718101

(deleted version)

3/8/77

Dave,

Enclosed is the original grant application which some members of the committee requested. I shall be glad to answer more questions and will try to arrange a meeting with the team from U of W on Thursday, March 24.

Paul Lange.

REPOSITORY LLNL B361 Rm B940A

COLLECTION Institutional Review Board

BOX No. IRB Protocol File

FOLDER ACTIVE GRANTS-Collaborative University of Washington OZONE Effects on overall lung function

2004780

ORIGINAL

Form Approved
Budget Bureau No. 68-R0249

SECTION I

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

GRANT APPLICATION

LEAVE BLANK		
TYPE	PROGRAM	NUMBER
REVIEW GROUP		FORMERLY
COUNCIL *(Month, Year)*		DATE RECEIVED

TO BE COMPLETED BY PRINCIPAL INVESTIGATOR *(Items 1 through 7 and 15A)*

1. TITLE OF PROPOSAL *(Do not exceed 53 typewriter spaces)*
Ozone Effects on Overall and Regional Lung Function

2. PRINCIPAL INVESTIGATOR

2A. NAME *(Last, First, Initial)*
FRANK, Robert

2B. TITLE OF POSITION
Professor of Environmental Health

2C. MAILING ADDRESS *(Street, City, State, Zip Code)*
Department of Environmental Health SC-34
School of Public Health and Community Medicine
University of Washington
Seattle, Washington 98195

2D. DEGREE
M.D.

2E. SOCIAL SECURITY NO.

2F. TELEPHONE DATA — Area Code: 206 — TELEPHONE NUMBER AND EXTENSION: 543-4383

2G. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT *(See Instructions)*
Department of Environmental Health

2H. MAJOR SUBDIVISION *(See Instructions)*
School of Public Health and Community Medicine

3. DATES OF ENTIRE PROPOSED PROJECT PERIOD *(This application)*
FROM 1/1/74 THROUGH 12/31/76

4. TOTAL DIRECT COSTS REQUESTED FOR PERIOD IN ITEM 3
$ 128,135

5. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH PERIOD
$ 43,770

6. PERFORMANCE SITE(S) *(See Instructions)*
Department of Environmental Health
School of Public Health and Community Medicine
University of Washington
Seattle, Washington 98195

1st Congressional District

Lawrence Livermore Laboratory
University of California
P. O. Box 808
Livermore, California 94550

8th Congressional District

7. Research Involving Human Subjects *(See Instructions)*
A. [XX] NO B. [ ] YES Approved: _____ Date
C. [ ] YES – Pending Review

8. Inventions *(Renewal Applicants Only - See Instructions)*
A. [XX] NO B. [ ] YES – Not previously reported
C. [ ] YES – Previously reported n/a

TO BE COMPLETED BY RESPONSIBLE ADMINISTRATIVE AUTHORITY *(Items 8 through 13 and 15B)*

9. APPLICANT ORGANIZATION(S) *(See Instructions)*
University of Washington
Seattle, Washington

1st Congressional District

IRS No. 91-6001537

10. NAME, TITLE, AND TELEPHONE NUMBER OF OFFICIAL(S) SIGNING FOR APPLICANT ORGANIZATION(S)
George W. Farwell
Vice-President for Research

Telephone Number (s) (206) 543-0151

11. TYPE OF ORGANIZATION *(Check applicable item)*
[ ] FEDERAL [XX] STATE [ ] LOCAL [ ] OTHER *(Specify)*

12. NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER OF OFFICIAL IN BUSINESS OFFICE WHO SHOULD ALSO BE NOTIFIED IF AN AWARD IS MADE
Mr. Donald Baldwin
Director, Grant & Contract Services
University of Washington
Seattle, Washington 98195

Telephone Number (206) 543-4043

13. IDENTIFY ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES *(See Instructions)*
School of Public Health and Community Medicine

14. PHS ACCOUNT NUMBER *(Enter if known)*

15. CERTIFICATION AND ACCEPTANCE. We, the undersigned, certify that the statements herein are true and complete to the best of our knowledge and accept, as to any grant awarded, the obligation to comply with Public Health Service terms and conditions in effect at the time of the award.

SIGNATURES (Signatures required on original copy only. *Use ink, "Per" signatures not acceptable)*	A. SIGNATURE OF PERSON NAMED IN ITEM 2A	DATE
	n/a	
	B. SIGNATURE(S) OF PERSON(S) NAMED IN ITEM 10	DATE

S-398
3-70

2004781

Note: Grant was awarded in May 1975, not 1974

SECTION 1

Frank

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

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PROJECT NUMBER

RESEARCH OBJECTIVES

PRIVACY ACT MATERIAL REMOVED

NAME AND ADDRESS OF APPLICANT ORGANIZATION

University of Washington, Seattle, Washington 98195

NAME, SOCIAL SECURITY NUMBER, OFFICIAL TITLE, AND DEPARTMENT OF ALL PROFESSIONAL PERSONNEL ENGAGED ON PROJECT, BEGINNING WITH PRINCIPAL INVESTIGATOR

R. Frank	Professor	Environmental Health, Univ. of Wash
S. Watanabe	Asst. Res. Professor	Internal Medicine, Univ. of Utah
P. Meyer	Physicist	Lawrence Livermore Lab.
E. Behrin	Electronics Engineer	Lawrence Livermore Lab.
D. Freeman	Sr. Applications Programmer	Lawrence Livermore Lab.
R. Holub	Research Associate	Environmental Health, Univ. of Wash

TITLE OF PROJECT

Ozone Effects on Overall and Regional Lung Function

USE THIS SPACE TO ABSTRACT YOUR PROPOSED RESEARCH. OUTLINE OBJECTIVES AND METHODS. UNDERSCORE THE KEY WORDS (NOT TO EXCEED 10) IN YOUR ABSTRACT.

Anesthetized, mechanically ventilated dogs will be acutely exposed to low concentrations (< 0.4 parts per million) of ozone (O_3) during resting ventilation and during increased ventilation simulating exercise. Alterations in pulmonary closing volume, flow resistance, dynamic compliance, and maximum flow versus lung volume will be monitored with standard respiratory techniques. Changes in regional ventilation, perfusion, diffusion capacity (carbon monoxide), and closing volume will be monitored with radioactive gases and an Anger positron scintillation camera. The regional and standard (overall) functional data will then be compared to determine the sequence and possible interrelations of early functional changes caused by O_3.

The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for provision of required progress reports if a grant is awarded as the result of this application.

29 May, 1973
(date)

Neal Blair Frank
(principal investigator/program director)

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PRIVACY ACT MATERIAL REMOVED

2004782

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Robert Frank	Professor	
PLACE OF BIRTH (City, State, Country)	**PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)**	**SEX**
	U. S. citizen	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
University of Virginia, Charlottesville, Virginia	A.B.	1941	
The New York Downstate Medical Center New York City, New York	M.D.	1945	respiratory physiology

HONORS

none

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
respiratory physiology, environmental health sciences	Principal Investigator

RESEARCH SUPPORT *(See instructions)*

Pulmonary Specialized Center of Research
PHS HL 14152 - J. Butler, Project Director
Source: NIH, NORDIC
Project Period: 6/1/71 to 5/31/76
Total Direct Costs: $182,769
Current Direct Costs: $39,685
Effort: 20%, 8 hours/week

Proposed:
Respiratory Effects of Inhaled Gases and Aerosols
Source: NIH
Project Period: 10/1/73 to 9/30/76
Total Direct Costs: $191,030
Current Direct Costs: (Beginning 10/1/73) $61,805
Effort: 20%, 8 hours/week

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1970-present	Professor of Environmental Health, University of Washington School of Public Health & Community Medicine, Seattle, Washington
1969-1970	Professor of Preventive Medicine, School of Medicine, University of Washington, Seattle, Washington
1968-1969	Professor of Environmental Medicine, University of Utah School of Medicine, Salt Lake City, Utah
1961-1968	Assistant Professor of Physiology, Harvard School of Public Health, Boston, Massachusetts
1958-1961	Associate in Physiology, Harvard School of Public Health, Boston, Massachusetts
1957-1958	Instructor in Physiology, Harvard School of Public Health, Boston, Massachusetts
1954-1957	Research Associate in Physiology, Department of Physiology, Harvard School of Public Health, Boston, Massachusetts
1950-1953	Assistant in Medicine, 2nd and 4th Harvard Medical Service, Boston City Hospital, Boston, Massachusetts

PRIVACY ACT MATERIAL REMOVED

DO NOT TYPE IN THIS SPACE-BINDING MARGIN

LIST OF PUBLICATIONS

R. Frank

1. Frank, N.R., M. O. Amdur, J. Worcester, and J. L. Whittenberger.: Effects of acute controlled exposure to SO_2 on respiratory mechanics in healthy male adults. J. Appl. Physiol. 17: 252-258, 1962.

2. Ferris, B. G., Jr., and N. R. Frank.: Pulmonary function in coal miners. J. Occup. Med. 4:274-281, 1962.

3. Ferris, B. G., and N. R. Frank.: Air pollution and disease. Anesthesiology 25:470, 1964.

4. Frank, N.R., M. O. Amdur, and J. L. Whittenberger.: A comparison of the acute effects of SO_2 administered alone or in combination with NaCl particles on the respiratory mechanics of healthy adults. J. Air and Water Poll. 8:2, 1964.

5. Frank, R., and F. E. Speizer.: SO_2 effect on the respiratory system in dogs. Arch. Environ. Health, 11:624, 1965.

6. Speizer, F.E., and N. R. Frank.: The uptake and release of SO_2 by the human nose. Arch. Environ. Health 12:725, 1966.

7. Speizer, F.E., and N. R. Frank.: A comparison of changes in pulmonary flow resistance in healthy volunteers acutely exposed to SO_2 by mouth and by nose. Brit. J. Indust. Med. 23:75, 1966.

8. Frank, N. R., R. E. Yoder, E. Yokoyama and F.E. Speizer: The diffusion of $^{35}SO_2$ from tissue fluids into the lungs following exposure of dogs to $^{35}SO_2$. Health Physics 13:31, 1967.

9. Brain, J. D., and N. R. Frank.: Recovery of free cells from rat lungs by repeated washings. J. Appl. Physiol. 25:63, 1968.

10. Brain, J. D., and N. R. Frank.: The relation of age on the number of free lung cells and on lung weight to body weight relations in rats. J. Gerontology 23:57, 1968.

11. Frank, N. R., R. E. Yoder, J. D. Brain, and F. Yokoyama.: SO_2(^{35}S labeled) absorption by the nose and mouth under conditions of varying concentration and flow. Arch. Environ. Health 18:315-322, 1969.

12. Woolcock, A. P., Macklem, P. T., Hogg, J. C., Wilson, N. J., Nadel, J. A., Frank, N. R., and Brain, J.: Effect of vagal stimulation on central and peripheral airways in dogs. J. Appl. Physiol. 26:806-813, 1969.

13. Frank, N. R.: Editorial in defense of lungs. Arch. Environ. Health 20:562-563, 1970.

14. Frank, N. R.: Effects of inhaled pollutants on nasal and pulmonary flow resistance. Ann. Otol. 79:1-7, 1970.

15. Yokoyama, E., Yoder, R. E., and Frank, N.R.: Distribution of ^{35}S in the blood and its excretion in urine of dogs exposed to $^{35}SO_2$. Arch. Environ. Health 22:389-395, 1971.

16. Frank, R., Flesch, J. P., and Brain, J.D.: Effect of ozone on elastic behavior of excised lungs of dogs. Environ. Res. 4:343-354, 1971.

17. Frank, N.R., Mead, J., and Whittenberger, J.L.: Comparative sensitivity of four methods of measuring changes in respiratory flow resistance in man. J. Appl. Physiol. 31:934-938, 1971.

18. Frank, R.: Clean and dirty lungs. pg. 323-338. In Brittin, W.E., West, R., and Williams, R. (eds.) Air and Water Pollution. Colorado Assoc. Univ. Press, Colo., 197.

19. Frank, R.: Health effects of air pollution. pg. 46-50. In Engineering for Resolution of the Energy-Environment Dilemma. Committee on Power Plant Siting. NAE, Washington, D.C., 1972.

20. Yokoyama, E. and Frank, R.: Respiratory uptake of ozone in dogs. Arch Environ. Health. 25:132-138, 1972.

21. Fisher, A. B., Frank, R., and Fisher, H.K.: Chapter 7 -- Action through channels other than airborne. In Environmental Factors in Respiratory Disease, 1972 (monograph).

22. Frank, N.R., Brain, J.D., and Yokoyama, E.: Compression atelectasis: A model for unilateral exposure of the lung. J. Appl. Physiol. (in press).

23. Brain, J.D., and Frank, R.,: Alveolar macrophage adhesion: wash electrotyte composition and free-cell yield. J. Appl. Physiol. 34:75-80, 1973.

24. Watanabe, S., Frank, R., and Yokoyama, E.: Acute effects of ozone on cats' lungs. I. Functional. (submitted for publication in Amer. Rev. Resp. Dis.).

ABSTRACTS

1. Frank, N.R., Brain, J.D., and Sherry, D.E.: Unilateral tolerance and altered elastic behavior in rabbits. Amer. Industr. Hyg. Conference, 1970. pg 31 (#102).

2. Yokoyama, E., and Frank, R.: Uptake of ozone by the upper and lower airways in dogs. Amer. Industr. Hyg. Conference, 1971. pg. 70 (#176).

3. Watanabe, S., Frank, R., Yokoyama, E., and Boatman, E.S.: Functional and structural effects of low concentrations of ozone in cats. Amer. Industr. Hyg. Ass. J. 33:20, 1972.

4. McJilton, D., Thielke, J., and Frank, R.: Ozone uptake model for the respiratory system. Amer. Industr. Hyg. Ass. J. 33:20, 1972.

5. Boatman, E.S., Sato, S., and Frank, R.: Structural changes in animal lungs exposed to low concentrations of ozone. 30th Ann. Proc. Electron Microscopy Soc. Amer. Los Angeles, Calif., 1972. C. J. Arceneaux (ed.).

6. McJilton, C.E., Charlson, R., and Frank, R.: Temperature and relative humidity: a possible role in the SO_2-aerosol synergism? (accepted for presentation at AIHA Conference, Boston, May, 1973.)

DO NOT TYPE IN THIS SPACE-BINDING MARGIN

 Frank

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE *(Mo., Day, Yr.)*
Suetaro Watanabe	Assistant Research Professor	
PLACE OF BIRTH *(City, State, Country)*	**PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)*	**SEX**
	U. S. citizen	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
Hokkaido University School of Medicine, Sapporo, Japan	M.D.	1955	medicine
Hokkaido University School of Medicine, Sapporo, Japan	Ph.D.	1963	medical science

HONORS
First Prize - Annual Award of Research Papers (1963). Medical Journal of Mutual Aid Association Hospitals, Tokyo, Japan

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
respiratory structure and function in man and animals	Investigator (Pulmonary Physiology)

RESEARCH SUPPORT *(See instructions)*

none

PRIVACY ACT MATERIAL REMOVED

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1972-present	Assistant Research Professor, Department of Internal Medicine, University of Utah College of Medicine, Salt Lake City, Utah
1967-1972	Research Associate, Department of Internal Medicine, University of Utah College of Medicine, Salt Lake City, Utah
1965-1967	Director, Pulmonary Function Laboratory, Konan Hospital, Sapporo, Japan
1963-1965	Fellow, Pulmonary Disease, Veterans Administration Hospital, Salt Lake City, Utah
1956-1963	Resident, Department of Internal Medicine, Hokkaido University Hospital, Sapporo, Japan
1955-1956	Intern, Hokkaido University Hospital, Sapporo, Japan

LIST OF PUBLICATIONS

S. Watanabe

1. Watanabe, S., Mitchell, M. M., and Renzetti, A. D., Jr.: Correlation of structure and function in chronic pulmonary emphysema. Amer. Rev. Resp. Dis. 92:221, 1965.

2. Beier, F. R., Renzetti, A. D., Jr., Mitchell, M. M., and Watanabe, S.: Pathophysiology of cystic fibrosis. Amer. Rev. Resp. Dis. 94:430, 1966.

3. Nicklaus, T. M., Watanabe, S., Mitchell, M. M., and Renzetti, A. D., Jr.: Roentgenologic, physiologic and structural estimates of the total lung capacity in normal and emphysematous subjects. Amer. J. Med. 42:547, 1967.

4. Mitchell, M. M., Watanabe, S., and Renzetti, A. D., Jr.: Evaluation of airway conductance measurements in normal subjects and patients with chronic obstructive pulmonary disease. Amer. Rev. Resp. Dis. 96:685, 1967.

5. Watanabe, S., Renzetti, A. D., Jr., and Bigler, A. D.: Bronchodilator and corticosteroid effect on regional and total airway resistance in patients with asthma, chronic bronchitis, and chronic pulmonary emphysema. Amer. Rev. Resp. Dis. 106:392, 1972.

6. Kanner, R. E., Klanbe, M. R., Watanabe, S., Renzetti, A. D., Jr., and Bigler, A. H.: The pathophysiologic patterns of chronic obstructive pulmonary disease in patients with normal and deficient levels of alphal antitrypsin. (accepted for publication in Amer. J. Med.).

7. Watanabe, S., Frank, R., and Yokoyama, E.: Acute effects of ozone on cats' lungs. I. Functional. (submitted for publication in Amer. Rev. Resp. Dis.).

8. Boatman, E. S., Frank, R., and Watanabe, S.: Acute effects of ozone on cats' lungs. II. Structural. (in preparation).

9. Watanabe, S., and Frank, R.: Pulmonary function in anesthetized cats; control data. (in preparation).

10. Watanabe, S., Begin, R., Renzetti, A. D., Jr., and Bigler, A. H.: The effects of a bronchodilator aerosol on airway responsiveness in 75 normal subjects. (in preparation).

11. Watanabe, S., Kanner, R. E., Bigler, A. H., and Renzetti, A. D., Jr.: Measurement of total lung capacity by radioactive Xenon ^{133}. (in preparation).

2004787

SECTION II – PRIVILEGED COMMUNICATION

Frank

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Paul Meyer	Physicist	
PLACE OF BIRTH (City, State, Country)	**PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)**	**SEX**
	U. S. citizen	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
University of Washington, Seattle	B.S.	1958	Physics
University of Washington, Seattle	M.S.	1960	Physics

HONORS

None

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
Photonuclear reactions	Radioactive gas production and operation of Anger camera

RESEARCH SUPPORT *(See instructions)*

None

PRIVACY ACT MATERIAL REMOVED

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List a or most representative publications. Do not exceed 3 pages for each individual.)*

1967-present Lawrence Livermore Laboratory, Livermore, California. Participation in photonuclear reaction experiments to measure neutron and fission yield cross sections. Development of gas activation experiments for bio-medical and other purposes; worked on problems in nuclear weapons effects, i.e. investigated X-ray induced blow-off impulse phenomenon.

1960-1967 General Electric, Vallecitos Nuclear Center, Pleasanton, California. Development of pulsed neutron application to reactor systems. Included design of neutron generators, neutron detectors and digital data acquisition systems and method evaluation; performed experiments in critical facilities and large power reactors.

1958-1960 University of Washington, Seattle, Washington. Masters thesis research on the 60" Cyclotron. Objective of work was to improve the horizontal focusing properties of the energy analyzing magnet. Specifically, all parts of the existing particle beam, for energies equal to within 0.1% were focused onto a target area about 1/8" wide. Work involved the use of nuclear magnetic resonance techniques to measure magnetic field strengths and differential ion chambers to maintain constant particle energy.

2004708

LIST OF PUBLICATIONS

P. Meyer

1. Meyer, P., and Ballowe, W.C.: An experimental parametric study of the effects of control rods on the prompt neutron decay constant in multiplying media. AEC Research and Development Report, GEAP-4019, 1962.

2. Meyer, P.: Pulsed neutron experiments in power reactors. Trans. Amer. Nucl. Soc. 6:287, 1963.

3. Meyer, P.: An experimental study of the ($\kappa\beta/\ell$) pulsed neutron source technique in light water assemblies. Pulsed Neutron Research, Vol. II, Internat'l. Atomic Energy Agency, Vienna, pp. 25-46, 1965.

4. Meyer, P., and Garelis, E.: Impulse response measurements with pseudo random source excitation. Proceedings of the Symposium on Neutron Noise, Waves and Pulse Propagation, University of Florida, p. 333, 1966.

5. Meyer, P.: Impulse response measurements using pseudo random source excitation. Proceedings of the Internat'l Conference on Research Reactor Utilization and Reactor Mathematics, Mexico City, p. 1590, 1967.

6. Meyer, P.: Precision magnetic field adjustments of the external beam analyzing magnet of the university of washington cyclotron. (A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science, unpublished, 1960).

7. Fultz, S.C., Alvarez, R.A., Meyer, P., and Berman, B.L.: The photoneutron cross sections for ^{58}Ni and ^{60}Ni and isospin splitting of the giant dipole resonance. Amer. Phys. Soc. 17:16, 1972.

8. Meyer, P.: Ozone-tagging for biomedical purposes. (To be published in the Proceedings of the Internat'l Conference on Photonuclear Reactions and Applications, Asilomar, California, March 26-30, 1973).

9. Alvarez, R.A., Berman, B.L., Lewis, F.H., and Meyer, P.: Photoneutron cross sections for ^{55}Mn. (To be published in the Proceedings of the Internat'l Conference on Photonuclear Reactions and Applications, Asilomar, California, March 26-30, 1973).

10. Alvarez, R.A., Berman, B.L., Lewis, F.H., and Meyer, P.: Photoneutron cross sections for ^{59}Co. (To be published in the Proceedings of the Internat'l Conference on Photonuclear Reactions and Applications, Asilomar, California, March 26-30, 1973).

2004789

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE *(Mo., Day Yr.)*
Richard Holub	Research Associate	
PLACE OF BIRTH *(City, State, Country)*	**PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* U.S. citizen	**SEX** ☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
University of Washington, Department of Preventive Medicine, Seattle, Wash.	B.S.	1969	Environmental health
University of California, Berkeley, Environmental Health Sciences	M.S.	1970	Environmental health

HONORS

None

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
The use and development of industrial hygiene, air pollution, and biomedical instruments and devices	Co-Investigator

RESEARCH SUPPORT *(See instructions)*

Proposed:
Respiratory Effects of Inhaled Gases and Aerosols
Source: NIH
Project Period: 10/1/73 to 9/30/76
Total Direct Costs: $191,030
Current Direct Costs: (Beginning 10/1/73) $61,805
Effort: 50%, 20 hours/week

PRIVACY ACT MATERIAL REMOVED

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1971-present Research Associate, Department of Environmental Health, University of Washington School of Public Health & Community Medicine, Seattle, Washington

Summer, 1969 Industrial Hygiene Trainee, Bremerton Naval Shipyard, Bremerton, Washington

Summer, 1968 Science Intern, Washington State Department of Health, Olympia, Washington

Summer, 1967 Sanitarian, Migrant Program, Pierce County Health Department, Tacoma, Washington

INTRODUCTION

Objective

Our objective is to describe the early effects of low concentrations of ozone (O_3) on pulmonary function in anesthetized, mechanically ventilated mongrel dogs. The study will have two parts. In the first, standard functional measurements including pulmonary flow resistance (R_L), dynamic compliance (Cdyn), and maximal flow-volume curves ($\dot{V}max$-V_L) will be made both during resting ventilation and hyperpnea, the latter to simulate exercise. In the second part, regional ventilation, perfusion, and diffusion capacity (carbon monoxide) will be studied using an Anger positron camera. The regional and standard (overall) functional data will then be compared to determine the sequence and possible interrelations of early functional changes caused by O_3.

Background, Rationale

Non-Radioactive Techniques

Ozone (O_3) has reached ambient levels of 0.4 parts per million (ppm) in a number of cities; [1] levels as high as 0.54 ppm have been reported in Los Angeles [2]. Such concentrations impair certain biochemical, structural, and functional properties of the lungs. The large numbers of persons exposed to these concentrations of O_3 underscore the need to expand and refine knowledge of its hazards. Evidence suggests that the peripheral airways are damaged by chronic exposure to O_3 [3]. While the influence of the peripheral airways[1] on the distribution of ventilation is generally acknowledged, there is difficulty in assessing their functional status with conventional tests. Indeed, the peripheral airways have been referred to as the "quiet zone" of the lungs [5]. Our intention is to assess their involvement in the early functional response to O_3. We also seek to determine the changes that O_3 may impose on the distribution of pulmonary blood flow. At present, virtually nothing is known about the latter.

The following are among the functional studies performed on man and laboratory animals which have shown significant alterations in one or more subjects during or following exposure to O_3 in the range 0.1 to 1.0 ppm.

A. Dynamic Measurements

1. Pulmonary flow resistance (R_L) in man [6,7] and in animals [8]
2. Maximum flow ($\dot{V}max$) related to lung volume (V_L) in man [6,9,10,11]
3. Dynamic compliance (Cdyn) in animals [8]
4. Closing volume (CV) in man [12]

---

[1] The term lacks anatomic, morphometric, or functional precision. Macklem and Mead [4] partitioned pulmonary flow resistance (R total) in the dog into central (R_C) and peripheral (Rp) components. Their peripheral component included airways about 3 mm in diameter and smaller. Rp/R total x 100 averaged about 10% at functional residual capacity (FRC).

B. Static (or Quasi-static) Measurements

1. Volume pressure (V/P) behavior in animals [8,13]
2. Maximum static elastic recoil pressure in man [6]

C. Diffusion Capacity (carbon monoxide) (D_{LCO}) in man [6,10,11] and in animals [8]

A. Dynamic Measurements

There have been two recent attempts to identify pulmonary functional parameters especially vulnerable to O_3. (Ample evidence exists that "non-respiratory" functions such as the resistance of the lungs to infection are impaired by low levels of O_3 [14,15].) One of these studies, on healthy volunteers, suggested that $\dot{V}max$ at 50% of vital capacity (VC) was more likely to be affected than either airway flow resistance (Raw) or D_{LCO} [6]. The other study, on anesthetized, mechanically ventilated cats, showed that pulmonary conductance, the reciprocal of R_L, decreased more often and more materially than did D_{LCO} (single breath) [8]. How much of the increase in R_L was owing to changes in caliber of the peripheral airways was uncertain. Light and electronic microscopic examination of the same lungs revealed damage at all levels of the airways [16]. Other evidence to suggest that the peripheral airways were implicated was the finding that the increase in R_L had a non-reflexive component; that is, about one-third of the increase in R_L persisted after atropine. (In dogs, vagal innervation stops short of the smaller airways [17]; we have no information about the extent of vagal innervation in cats.) Some reflexive narrowing of peripheral airways may be caused by submucosal edema, excessive secretions, or an increase in smooth muscle tone following the release of agents like histamine [18]. It is of interest that a computer program [19] based on an idealized model of the lungs [20] predicts that the dosage of inspired O_3 to the airways, both central and peripheral, should exceed the alveolar dosage.

There are at present two principal "non-invasive" means of adducing evidence for damage to the small airways; measurement of Cdyn [21] and measurement of CV [22-24]. Both measurements are useful only if the total R_L is not significantly elevated [21]. (In a study on the effects of O_3 it might therefore be worth performing these tests on the exposed animal following vagotomy or atropine.) In the cat, Cdyn is not sensitive to respiratory frequency even after total R_L is elevated significantly [8]; the factors which act to mitigate this Cdyn-frequency have been discussed by Macklem [25]. The cat may be inappropriate for our experiments for still another reason: its lungs are probably too small to demonstrate the CV phenomenon. The latter requires a relatively large gradient in pleural pressure from apex-to-base, which in turn implies a long vertical axis of the lungs (upright position) [26-27]. The dog, because of its larger thorax, is a more appropriate choice than the cat.

B. Static (or Quasi-static) Measurements

For the sake of simplicity, we will not measure the quasi-static V/P behavior of the lungs. We think the omission is justified on the basis of earlier in vivo studies [8] showing that, in the absence of intra-alveolar edema, the deflation limb of the V/P curve and the VC are not affected by acute exposure

to O_3. Intra-alveolar edema is unlikely at the concentrations of O_3 to be used in this study. If the study is enlarged to include functional measurements for as long as one to two weeks following the exposure, the quasi-static elastic behavior will then be studied. There is evidence obtained in rabbits [13] that significant changes in this functional parameter appear days after the exposure.

C. Diffusion Capacity

The overall D_{LCO} (non-radioactive technique) will not be measured since there is evidence to show that this function is less sensitive to change from O_3 than is R_L [8]. Regional diffusion capacity (radioactive technique) will be studied.

Radioactive Techniques

The use of a radioactive gas for assessing regional ventilation was reported as early as 1957 by Knipping et al [28]. Count rates were recorded over multiple areas of each lung field during inhalation of a mixture of xenon 133 (^{133}Xe) and air. With these data, Knipping et al demonstrated the presence of unventilated areas in chonically diseased lungs. The use of multiple arrays of individual scintillation counters for the detection of the positron emitting radioisotopes, nitrogen 13 (^{13}N), carbon 11 (^{11}C), and oxygen 15 (^{15}O) was developed by West [29-36], Dollery [37-43], and Dyson [44-46] et al at Hammersmith Hospital, London, England. Individual counters allowed the simultaneous assessment of regional ventilation and perfusion in four distinct lung zones (upper and lower zones in each lung). Later, a system was developed for the sequential scanning of the whole lung field. Simultaneous measurements from multiple regions of the lung are not practicable with this system.

In 1958 Anger described a gamma-ray and positron scintillation camera [47]. The camera was basically an improvement on his earlier gamma-ray pin hole camera with image amplifier [48,49]. Present models of the Anger gamma camera make it possible to obtain data simultaneously from a field having an approximate diameter of 23 cm [50]. The data may be processed by a computer so that regions as small (vascular) liquids, the ventilation/perfusion ratio ($\dot{V}/Q$) may be obtained for each specified regional area [35,51,52]. It is also possible to determine with an Anger positron camera[2] the relative sites of uptake of any positron emitting material such as gas tagged with: ^{15}O, ^{11}C, or ^{13}N.

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[2] Most Anger cameras are single-headed gamma scintillation cameras. The Anger positron scintillation camera consists of two identical camera heads each placed exactly opposite the other on separate supports. When a positron is annihilated, two 0.51 MEV gamma rays are produced which travel in opposite directions. These rays must simultaneously hit both cameras before a valid positron event is registered. A method for locating the "plane of best focus" between the two cameras makes it possible to describe the site of the positron annihilation in three dimensions.

Since O_3 affects the conducting airways at all levels [53-56], one would expect alterations in the $\dot{V}/Q$ ratio as a consequence. With the Anger positron scintillation camera, the approximate sites of early $\dot{V}/Q$ alterations with exposure to ozone should be identifiable.

Exercise

O_3 penetrates the upper airways more completely if the flow rate is increased or if breathing is oral rather than nasal [57]. Bates et al [6] showed that exercise exaggerated the functional response of healthy volunteers to O_3, particularly by causing a reduction in $\dot{V}max$ at 50% of VC. These observations offer a basis for the impaired performance of high school track teams in Los Angeles found in association with elevated ambient oxidant levels [58]. Children, because they are frequently outdoors and exercising, may be especially vulnerable to community air pollution. We plan to examine the effects of increased minute ventilation (controlled with a respiratory pump and balanced by the addition of CO_2 to inspired air (hyperpnea)) on all functional parameters.

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SPECIFIC AIMS

1. To determine the most sensitive pulmonary functional measurements for the detection of the early effects of low levels of O_3 (< 0.5 ppm).

2. To determine the effect of low levels of O_3 (< 0.5 ppm) on regional $\dot{V}/Q$ ratios and regional diffusion capacity (carbon monoxide) using an Anger positron camera and radioactive positron emitting gases.

3. To compare functional effects of low levels of O_3 (< 0.5 ppm) during resting ventilation and during increased ventilation simulating light-to-moderate exercise.

METHODS OF PROCEDURE

The study will be divided into two parts--non-radioactive techniques, to be done at University of Washington (U of W) and radioactive techniques, to be done at Lawrence Livermore Laboratory (LLL). The non-radioactive experiments will be completed during the first year and a half (January 1974 to mid-1975). The radioactive experiments will begin during the second year (1975) and be completed by December of 1976.

Non-radioactive Techniques

Mongrel dogs of approximately 15 kg will be used in both phases of the study (U of W and LLL). Animals this large are needed to fill most of the camera's field of view (about 10 x 10 inches) with the respiratory system. Preliminary experiments will be done to determine whether dogs respond to low concentrations of O_3 with changes in R_L, as do human subjects and other laboratory animals. If not, other medium-sized animals such as sheep or monkeys will be tried. The animals will be anesthetized (sodium pentothal initial dose: 30 mg/kg, i.v.), paralyzed (gallamine HCl) and mechanically ventilated with a Harvard Apparatus pump through a steel tracheal cannula inserted just below the larynx. The pump will be modified to minimize the uptake of O_3. An infusion of 5% glucose in saline will be administered slowly throughout the experiment.

Pleural pressure will be measured with a differential inductance transducer (P 268B, Hewlett-Packard Co.) through a rubber mushroom catheter. The catheter will be inserted in the right anterio-medial fourth - fifth intercostal space after initiation of a pneumothorax (50 ml) intended to prevent injury to the lung. Approximately 10 ml of gas will be maintained in the pleural space throughout the experiment. Flow rate will be monitored with a suitably sized Fleish pneumotachograph (Instrument Associates, Inc.) and differential inductance transducer (P270, Hewlett-Packard Co.). Volume will be obtained by integrating the pneumotachograph flow signal with a Lexington Model A-123 integrator. All three signals will be amplified and recorded on a thermal oscillograph (Hewlett-Packard, Co.) and on computer tape through an analog-to-digital converter and the School of Public Health's General Automation SPC-16 computer. Blood samples will be analyzed for pH, P_{O_2} and P_{CO_2} approximately every 30 minutes with electrodes.

The dogs will be supported in an upright position throughout the experiment, since normally gravity appears to be the principal determinant both of the uneven distribution of ventilation and perfusion, and of CV [1,2].

We intend to make the following functional measurements: CV, R_L, Cdyn (at 2 to 3 frequencies), $\dot{V}max$ vs V_L (later measurements such as VC, FEV_1, MEF, etc. will be computed from these data), functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC), and nitrogen (N_2) washout.

CV will be measured using the technique of Green et al [3]. At RV (P_{airway}: -5 to -7 cm H_2O) a 75 cc bolus of helium will be injected into the airways and the lungs inflated to 30 cm H_2O or TLC. The lung will then be deflated at a constant rate (60-100 ml/sec). A portion of the air will be sampled with a critical orifice helium analyzer (Mead and Collier [4]).

R_L will be calculated as an average value for inspiration and expiration at iso-volumes, in the range of mid-tidal breathing.

$$R_L = \frac{[P_{ao} - P_{pl}],\ \text{cm } H_2O}{[\dot{V}\ (\text{insp}) + \dot{V}\ (\text{exp})],\ \text{l/sec}}$$

where $\dot{V}$ = instantaneous flow rates during inspiration and expiration at iso-volumes, P_{ao} = pressure at the airway opening or trachea, and P_{pl} = pleural pressure. The values for R_L will be obtained 3-4 minutes after the application of two deep inspirations and will be based on averages of three consecutive breaths.

Cdyn will be calculated as the ratio of the tidal volume (V_T) to the change in transpulmonary pressure at the instant of zero flow:

$$\text{Cdyn} = \frac{V_T,\ \text{ml}}{(P_{ao} - {}_{pl}),\ \text{cm } H_2O}$$

The measurements will be made at 10, 25, and 50 breaths/min.; an average value for Cdyn will be calculated from three successive breaths. The resistance of the expiratory tubing will be adjusted to minimize shifts in end-expiratory lung volume over this range of breathing frequency. Cdyn and R_L will be measured simultaneously.

$\dot{V}max$ will be obtained by expanding the lungs to TLC ($P_{distending}$ = 30 cm H_2O) with the commercial vacuum cleaner maintaining the peak pressure for 10 seconds, and then connecting the airway through an electrically operated solenoid valve to a 40 liter bottle evacuated to a vacuum of approximately - 20 inches mercury. $\dot{V}max$ and lung volume (V_L) will be recorded simultaneously.[2a] The data will later be analyzed by computer to obtain the values for VC, FEV_1 second, MEFR, etc.

RV and VC will also be determined in conjunction with the measurement of $\dot{V}max$ and V_L. (In these experiments we define VC as the volume of gas emitted from the

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[2a] Reflex bronchoconstriction may be temporarily reduced or abolished by a deep breath [5]; consequently, we may also measure $\dot{V}max$ from with FRC or FRC plus V_T.

lungs as the distending pressure is lowered from a peak level of 30 cm H_2O (TLC) to a level at which P_{airway} is subatmospheric (approximately -5 to -7 cm H_2O) and no additional gas can be suctioned from the lungs.)

The "communicating" FRC will be determined with the single breath method as is customarily done in the measurement of D_{LCO}[3]; a 500 cc bolus of a gas mixture containing 0.625% neon (Ne), 23.8% oxygen (O_2), and the balance, nitrogen (N_2), will be delivered from a large syringe into the lungs through the tracheal cannula. After a lapse of 10 seconds, 100 ml of gas will be withdrawn to be discarded (dead space volume) and the next 500 ml will be quickly withdrawn for analysis. The concentration of the gases will be analyzed with a gas chromatograph.

$$FRC_{ATPD} = 500 \left[\frac{F_{I_{Ne}}}{F_{E_{Ne}}} - 1 \right], \text{ ml}$$

where 500 = size of test gas bolus, FI_{Ne} = neon concentration in injection test gas, and $F_{E_{Ne}}$ = neon concentration in the expiratory sample.

Immediately following the measurement, the lungs will be evacuated to RV by reducing airway pressure to a subatmospheric level (P_{airway} -5 to -7 cm H_2O). The volume of gas removed from the lungs with this maneuver is analogous to the expiratory reserve volume (ERV). RV will be calculated as FRC-ERV.

Breath by breath analysis of N_2 washout curves will be made to test the even distribution of inspired air. For this measurement the animal will be ventilated with O_2. We estimate that 40-60 consecutive breaths may be needed to describe "fast" and "slow" emptying alveolar space, should a "slow" space appear following O_3. In preliminary experiments we will test the value and feasibility of measuring the N_2 washout at more than one pump frequency and during a single slow breath [6].

The wet/dry lung weight ratio will also be determined as an index of edema.

FRC will be measured once every 20 minutes. All other functional measurements will be repeated twice at 20 minute intervals. The measurements will be staggered so that the exposure to O_3 will only be interrupted for a maximum two-minute period of time.

O_3 will be generated from filtered air with an ultraviolet Orec Model 03U1 O_3 generator (Ozone Research and Equipment Corp.). O_3 concentration will be continuously monitored with a pre-calibrated Dasibi Model 8000 ozone analyzer. Glass, stainless steel and teflon fittings will be used throughout the preparation.

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[3] We found that FRC measured this way in cats [7] was almost identical with FRC measured by gas compression. The only exception occurred when R_L rose at least several hundred precent. Such exaggerated increases in R_L are not expected at the low concentrations of O_3 to be used in these experiments.

About 0.4 ppm of O_3 will be administered. If this concentration evokes a considerable response, a lower concentration may be substituted. Previous experience suggests that 0.4 ppm is close to the threshold for changes in R_L during resting ventilation [7]. A preliminary test at a concentration of approximately 1 ppm will be done on one or two animals to test all procedures and measurements.

Exposure to O_3 will last three hours. A one-half hour control period (air) with the animal on the pump will precede the exposure during which at least two complete sets of functional measurements will be made. Tidal volume (V_T) and respiratory frequency (f) will be based on the Kleinman-Radford Nomograph [8].

One set of animals will be studied with O_3 under conditions of "resting ventilation , another set during "hyperpnea." Two sets of control animals with no O_3 exposure will also be done (rest and hyperpnea). To achieve hyperpnea, tidal volume (V_T) and pump frequency (f) will be increased so that minute ventilation is about three-fold above resting levels. (In the experiments on human subjects by Bates et al [9], the average increase in minute ventilation during exercise was about two-fold.) CO_2 (2-4%) will be added to the inspired gas to maintain P_{aCO_2} at pre-hyperpnea levels. The inspired gas will be humidified periodically.

Radioactive Techniques

The radioactive experiments will be performed at the LLL 100 MEV Linear Electron Accelerator (Linac) facility. This facility contains, in addition to the Linac, an Anger positron scintillation camera system (two 16-inch cameras) and a PDP-15 computer for data collection and analysis. (See "Facilities Available".)

We intend to use a coincidence detection system with the Anger camera (Appendix I). This will allow us to use low activity gases while retaining the best combination of camera sensitivity and resolution. The PDP-15 computer can be programmed to store the camera data in sectors containing all counts detected in a specific period of time ($\geq$ 1/10 sec) or for every complete breath.

Positron emitting isotopes will be obtained by irradiating stable elements with X-rays from the 100 MEV Linac (Appendix III). $^{13}N_2$ will be obtained by using pure N_2 (> 99.999% purity) as a target gas. No contaminants such as ^{11}C have been found in significant amounts in the $^{13}N_2$ produced.

The animals will be anesthetized, paralyzed, and ventilated mechanically as in the non-radioactive experiments. O_3 exposure (about 0.4 ppm) and CO_2 levels will be maintained with the same methods as in the earlier experiments. Total O_3 exposure will be three hours with a one-half hour control period (air) preceding the exposure.

Three small low level point sources (sodium 22) will be attached to the shaved skin of the animal. The point sources will be positioned in a triangular configuration that is outside of the Anger camera's view of the lung but still within the camera's field of view (10 x 10 inches). Anterior-posterior and lateral chest X-rays will be taken with the animal supported in an upright position. The X-rays will later be used to superimpose the anatomic boundaries of the respiratory system onto the scintigraphic printout, using the basic techniques of Coulum et al [10].

The initial experiments will include: standard (non-radioactive) pulmonary function measurements; regional ventilation, dynamic compliance, and closing volume measurements using $^{13}N_2$; and regional perfusion measurements using ^{133}Xe dissolved in saline.

The choice of standard pulmonary function measurements (non-radioactive techniques) will be based on our experience with the non-radioactive experiments. We will rely on those tests that have proven to be most sensitive to O_3.

Regional ventilation and closing volume will be measured simultaneously with $^{13}N_2$. The respiratory pump will be stopped with the lungs at FRC and the lungs evacuated to RV. The lungs will then be inflated with a mixture of air and $^{13}N_2$ from a spirometer at a slow steady flow rate (about 75 ml/sec) measured with a Fleish phenumotachograph until P_{airway} is 30 cm H_2O. Peak inspiration will be maintained for 10 seconds before the lungs are deflated at the same flow rate to RV. The animal will then be placed back on the pump set at the normal respiratory frequency. A separate external scintillation counter will be placed over the tracheal cannula to monitor the activity of the inspired and expired gases.

Closing volume will be determined using the technique of Greene et al [11] by monitoring the expired gas from the slow inspiration/expiration maneuver. Inspiratory data starting from RV will be obtained by sampling the camera's output every second starting approximately two seconds before the inspiration of $^{13}N_2$. $^{13}N_2$ washout data will be obtained from the time the animal is placed back on the O_3 pump until activity has reached background levels. Each sample of camera output will contain the total number of positron events and their approximate locations that occur during the one second interval.

Regional perfusion will be determined by using the technique of Dugard et al [12] (injection of ^{133}Xe in saline into the bloodstream). The Anger camera will again record the total number and location of all events for each one second interval before, during, and after injection until background levels of activity have been obtained.

An index of regional dynamic ventilation will be sought in conjunction with the regional perfusion measurements in the following manner: the injected ^{133}Xe will be washed out (with the O_3 pump) at 3 different frequencies for 4-5 breaths at each frequency (10, 25, 50 breaths/minute, rotated randomly) and then returned to the normal operating frequency. The rate at which the regional radioactivity falls per breath as a function of frequency may prove to be a useful measure of dynamic ventilation.

$^{13}N_2$ washin curves will be obtained by administering by pump a mixture of approximately 80% $^{13}N_2$ and 20% O_2. Tidal volume will be constant; initially, the standard pump frequency will be used (approximately 25 breaths/minute); we may also test $^{13}N_2$ washin at more than one frequency.

A number of individual lung sites will be chosen on the basis of their location and alterations in the $\dot{V}/Q$ ratios will be followed throughout the O_3 exposure. The data from the ventilation and perfusion measurements will be corrected for camera non-uniformity [13] before $\dot{V}/Q$ ratios are computed.

One set of animals will be studied with O_3 under conditions of "resting ventilation", another set during "hyperpnea." Two sets of control animals with no O_3 exposure will also be done (rest and hyperpnea). Preliminary tests at a

concentration of approximately 1 ppm will be done on two to four animals to test all procedures and measurements. All measurements will be done in duplicate every 30 minutes throughout the control and exposure periods. The measurements will be staggered so that exposure is not interrupted for more than two minutes.

After the initial radioactive experiments a second series of regional diffusion experiments will be done on two groups of animals (rest and hyperpnea) exposed to O_3. Regional diffusion will be measured using the techniques of Dollery et al [14] with $^{15}O_2$ labelled carbon monoxide (CO*). This technique basically involves: inspiration of a CO* and air mixture (∿ 500 ml) after a normal expiration, holding the maximum inspiration for 10 to 15 seconds and expiration of the breath.

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SIGNIFICANCE

Our hypothesis is that low concentrations of O_3 may alter functions that are related to the patency of the peripheral airways in the absence of significant increases in resistance of the central airways (i.e. in the presence of only minor increases in R_L). To what extent regional $\dot{V}/Q$ relations and regional diffusion are altered by O_3 is not known. The hypothesis, if substantiated, may signal a direction for functional tests that are used in epidemiological studies.

The peripheral airways represent a critical anatomic site in the lungs. Mead [1] has suggested that they are probably implicated in most, or all, forms of "bronchitis". Whether "bronchitis", or "bronchiolitis", is diagnosed depends in large measure on the age of the patient and, consequently, on the relative contributions of his central and peripheral airways to R_L. Changes in elastic recoil of the lungs associated with aging and emphysema also influence the patency of the peripheral airways. It is possible that the most accessible early evidence of a reduction in elastic recoil may be an increase in RV, or CV, and that changes in these volumes may in turn reflect the collapse of small airways.

Acute exposure to O_3 damages the small airway histologically [2-4], and may also affect their patency [5]. Such damage, if repeated many times, could lead to permanent distortion. O_3 also attacks the alveolar-capillary membranes [6-9]: for one-two weeks following a single exposure, the distensibility of the lungs may be reduced [10]. How kindred these events at the two structural levels may be is not known. To date, the techniques employed in surveys of populations exposed to oxidant air pollution have been largely insensitive to early functional changes at these lung sites.

The study also should indicate the importance of increased minute ventilation (analogous to exercise) in determining the functional response to O_3. It is possible that the type of response, as well as the magnitude, may change if hyperpnea is associated with a change in the site of uptake of O_3.

The resources at Lawrence Livermore Laboratory should add considerable precision and analytic strength to the study. If the initial phase of the study is successful, we hope to extend the studies in time to assess the delayed effects of O_3 and, perhaps, to study the effects of other oxidants such as nitrogen dioxide.

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FACILITIES AVAILABLE

University of Washington

The PI and associates occupy two separate laboratories within the Department of Environmental Health. These well-equipped respiratory physiology laboratories contain two Hewlett-Packard six channel oscillographic recorders with appropriate preamplifiers and transducers, two Textronix storage oscilloscopes, one Harvard Apparatus dog pump, two Orec Corp. ozone generators, one Beckman infrared CO_2 analyzer and ancillary equipment. An analog-to-digital data storage and analysis system is presently being installed in the School of Public Health and Community Medicine's General Automation SPC-16 computer. Cabling to both laboratories will allow up to 15 separate instruments to be monitored by the system. Programs will be developed with other funds to compute such measurements as Cdyn, FRC, RV, R_L, FEV, MMFR, etc., from the incoming raw data. A teletype data terminal will be placed in one of the laboratories for communication with the computer.

The Department has available for our use a biochemistry laboratory, electron microscopy laboratory, and a fully-equipped industrial hygiene laboratory containing a mass spectrophotometer, X-ray spectrophotometer, infrared spectrophotometer, atomic absorption spectrophotometer, and four gas chromatographs.

Lawrence Livermore Laboratory

We plan to utilize an Anger positron scintillation camera and data acquisition and display systems located at the Lawrence Livermore Laboratory 100 MEV Linac facility (see Appendix I). The camera consists of two identical 16" diameter Anger scintillation detectors, each having a close-packed array of 37 photomultiplier tubes. The camera's output is sampled, digitized, and routed through a PDP-15 computer onto a high-speed drum storage device (capacity 3×10^6 scintillation events). All data are stored on magnetic tape which may later be analyzed using the laboratory's "Octopus" computer network. This computer network, consisting of nine major processors, has a total primary (core) storage capacity of

approximately 144 million bits and a secondary (rotating) storage capacity of approximately 45 billion bits [1] and will permit a variety of methods of data analysis and presentation. Programs have already been developed for the preliminary O_3 uptake work of November, 1972, (Appendix II) which allow three dimensional plots of the data (corrected for camera efficiency), as well as more standard data presentations (Appendix I). By mid-1975 we plan to have available programs for iso-activity contour plots of the data [2] and methods of determining V/Q ratios foras many as 300 1 cm^2, or larger, sites within the lung.

The tagged $^{13}N_2$ will be produced using the laboratory's 100 MEV Linac. Production of other positron emitting gases, such as $C^{15}O_2$, $^{11}CO_2$, $^{15}O_2$, and O_3^*, for future experiments, is also possible with the Linac facility.

A well-equipped vivarium with facilities for animal surgery, as well as numerous pieces of ancillary equipment (8 channel Grass biomedical recorder, scintillation detectors, etc.) will be available for the experiments. Technical assistance from in-house personnel in electronics, health physics, programming, and hazards control will also be available.

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COLLABORATIVE ARRANGEMENTS

Dr. Suetaro Watanabe, University of Utah Medical Center, will assist with the respiratory functional measurements at both the University of Washington and Lawrence Livermore Laboratory. During 1970-71, he collaborated with the PI, University of Washington, on other experiments utilizing O_3. (See Watanabe, Frank, and Yokoyama [1]). Dr. Watanabe also has experience with radioactive techniques applied to respiratory functional measurements [2,3].

Mr. Holub, Dr. McJilton, and the PI did preliminary experiments in November, 1972, with Mr. Paul Meyer and Mr. Ervin Behrin of LLL. The purpose of these experiments was to measure the penetration of radioactive O_3 into the lower airways and parenchyma. The results are summarized in Appendix II. A letter from LLL indicating their willingness to collaborate on this project is included in in Appendix IV.

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Appendix II

During November of 1972, a series of experiments were completed by Mr. Meyer and Mr. Behrin (LLL), and Dr. McJilton, Mr. Holub, and the P.I. (U of W) at LLL. The experimental plan was basically to expose anesthetized, mechanically ventilated beagles to alternating doses of $^{13}N_2$ and $^{15}O_2$ tagged O_3* in air and follow the uptake and washout of the gases. $^{13}N_2$ should show the normal distribution of ventilation for each dog and by comparison with the O_3* data, the relative sites of O_3 uptake should be apparent.

A large amount of preliminary work by LLL was necessary before these experiments could be completed. This work included: development of a method to produce $^{15}O_2$ tagged O_3* (Appendix III) and development of data-gathering and display programs for the Anger camera system (Appendix I). After the experiments were completed, additional time was spent by LLL developing data analysis and display programs for use with the LLL "Octopus" computer system [1].

Preliminary results are shown in figures 1 to 6.[1] The results do indicate that the distribution of $^{13}N_2$ (ventilation) is altered by O_3* exposure.

Later, more advanced computer display programs will enable us to produce contour plots of the data [2] as well as superimpose anatomical boundaries on the displays.

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[1] The figures are three dimensional plots of the data with the vertical axis being the relative activity at each site. Each square approximately represents an 1/2 x 1/2 inch area of the camera's field of view.