's Health, Safety and Environment Advisory Committee, which oversees the subject areas at the National Laboratories managed by the University, appointed a Working Group on Malignant Melanoma to work with the Laboratory and with the parent committee to address the issue of melanoma at LLNL. The Oversight Committee conducted two thorough reviews at LLNL during the past sixteen months. The Committee recommends that a detailed occupational workplace study be conducted at LLNL to examine the specific

factors mentioned in the Austin/Reynolds Report No. 3 and any other workplace factors that may distinguish cases from controls.

Much effort has already gone into evaluating possible workplace exposures that might be related to melanoma incidence at LLNL, but no credible factors have been identified. Direct intensive interviews are necessary before we can be satisfied that we have exhausted all avenues of study of possible workplace exposures that might be related to melanoma incidence.

To investigate in depth the conclusion of the Austin Report No. 3 that several exposure factors in the LLNL workplace account for the increased incidence of melanoma, we are undertaking in-depth occupational interviews of our cases and selected matched controls. These will be conducted by an industrial hygienist well experienced in weapons testing and other major programs, together with the Deputy Medical Director. Question modules have been designed for work history (non-LLNL), LLNL work history including specific projects and programs and possible incidents of exposure, military service, residential and educational history, hobbies and leisure activities, non-occupational exposure to pesticides and herbicides, and non-job related travel. Interviews will begin in February 1987, together with dermatologic examinations by our consultant dermatologist and a questionnaire on lifetime solar exposure and reactions thereto based on a design by Armstrong.

Approximately 35 LLNL employees will be interviewed. The first part of the program involves completion of an initial brief mailed questionnaire (for melanoma cases only); an examination by a dermatologist in Health Services; and an interview about previous sun exposure administered by a Health Services staff member.

The second part of the program consists of completion of a questionnaire concerning previous residence, education, and work history; and an extensive work history interview, with a brief followup interview to verify the recorded data.

The time and effort required of the research subjects asked to participate in the workplace investigation will vary with the complexity of each individual's work history. We estimate that an average of twelve hours of effort will be required.

The main objectives of this study are (1) detection of common threads of experience among cases that are not common to controls and (2) hypothesis generation concerning any workplace factors that may have contributed to increased incidence of melanoma.

UNIVERSITY OF CALIFORNIA
LAWRENCE LIVERMORE NATIONAL LABORATORY
Consent to Act as a Human Subject

LLNL Human Subjects Committee

Approval Date: November 25, 1986

Project: Occupational Medical Investigation of Malignant Melanoma

Principal Investigator: Dr. David P. Discher
Deputy Medical Director
Office of Health Services
L-423, Ext. 27459

Subject's Name: _____

L-Code: L- _____ Telephone Ext.: _____

Date: _____

1. I hereby authorize Dr. Jeffrey Schneider to obtain from me questionnaire data concerning my medical history, lifestyle, residential history, and history of exposure to the sun, and to conduct a complete dermatologic examination, including skin photographs, if indicated.
2. I understand that the purpose of this investigation is to obtain comprehensive information on possible workplace exposures or other factors that could contribute to the apparent increased diagnosis rate of malignant melanoma at LLNL.
3. I understand that the reason for my selection for this project is either that I am a melanoma case or I match such a person on the basis of age, sex, time at the Laboratory, and educational degree.
4. I understand that all the information I provide will be protected as medically confidential by the Office of Health Services. It will be made available to Health Services staff assigned to the project and to members of the Melanoma Investigation Task Group who are involved in the investigation. To the extent possible it will be worked with in coded form with my name removed. No use of the information, other than that required for evaluating possible contributory factors to melanoma incidence, will be made.
5. I understand that the risk associated with my participation in this study is the remote chance of inadvertent release of confidential information.
6. I understand that this study may result in no direct benefit to me but that it may contribute to understanding the possible causes of melanoma and to making the work environment at LLNL as safe as possible.

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7. I understand that Dr. Schneider and/or Dr. David Discher will answer any inquiries I may have at any time about this investigation.
8. Any publication or report arising from this study will be made without specific reference to my name.
9. I recognize that my participation in this investigation is entirely voluntary and that I may refuse to participate or withdraw at any time without jeopardy of any kind. The principal investigator may, according to his judgment, terminate my participation at any time.
10. Dr. David Discher, Deputy Medical Director, is responsible for the conduct of this investigation. The study is sponsored by LLNL solely for increasing the understanding of the apparent increase in melanoma among LLNL employees.
11. I understand that I am entitled to receive a copy of this consent form and the Experimental Subjects Bill of Rights.
12. I understand that if I have any complaints or concerns about the procedures I may address them to Vivian L. Shepherd, Secretary of the Human Subjects Committee, in person, by telephone, or in writing. She can be reached at extension 3-2887, or L-319 at LLNL.

Subject's signature: _____

Witnessed: _____

UNIVERSITY OF CALIFORNIA
LAWRENCE LIVERMORE NATIONAL LABORATORY
Consent to Act as a Human Subject

LLNL Human Subjects Committee

Approval Date: November 25, 1986

Project: Occupational Medical Investigation of Malignant Melanoma

Principal Investigator: Dr. David P. Discher
Deputy Medical Director
Office of Health Services
L-423, Ext. 27459

Subject's Name: _____

L-Code: L- _____ Telephone Ext.: _____

Date: _____

1. I hereby authorize H. Wade Patterson and/or David Discher to obtain from me questionnaire data concerning my medical history, work experience, lifestyle, residential history, and other relevant information, and to conduct an interview with me that will probe, to the extent deemed necessary, my workplace experiences at LLNL and elsewhere. I understand that the interview may be recorded stenographically for the purpose of accurate record maintenance, and that I will have an opportunity to review the transcript and correct it, if necessary.
2. I understand that the purpose of this investigation is to obtain comprehensive information on possible workplace exposures or other factors that could contribute to the apparent increased diagnosis rate of malignant melanoma at LLNL.
3. I understand that the reason for my selection for this project is either that I am a melanoma case or I match such a person on the basis of age, sex, time at the Laboratory, and educational degree.
4. I understand that all the information I provide will be protected as medically confidential by the Office of Health Services. It will be made available to Health Services staff assigned to the project and to members of the Melanoma Investigation Task Group who are involved in the investigation. To the extent possible it will be worked with in coded form with my name removed. No use of the information, other than that required for evaluating possible contributory factors to melanoma incidence, will be made.
5. I understand that the risks associated with my participation in this study are the possibility of psychological discomfort associated with detailed discussion of past activities and the remote chance of inadvertent release of confidential information.

6. I understand that this study may result in no direct benefit to me but that it may contribute to understanding the possible causes of melanoma and to making the work environment at LLNL as safe as possible.
7. I understand that Dr. Discher and/or Mr. Patterson will answer any inquiries I may have at any time about this investigation.
8. Any publication or report arising from this study will be made without specific reference to my name.
9. I recognize that my participation in this investigation is entirely voluntary and that I may refuse to participate or withdraw at any time without jeopardy of any kind. The principal investigator may, according to his judgment, terminate my participation at any time.
10. Dr. David Discher, Deputy Medical Director, is responsible for the conduct of this investigation. The study is sponsored by LLNL solely for increasing the understanding of the apparent increase in melanoma among LLNL employees.
11. I understand that I am entitled to receive a copy of this consent form and the Experimental Subjects Bill of Rights.
12. I understand that if I have any complaints or concerns about the procedures I may address them to Vivian L. Shepherd, Secretary of the Human Subjects Committee, in person, by telephone, or in writing. She can be reached at extension 3-2887, or L-319 at LLNL.

Subject's signature: _____

Witnessed: _____

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The management and staff of the University of California, Lawrence Livermore National Laboratory, wish you to know:

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.
3. Be given a description of any attendant discomforts and risks reasonably expected from the experiment, if applicable.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment, if complications should arise.
7. Be given the opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of the signed and dated written consent form.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

If at any time you have any questions regarding a research study, the researcher or his/her collaborators will be glad to answer them. You may also seek assistance from the Human Subjects Committee which was established for the protection of volunteers in research projects. The Secretary of the Committee, Vivian L. Shepherd, may be reached by calling, (415) 423-2887, from 8:00 a.m. until 5:00 p.m., Monday through Friday, or writing to the Human Subjects Committee, L-319, Lawrence Livermore National Laboratory, P.O. Box 808, Livermore, CA 94550.

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