Interdepartmental letterhead

Mail Station L- 280

Ext: 7226

BUSINESS OFFICE
LLL, LIVERMORE
FEB 8 2 24 PM '77

718116

February 8, 1977

MEMORANDUM

TO: Dave C. Shepherd L-54

FROM: Paul Meyer

This is a copy of the application for the use of radioactive tracers, which the University of Washington group submitted to their committee. The ozone exposure of humans has been going on for a few years at Seattle; the only new thing is the application of radioactive tracers.

I hope that your committee can consider this application in the near future.

Paul Meyer.

PM:lo

REPOSITORY LLNL B361 Rm B940A
COLLECTION Institutional Review Board
BOX No. IRB Minutes
FOLDER Human Subjects Minutes and Approvals 1965-1977

University of California
LAWRENCE LIVERMORE LABORATORY

2004057

APPLICATION FOR AUTHORIZATION TO USE RADIATION WITH HUMAN SUBJECTS

Submitted Feb 3 1977

Form RSC 30(76)

Docket Number _____

Applicant _____

Provide Identical Information From Form UW 13-11 For First Section

	Investigator	Department	Mail Stop	Telephone
I.	Robert Frank, Professor	Environmental Health	SC-34	543-4383

Associates
U. of W: Michael Morgan, Dick Holub, Jane Koenig, Neil Horike

II. *Names of Persons Responsible for Procedures (other than I.)*

Paul Meyer, University of California, Lawrence Livermore Laboratory, Livermore, California (415) 447-1100 ext. 7226

III. *Title of Proposed Activity*

Ozone Effects on Overall and Regional Lung Function

IV. *Beginning Date of Proposed Activity* 7/1/77

[✓] VIII. *Subjects (attach copy of response to 13-11)*

[✓] XI. *Outline of Activity (attach copy of response to 13-11)*

[✓] *Attach Copy of Consent Form*

If radiation source is not a standard clinical facility an Application for Authorization to Use Radiation will be required in addition to the application (Form RSC 10(76).

The applicant should attach information relative to each point below. Please use the same numbers and subtitles. For more complete instruction refer to Guidelines for Application for Authorization to Use Radiation with Human Subjects

[✓] 1. *Education and Training (Form RSC 20(76)*

[ ] 2. *Description of Research Project*

[✓] 3. *Description of Subjects*

[✓] 4. *Benefit to Subjects*

[✓] 5. *Limits of Study*

[✓] 6. *Basis for Selecting (and Rejecting) Potential Subjects.*

[ ] 7. *Radiation Protection Measures for the Subject*

[ ] 8. *Radiation Dosimetry*

[ ] 9. *Summary of Risk to Subject*

[✓] 10. *Consultation with Radiation Specialist*

[ ] 11. *Report of Progress or Completion of Project.*

Other Attachments (list).

References: (1) Meyer, P.; Behrin, E; Frank, R.; Holub, R.; and McJilton, C.E. Biomedical Application of Shortlived Positron Emitting Isotopes. Preprint: 1-3. February 1975

(2) Meyer, P. Ozone-Tagging for Biomedical Purposes, Lawrence Livermore Laboratory, 7-20-72.

This application and attachments are provided to the Radiation Safety Committee for approval.

Department Chairman _____

Applicant Robert Frank

2004853

Date 1/25/77

UNIVERSITY OF WASHINGTON

Human Subjects Review Committee Application

Date February 2, 1977

Please type; use supplemental sheets, as needed. Submit 15 copies, including a signature copy to Research Services, AG-10. Each copy should have all relevant materials, e.g., consent form(s), questionnaires, other, unless otherwise specified in this application form.

	Name and position	Department/Division	Mail Stop	Telephon
I. Investigator:	Robert Frank, Professor	Environmental Health	SC-34	543-4383

Associates: (U. of W.): Michael Morgan, Dick Holub, Jane Koenig, Neil Horike

(Lawrence Livermore Labs): Paul Meyer

II. Names of other persons responsible for performing or supervising procedures.

III. Title of proposed activity.

Ozone Effects on Overall and Regional Lung Function

IV. Beginning date of proposed activity. 7/1/77

V. Is this activity related to a grant or contract? Yes x No ____ If yes, complete A-J.

A. Is it related to a training grant? Yes ___ No x If no, ATTACH ONE COPY (without budget).

B. Is it related to a fellowship? Yes ____ No x

C. Has proposal been submitted? Yes x No ____

D. Has award been made? Yes x No ____

E. Name of Principal Investigator shown (or to be shown) on proposal: Robert Frank

F. Name of agency to which proposal was (or will be) submitted: NIH

G. If continuation (or already awarded), what is the agency's grant or contract number? S R01 HL 18925-02

H. Title of proposal shown (or to be shown) on GC-1 form:

I. Inclusive dates of grant or contract:
From 7/1/75, through 6/30/78.

J. Will activity be performed if funding is not received? Yes x No ____

VI. Recommendations and action:

		Date	Approve	Disapprove
A. Department Chairman	John T. Wilson, Jr. (Typed name, plus signature)			
B. Faculty Sponsor (for student)	Typed name, plus signature			
C. Human Subjects Review Committee	Chairman's signature			

Subject to the following conditions: _____

Period of approval from _____, through _____.
Valid only as long as approved procedures are followed.

Research Services
April, 1975

2004859

I. Checklist to be completed by investigator:

	Yes	No
A. Will another organization or agency be involved (Veterans Administration Hospital, Department of Social and Health Services, or others)? Name of other organization or agency:	x	
B. Will materials with potential radiation risk be used, e.g., X-rays, radioisotopes? If yes,	x	
1. Status of review by Radiation Safety Committee (RSC). (If approved, ATTACH ONE COPY of approval.)		
2. Title of application submitted to RSC.		
C. Will an investigational new drug (IND) be used? If yes, name, proposed dosage, status with Food and Drug Administration, and IND number. ENCLOSE ONE COPY of available toxicity data.		x
D. Will other drugs be used? If yes, names and dosages.		x
E. Should this activity be covered by the adverse effects' insurance?	x	
F. Will a written consent form(s) be used? (Required in most cases.)	x	
1. If no, explain why a written consent form will not be used.		
2. If no, is a statement attached describing what participants will be told? Participants must be informed of all elements of VII.G. below.		
G. Does (Do) the consent form(s) include: (Page 4 provides a sample format--tear off, do not submit to Research Services).		
"University of Washington" heading?	x	
Name, position, department, and telephone number of investigator?	x	
Date?	x	
Copy for subject?	x	
Signature and date lines to be completed by subject (and legal guardian, if subject is a minor or is legally incompetent), and investigator?	x	
The following elements of consent expressed in lay terms:	x	
1. Purpose--benefits to be expected or knowledge hoped to be gained?		
2. Procedures to be followed, including identification of those which will be performed only for the purposes of this activity, and time involved?	x	
3. Nature and amount of risk, or substantial stress or discomfort involved?	x	
4. Appropriate alternate procedures that might be advantageous or available to subject? (Show "N/A" (not applicable) when there are none.)	N/A	
5. Costs the subject may immediately or ultimately be forced to bear and what reimbursement of costs or other compensation the subject will receive as the result of participation in this activity?	N/A	
6. Voluntary nature of participation and freedom to withdraw at any point without penalty?	x	
7. Opportunity to ask questions before consenting?	x	
8. Assurance that subject's identity will remain confidential?	x	

2004660

II. Subjects.

A. Approximate number and ages: Normal, patient, either. 16 health subjects per year; ages 20 to 65

B. Criteria for selection and exclusion. Healthy subjects with no history or X-ray of chronic or recent cardiopulmonary disease. Minors and pregnant women will be exclu

C. Source of subjects (including patients), and how they will be approached.
Healthy subjects announcements posted on bulletin boards at UC, San Francisco and Lawrence Livermore Labs, Livermore, California

D. Will subjects be paid or otherwise compensated? If so, what amount? and what is the reason for payment?

Healthy subjects will be compensated $50 for the time and travel involved.

E. Location where procedures will be carried out. why?
Linear Accelerator Bldg., #194, Lawrence Livermore Labs, Livermore, California

X. Confidentiality and anonymity.

A. Steps to insure that participation by subjects will be kept confidential.
Anonymity of documents and data how?

B. Provisions to insure anonymity of documents and data.
Data will be identified by number and available to authorized personnel only

C. Provision for controls over access to documents and data.
Data and documents will be stored in a locked file

X. What publications might be helpful to the committee in consideration of this application? (Answer only if these might expedite review.)

I. Outline of activity (circle OPTION you will use in responding):
FIRST OPTION: Provide answers in spaces following A-F below (add sheets, when needed).
SECOND OPTION: Provide answers in attached summary statement (reference, if over one page

A. Background or rationale for this activity.
To determine the respiratory effects of low levels of ozone in healthy adults at rest and during exercise.

B. Objectives.
See add. sheet

C. Procedures involved.
(Which of these will be performed only for the purposes of this activity, e.g., volume of blood, size of biopsy, questionnaire, name of psychological test?)

See add. sheet

D. Identify alternate procedures, if any, not proposed for this activity that might be advantageous to the subject. none

E. If any deception (withholding complete information) is required for the validity of this activity, explain why this is necessary and attach debriefing statement.
N/A

F. Nature and amount of risk (include side effects), or substantial stress or discomfort involved.

See add. sheet

1. Follow-up planned for procedures and possible adverse effects. If symptoms occur and persist, daily interview by phone will be made until all symptoms have abated

2. Arrangements for financial responsibility for adverse effects.
To be assumed by Univ. of Calif. ?

2004061

XI. B. Objectives

To study the effects of acute low level exposure to ozone (< 0.5 ppm) on overall and regional lung function

C. Procedures Involved

Non radioactive measurements (overall function)

The subject will be seated, at rest in a conventional body plethysmograph breathing quietly. For the measurements of pulmonary compliance and flow resistance, a thin balloon tipped esophageal catheter is to be swallowed so that the tip lies in the lower third of the esophagus. Some subjects may experience slight discomfort while the catheter passes through the posterior pharynx; otherwise the procedure is harmless. A nose clip is worn to anchor the catheter in place. The catheter is used to measure the pressure gradient between the esophagus (analogous to the pleural surface) and the mouth. The other two parameters required to calculate compliance and flow-resistance, the tidal volume and the rate of flow, will be measured with a flow meter attached to a conventional mouthpiece. Each set of measurements requires 5-10 minutes. Between measurements, the subject will breathe the ozone through a mask.

Following the end of exposure, all measurements will be repeated until the control values are re-established.

Exercise will be achieved by working on a treadmill at about 3 mph on a 5% grade for 10-15 minutes. The periods of exercise may be repeated for a total of four 10-15 minute sessions interspersed with quiet breathing (total exposure = 2 hours). Ventilation and heart rate will be measured.

Radioactive measurements (regional function) based on the technique of West et al.

The subject will be standing at rest between the two heads of the Anger Position Camera. A single breath of $^{13}N_2$ or $C^{15}O_2$ will be inspired from a plastic bag and the subject will hold his breath for 15 to 20 seconds. The Anger camera will record the distribution of the radioactive gas.

F. We intend to administer concentrations of ozone (0.2 - 0.5 ppm) that have been employed in a number of previous investigations on healthy volunteers (2-7). These concentrations of ozone may produce changes in pulmonary function which are completely reversed within 24 hours and which are not perceived by the subject (the subject is not aware of the slight increase in pulmonary flow resistance, slight decrease in maximal forced expiratory flow rates, or slight decrease in diffusing capacity that may occur. is not unusual for subjects to experience throat irritation, tickling sensation in the throat, and cough at these concentrations. Such symptoms also regress within 24 hours. There has never been a report of unusual

distress or hospitalization arising from such exposures. While exercise tends to increase the functional effects and symptoms, there are no reports of untoward reactions associated with this procedure. Concentrations of 0.2 - 0.5 ppm of O_3 have been reached on numerous occasions in the Los Angeles basin and are exceeded in a number of occupational and industrial settings.

The radioactivity tagged gas $^{13}N_2$ and $C^{15}O_2$ will be produced using the techniques of West et al. (2 and 9). Each bag of gas will be tested for any radioactive and non radioactive contaminants by personnel from the Hazards Control Section, Lawrence Livermore Laboratory, before administration to the subject.

REFERENCES

1. West, J.B.: Pulmonary function studies with O^{15}, C^{11} and N^{13}. In Dynamic Clinical Studies with Radioisotopes. U. S. Atomic Energy Commission. Oak Ridge, 1964, pp. 213-236.

2. Young, W.A.; Shaw, D.B.; and Bates, D.V.: Effect of low concentrations of ozone on pulmonary function in man. J. Appl. Physiol. 19, 765-768, 1964.

3. Goldsmith, J.R., and Nadel, J.A.: Experimental exposure of human subjects to ozone. J. Air Pollution Control Assoc. 19, 329-330, 1969.

4. Bates, D.V.; Bell, G.M.; Burnham, C.D.; Hazucha, M; Mantha, J.; Pengelly, L.D.; and Silverman, F.: Short-term effects of ozone on the lung. J. Appl. Physiol. 32:176-181. February 1972.

5. Hazucha, Milan, M.D.; Silverman, Frances, MSc; Parent, Claude, BSpSc; Field, Stephen, BSc; and Bates, David V., M.D.: Pulmonary Function in Man after Short-Term Exposure to Ozone, Montreal, Canada. Sept., 1973. 27:183-188.

6. Kerr, H.D.; Kulle, T.J.; McIlhany, M.L.; and Swidersky, P.: Effects of Ozone on Pulmonary Function in Normal Subjects, an Environmental-Chamber Study. Amer. Review of Respiratory Disease, 3:763-773, 1975.

7. Folinsbee, L.J.; Silverman, F.; and Shephard, R.J.: Exercise responses following ozone exposure. J. of Appl. Physiol.; Toronto, Ontario, Canada. 38 no. 6:996-1001; June, 1975.

8. DeLucia, A.J., and Adams, W.C.: Effects of O_3 Inhalation During Exercise on Pulmonary Function and Blood Biochemistry. Submitted to J. Appl. Physiol., 1976.

9. Buckingham, P.D., and Forse, G.R.: The preparation and processing of radioactive gases for clinical use. Int. J. of Appl. Rad. and Isotopes. 14:439-445, 1963.

2004864

UNIVERSITY OF WASHINGTON

& UNIVERSITY OF CALIFORNIA, LAWRENCE LIVERMORE LABORATORY

CONSENT FORM FOR INHALATION OF OZONE AND SPECIFIC RADIOACTIVE GASES FOR RESEARCH

Ozone Effects on Overall and Regional Lung Function

Principal Investigator: Robert Frank, M.D. , Department of Environmental Health
University of Washington (206)543-4383

Associates:
Jane Koenig, Ph.D., Department of Environmental Health 543-4383
Michael Morgan, Sc.D. Department of Environmental Health 543-4383
Dick Holub, M.S. , Department of Environmental Health 543-4383
Neil Horike, M.S. , Department of Environmental Health 543-4383
Paul Meyer, M.S., Lawrence Livermore Laboratory (415)447-1100 ext. 7226

The purpose of this study is to test the effect of ozone, an important air pollutant, on the pulmonary function of normal, healthy humans.

Persons who have chronic heart disease, lung disease including asthma, or have had any respiratory infection during the past six weeks may not participate. Pregnant women may not participate.

Procedure: The study will involve breathing low concentrations of ozone for two hours. The subject will sit in a small chamber shaped somewhat like a telephone booth and breathe through a mouthpiece. Before the subject enters the chamber, a narrow tube (catheter) will be passed through the nose into the rear of the throat. The subject will then swallow the catheter until the tip lies just above the stomach. The catheter is necessary to estimate intrapleural pressure (the pressure in the space between the lungs and the chest wall) which is used to calculate flow resistance (a measure of the effort required to move air through the airways). Flow resistance will also be measured by a non-evasive method using pressure waves created by a pump (forced pressure oscillatory method). The flow resistance measures require only quiet breathing on the part of the subject. Other functional measurements will require such simple maneuvers as inhaling and exhaling maximally, exhaling at a given flow rate and occasional breath holding or panting. The radioactive measurements require the subject to inspire a single breath of gas tagged with a low level of radioactivity and hold his breath for 15 to 20 seconds. Following the breathing of the pollutant the subject will come out of the chamber for one hour and thereafter re-enter for another set of measurements lasting 10-15 minutes. The total length of the procedure will be 4-5 hours. Some subjects will be asked to exercise moderately on a treadmill for 10-15 minutes while breathing the pollutant.

The risks involved in the study are negligible. Discomforts that may arise are as follows: nasal irritation may be felt when the catheter is first passed; the nose clip may occasionally feel tight; sitting in the chamber may be tedious. The pollutants may cause burning of the throat and anterior chest, or cough, and rarely, difficulty in breathing. Should the symptoms occur, they are likely to be slight and to disappear within minutes or hours. The radioactive gas needed for the measurements will be tested before each procedure and maintained at a level low enough to cause no harmful effects.

2004865

If the subject experiences excessive symptoms the experiment will be terminated. A doctor will be present throughout the experiment and will question the subject at least once daily until all symptoms are gone.

The subjects retain the right to withdraw from the study at any point. The subject will be paid $50 per two-hour exposure session. There are no personal benefits deriving from participation in the study. The rights to withdraw from the test at any time and to withhold information from non-medical persons without additional consent are protected. The subject's welfare is protected by the presence of the physician before and during the test, and by the availability of emergency hospital treatment if the need arises. The subject's identity and all information about him or her are to remain confidential.

Signature of investigator _____ Date _____

Subject's statement

I voluntarily consent to participate in this study. I have had an opportunity to ask questions.

Signature of subject _____ Date _____

Copies: Subject
File

We must revise this

2004866

STATEMENT OF TRAINING AND EXPERIENCE IN RADIATION WORK

Form RSC 20(76)

PRIVACY ACT MATERIAL REMOVED

Name Paul Meyer

Social Security Number

Title/Position Physicist

Address Lawrence Livermore Laboratory, Livermore, CA 94550

TYPE OF TRAINING	FORMAL COURSE yes	FORMAL COURSE no	ON THE JOB yes	ON THE JOB no	WHERE	DURATION
a) Principles and Practices of Radiation Protection			X		LLL, Livermore	10 years
b) Radiation Measurements Monitoring Techniques and Instruments	X		X		LLL, Livermore	10 years
C) Mathematical and Calculations Basic to use and Measurement of Radiation	X		X			
d) Biological Effects of Radiation	X				LLL, Livermore	

FORMAL COURSES *Please describe by title and course content each formal course indicated by "yes" in the first column. (For additional space use reverse side.)*

Courses providing the type of training listed under (b) and (c) above where part of the curriculum required for my Master of Science in Physics degree granted by the University of Washington in 1960.

(d) Biological effects of ionizing radiation (CE 4300): A survey course in radiation biology designed to provide a basic understanding of radiation effects on biological systems. Emphasis was on biological phenomena with special reference to human dose-effect relationships.

EXPERIENCE *Describe actual use of radiation either as part of a formal course or as laboratory employee. Indicate type of radiation or radioactive material, amounts, uses, duration of work and your involvement and where experience occured. (For additional space use reverse side.)* As an experimental physicist at the Linear Electron Accelerator at LLL, I have been producing radioisotopes like ^{11}C, ^{13}N, ^{15}O and other gases to be used in physics experiments as well as in biomedical applications with live dogs over the past four years at Livermore.

HUMAN USE *Describe your experience in administration of radiation to humans that qualifies you for work described in the application. Provide name of preceptor physicians who supervised this training. (Use reverse side for additional space.)*

2084867

Signed Paul Meyer Date [illegible]

TO THIS RADIATION SAFETY OFFICE 4725 30th NE SEATTLE, WA 98105 (543-7262)

3. Description of Subjects: Healthy Subjects, male or female, 20 to 65 years in age.

4. Benefit to Subjects: Participation in experiment designed to measure the effects of a common air pollutant at levels which are currently found in many of our larger cities and urban areas.

5. Limits of Study: 16 subjects for one year.

6. Basis for Selecting(and Rejecting) Potential Subjects: Healthy subjects with no history or X-ray of chronic or recent cardiopulmonary disease. Minors and pregnant women will be excluded.

7-10 See attached memo to Paul Meyer

2004868

Interdepartmental letterhead

Mail Station L 518

Ext. 3824

December 13, 1976

TO: Paul Meyer

FROM: M. S. Singh/T. R. Crites

SUBJECT: Estimates of Dose to the Lungs From ^{13}N and ^{15}O Due to Inhalation

Radionuclides ^{13}N and ^{15}O are both positron emitters and decay into the ground state of ^{13}C and ^{15}N, respectively, as follows:

$$^{13}N \rightarrow \beta^+ + {}^{13}C + \nu \qquad \text{ground state, } E_{\beta^+,max} = 1.19 \text{ MeV}$$

$$^{15}O \rightarrow \beta^+ + {}^{15}N + \nu \qquad \text{ground state, } E_{\beta^+,max} = 1.72 \text{ MeV}$$

As the positron moves through matter it loses kinetic energy and finally combines with an electron to form a positronium atom which decays into two 0.51 MeV gammas.

Dose delivered to the lungs is thus primarily from positrons and 0.51 MeV gammas.

The effective absorbed energy from positron emitters can be estimated to be[1]

$$E = 0.33\, E_{\beta^+,max}\, f \left(1 + \frac{E^{0.5}_{\beta^+,max}}{4}\right) + 2(0.51)\, f_a f$$

where f_a is the fraction of 0.51 MeV gamma energy absorbed in the lungs and f is the number of positrons per disintegration, which is equal to one in our case.

The absorbed fraction of 0.51 MeV gamma energy in the lungs (mass of lungs is approximately 600 g, excluding arterial and venous blood) is 3.05%.[2] Therefore, the effective absorbed energy in lungs from positron emitters becomes

$$E = 0.33\, E_{\beta^+,max} \left(1 + \frac{E^{0.5}_{\beta^+,max}}{4}\right) + 0.031$$

$$= 0.531 \text{ MeV for } ^{13}N, \text{ and} \qquad (E^{13N}_{max} = 1.20 \text{ MeV})$$

$$= 0.785 \text{ MeV for } ^{15}O. \qquad (E^{15O}_{max} = 1.74 \text{ MeV})$$

2004869

University of California
LAWRENCE LIVERMORE LABORATORY

Dose rate per mCi maintained in the lungs is

$$D_R = \frac{E(\text{MeV/d})}{600\ \text{g}} \times \frac{1.6\times10^{-6}\ \text{erg}}{\text{g}} \times \frac{\text{rad-g}}{100\ \text{erg}} \times \frac{3.7\times10^{7}\ \text{d/s}}{\text{mCi}}$$

$$= E \times 9.87\times10^{-4}\ \frac{\text{rad/s}}{\text{mCi}}$$

For a one time exposure with radionuclides retained in the lungs, the absorbed dose is simply

$$D = D_R \times \frac{1-e^{-\lambda t}}{\lambda}\ \frac{\text{rad}}{\text{mCi}}$$

where λ is the effective decay constant and t is the residence time for nuclides in the lungs.

The integrated dose per mCi for one breath held for time, t_h, and then normal breathing resumed is

$$D_I = D_R \times \left(\frac{1-e^{-\lambda_h t_h}}{\lambda_h} + \frac{e^{-\lambda_h t_h}}{\lambda_h + \lambda_c}\right)$$

where λ_h is the effective decay constant while holding breath and λ_c is the clearance decay constant once breathing is resumed.

Table 1 summarizes the calculated dose rates and integrated dose equivalents delivered to the lungs for various breath hold-up times.

Table 1. Calculated dose to the lungs due to inhalation of ^{13}N and ^{15}O.

Radio-nuclide	$T_{1/2}$ (s)	λ_h (s^{-1})	λ_c (s^{-1})	D_R rad-s^{-1}-mCi^{-1}	D rad-mCi^{-1}	D_I t_h (s)	D_I rad-mCi^{-1}
^{13}N	600	1.16×10^{-3}	2.31×10^{-1}	5.24×10^{-4}	4.52×10^{-1}	15	9.98×10^{-3}
						30	1.75×10^{-2}
						45	2.51×10^{-2}
						60	3.25×10^{-2}
^{15}O	120	5.78×10^{-3}	2.31×10^{-1}	7.75×10^{-4}	1.34×10^{-1}	15	1.42×10^{-2}
						30	2.42×10^{-2}
						45	3.33×10^{-2}
						60	4.17×10^{-2}

A review of the literature reveals a few additional calculational methods producing about the same estimate.

ICRP #13, Protection of the Patient in Radionuclide Investigations, reports the total dose to the lungs due to a single breath of ^{15}O to be 16 mrad/mCi/ℓ and 3.6 mrad/mCi/ℓ to the gonads. Holding the gas in the lungs for 15 seconds will increase this dose less than a factor of two. They also report the total dose from breathing 1 mCi/ℓ ^{13}N for 1 minute to be 68 mrad to the lungs and less than 1 mrad to the gonads. The designed experiment will result in doses less than this.

Publications of the Medical Internal Radiation Dose Committee (MIRD) pamphlets list 3.06×10^{-4} rad $mCi^{-1}s^{-1}$ due to ^{15}O, and 4.4×10^{-4} rad $mCi^{-1}s^{-1}$ due to ^{13}N. The difference between the dose rate, D_R, that appears in Table 1 and this one is attributable to the basic assumption made in considering the mass of the lungs. In our case we have excluded the arterial and venous blood, whereas MIRD Committee included this mass in their calculations. Other than this, the results are agreeable.

An additional reference by W. H. Blahd in Nuclear Medicine indicates a procedure of the type proposed will result in 35 mrad/mCi ^{13}N. We feel this is a somewhat conservative estimate.

Table 2 lists the current acceptable dose limits for various conditions.

Table 2. Acceptable dose limits to the lungs.

Condition	Dose
Occupational	15 rem/y (5 rem/qtr)*
Individual	0.5 rem/y*
Population	0.17 rem/y*
Clinical	4000 rad**

* Current NCRP dose limits.

** 4000 rads is the minimal clinical tolerance dose to lungs which results in no more than 5% severe complications, i.e., radiation pneumonitis and fibrosis, within five years following treatment.

M S Singh
M. S. Singh
Health Physics Group
Hazards Control Department

T. R. Crites, Leader
Special Projects Division
Hazards Control Department

MSS:TRC:gw
cc: R. Alvarez
D. Myers
J. Powell

2004611

References

1. Report of Committee II on Permissible Dose for Internal Radiation, ICRP, Pub. 2 (Pergamon Press, Oxford, 1960).

2. Report of the Task Group on Reference Man, ICRP, Pub. 23 (Pergamon Press, Oxford, 1975).

TO USE RADIATION

For RSC 10(76)

☐ New ☐ Renew 1. ☐ Amendment

2). *Name, Title, Department of Applicant	1(b). Building (s) and Room (s) For Use
Robert Frank, Professor Department of Environmental Health School of Public Health & Community Medicine	Experiments will be performed at University of California, Lawrence Livermore Laboratory, Livermore, Calif. Linear Accelerator Bldg. #294 (415) 457-1100, ext. 7226
a). Mailing address and Office Address	2(b). Telephone
SC-34, F-561F, Health Sciences Bldg.	543-4383

Other Radiation Used by Applicant

none

*Individual Users (Name and Title)

Paul Meyer, Physicist, Lawrence Livermore Laboratory

(a). *Local Radiation Safety Agent	5(b). Emergency Phone Numbers
Hazards Control, LLL	

. RADIATION SOURCE (S)

(a). Radionuclide	6(b). Chemical/ Physical Form	6(c). * Maximum Activity mCi/liter	6(d). Dose/exposure (30 sec)
^{13}N	Gaseous	.072 mCi/liter	1.34 mrads/liter 30 sec([illegible])
^{15}O	"	.0037 mCi/liter	.091 mrads/liter 30 sec([illegible])

*Based on calibration measurements by LLL-Hazards Control personnel.

(e). Describe other radiation sources (e.g., X-ray machine, neutron generator)

(f). List Title(s) of Projects (Include grant/contract numbers).

Ozone Effects on Overall and Regional Lung Function, S R01 HL 18925-02

2004873

*Training and Experience Records for each individual should be submitted if not on file with the Radiation Safety Office. Use Form RSC 20(76).

APPLICATION FOR AUTHORIZATION
TO USE RADIATION

Form RSC 10(70)

Docket Number _____

Applicant _____

8. RADIATION INSTRUMENTS

TYPE Manufacturer & Model	DETECTS α β (γ) n	SENSITIVITY	WINDOW mg/cm²	PROBE TYPE (e.g., G.M., NaI)	LOCATION Room & Bldg.
Auger Positron Camera				NaI	Livermore

9. SPECIAL FACILITIES. Describe special facilities and equipment (e.g., fume hood, shieldin

0. SPECIAL PRACTICES. Describe special lab radiation safety practices (e.g., monitoring, bioassay).

Continuous monitoring of experimental area.

1. WASTE DISPOSAL. Describe waste disposal program. Estimate quantities per month of liquid, solid, perishables.

The applicant accepts full responsibility for the safe use of radiation described in this application. The applicant further agrees to conform to Rules and Regulations for Radiation Protection, WAC 402, U of W Radioactive Material License Conditions, and U of W Radiation Safety Committee policies.

Department Chairman _____ Date _____

Applicant _____ Date _____

2004674

REPRINTED FROM NBS SP 425 Volumes I and II

Nuclear Cross Sections and Technology

Proceedings of a Conference
Washington, D.C.
March 3-7, 1975

Edited by

R. A. Schrack and C. D. Bowman

Center for Radiation Research
National Bureau of Standards
Washington, D.C. 20234

U.S. DEPARTMENT OF COMMERCE, Rogers C. B. Morton, *Secretary*
NATIONAL BUREAU OF STANDARDS, Ernest Ambler, *Acting Director*

Issued October 1975

2004675

BIOMEDICAL APPLICATION OF SHORTLIVED POSITRON EMITTING ISOTOPES†

P. Meyer and E. Behrin
Lawrence Livermore Laboratory
Livermore, California 94550

R. Frank, R. Holub and C. E. McJilton
University of Washington
Seattle, Washington 98105

Radioactive nitrogen, oxygen and ozone have been used for dynamic lung-function studies on live dogs with an Anger positron camera. In particular an attempt was made to determine the feasibility of this method to study early functional changes caused by ozone.

(Radioactive tracers; Anger positron camera, lung function)

Introduction

Ozone has been identified as a significant component of ambient air pollution where atmospheric photochemical activity occurs. The importance of ozone,[1] (O_3), as a toxicant has been investigated and several of its effects have been defined, although the mechanism is still uncertain.[2]

The results of this research have led, in part, to an interest in where the ozone is taken up in the respiratory system. At present the distribution of the ozone-uptake throughout the airways is unknown. By tagging ozone with an ^{15}O isotope, actual sites of O_3-uptake may be discovered.

More information as to the effects of ozone on the lung function can possibly be obtained by the use of ^{13}N tracers in a breathing gas. Nitrogen is not usually soluble in the blood, stays in the lungs until recirculated and, labeled with a ^{13}N tracer its distribution can provide a useful image of a lung. Using radioactive Nitrogen periodically, functional changes in the respiratory system due to, for instance, ozone may perhaps be detected early.

The ^{13}N and ^{15}O isotopes were produced by bremsstrahlung from the 100 MeV Livermore Electron Accelerator (Linac) via $^{14}N(\gamma,n)\ ^{13}N$ and $^{16}O(\gamma,n)\ ^{15}O$.[3,4] Thresholds for these reactions are 10.4 MeV (^{14}N) and 15.7 MeV (^{16}O). Both isotopes decay by positron emission with half lives of 10 min. and 2 min., respectively. After irradiation, the tracer gas was pumped to the anesthetized, mechanically ventilated animal which was placed between the two detector crystals of the positron camera. The camera detects the two .51 MeV annihilation gamma rays in coincidence and stores the information in the memory of an on-line PDP-15 computer. Data transfer from the computer to a magnetic drum is initiated breath by breath so that, in principle, single breath studies can be made, the quality depending primarily on the level of activity of the gas.

Radioactive Gas Production

A stainless steel bottle of 2 liters volume, located downstream behind the tantalum bremsstrahlung target of the Linac, was pressurized with pure O_2 and irradiated with γ-rays of about 30 MeV end-point energy having a typical bremsstrahlung spectrum. To minimize the production of ^{11}C from the reaction $^{15}O(\gamma,n\alpha)\ ^{11}C$ it was desirable to keep the maximum γ-ray energy near the 26.5 MeV threshold for this reaction. After an irradiation time of about 2 half-lives (4 minutes) the exposed gas, now a mixture of O_2, $^*O_2$, O_3 and $^*O_3$, (the astericks refer to molecules with an ^{15}O atom) has nearly reached saturation activity. Since there is no way to differentiate between the decay of $^*O_2$ or $^*O_3$ it was necessary to eliminate the activated oxygen. This was accomplished by passing the mixture through an ozone trap of silica gel at dry-ice temperature (-78°C). After collecting sufficient amounts of ozone, the trap was flushed with clean oxygen to remove all $^*O_2$, then heated to release the ozone which then was mixed with air to the desired concentration, 1ppm or 5ppm, for an animal exposure.

Similarly, $^*N_2$ was produced by using N_2 as a target gas to which clean oxygen was added after irradiation.

Anger Positron Camera[5]

The camera's operation depends on detecting, in coincidence, the two back-to-back gamma rays from a positron-electron annihilation and thus defining a line between the two detector crystals along which the event took place. Many events allow then, in principle to determine the point or points of intercept and thus the location of the source of activity.

The Livermore camera[6] consists of two identical detector heads, each with 37 photomultiplier tubes mounted on a 40 cm dia. NaI-crystal of 1.25 cm thickness (Figs. 1a,b). Each head derives position information, i.e. where on the X-tal the gamma rays hit, from a precision-capacitor network coupled with the P.M.T.-outputs. These outputs are sampled, digitized and stored on a high-speed drum by the PDP-15. The camera heads can also be used independently as scintillators with position sensitivity. Maximum count-rate capability is 2×10^5 positron events per second.

Annihilation pairs are ordered into a 100 x 100 matrix permitting, in principle, a spatial resolution of about .3 cm. In practice, the camera's point-source resolution is only about 1.5 cm. However, the extrapolated range[7] of the ^{15}O-positron (E_{max} = 1.74 MeV) in lung tissue of density $\approx$ .23g/cc is about 3.5 cm and the resolution is thus limited by this fact. For the ^{13}N-positron the max. range is somewhat shorter.

During collection, data is displayed on an oscilloscope with four brightness levels controlled by the PDP-15. Hard-data-output is available in graphical form as well as in a digital map, giving the number of annihilation events versus matrix location. Corrections for decreased counting efficiency near the edges of the detectors can be applied as a function of

2004876

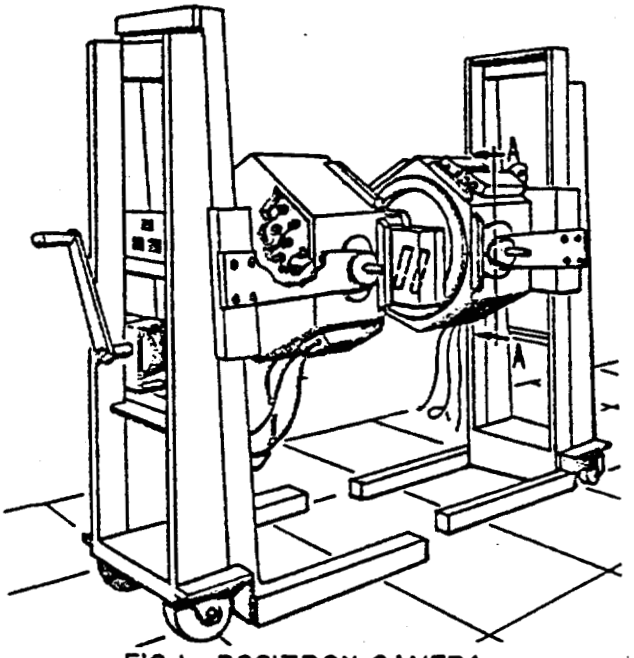

FIG. 1a, POSITRON CAMERA

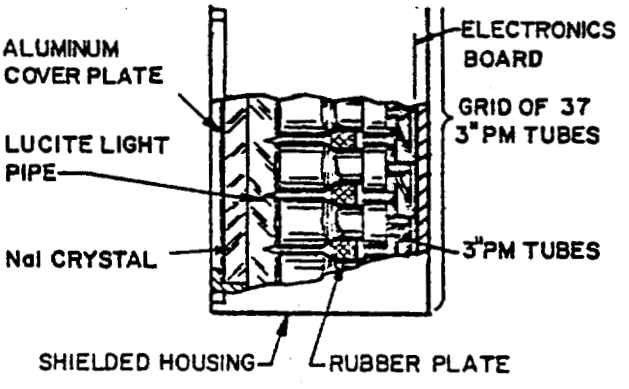

FIG. 1b, POSITRON CAMERA, DETAIL A-A

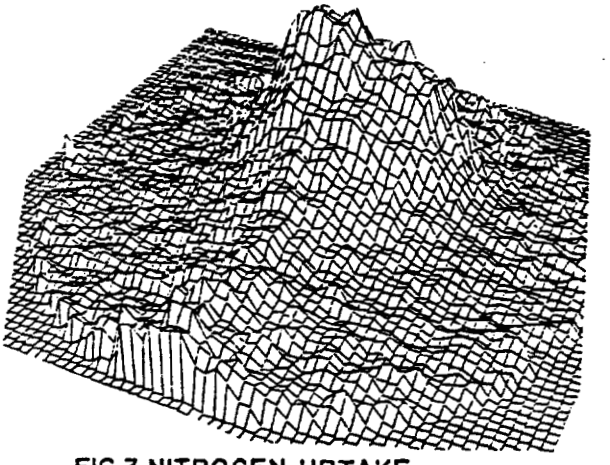

FIG. 3, NITROGEN UPTAKE POST 1PPM OZONE EXPOSURE

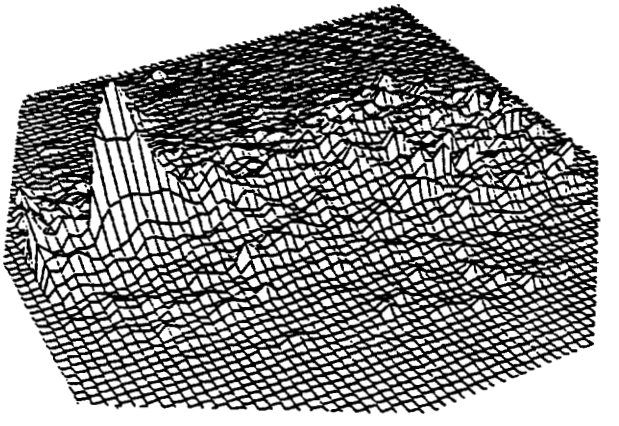

FIG. 4, 5PPM OZONE UPTAKE

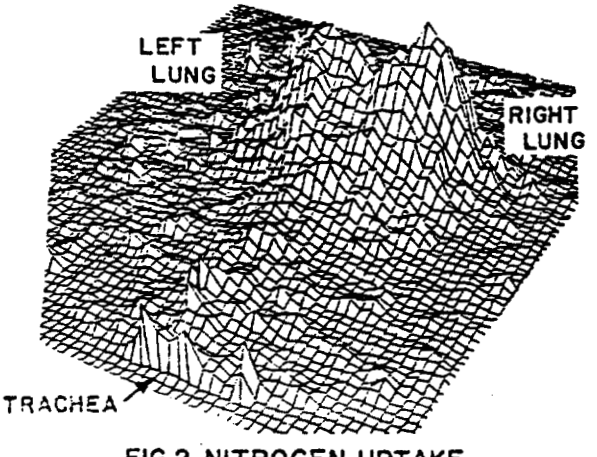

FIG. 2, NITROGEN UPTAKE PRE-OZONE EXPOSURE

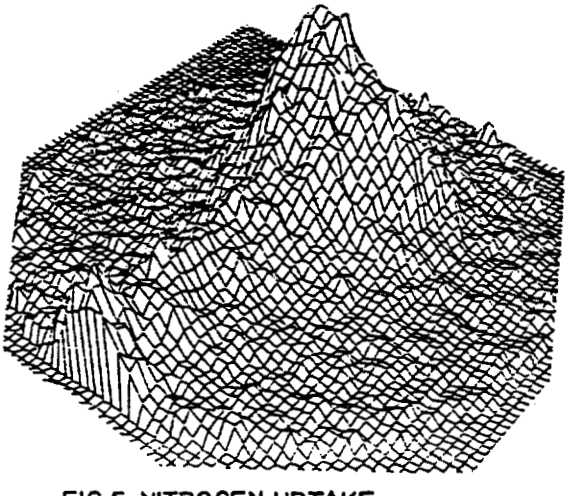

FIG. 5, NITROGEN UPTAKE POST 5PPM OZONE EXPOSURE

2004877

Alan B. Varley, M.D.

Protection of Human Research Subjects: Are Ethics Necessary?

AS ONE CONSIDERS the changing role of medical ethics as applied to human research, one cannot help being struck by a mixed sense of nostalgia, futility, and alarm. Although we as a society seem to be talking much more about the *importance* of ethical standards, we seem increasingly reluctant to have much *trust* in them, and we seem to have more confidence if they are replaced with rules, regulations, and committees. Unquestionably, the concepts of peer review and regulatory scrutiny are important elements in protecting research patients, but one gets the distinct impression that we are approaching a state of mind that says: "If it passes review and is legal it *must* be ethical."

Perhaps this is the route we are following, but I am inclined to agree with Henry Beecher when he says: "Ultimately the problem of ethical standards comes down to the integrity and judgment of the individual professional."[1] Law Professor Douglas Whalen has also succinctly summed up this concern: "Codes of ethics can be drawn up, review committees can be established, regulations can be promulgated, laws can be passed, a whole pile of consent forms can be signed, but I believe that the best guarantee of all is the conscience of the properly qualified investigator."[2]

In no way should one discount the value and importance of peer review, but as such human protection systems are implemented we should keep firmly in mind that the principal objective is to examine the competence and conscience of the investigator, not to serve as a substitute for it.

The rising near-hysteria that nowadays seems to surround the subject of conduct in human research studies is puzzling. Certainly, by any standard, the overwhelming majority of clinical investigators are conscientious, compassionate physicians, truly humane in their practice and behavior. Further, if we live in an environment of uncontrolled disregard for subject safety, one is hard pressed to observe the expected ravages. True, there have been a few serious and inexcusable abuses, but their frequency has been rare enough to class them as genuine research scandals.

Finally, let us look at the most important track record of all; genuine physical or mental harm secondary to research participation has been amazingly rare. A recent review of a decade's experience in a prison research setting disclosed that of approximately 13,000 studied subjects, only eight required hospitalization while participating in experiments, and only three of the eight were determined to have problems unequivocally related to their research participation. A recent examination of similar records by both industry and government failed to uncover a single fatality occurring in Phase I Studies—presumably the most risky part of a new drug evaluation. Considering the magnitude of the total drug research effort over the past decade, this appears to be a most responsible safety record, particularly when compared with other commonly undertaken and socially acceptable everyday risk situations.

Then why are we so uptight on this issue? Why does Frederick Carney, professor of ethics at Southern Methodist University, write an editorial in *Clinical Research*[3] claiming that human research is in the midst of a "crisis of legitimacy" that could soon lead to social withdrawal of the authority and independence necessary for continuation? The reasons are obviously complex,

2004878

and "crises of legitimacy" are by no means reserved exclusively for human experimentation. But certainly three steps in the process include (1) the poor documentation of the problem in the first instance, (2) the conviction that problems can be promptly solved by developing rules, and (3) the belief that rules can really only be written by lawyers.

A Societal Problem

As has been noted many times, the proper management of human experimentation requires a wise respect for both societal and individual rights. But one of the pressing questions of our time is: "Who speaks for society's rights and the best interest of all people?" For nearly two centuries the answer seemed clear—elected officials of government. If opinion surveys have significance, public confidence in politicians as their representatives has eroded markedly over the past decade.

As confidence in politicians has decreased and the complexity of issues increased, it has become increasingly difficult for society to articulate its wishes and perhaps even more difficult for anyone truly to determine what they are. This situation is ready-made for the self-elected spokesman who claims to be the true representative of the people. Unfortunately, the positions presented may not always be totally accurate statements of societal concern.

Resolution of problems of individual patient protection is made difficult, if not impossible, in the absence of some genuine expression of society's opinion on the basic legitimacy of human experimentation. If many current consumerist spokesmen for society, the media, or selected government officials are correct in their representation, there is today a genuine societal concern that the benefits of human research do not merit the presumed risk. On the other hand, in a recent poll,[4] two-thirds of a public sample who expressed an opinion favored continued human experimentation as a way to better medicine for the future.

In a book widely cited as confirming the inadequacy of research standards,[5] Barber acknowledges that 70 per cent of institutions polled actually had human use review committees before government requirements and that 76 per cent thought the review system was "very effective."

Which benefit-to-risk position most closely approximates public opinion and concern? The answers to these critical, basic questions are too important to be left to professional spokesmen—be they consumerists, politicians, journalists, or medical researchers.

Rules of Ethical Conduct

In the absence of an expressed social consensus on human experimentation, specific crises must be handled as they occur. Many people, unfortunately, are convinced that for every problem there is a rule (or a committee) that can solve it. In practice, this seldom seems to work; rules (or committees) often seem to create more, not fewer, problems. The process also seems to increase confusion, cost, and frustration.

Perhaps it is still too early to tell, but in our zeal to instantly correct all real and imagined abuses of research patient protection, we may well be overregulating the problem to the benefit of no one. If one presumes medical researcher competency (which is another issue) and societal approval of human research, the fundamental ethics of an individual investigation are really not all that complicated. The patient has a right

- To know about the experiment
- To have all questions answered promptly and truthfully
- To refuse to participate (or to agree to participate)
- And, to change his or her mind and withdraw from the study.

The House of Delegates of the American Medical Association adopted an almost identical statement nearly 10 years ago.

Yet, today we are drafting rules and regulations that tend to obscure these simple conditions and the critical role of the conscience and ethics of the investigator. Congress directs that "consent" be obtained when experimental drugs are used, and FDA is obligated to provide nine paragraphs of definition. The August HEW Patient Protection Regulations (applicable only to fetuses, pregnant women, and *in vitro* fertilization) run 26 pages of "bible" print and severely tax the reader's perseverance.

Considering our success in regulating other types of behavior, it seems possible the net result of commissions, committees, and volumes of rules will add appreciably to the cost and confusion, will discourage some research, and give an aura of doing something. In reality, it probably will do little to change bad ethical principles of poor investigators.

Unquestionably, a ponderous system also will generate dozens of new problems that, in turn, will require more rules and even further obscure the importance of investigator ethics. For example, recent deliberations over rules for patient protection have focused on the details of composition and function of protocol reviewing committees. It has been seriously proposed that (1) "professional outsiders" be trained to staff such committees because even the clergy cannot be trusted,[5] (2) the review committees must take an active role in patient selection because investigators cannot be trusted to obtain consent[6] (even though it is part of the study protocol), and (3) tests must be developed for committees to check patient comprehension to be absolutely sure patients also understand the details of the study. Surely a simpler scheme must prevail that allows for "peer review" but keeps accountability where it belongs—with the investigator.

2004679

Informed Consent

As we turn to lawyers to articulate these rules and procedures, it must be recognized that law has at least three fundamental concepts that differ markedly from those of medicine. Regulations drafted by lawyers will surely reflect these differences. Law is essentially retrospective in its outlook, while medicine must focus prospectively. Law can define issues in black or white, guilty or not guilty, while medicine must almost always deal in shades of gray. And, finally, law in its conception is generally able to deal with people as true equals whereas medicine by its nature must constantly recognize vast differences in human behavior and composition.

Perhaps nowhere are these differences in perspective more clearly demonstrated, and more applicable to medical research ethics, than in the concept of "informed consent." In a discussion of this concept, it has been explained: "Where a professional has a much higher knowledge than the person with whom he is dealing, the professional picks up a duty to at least semiprotect the ordinary person with whom he has business."[7] This seems a most reasonable position and not at all at variance with generations of medical ethics. It has recently been legally reasoned,[8] however, that inasmuch as a patient has the right to decide what will be done with his body (at least insofar as medicine is concerned), he has the right to all information necessary to allow him to make that decision intelligently. It is then reasoned that it is the physician's duty to be *sure* the patient is "fully informed" and capable of making the decision that more often than not he probably thought the physician was supposed to make in the first place.

Aside from the tortured medical logic involved and the fact that *all* risks are either not known or *all* are at least potentially possible, two other aspects of this doctrine are disturbing to physician-investigators. Obviously "informed consent" is a synergistic concept involving more than simply informing and consenting. Yet precisely and practically what is intended seems to defy crisp statement. Perhaps the most precise help comes from the celebrated *Canterbury v. Spence* decision.[9] "All risks potentially affecting the decision must be unmasked," declares Judge Robinson. Clearly, he expects a legally comprehensive review of *all* risk factors and options, although in another important case the full disclosure rule was discarded as "obviously prohibitive and unrealistic."[10] Finally, there is the uneasy feeling that the specific definition of informed consent can only be made in retrospect: If no problems develop, the informing was probably sufficient, but if an untoward event occurred, the informing was probably insufficient, else the patient would never have consented. A frightening addendum to this medically confused state is the more recent legal speculation that harm may not be necessary to prove malpractice.[11] Merely the failure to "adequately inform" may be construed as evidence of negligence.

If the preceding is considered exaggeration, it may be worth "fully informing" your lawyer and asking him to write an informed consent statement that will stand retrospective legal scrutiny and is also medically ethical and feasible.

The point is that "informed consent" has replaced "ethics" as a standard for medical behavior, or is rapidly doing so. Is there an alternative? Perhaps there is. Without a crisis, however, one would seem unlikely to occur.

Surely in our sophisticated world, medicine is not the *only* area where the consumer is at a technical disadvantage and needs extra information if he wishes to make an informed decision. Yet in no other area do courts require "informed consent" as a prerequisite to agreement. In all other areas, a legal policy of "assumption of risk" prevails.

Why not treat medicine and human research in the same legal fashion as other technical events with acknowledged human risk? The patient would then need enough information to understand that risk is involved, rather than an impossible "fully informed" disclosure of all "potentially" relevant information necessary to make an "intelligent choice." The consequences of an assumption of risk doctrine might well be even more salubrious than merely relieving the investigator of an impossible task. The investigator would retain his ethical medical "duty to inform," now much more realistic and probably more understandable and binding on him than a legal document needing a signature. The patient or subject likely would be inclined to ask more relevant questions and take them seriously if it were understood it was *his* duty to ask questions and satisfy himself before consenting. Instead of the present impossible test of "unmasking all potential risks," the consent test would be: "Was the subject fully aware that risks were being assumed and was [illegible] information denied?"

With a more realistic role to fill, physician-investigators perhaps actually would respond more positively, more ethically, and the intended objective of

Alan B. Varley, M.D., is chairman of the American Medical Association's Section Council on Clinical Pharmacology and Therapeutics. He is also a member of the board of directors of the American Society for Clinical Pharmacology and Therapeutics. He is [illegible] chairman of the medical [illegible] Michigan State Medical Society. He is currently the director of medical affairs of the Upjohn Company, Kalamazoo, Mich. The views expressed in this article are Dr. Varley's own and do not necessarily represent those of the Upjohn Company.

2004880

protecting patients' rights be better accomplished. The present atmosphere of mounting mutual distrust and confusion might be replaced by a mature recognition of the patient-subject as an acceptor of risk and the physician-investigator as an ethical and medical advisor.

Conclusions

This critique of our current medical-ethical environment has intentionally tried to be provocative. Our present path for assuring patient protection may well be leading down an ultimately impossible avenue that is in the best interest of neither patient, investigator, nor society. New thinking and different solutions to patient protection surely will be necessary if human research is not to stagnate. Summarized below are some thoughts on these difficult ethical questions.

1. In the broadest sense, both the costs and the benefits of a dynamic, productive human medical research program are borne by society. Yet society has no satisfactory method for expressing approval or disapproval of health research policy. The professional spokesmen of the day must all be considered suspect. Indeed, it is not truly known if, in the mind of society, there *is* a problem. This void in social direction needs to be filled. An effort to develop a positive congressional "informed consent" that clearly establishes society's objectives and limitations might be attempted. Absent such guiding governmental policy statement, could the approval and direction of society be determined through periodic, large-scale, expertly and objectively administered opinion polls having the stature of a national referendum?

2. Scholars of patients' rights and human experimentation seem agreed on one point—despite all the trappings, it is the conscience and concern of the investigator that will really determine if the patient is fairly treated. Yet we are in the process of assembling a massive national system of committees upon committees that at best seems determined to dilute this commonly held and important precept. Would the monies and energies now going into creating and maintaining this research policing system be better spent supporting a few centers for research ethics and requiring each investigator as a prerequisite to research endeavors to present evidence that he or she had attended and passed such a period of thoughtful review of ethical problems? Would such have a greater impact on outcome than the scheme of depersonalized diffusion of responsibility we are developing?

3. "Informed consent" is or has replaced medical ethics as a standard; yet no one seems able to realistically and prospectively define it. If pushed to its ultimate—as it must be by lawyers and regulators—it is clearly neither practical, respectful of society's interests, nor likely to stimulate optimal personalized ethical treatment from the investigator. Would it not be better to terminate the ill-conceived notion that one can give *fully* "informed consent" to any medical research experiment and rely instead on the already established "assumption of risk" concept? Under this precept, it is the investigator's responsibility to be sure the patient-subject understands that a level of risk is involved and that the patient-subject accepts this risk—without illusion of comprehensive understanding—just as he accepts many risks of our day.

4. Inasmuch as collective society is the benefactor of the good results of human research and the patient is asked to assume the risk, is it not time for society to express its willingness to pay individual, no-fault costs through some form of a research insurance system? Such delegalization of our system would probably do more to create an honest, trustful atmosphere and high ethical principles than almost any other single effort.

As we grope for new solutions to these complex problems, perhaps we can be encouraged by Warren Burger's comments some eight years ago. The man who is now Chief Justice of the United States said: "[I]t is not the role and function of the law to keep pace with science. Yet the law has demonstrated its capacity over the years to develop new techniques to meet new problems."[12] It might also be well to keep in mind recent comments of former Senator Sam Ervin, Jr., expressing concern about legislation to create the Consumer Protection Agency: "The act is based upon two premises which I don't think exist. The first premise is that every businessman [In this context, substitute *investigator*] sits up nights trying to devise new ways to defraud his customers. The second premise is that all American people are mentally inferior to the point where they can't look after their own interests and have to be put under some kind of bureaucratic guardianship."[13]

Research subjects and patients deserve the very best medicine has to give. Let us be sure we develop an ethical protection system that does not prevent their getting it. ■

REFERENCES

1. BEECHER HK quoted in NORTON ML: When does an experimental, innovative procedure become an accepted procedure? *Pharos* October 1975, p. 163
2. WHALEN DJ: The Ethics and morality of clinical trials in man. *Med J of Aust* 1:161:494
3. CARNEY FS: The crises of legitimacy in human experimentation. *Clin Res*, September 1975, p. 202
4. YANKELOVICH: Annual Business Priorities Poll (1975)
5. BARBER B, LALY JJ, MAKARUSHKA J, SULLIVAN D: *Research on Human Subjects*. New York: Russel Sage Foundation, 1973, pp. 162, 172, 195-196
6. GRAY B: An assessment of institutional review committees in human experimentation. *Med Care* 13:325, 1975
7. ROSENBERG AR: Informed consent—the latest threat? *J Leg Med* 1:2:18, 1975
8. BRECKLER JA, PRICE EN, SHORE S: Informed consent: a new majority position. *J Leg Med* 1:1:39, 1973
9. Canterbury v. Spence, 464 F 2d 772 (D.C. Cir. 1972)
10. Salgo v. Leland Stanford Hospital, 154 Cal. App. 2d 560, 317 P.2d 170, 181 (1957)
11. Meyers, Informed Consent in Medical Malpractice, 55 CALIF. L. REV. 1397 (1967)
12. BURGER WE: The law and medical advances. *Ann Intern Med* 67:2:16, September 1967
13. ERVIN: The Most Dangerous Piece of Legislation Ever Presented to the Congress (editorial). NATIONAL BUSINESS, November 1975, p. 80

Dave Shepherd

RE: Use of Radioactive
TRACERS + OZONE
exposure to humans

This would seem to be a
very dangerous area with
substantial legal risk.
If any of these human
subjects develope any form
of cancer or similar illness
we could be open to
possible suit. Those problems
could occur years later.
It would be a jury
question whether the exposure
caused the illness.

Jim
3-9-77

(e.g. Rosenkrantz + Martin case just going to UL for lung damage from working in plutonium area

Interdepartmental letterhead

Mail Station L- 54

Ext: 7861

Sam's response

February 24, 1977

TO: Human Subjects Committee

SUBJECT: Next Scheduled Meeting

A meeting of the Lawrence Livermore Laboratory Human Subjects Committee has been scheduled for March 7, 1977 at 2:00 p.m. in the Jade Room. The topic for discussion will be ozone exposure in humans. Additional subject matter is attached for your information.

Also attached is an article titled "Protection of Human Research Subjects: Are Ethics Necessary?", which you may find of interest.

Will you please let me know if you will not be able to attend this meeting.

Vivian L. James

Vivian L. James

Distribution:
J. O. Beatty
M. W. Biggs
S. D. Cole
R. L. Dobson
D. B. Gordon
F. T. Hatch
J. S. Johnson
P. Meyer w/o attachments
attachments

University of California
LAWRENCE LIVERMORE LABORATORY

2004883

LAWRENCE LIVERMORE LABORATORY

March 17, 1977

Mr. David A. Dorinson
Assistant Counsel
Office of the General Counsel
590 University Hall
Systemwide Administration

Re: Medical Practice in California

Dear Mr. Dorinson:

A question has been raised by our Research on Human Subjects Committee as to whether a visiting M.D. may participate in research on human subjects, which may involve some medical practice, when he is licensed to practice medicine in another state, but not in California.

May we have your opinion on this question.

Very truly yours,

ORIGINAL SIGNED BY
R. H. DYER

R. H. Dyer
Legal Liaison

RHD:em
cc: D. Shepherd

Vivian
Would you hold this in pending
Thanks

University of California P.O. Box 808 Livermore, California 94550 □ Telephone (415) 447-1100 □ Telex 34-6407 AEC LLL LVMR □ Twx 910-386-8339 AEC LLL LVMR

2004084

'CE OF THE GENERAL COUNSEL
JNIVERSITY HALL
BERKELEY—EXTENSION 2-2822

BUSINESS MANAGER
L.L.L. LIVERMORE
MAR 25 9 00 AM '77

March 22, 1977

LEGAL LIAISON R. H. DYER
Lawrence Livermore Laboratory

Re: Medical Practice in California

COPY

Your memorandum of March 17, 1977 notes that a question has been raised by the LLL Research on Human Subjects Committee as to whether a visiting M.D. may participate in research on human subjects, which may involve some medical practice, when he is licensed to practice medicine in another state, but not in California.

A person may only practice medicine in the State of California if she or he holds a valid certificate as a physician and surgeon or is authorized to practice medicine under an express exemption from certification. There is no express exemption for physicians licensed in another state when participating in human subject research.

Please let me know if you have any questions.

ORIGINAL SIGNED BY
DAVID A. DORINSON

David A. Dorinson
Assistant Counsel

cc: Director Batzel
D. Shepherd ✓

2004885

No hlth employees may participate

Strike hlth employees on VIII c

Committee wants more data on dog studies

More data from people up north

Want to do experiments in August

Then work in wkr a 3 yr grant

UC will ~~screen~~ ~~examine~~ for
~~off~~ on health

Tovey wants a committee meeting
with Engineering ~~frame~~ U of Wash
people

Own physician
— Meeting March 17th

2004886

QV seems to assume that
1 Meteorology levels
2 Ozone levels
are not exceeded

① What will be done to screen out

② Who will MD be

③ Is this a 189 project
who will pay.

4 We must redo the consist form

Is this a federal installation does the
physician need to be licensed for State

Permission w/o a coly license?
WFO agreement.
Can QVex be an already Robert Stuart.

2004687

ADMINISTRATIVE ESCORT REQUEST

(PLEASE TYPE)

NO. 11445

DATE REQUIRED: Mar. 7, 1977 TIME: FROM: 1:30 TO: 4:00

VISITOR(S) NAME AND AFFILIATION: Dr. David B. Gordon
Veterans Hospital, Livermore

BUILDING(S) AND ROOM(S) TO BE VISITED: B-125 Jade Room

MEET AT: SOUTH BADGE OFFICE ☐ WEST BADGE OFFICE ☒

PRIMARY ADMINISTRATIVE ESCORT: Vivian L. Hames DEPT. DO EXT. 7861 BLDG. 111 RM. 415

ADMINISTRATIVE ESCORTS: David C. Shepherd

PURPOSE OF VISIT: Attend meeting of the Human Subjects Committee

IF CAR PASS IS REQUIRED PLEASE EXPLAIN:

LIST BUILDING COORDINATOR THE PRIMARY A.E. HAS CONTACTED FOR EACH BUILDING THE VISITOR WILL ENTER:

David C. Shepherd	54		D O	7861
AUTHORIZED REQUESTER	MAIL CODE	SIGNATURE	DEPARTMENT	EXT.

MAIL REQUEST TO BADGE OFFICE, BLDG. 310, RM. 120-L-370. THIS REQUEST MUST BE IN THE HANDS OF ISSUE OFFICE PRIOR TO VISIT. IF NECESSARY, PLEASE HAND CARRY TO ASSURE PROMPT SERVICE.

LL3931 (REV 3/76)

REQUESTING DEPARTMENT COPY(YELLOW)

2004888