717816

WRITE IT – DON'T SAY IT

TO Vivian Shepherd

RE: Renewal of H.S. Approval 80P-109-02

Enclosed is the Navy's Human Subjects form. approval for the radioactive tracer experiments. The LLNL H.S. Committee in its meeting of Aug. 23, 84 approved, in principle, the experiments. A change in the Consent-Form was suggested and is now in Dr. Hatch's hands.

FROM Paul Meyer x29678

DATE 9/11/84

RL-2447(REV.4/62)

REPOSITORY LLNL B361, Rm. B940A

COLLECTION Institutional Review Board

BOX No. IRB Protocol File

FOLDER Meyer, P. IRM No. 80P-109
Decompression Sickness Studies
with Radioactive Gases
Folder 1 of 2

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NAVV 5216/144A (Rev. 8-81)
S/N 0107-LF-062-2320

Memorandum

DATE: 11 June 1984

FROM: Chairman, Committee for the Protection of Human Subjects, NMRI

TO: Director, Hyperbaric Medicine Program Center

VIA: Scientific Director, NMRI 6/18/84

SUBJ: Hyperbaric Medicine Program Center protocols involving human use, review and approval of

Incls: Approvals and consent forms for:

(1) Work tolerance in the hyperbaric environment (M0099.01A.0007)

(2) Thermal balance and performance in divers during cold exposure (M0099.01B.0008)

(3) Scientifically based decompression tables for air diving (M0099.01A.0005)

(4) Physiological design criteria for underwater breathing (M0099.01B.0010)

1. The Committee for the Protection of Human Subjects has reviewed and approved the Hyperbaric Medicine Program Center protocols involving human use.

2. The signed Committee approval forms are enclosed together with the appropriate consent forms to be used in the study.

L. J. Yaffe

L. J. YAFFE

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☆U.S. GPO: 1982-539-003/2091 Region 3

DEPARTMENT OF THE NAVY
NAVAL MEDICAL RESEARCH INSTITUTE
NATIONAL NAVAL MEDICAL CENTER
BETHESDA, MD 20814

IN REPLY REFER TO
SECNAVINST 3900.39B
NMRIINST 3900.6A

Certification of Research Protocol
Review and Approval
Committee for the Protection of Human Subjects

Research Protocol: Scientifically based decompression tables for air diving (M0099.01A.0005)

Investigator(s): M. Bradley, P. Weathersby, R. Lillo

1. The listed research protocol has been reviewed and approved by the members of the Committee for the Protection of Human Subjects, Naval Medical Research Institute in accordance with the directives of SECNAVINST 3900.39B.

2. The Committee has determined that the risks to the subjects participating in this study have been adequately assessed and appropriate safeguards instituted.

3. The attached, approved consent form(s) must be adequately explained and provided to each subject participating in the study to fulfill the requirements for both effective, informed consent and proper documentation.

4. The risks, if any, to the subjects in this study are sufficiently outweighed by the knowledge to be gained as to merit acceptance of the risks by the subject. The Institute will have emergency professional care and facilities available as may be needed for subjects who may suffer physical, psychological, or other injury as a result of participation in the study.

5. The Committee Chairman must be notified by the investigator(s) of any serious adverse reactions or accidents occurring to subjects during the study.

6. The signatories certify that the review and approval of the listed protocol were carried out in accordance with the requirements of SECNAVINST 3900.39B.

Pen Yaffe 8 June 84
L. YAFFE, CDR, MC, USN
Chairman

Members:

M. Caldwell
M. Caldwell, LT, MC, USNR

D. Seeland, CDR, CHC, USN

T. Palmer, LCDR, MSC, USN

Donald Hagengruber, J.D.
D. Hagengruber

W. Shurtz, HMCS, USN

P S Matthews 8 JUNE 84
P. Matthews

Alternates:

J. Nanfro, LCDR, MC, USNR

R. Lillo

1121766

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-N, 15-O, 37-Ar, and 85-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.

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

IN REPLY REFER TO

CONSENT FOR VOLUNTARY PARTICIPATION IN AN EXPERIMENTAL STUDY

Date: _____

1. I, _____, HAVE BEEN ASKED TO VOLUNTARILY PARTICIPATE IN A RESEARCH STUDY.

2. THIS PROJECT IS SUBTITLED, "Tracer gas kinetic studies for decompression table design."

3. THE PURPOSE OF THIS RESEARCH STUDY HAS BEEN EXPLAINED TO ME. I understand that the study is designed to measure how fast inert gas enters and leaves parts of the human body. This information is needed to develop safer diver decompression schedules.

4. I WILL BE MAINTAINED IN THIS STUDY FOR A PERIOD OF one year.

5. THE PROCEDURE FOR THIS STUDY HAS BEEN EXPLAINED TO ME AS FOLLOWS: I will travel to the Lawrence Livermore Laboratory where I will breathe a mixture of gases that include radioactive nitrogen and/or radioactive argon. During the breathing (up to 2½ hr) I will breathe through a mouthpiece, wear nose clips, and sit very still in front of the radiation detection equipment. I may be asked to repeat the study, and I may receive a standard x-ray for reference purposes.

6. SPECIFICALLY, I AM AWARE THAT THE ENTIRE PROCEDURE IS EXPERIMENTAL.

7. THE INVESTIGATOR HAS INFORMED ME THAT A TOTAL OF 4 TO 10 SUBJECTS WILL BE ENROLLED IN THIS PROJECT THIS YEAR. The subjects will be active duty U.S. Navy personnel, primarily male divers from the Naval Medical Research Institute (NMRI).

8. THE RISKS THAT ARE POSSIBLE ARE AS FOLLOWS: There is a small risk of breathing a chemically harmful gas such as ozone or nitrogen dioxide. I understand that the gas will be analyzed for these substances before I breathe it. There is a risk of illness from the radiation exposure. The exposure will be kept below 0.5 rad, which is below the amount of radiation allowed by law for people who work in radiation occupations. Some scientists believe, however, that even such small doses of radiation give a very slightly higher risk of cancer later in life.

9. THIS RESEARCH WILL NOT BE OF DIRECT BENEFIT TO ME; HOWEVER, THE RESULTS MAY PROVIDE IMPORTANT INFORMATION OF BENEFIT TO OTHERS.

10. I AM AWARE THAT THIS STUDY MAY INVOLVE RISKS TO ME (OR TO THE EMBRYO OR FETUS IF I BECOME PREGNANT) THAT ARE CURRENTLY UNFORESEEABLE. I AM AWARE THAT I SHOULD PROMPTLY ADVISE THE INVESTIGATOR IF I BECOME PREGNANT OR CONTEMPLATE BREAST-FEEDING.

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11. BECAUSE THIS IS NOT A MEDICAL TREATMENT, I MAY DECLINE ENROLLMENT INTO THIS STUDY, OR WITHDRAW AT ANY TIME.

12. IF I HAVE ANY QUESTIONS CONCERNING THIS RESEARCH STUDY, I MAY CONTACT DR. WEATHERSBY AT 295-5898.

13. I UNDERSTAND THAT PARTICIPATION IS VOLUNTARY AND, IF I DO REFUSE TO ENROLL, NO LOSS OF BENEFITS OR CARE TO WHICH I AM ENTITLED WILL OCCUR.

14. THE INVESTIGATOR MAY TERMINATE MY PARTICIPATION IN THIS STUDY FOR ANY REASON AT HIS DISCRETION.

15. IF I SHOULD DECIDE TO WITHDRAW FROM THE RESEARCH STUDY, I WILL NOTIFY DR. WEATHERSBY AT 295-5898 TO ENSURE AN ORDERLY TERMINATION PROCESS.

16. ANY NEW SIGNIFICANT FINDING DURING THE COURSE OF THE RESEARCH THAT MAY EFFECT MY WILLINGNESS TO PARTICIPATE FURTHER WILL BE EXPLAINED TO ME.

17. IN ALL PUBLICATIONS AND PRESENTATIONS RESULTING FROM THIS RESEARCH STUDY, MY ANONYMITY IS GUARANTEED, ALTHOUGH I REALIZE THAT AN APPROPRIATE AUTHORITY HAS THE RIGHT TO INSPECT THE RECORDS.

18. I REALIZE THAT BECAUSE I AM ON ACTIVE DUTY, THE DEPARTMENT OF DEFENSE WILL PROVIDE BOTH SHORT-TERM AND LONG-TERM MEDICAL CARE FOR ANY INJURY THAT RESULTS FROM MY PARTICIPATION IN THIS STUDY.

19. I CERTIFY THAT I HAVE READ AND RECEIVED A COPY OF THIS CONSENT FORM

_____.
SUBJECT INITIALS

_____	_____
DATE SIGNED	SUBJECT SIGNATURE
	_____
	TYPED NAME - STATUS
_____	_____
WITNESS SIGNATURE	INVESTIGATOR SIGNATURE
_____	_____
TYPED NAME - RANK - S.S. #	TYPED NAME - RANK - S.S. #

1121770

October 8, 1984
To: IRB File on P. Meyer Project
From: Fred Hatch, Chair, IRB F.T. Hatch, MD
Subject: Update on review of project

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

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."

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ENVIRONMENTAL SC ENCES DIVISION

Interdepartmental letterhead

Mail Station L- 453

Ext: 23840

September 13, 1984

To: Fred Hatch

From: Lynn Anspaugh

Subject: Risk of Developing Lung Cancer Following a Dose of 0.45 rad

At your request, I have examined what the probability might be of developing lung cancer following a dose of 0.45 rad. The most recent consideration of this problem has been done by Rall, et al., (Ref. 1) in order to derive probability of causation for individuals who have already developed cancer.

For lung cancer, Rall, et al., have adopted a nonthreshold linear-quadratic dose-response model to aid them in calculating basic risk coefficients from the radioepidemiological studies done on people who received high doses of radiation. Their tabulated risk coefficient for lung cancer for men exposed at ages of 20 to 34 years is 0.116 excess cancers per 100,000 persons per year per rad for low doses of low-LET radiation (Table VI-1 on p. 97). This number is based upon follow-up of individuals over the period of 10 to 30 years post exposure and accounts for a presumed latent period of 10 years. Thus, if we assume an individual is exposed at the age of 20 years and we want to calculate the risk of developing lung cancer over the next 50 years, the result is

$$\frac{0.116}{100{,}000 \text{ persons} \bullet \text{yr} \bullet \text{rad}} \times 0.45 \text{ rad} \times (50-10) \text{ yrs} = 2\times10^{-5}$$

This approach differs somewhat from that taken by the National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR) in the BEIR-III report (Ref. 2). They used a nonthreshold linear dose-response model to calculate a risk coefficient and derived a value of 2.45 excess cases per million persons per year per rad for males aged 20 to 34 years at exposure 11 to 30 years after exposure. The risk calculated from this is then

$$\frac{2.45}{1{,}000{,}000 \text{ persons} \bullet \text{yr} \bullet \text{rad}} \times 0.45 \text{ rad} \times (50-10) \text{ yr} = 4\times10^{-5}$$

University of California
Lawrence Livermore National Laboratory

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In my opinion, these risk calculations are subject to a great deal of uncertainty. The true risk might be zero as radiation has not been demonstrated as a carcinogenic agent at such low doses (Refs. 2 and 3). The true risk might also be substantially higher as data for follow up periods beyond 30 years are considered. My understanding from Mort Mendelsohn is that the rate of occurrence of excess cancers attributable to radiation is increasing as the Japanese A-bomb survivor population ages beyond the 30-year follow-up point.

I would conclude that a reasonable estimate of the excess risk of lung cancer from 0.45 rad is between $1x10^{-5}$ and $1x10^{-4}$.

Presently, I have no knowledge of the benefits of the proposed study wherein members of the Armed Forces might receive such doses. However, I do want to call your attention to another area of risk to LLNL. At the present time, the University is being sued by many (hundreds?) of "atomic veterans" who allege injury from doses smaller than 0.45 rad. They, and the "downwind people", allege that they were "human guinea pigs" and the US Congress has supported this allegation (e.g., Ref. 4). The atomic veterans and the downwind people allege, of course, that their doses were much higher (without validity, in my opinion); and you can be sure that the new "guinea pigs" will also allege in years subsequent that their doses were much higher than 0.45 rad.

As several of these "atomic veteran" cases are now in litigation and the Veterans Administration has already provided compensation for harm alleged to be due to radiation doses of less than one rad, I think the conduct of such a study on humans would be ill advised. It is clear that, at the present time, a veteran cannot sue the US government for injury alleged to have resulted from such exposure and his recourse would be to sue the University of California.

If such studies are carried out, I suggest that heroic measures be made to document the dose received by every individual and that a committee of qualified persons review such calculations and plans before anyone is exposed.

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References

1. J.E. Rall, G.W. Beebe, D.G. Hoel, S. Jablon, C.F. Lord, O.F. Nygaard, A.C. Upton, R.S. Yalow, and V.H. Zeve, Draft Report of the Ad Hoc Working Group to Develop Radioepidemiological Tables, National Institutes of Health, Bethesda, MD (July 1984).

2. Committee on the Biological Effects of Ionizing Radiations, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980, National Academy Press, Washington, DC (1980).

3. High Background Radiation Research Group, China, "Health Survey in High Background Radiation Areas in China," Science 209, 877-880 (1980).

4. Committee on Interstate and Foreign Commerce, US House of Representatives, The Forgotten Guiena Pigs, US Government Printing Office, Washington, DC, Committee Print 96-IFC53 (1980).

Lynn R. Anspaugh
Division Leader

LRA:vs