ENVIRONMENTAL HEALTH SCIENCES

HEARING

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON GOVERNMENT OPERATIONS HOUSE OF REPRESENTATIVES

NINETY-SECOND CONGRESS

SECOND SESSION

APRIL 24, 1972

Printed for the use of the Committee on Government Operations

U.S. GOVERNMENT PRINTING OFFICE
WASHINGTON : 1972

80-012 O

COMMITTEE ON GOVERNMENT OPERATIONS

CHET HOLIFIELD, California, *Chairman*

JACK BROOKS, Texas
L. H. FOUNTAIN, North Carolina
ROBERT E. JONES, Alabama
EDWARD A. GARMATZ, Maryland
JOHN E. MOSS, California
DANTE B. FASCELL, Florida
HENRY S. REUSS, Wisconsin
JOHN S. MONAGAN, Connecticut
TORBERT H. MACDONALD, Massachusetts
WILLIAM S. MOORHEAD, Pennsylvania
CORNELIUS E. GALLAGHER, New Jersey
WM. J. RANDALL, Missouri
BENJAMIN S. ROSENTHAL, New York
JIM WRIGHT, Texas
FERNAND J. ST GERMAIN, Rhode Island
JOHN C. CULVER, Iowa
FLOYD V. HICKS, Washington
GEORGE W. COLLINS, Illinois
DON FUQUA, Florida
JOHN CONYERS, JR., Michigan
BILL ALEXANDER, Arkansas
BELLA S. ABZUG, New York

FLORENCE P. DWYER, New Jersey
FRANK HORTON, New York
JOHN N. ERLENBORN, Illinois
JOHN W. WYDLER, New York
CLARENCE J. BROWN, Ohio
GUY VANDER JAGT, Michigan
GILBERT GUDE, Maryland
PAUL N. McCLOSKEY, JR., California
JOHN H. BUCHANAN, JR., Alabama
SAM STEIGER, Arizona
GARRY BROWN, Michigan
BARRY M. GOLDWATER, JR., California
CHARLES THONE, Nebraska
H. JOHN HEINZ III, Pennsylvania
RICHARD W. MALLARY, Vermont

HERBERT ROBACK, *Staff Director*
CHRISTINE RAY DAVIS, *Staff Administrator*
JAMES A. LANIGAN, *General Counsel*
MILES Q. ROMNEY, *Associate General Counsel*
J. P. CARLSON, *Minority Counsel*
WILLIAM H. COPENHAVER, *Minority Professional Staff*

INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE

L. H. FOUNTAIN, North Carolina, *Chairman*

ROBERT E. JONES, Alabama
BENJAMIN S. ROSENTHAL, New York
JOHN C. CULVER, Iowa
DON FUQUA, Florida
BILL ALEXANDER, Arkansas

FLORENCE P. DWYER, New Jersey
CLARENCE J. BROWN, Ohio
GUY VANDER JAGT, Michigan
JOHN H. BUCHANAN, JR., Alabama
GARRY BROWN, Michigan

EX OFFICIO

CHET HOLIFIELD, California

DELPHIS C. GOLDBERG, *Professional Staff Member*
JAMES R. NAUGHTON, *Counsel*
GILBERT S. GOLDHAMMER, *Consultant*

CONTENTS

APPENDIX

ENVIRONMENTAL HEALTH SCIENCES

MONDAY, APRIL 24, 1972

HOUSE OF REPRESENTATIVES,
INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE
OF THE COMMITTEE ON GOVERNMENT OPERATIONS,
Raleigh, N.C.

The subcommittee met, pursuant to call, at 9:30 a.m. in the auditorium of the North Carolina Department of Archives and History, Raleigh, N.C., Hon. L. H. Fountain (chairman of the subcommittee) presiding.

Present: Representatives L. H. Fountain, Don Fuqua, Bill Alexander, and John Buchanan.

Professional staff present: Dr. Delphis C. Goldberg, professional staff member; and Gilbert S. Goldhammer, consultant.

Mr. FOUNTAIN. The meeting will come to order, and the record will show that a quorum is present. Before proceeding with some preliminary remarks concerning the purpose of this hearing, I'd like to say it gives me a great deal of pleasure to introduce to the people of my home State the members of the subcommittee who are with us today. On my right are Congressman Fuqua of Florida and Congressman Alexander of Arkansas; on my left is Congressman John Buchanan of Alabama. They are all very able Members, not only of their respective committees, but also of the Congress. I am delighted they can be in Raleigh with us, in view of all the other demands on their time.

Although all of the members able to be present happen to be from the South, I'd like the record to show that a majority of the committee's 11 members are from other sections of the country.

The subcommittee's professional staff is represented here today by two highly competent men, Dr. Goldberg and Mr. Goldhammer. Dr. Goldberg has been with the subcommittee for some 16 years, so he and I have worked together for quite some time; and Mr. Goldhammer serves in an advisory capacity. Before joining the subcommittee, he served with the Food and Drug Administration on regulatory administration. He also teaches chemistry at Montgomery College in Maryland.

This is the second time, incidentally, that this subcommittee has held a hearing here in our capital city of Raleigh. On the previous occasion, in December 1957, we had the great honor of taking testimony from Gov. Luther Hodges and from other State and local government officials. Governor Hodges, as many of you know, is a great booster of the Research Triangle Park and has been instrumental in bringing many science-related industries to North Carolina. In fact, I think of him as the founder or the father of the Research Triangle.

We regret very much the inconvenience which the change of location of this hearing may have caused any of you here this morning. We did not learn until last Thursday that the courtroom in the Federal Building, which had been reserved, would not be available because it was needed for the continuation of a trial. The subcommittee sent out a press release announcing the change as soon as we obtained the use of this auditorium on Friday. However, that news release may not have reached some of you, or all of you.

For the benefit of those not familiar with the work of this subcommittee, I'd like to say that under the Rules of the House of Representatives, our parent Committee on Government Operations has the responsibility for studying the operations of Government activities at all levels, from the standpoint of economy and efficiency. This responsibility, as it relates to the Departments of Health, Education, and Welfare, Labor, and Agriculture, and a number of other Federal agencies, has been assigned to this subcommittee. The subcommittee also has been assigned the responsibility within the House of Representatives for studying relations between the Federal Government and the States and their political subdivisions. It is in connection with the subcommittee's oversight responsibilities for the Department of Health, Education, and Welfare that we are reviewing this morning the activities of the National Institute of Environmental Health Sciences.

The past few years have ushered in a new era in man's attitude toward his environment. This environmental awakening has brought marked changes in our social values, in our laws, and in our institutional arrangements—both governmental and private—for protecting the environment.

We Americans have been much more fortunate than the citizens of most nations, not only because of our enormous economic resources and productivity, but also ecologically because we have had an abundance of land and water for disposing of waste products. We were not very concerned until quite recently, about the use of our land, streams, and air for waste-disposal purposes. In fact, neither our industrial plants nor our governmental facilities ordinarily took into account the social consequences of the water and the air they polluted.

Those attitudes which were acceptable in an earlier period are no longer acceptable today. Our productivity and affluence in themselves contribute to the pollution which we seek to control. The public is demanding increased protection from a wide variety of environmental dangers involving, among other things, air, water, radiation, noise, toxic industrial chemicals, food additives, and pesticides. And the Congress, as well as State and local governments, are responding to these demands. The establishment of the National Institute of Environmental Health Sciences and of the Environmental Protection Agency are examples of the Federal response to this challenge.

The strong industrial growth and rapid technological change which have characterized the American economy have brought tremendous material benefits to the people of this Nation. However, in conjunction with population growth and accelerated urbanization, these trends have also increased the difficulty of maintaining a safe and healthful environment.

Earth Week, which was officially observed last week, is a reminder to the Nation that we must give serious thought to the environmental effects of economic progress, and that we must do whatever is necessary to minimize or eliminate any resulting health dangers.

This subcommittee has devoted a great deal of time during the past year to reviewing the activities of Federal agencies with respect to assuring the safety of food additives and of those drugs added to animal feeds which may carry over into the products we consume. The safety of our food is becoming of increasing concern to the American people as more chemicals are introduced into the food supply, intentionally as useful additives, or unintentionally from the soil and through processing.

In 1958, Congress passed the food additives amendment to the Federal Food, Drug, and Cosmetic Act for the purpose of assuring that chemicals used in or on foods would be subject to substantially the same safety requirements as apply to new drugs. Since this amendment became effective, thousands of chemical substances have been approved by the Food and Drug Administration for food use. Many of these are quite toxic and tolerances for their use have been established. Moreover, some food additives and chemicals used in animal feeds are suspected by scientists to have the capability of promoting cancer in man.

The subcommittee's investigation has sought to evaluate the effectiveness of the programs of the Food and Drug Administration and the Department of Agriculture for protecting the public from potentially unsafe food additives and medicated animal feeds. The subcommittee's hearings have focused special attention on the use of nitrites in meat and fish products and of diethylstilbestrol (DES) in the feed of cattle and sheep. DES, a synthetic female hormone, has been shown to cause cancer in laboratory animals and has been linked to a rare form of vaginal cancer found quite recently in a large number of young women whose mothers were treated with DES during pregnancy.

The subcommittee's investigation, which included 7 days of public hearings last year, has already produced a greater effort by the regulatory agencies to improve their liaison, testing methods, and enforcement procedures. It is my expectation and hope that this investigation, when it is completed this year, will result in substantially increased protection for the consumer, with respect to both food and drugs.

The agency within the Federal Government which has been given a major responsibility for conducting and sponsoring fundamental biomedical research in this general area is the National Institute of Environmental Health Sciences. The Institute, as I understand it, is particularly concerned with the adverse effects on human health of long-term exposure to low-level concentrations of biological, chemical, and physical substances. The work of the Institute is intended to provide a scientific basis for the protective and preventive measures taken by the regulatory agencies operating in the environmental field. This is an awesome responsibility for a relatively small agency, and it is the subcommittee's purpose to find out how this responsibility is being performed.

Those of us in the Congress from North Carolina were very proud when the Department of Health, Education, and Welfare decided to

locate this agency at the Research Triangle Park on land which the State gave to the Federal Government without charge for this important purpose.

I was happy to join all of my colleagues from North Carolina in encouraging the Congress to seriously consider that area for the Institute, and I am happy to note that the Institute was located in the Research Triangle, not on the basis of pressure from us, but on the basis of merit. It was shown to be a logical spot for the Institute, and I believe the Institute is widely regarded by the residents of this area as a welcome addition to the total life of the community.

I am pleased at this time to call upon Dr. David P. Rall, the Director of the National Institute of Environmental Health Sciences, for a report on the programs and progress of the Institute during the past 5 years. If Dr. Rall will come up, we will be glad to hear him.

Before you proceed, Dr. Rall, I would like to recognize Dr. Robert Marston, the Director of the National Institutes of Health, who is with us this morning. NIH is the parent agency of which Dr. Rall's Institute is a part. We understand that Dr. Marston will have to leave for Washington in about an hour.

We appreciate your being here for this hearing, Dr. Marston, and we will be pleased to hear whatever preliminary remarks you might wish to make before Dr. Rall proceeds with his statement.

STATEMENT OF DR. ROBERT MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Dr. MARSTON. Thank you very much, Mr. Chairman, and members of the committee. I will be brief, but I did want to say how pleased I am to be with you today. The National Institute of Environmental Health Sciences is the only Institute among the 10 National Institutes and six divisions of NIH which is located other than in Bethesda. In addition to the research institutes, of course, as you are well aware, we have the Bureau of Health Manpower Education, and the National Library of Medicine also.

The National Institute of Environmental Health Sciences has found North Carolina to be a hospitable area, both from the intellectual and scientific standpoint, as well as a pleasant place to live, which I believe, Dr. Rall, has made your job of recruiting the top scientists that are needed to carry out this work somewhat easier. The importance of the subject you have spoken to very well; but the fact that environmental problems are so important made it very easy for me in 1968 to make the decision to recommend that the Environmental Health Sciences Division, as it was called that time, be elevated to full Institute status, and that has been a very happy decision; it has worked out well with the development, as we will hear later today, of that Institute. I would close simply by calling to the committee's attention my belief that this Institute will have to develop in a somewhat different fashion than the other research institutes at NIH. The nature of the problem is a much broader one even than areas such as cancer or heart and lung disease, or infectious diseases. From our own operational standpoint, I have given Dr. Rall and his staff, encouragement,

and have given them the opportunity to exploit the full range of research opportunities among those in related areas in the Federal Government and outside the Federal Government in carrying out his work. I don't think that 10 years from now as one looks at this Institute that it will look the same as other Institutes, in program structure—not even in grants—because I think they will have to develop their in-house capability to a far greater extent than any of the existing Institutes in order to carry out the types of responsibilities that you have touched on in your comments and which Dr. Rall will speak to later. It is a young Institute; it is a small Institute; it is in a period of critical growth at present, and it is faced with perhaps the most important problems that face any of us in this world today.

I am pleased to be here and to meet with you. Thank you.

Mr. FOUNTAIN. Thank you very much, Dr. Marston. And for the benefit of those who will read the record—quite often they read a person's testimony but don't know too much about his background—I wonder if you would provide a description of your experience and training in this area.

Dr. MARSTON. Yes, sir.

(The information requested follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, NATIONAL INSTITUTES OF HEALTH

BIOGRAPHICAL SKETCH

Name: Robert Quarles Marston.

Position: Director, National Institutes of Health.

Birthplace and date: Toano, Va., February 12, 1923.

Education: B.S., Virginia Military Institute, 1943; M.D., Medical College of Virginia, 1947; B.Sc., Oxford University, 1949.

Experience: Director, National Institutes of Health, September 1968–present; Administrator, Health Services and Mental Health Administration, April-September 1968; Associate Director, National Institutes of Health, and Director, Division of Regional Medical Programs, 1966–1968; vice chancellor, The University of Mississippi, and Dean, School of Medicine, 1965–1966; director of the University of Mississippi Medical Center and dean, School of Medicine, 1961–1965; associate professor of medicine and assistant dean in charge of student affairs, Medical College of Virginia, 1959–1961; Assistant Professor of Bacteriology and Immunology, University of Minnesota, 1958–1959; Assistant professor of medicine, Medical College of Virginia, 1954–1957; assistant resident, Medical College of Virginia, 1953–1954; assistant resident, Vanderbilt University Hospital, 1950–1951; intern, Johns Hopkins University, 1949–1950.

Association memberships: Alpha Omega Alpha, Association of American Medical Colleges (Executive Council: 1964–1967), American Federation for Clinical Research; Society for Experimental Biology and Medicine, Tissue Culture Association; American Society for Cell Biology; American Association for the Advancement of Science; Association of American Rhodes Scholars; American Medical Association; American Public Health Association Fellow; Association of American Physicians.

Special awards, citations, or publications: Rhodes Scholar, 1947–1949; Markle Scholar, 1954–1959; honorary membership in the National Medical Association 1969; honorary membership in the American Hospital Association.

Mr. FOUNTAIN. Are there any questions from any members of the committee?

Thank you very much, Dr. Marston. We are delighted to have you with us.

Now, I believe, Dr. Rall, you have a prepared statement.

STATEMENT OF DR. DAVID P. RALL, DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Dr. RALL. Yes, sir, I do.

Mr. FOUNTAIN. Before you proceed with your statement, will you identify for the record the individuals accompanying you this morning and their respective positions.

Dr. RALL. Yes, sir, I will be delighted to introduce them. On my far left, Dr. Marston; Dr. Payne, the Deputy Director of the National Institute of Environmental Health Sciences; on my left, Dr. Hans Falk, Associate Director for Program; and on my right, Mr. George Kingman, the Executive Officer.

(The curriculum vitae of each of the above follows.)

CURRICULUM VITAE

Name: David Platt Rall.

Date and place of birth: August 3, 1926; Aurora, Ill.

Marital status: Married; two children.

Education: Public schools, Naperville, Ill.; B.A., North Central College, Naperville, 1946; M.S. (Pharmacology), Northwestern University, 1948; Ph.D. (Pharmacology), Northwestern University, 1951; M.D., Northwestern University School of Medicine, 1951.

Professional training: Internship; Second (Cornell) Medical Division, Bellevue Hospital 1952–53.

Positions held: 1947–1949: Baxter Fellow in Pharmacology, Northwestern University; 1949–1950: Assistant in Pharmacology, Northwestern University; 1950: Research Associate in Pharmacology, Northwestern University; 1953–1955: Senior Assistant Surgeon, USPHS; 1953–1955: National Cancer Institute, Laboratory of Chemical Pharmacology; 1955–1963: National Cancer Institute, Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch; 1955–1959: Surgeon, USPHS; 1958–1962: Lecturer in Physiology, The School of Medicine, George Washington University; 1958–1963: Head, Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch, National Cancer Institute; 1959–1963: Senior Surgeon, USPHS; 1962–1965: Editorial Board, Proceedings of the Society for Experimental Biology and Medicine. 1962–date: Member of Graduate Council, George Washington University; 1963–1969: Chief, Laboratory of Chemical Pharmacology, National Cancer Institute; 1963–1971: Medical Director, USPHS; 1964–date: Editorial Board, Cancer Research; 1966–1971: Associate Scientific Director for Experimental Therapeutics, National Cancer Institute; 1967–1969: Chairman, National Institute of General Medical Sciences, Pharmacology-Toxicology Review Committee; 1969–date: Editorial board, Pharmacological Reviews; 1970: Chairman, HEW Departmental Committee on Drug Research and Regulation; 1971– : Director, National Institute of Environmental Health Sciences, DHEW; 1971– : Assistant Surgeon General, USPHS.

Memberships: American Association for the Advancement of Science; Society of Experimental Biology and Medicine; American Society of Pharmacology and Experimental Therapeutics; American Association for Cancer Research; Washington Academy of Science; American Society for Clinical Investigation; Federation of American Societies for Experimental Biology; Society of Toxicology.

Research Interests: Comparative pharmacology; cancer chemotherapy; blood-brain barrier; blood CSF barrier; pesticide toxicology; drug research and regulation.

CURRICULUM VITAE

Name: William Walker Payne.

Date and place of birth: June 1, 1913; Calverton, Va.

Marital status: Married, three children.

Education: University of Virginia, B.S.E., 1935; University of Michigan, M.S.E., 1947; University of Pittsburgh, M.P.H., 1956; University of Pittsburgh, Sc.D., 1959.

Positions: 1935–1943: Engineer, Montgomery County, Md.; 1943–1948: Sanitary Engineer, Public Health Service; 1948–1954: Research Facilities Engineer,

National Cancer Institute; 1954–1962: Environmental Cancer Section, National Cancer Institute; 1963: Carcinogenesis Studies Branch, National Cancer Institute; 1963–1965: Deputy Associate Director, Field Studies, National Cancer Institute; 1966–1967: Deputy Scientific Director, Etiology, National Cancer Institute; 1967–Date: Deputy Director, National Institute of Environmental Health Sciences.

Memberships in professional societies: American Association for Cancer Research; American Academy of Sanitary Engineers; Conference of Federal Sanitary Engineers; American Industrial Hygiene Association; American Public Health Association.

CURRICULUM VITAE

Name: Dr. Hans L. Falk.

Date and place of birth: September 15, 1919, Breslau, Germany.

Citizenship: United States.

Marital status: Married, 1950, three children.

Education: April 1937: Graduated from high school, Gymnasium am Zwinger, Breslau, Germany; 1938–1940: University of London, London, Great Britain; 1942–1944: B.Sc. (First class honors in biochemistry), McGill University, Montreal, P.Q., Canada; 1944–1947: Ph.D. (Biochemistry), McGill University (Thesis: Synthesis of Corticosteroids and Spectrophotometric Studies of Steroid Hormones); 1957: One month course in Isotope Techniques, Oak Ridge Institute for Nuclear Studies, Oak Ridge, Tenn.

Brief chronology of employment: 1947–1952: Instructor, Department of Pathology, University of Chicago, Chicago, Ill.; 1952–1962: Adjunct Assistant and Associate Professor of Pathology, University of Southern California, Los Angeles, Calif.; 1962–1963: Head, Chemistry Section, Carcinogenesis Studies Branch, Field Studies, National Cancer Institute, NIH, Bethesda, Md.; 1963–1966: Chief, Carcinogenesis Studies Branch, Field Studies, National Cancer Institute, NIH, Bethesda, Md.; 1966–1968: Associate Scientific Director for Carcinogenesis, Etiology, National Cancer Institute, NIH, Bethesda, Md.; 1968–1971: Associate Director for Laboratory Research, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, N.C.; 1971–: Associate Director for Program, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, N.C.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

BIOGRAPHICAL SKETCH

Name: George M. Kingman.

Position: Executive Officer, National Institute of Environmental Health Sciences.

Birthplace and date: Ft. Leavenworth, Kans., December 25, 1929.

Education: B.S. Northwestern University, 1955.

Experience: Executive Officer, National Institute of Environmental Health Sciences, 1967 to present; Assistant Executive Officer, National Institute of Mental Health, 1963–67; Administrative Officer for Extramural Programs, National Institute of Mental Health, 1961–63; Budget Officer, National Institute of Mental Health, 1958–61; Budget Examiner, National Institute of Dental Research, 1958; Budget Examiner (trainee), National Institute of Neurological Diseases and Blindness, 1957–58; Management Intern, Division of Business Operations, 1956–57; private industry, 1955–56; military service, 1950–53.

Association memberships: American Society for Public Administration, the Academy of Political Science.

Special awards, citations, or publications: 1962—Department of Health, Education, and Welfare Candidate for William A. Jump Award; 1971—Department of Health, Education, and Welfare Superior Service Award.

Dr. RALL. Let me also welcome the members of the committee to North Carolina. As a very recent resident of this very lovely State, I find I am rapidly becoming an enthusiastic "Tarheel." I am delighted to have this opportunity to tell you about the programs and progress of the National Institute of Environmental Health Sciences. The first 5

years have been exciting and fruitful and we face the coming years with eagerness and certainty of continued progress. Let me begin by giving a brief summary of the Institute's short history.

HISTORICAL BACKGROUND

Following the Korean War, several Public Health Service advisory committees called attention to the fact that changing environmental factors would have an increasingly serious effect on human health. They recommended that the Public Health Service embark on major new research efforts in environmental health. The report of the committee chaired by Dr. Paul Gross of Duke University was specific. It recommended establishment of a major new organization: the National Environmental Health Sciences Center. This led first in 1961, to the appropriation of an initial $785,000 dollars for planning and construction of the center; second to the Surgeon General's decision in 1965 to establish within the NIH a Division of Environmental Health Sciences; and third to the leasing in 1966 of the first increment of laboratory space for the center in North Carolina's Research Triangle Park. Three factors led to the locating of the Division in the Research Triangle: First, the congressional mandate that the center be located at least 50 miles from Washington; second, the proximity of the three Triangle universities, and others in North Carolina, represented a superior resource; and third, a 509-acre site for construction of the full center envisioned by the Gross committee was made available to the Public Health Service at no cost to the Federal Government.

In recognition of the Division's program and organizational development, in January of 1969 HEW Secretary Cohen redesignated it as the National Institute of Environmental Health Sciences. Staffing has increased from a mere handful in June of 1966 to a projected 267 in June of this year; the budget has grown from $16 million in 1966 to more than $26 million in the current year; available space has been expanded from an initial 36,000 square feet to the nearly 90,000 square feet available today. Construction plans for the first increment of permanent, Government-owned facilities are expected to be completed next calendar year. And we will tell the committee more about the facilities as they tour the Institute this afternoon.

PROGRAMS

The program encompasses the study of environmental health science; that is, the study of the interaction of man with external noninfectious factors, both chemical and physical.

This study includes investigation of the effects of such factors on man as well as the mechanisms by which man can, through detoxification, protect himself from their deleterious effects. Our specific concerns include such diverse topics as pesticides, carcinogenesis (the production of cancer), microwaves, teratogenesis (the production of physical defects in the developing embryo), noise, radiation, occupational hazards, and mutagenesis (the induction of genetic damage).

The interdependencies and potential interactions of the various environmental factors have made it mandatory to describe the science

of environmental health research, and therefore the mission of the Institute, more broadly than any single discipline could encompass.

Thus, the primary goal of the NIEHS is to provide that information necessary to insure that the environment is as free as possible from dangerous concentrations of noxious agents or factors. Operationally, it seeks first to identify those agents or factors which are potentially noxious and then to assess the degree of their hazard to man.

We are as concerned with the underlying principles of action of environmental agents as we are with their sources and characteristics; we are as mindful of the long-term effects of low-level exposures as we are of the acute episodes of massive exposure; we are as interested in the "how" and the "why" of harmful effects as we are in the "what" of their causes.

Research on the development and refinement of testing procedures is also an important aspect of environmental health research. This category of research is becoming increasingly sophisticated, as all research is. The tests of the 1960's are inadequate for the 1970's, just as the tests of the 1970's will be inadequate in the 1980's. The end products of this research become the basis for the regulatory actions and control measures that will ultimately protect human health.

The primary focus of our research program is, of course, man. Most of the research, however, must be performed using laboratory test systems, including laboratory animals rather than man since proper ethical considerations properly prohibit the deliberate administration of noxious agents to man if there is no hope of benefit to that man.

Environmental health research must do more than simply provide interesting and important basic biomedical information. We need also to identify and quantitate those agents in the environment to which man is exposed. Thus the NIEHS' effort must be buttressed by efforts to identify agents that are entering the environment and by efforts to sample or monitor the environment for the presence of various agents. In this our sister agencies—especially those within the Environmental Protection Agency—provide vital and essential assistance.

Environmental health research may be viewed as the apex of a surveillance triangle. This apex consists of biological research related to the biological effects of the agents or factors, the mechanisms by which they may be disposed of or eliminated from the body, and the development of the necessary methodology to test the agents or factors for toxicity. This role I like to call toxicological surveillance.

At the base of the triangle are efforts on the one corner to identify all agents or factors entering man's environment, generally as a result of man's technology, and this I call technological surveillance. On the third corner are efforts to monitor man and his environment for the presence and concentration of potentially toxic agents or factors to which humans are exposed—environmental surveillance.

As a component of the NIH our approach to accomplishing our mission is similar to that of the other institutes. Three aspects of that similarity are especially important:

Our primary task is performing the basic biomedical research which I have described as being at the apex of the triangle;

Fulfillment of this task precludes our heavy involvement in the activities of the other agencies whose tasks encompass ecological, conservation, monitoring, or control technology responsibilities and whose activities represent the base of the triangle;

Our role vis-a-vis the control of environmental hazards is generally one of providing advice and assistance to the agencies (like EPA and FDA) whose major responsibilities include regulation and control.

We publicize the results of our research as do the other institutes and all basic research organizations; our vehicle of communication is more often the journal of science than the press release or institutional report. Consequently, our findings are subjected to scrutiny by peers before more widespread dissemination. Like all Institutes of NIH, we perform our mission primarily through the use of three mechanisms: Grants, contracts, and work performed in our own laboratories by our own staff. For the current (1972) fiscal year, we have allocated about $16 million for grant programs; about $2 million for contracts; and about $7 million for intramural, that is, in-house research.

As with other Institutes, ideas for specific programs arise from a variety of sources. Our scientists continuously review the literature of their specialties in order to discover new leads and gaps in basic knowledge which we might help to fill. We are also alert to requirements for research identified by other agencies, by congressional sources, and those resultant from public alarms or press coverage. There are more formal mechanisms of selection which can come into play as well.

MAN'S HEALTH AND THE ENVIRONMENT

You may be interested in seeing the fruits of one of our most ambitious—and I believe successful—efforts at employing one of these mechanisms. In 1968 my predecessor, Dr. Kotin, convened a Task Force on Research Planning in Environmental Health Science. Drs. Norton Nelson of New York University and James Whittenberger of Harvard cochaired the task force and supervised preparation of a very exhaustive document summarizing its recommendations. That document, entitled "Man's Health and the Environment—Some Research Needs," was published in March of 1970. Within its nearly 260 pages is a very comprehensive exposition of the full scope of needs for research. We rely upon its recommendations as one important guide to planning, although we recognize that full implementation of its suggestions will take many years and far greater resources than can be made available at the present time.

Copies of the report have been provided to the committee.

Incidentally, I have noted in my visits with officials of other environmental programs how widely known this report has become. In addition, the report has formed the basis for several reviews of Federal environmental health research. It apparently is as useful to others as it is to us.

PRINCIPLES OF OPERATION

I hope that this gives some idea about the sources for content of our programs. Certain very important principles are applied in order to insure that our selections among the many opportunities for use of our limited resources are good ones.

The first of these principles is that our society desires constant and immediate access to the fruits of advanced technology along with assurance that the risks of such access will not outweigh the benefits and that the fruits will not be poisoned.

Second, maximum protection of the public health demands that the less we know about the health effects of a given product, the more stringent and conservative must be the standards regulating its use. Conversely, the more we know, the greater is the likelihood that the standards can be liberalized.

Finally, we recognize that science rarely discovers absolutes, that there is room for a heterogeneity of opinion among experts, and that consequently we must listen outside of the scientific community as well as within it in order to arrive at sensible resolutions of environmental issues.

These key principles, inputs from other Government agencies, and suggestions from advisory and congressional sources, all are combined in developing an optimum mix of a program to be performed within available resources.

PROJECT EXAMPLES

The actual programs which result from these planning operations are, as you might imagine, many and varied. I would like very quickly to list some representative projects and then to go into greater detail about several which we think are particularly important.

We have devoted major resources to the study of a full spectrum of pesticides and their metabolic products; we have gone deeply into the mechanisms of action and metabolic fate of numerous trace metals and their compounds; we have carefully examined many of the hydrocarbons and their reaction products; we have examined the disposition and effects of polymer dusts, beryllium, asbestos, and fiberglass; and we are launching important investigations into the health effects of such physical factors as microwaves, alpha radiation, and noise.

We are starting a major new effort concentrated on vastly increasing our knowledge and understanding of mutagenesis—genetic alterations—which could result from many types of environmental exposures. Additionally, we are improving our ability to react to requirements for brief ad hoc projects needed to supply information essential to unanticipated regulatory decisions of high priority.

In pursuit of activities of the latter sort, we have been fortunate enough to be able to call upon experts on our staff for short periods of time to fulfill requests for exploratory research on adventitious problems of an immediate nature. We have in fact done this in the cases of 2,4,5-T (2,4,5-trichlorphenoxyacetic acid) and NTA (nitrilotriacetic acid), and also in investigations of babyfoods suspected of high nitrite content and household detergents suspected of unusual irritation characteristics. Projects of this type often become topics of widespread interest and discussion, though sometimes, however, they yield negative results (as was the case with the babyfood study) and actually lead to a quieting of public outcry.

We welcome these opportunities in which we can contribute to the resolution of immediate problems without losing sight of the long term research which is vital to avoiding future problems.

Two of the programs in which we take special pride are programs which don't appear on organizational charts and which might not even appear to the casual observer to be unified. The first is just beginning to take form, the second is already supplying useful and important results.

NEW TESTING METHODS

As one might imagine, one of our greatest needs is to have available a series of rapid, accurate, economical, and effective methods for testing new chemicals and chemicals nominated for more widespread use. Chemical products are perhaps the most significant category of technological innovation available to the public. Indeed it has been estimated that some 2,000 new chemicals are developed annually and that 300 to 500 of these will significantly come in contact with man.

As I mentioned earlier, however, testing methods must change in order to meet our changing needs. Current testing methods have serious shortcomings; they involve use of animals whose similarity to man is questionable; they require speculative alteration of dose levels, leaving doubt in the minds of some about their pertinence to man; they involve intolerable time intervals for completion; and they are expensive, often prohibitively so. To resolve these problems we are actively pursuing research directed towards:

Development of better laboratory animal models and better characterization of the models we now have;

Improved statistical and analytical techniques;

Refined instrumentation; and

Expanded information about the relationships of *in vitro* (test tube) testing to *in vivo* results (that is, within the living body).

EXAMPLES

Several examples of these activities are underway in separate NIEHS projects which together encompass a program. One of these is the characterization and breeding of the Virginia opossum for use as a research model. This effort has great potential because of the fact the opossum provides a unique opportunity for observation of the young developing during gestation. This is because very early in the development of baby opossums—12 days after conception when they are about ¼ inch long—they migrate from the uterus and attach themselves to their mother's breasts for the balance of gestation for an additional 45–50 days. Thus during most of their embryonic development they are external and available. Thus, the effects on offspring of compounds fed to their mothers or directly fed to the babies can be observed as they take place. This is a particular advantage in studies of teratogenesis or production of physical defects in the developing embryo, which is one of our greatest concerns.

Another project involves development of a device to sense and measure microwave dose levels without the device itself becoming a part of the effects measured. We have under contract a project for design of a physical model of the lung which will enable accurate determination of the deposition of inhaled pollutants. Other activities are underway both in-house and on contract which will enable more accurate,

safe, and rapid detection of mammalian mutagenesis than is now possible.

All of these projects and others can be considered together as a significant contribution to the essential development of improved test systems. This is one area we plan to expand as resources become available.

METHYL MERCURY PROGRAM

The second program of major interest is one directed toward increasing our understanding of methyl mercury toxicity in man. You will recall that mercury was in the news last year because of the realization that the relatively safe elemental and salt forms which are widespread in the environment can be converted in nature to the methylated form, which is highly toxic.

The source of our pride, however, is the effectiveness with which we have been able to assemble a multidisciplinary team to thoroughly consider the body's reactions to methyl mercury ingestion:

Pathologists and veterinarians are examining in animal models, at both the gross and molecular levels, the pathologic changes from ingestion of the compound to determine fundamental mechanisms of action in brain, kidney, liver, spleen, and other organs and to relate blood concentration of the compound to toxicity;

Biochemists are studying the effects of methyl mercury on cell components and enzyme systems; and

Pharmacologists are studying the effects of the compound on fetal development in experimental animals.

All of these efforts seek methods for earlier diagnosis and possible reversal and repair of what today are the inevitable and dreadful results of methyl mercury ingestion.

The results of this program, now underway less than 18 months, are most gratifying:

An effective laboratory animal model system has been developed;

Evidence has been found which indicates that methyl mercury interferes with protein synthesis in rats; and

It has been demonstrated that the compound interferes with enzyme induction, thereby upsetting crucial natural detoxification processes and rendering the victim more susceptible to other normally harmless substances.

Much of what we learn in these studies can be of great value in gaining understanding of other important environmental compounds as well.

RELATIONSHIPS WITH OTHER PROGRAMS

I spoke earlier about the triangle which constitutes a representation of environmental health research. As indicated, our mission is to exercise responsibility primarily at the apex—concern with research on the biomedical effects of environmental exposure. We are equally interested in the maintenance of close, continuing, and effective relationships with those programs whose responsibilities interface with ours at the base of the triangle.

We devote considerable effort to nurturing these vital relationships. Through the first few years we did this by maintaining continuing

person-to-person contact with the control and research programs of the PHS, the Department of Agriculture, and the Interior Department. The exchange of information was deliberate and productive, but relatively informal. During that time, however, environmental programs and environmental aspects of others programs have proliferated and expanded. Recognizing this difficulty and the importance of effective liaison, the Office of Science and Technology and the Council on Environmental Quality asked us earlier this year to help establish and chair on their behalf a more formal ad hoc committee on environmental health research. Illustrating the pervasiveness of programs with environmental health aspects, this group has membership from nearly every executive agency. Directors of the programs which are most directly impinging on environmental concerns are the usual representatives on the committee, and our expectations are that the endeavor will result, in the final analysis, in the improved utilization of Federal resources available for environmental research.

In addition, NIEHS staff frequently provide assistance in efforts directed toward the resolution of pressing environmental health problems. For example, we are or were represented on: the HEW Secretary's Commission on Pesticides (Mrak Commission); the Secretary's Pesticide Advisory Committee; the National Advisory Committee on Oceans and Atmosphere; the DDT Advisory Committee to the EPA; and the Interagency Uranium Mining Task Force, among many others. We are also regularly consulted by control agencies during their preparation of standards about which we may have knowledge. Needless to say, the consultations are two-way and we find ourselves regularly seeking advice from other agencies in the formulation of our own program plans as well.

PCB'S CONFERENCE

Last December we convened a conference on research into PCB's (polychlorobiphenyls) in cooperation with several other agencies and we will be publishing the proceedings very shortly. This conference was unusual in that we invited all segments involved: industry, academia, Federal and private research, and representatives of the press.

I hope I have made evident the pleasure and pride I experience in discussing the NIEHS. Without difficulty I could continue to express my pleasure and pride for the balance of this hearing. Instead, I think you might prefer to pose questions of your own. Again, I thank you for the opportunity of discussing our programs, and I will be delighted to answer any questions.

Mr. FOUNTAIN. Thank you, Dr. Rall, for a very informative statement. Before the subcommittee begins questioning on your testimony, I'd like to ask if any of your senior scientists care to supplement anything you have said at this point.

Dr. PAYNE. Not right now. We will have more to say this afternoon.

Mr. FOUNTAIN. During the course of the tour?

Dr. PAYNE. Yes, sir.

Mr. FOUNTAIN. Before asking questions, I'd like to yield to Congressman Buchanan for any questions he might have at this time because he has to leave early.

Mr. BUCHANAN. Thank you, Mr. Chairman. Let me say first that it is a pleasure to be here in North Carolina. I appreciate the chairman's leadership in setting up this hearing and your presence here, Doctor, this morning, as well as the work of your Institute.

The chairman, in his opening statement, said, and I concur, "Our productivity and affluence in themselves contribute to the pollution which we seek to control." It seems to be an irony of our time that the very technology which has caused us to keep at least the early lead in space and to place man's footprints on the moon has at the same time also created problems for man's survival and great problems of environmental quality here on earth; and it is my profound hope that you can find the ways to combat the pollution and the harmful influences that this technology has helped create without sacrificing civilization in the process. I would hope that you are basically optimistic about our ability to get that job done, Doctor.

Dr. RALL. I am a very optimistic person.

Mr. BUCHANAN. Doctor, specifically, from your prepared statement, I note on page 11 your discussion of the relationship—you mentioned the relationship between test tube testing to results within the living body; *in vivo* and *in vitro*; is that correct?

Dr. RALL. Absolutely.

Mr. BUCHANAN. What is the current status of *in vitro* tissue culture tests and how reliable is this method for testing carcinogenesis in human tissue?

Dr. RALL. There have been a number of tests involving *in vitro* cell culture transformations; tests in which you add suspected carcinogens and follow the developing tissue culture cells to see if they undergo what's called malignant transformation. These tests are just becoming standardized, and the next step then is to carefully test a variety of known carcinogens and compounds which are known, as best we can tell, not to be carcinogens. This process is just about to start right now, and I would hope within a year or two we will have a very good idea as to whether these tests would give us a quick presumptive screening type answer as to whether a compound is likely to be carcinogenic or not. One problem with these tests is related to the fact that many carcinogens are actually made in the body. The compound that's administered is perfectly safe, but the metabolic processes of the body convert it into a more toxic compound which is in fact carcinogenic. One of the major efforts then will be to build some sort of metabolic system into these *in vitro* tests. Dr. Falk, would you care to elaborate on this?

Dr. FALK. Yes, the chemicals on test that are put into a tissue culture system, as mentioned before, are often not the true carcinogenic compounds, that we have to deal with. This represents a problem because the tissue culture cell has no way of changing it to the true carcinogen. We may thus at times miss very important chemicals which are effective transforming agents. On the other hand, the realization of this difference in effectiveness gives us a chance to distinguish between those chemicals that are carcinogenic per se and those that have to be metabolized first. As a secondary test system it therefore has an additional advantage in the further elucidation of the nature of the chemical in question, i.e., whether it is a carcinogen or a precursor.

Mr. ALEXANDER. I have a question as a followup to that, if I may. Dr. Rall, you said that the tests of the sixties are inadequate for the seventies, and the seventies for the eighties; are the tests for carcinogenicity, as practiced today, adequate, in your opinion?

Dr. RALL. Yes, as practiced today, as recommended by the experts from the Cancer Institute and their advisory committees. This includes use of two species of animals, males and females, and an adequate number of test animals in each group and enough different dose levels to get up to one that is fairly near the maximum tolerated dose. These tests have only been used in the last few years. The typical carcinogenicity test of 10 years ago utilized one strain of animals, relatively few animals, and was not a lifetime test at all, so this, I think, is a problem. Many of the compounds we are considering today were tested by the simpler, old-fashioned tests using only rats.

Mr. ALEXANDER. What about the tests for mutagenicity? Do you consider them adequate as well?

Dr. RALL. I think the tests as of today for mutagenicity are not adequate. One of our major efforts this year and next year will be to set up a Mutagenesis Branch, and I hope this Branch will provide great assistance, will provide more and better development of mutagenesis tests.

Mr. BUCHANAN. One more general question along this line. There are times in the conducting of our hearings that I almost come to the conclusion that a large enough dose of practically anything given to a rat will become toxic or carcinogenic. Just basically, or broadly, where a test reveals a massive dose of a substance is apparently associated with the development of cancer in a rat, how good is this evidence toward the establishment of carcinogenicity of this in very small doses in a human being?

Dr. RALL. That's quite a question. First, any compound, if given in large enough doses, will be toxic—not carcinogenic but toxic—and I think that's important as sort of a starting fact. Second, how many compounds are carcinogenic. Well, I think the best evidence on that question comes from the study that Dr. Falk initiated some years ago with Bionetic Research Laboratories, and I probably will get the numbers wrong. They tested about 130 industrial pesticides in two strains of mice for carcinogenicity. These were lifelong studies and quite well done. Of these 130, about 15 were clearly positive for carcinogensis. About 15 were borderline, and the rest were negative. So I think this will give you a rough order of magnitude as to what the likelihood will be that any one will be carcinogenic. But this really is not answering the question what it means when a very large dose of a compound is given and causes toxicity in an animal. Let's look at this. There are problems, as we all know, in extrapolating animal data to man. If man is more susceptible than the animals then we can be in trouble, and so this, I think, is one reason why I think people try to use very large doses. Second, the very large number of people in the United States that can be exposed to any compound that has widespread distribution. As you know, we all carry DDT, about five parts per million, we carry about that much PCB, and recently it appears that we carry a fair amount of phthalate esters. So when 200 million people are exposed, it's hard to project from results of 50 or 100 rats exactly what's going to happen.

Most scientists seem to be somewhat conservative when it comes to human health so they feel a very large dose is appropriate in safety testing. Now, the other problem is the heterogeneity of the human species. We are biologically very heterogeneous. The best example of this is a study of this some years ago when a series of patients were given the same dose of a tranquilizing agent—imipramine, as I remember—and this dose was continued for a number of days, and then the plasma level, the concentration of the drug was determined in the plasma; in this group of about 50, the plasma varied about 50-fold from the lowest to the highest. Now, the very highest plasma concentrations were in the people most susceptible and they were about 30 times as susceptible as the low level. So in human beings, the important thing is paying attention to those very high doses.

Mr. BUCHANAN. Thank you.

Mr. FOUNTAIN. We will ask if Mr. Fuqua has any questions next; but before doing so, I'd like to ask you, Dr. Rall, just one question supplementing what Congressman Buchanan was asking about. Is a carcinogen carcinogenic at any dose, no matter how small?

Dr. RALL. I don't know. I think this is one of the most important questions we have to study and find out about. I am not sure we can do it directly by the so-called megamouse experiment where you look at thousands and thousands of mice at once, because these mice will be genetically very homogeneous—all the same strain, you know, just as similar as they can be—whereas, as I suggested earlier, man, the species we are concerned about—I am concerned about—is a very heterogeneous species. I think the answer to that will come from research, first, on what I call the pharmacology of the agent. Now, pharmacology has a drug implication, and I don't mean this. I mean, how is it absorbed; how is it excreted from the body, metabolized; and then after that, what is its mechanism; how does it work on molecular terms? It's this sort of study I think that will finally let us answer the very important question you posed.

Mr. FOUNTAIN. Mr. Fuqua.

Mr. FUQUA. Thank you, Mr. Chairman, and let me say that it is a pleasure for me to be in North Carolina and the State capital. I have been a great admirer of your State for a long time and had the benefit of football and basketball at the great universities in this State inflicted upon little schools in my district and vice versa during the past basketball season. But it is a pleasure to be here, and particularly because it is the home State of our chairman who has played a tremendous role in this health-related field. I think his praise, and the leadership that he has taken in this field, has been undersung.

I want to say also that I was quite surprised in your statement that scientists here go opossum-hunting to get their samples they use. I assume you get the enjoyment out of it that many people in my district still do.

I am fascinated by the very interesting and important work you are doing at the Institute and I am looking forward to visiting it this afternoon.

Dr. Rall, in December of 1970, I think it was, the Surgeon General of the Public Health Service, speaking in the environmental area, asked the detergent manufacturers not to market NTA as a substitute for phosphates in laundry products. This past spring or last summer

sometime, and in the fall also, there were comments in the press relating to the harmful effects that NTA may have on young children and the causing of birth defects, and so forth. Was the action of the Surgeon General taken because of research findings by your Institute concerning the dangers of NTA?

Dr. RALL. The initial studies in leading up to the decision in December of 1970, which cast some doubt on the eventual safety of NTA, were performed by our Institute; yes.

Mr. FUQUA. What were your findings in this connection?

Dr. RALL. Using teratology experiments in mice and rats, we found that certain combinations of heavy metals—mercury and cadmium in particular—with certain doses of NTA—could cause an apparent increase in birth defects and fetal mortality. As these were studies done on a sort of a firefighting, crash basis, the answers were looked for in a very short time line. These studies, I think, pointed out the problems of an agent which can tie up heavy metals and perhaps alter the toxicity of those metals, becoming widely dispersed in the environment. Now, later, when much more careful studies were performed, it turned out that although our results were repeated by industry and other groups, they probably—the experiments—were probably unrealistic; that is, there would be very, very much less NTA present in the environment than had been used in these studies. So the concerns about NTA in terms of specific problems of teratogenesis were resolved, but, unfortunately, other problems arose during the course of these and other studies. The primary problems under consideration now, and a problem which is largely being handled by the National Cancer Institute, is whether or not NTA is potentially carcinogenic.

Mr. FUQUA. So you have not made any conclusive findings; you are still looking?

Dr. RALL. That's right.

Mr. FUQUA. Have any of these findings been published?

Dr. RALL. I don't think so; no. No, they have not.

Mr. FUQUA. Would you object to submitting them to the subcommittee and making them a part of this record?

Dr. RALL. Oh, no; not at all.

(The information referred to follows:)

SUMMARY

NTA has a low acute and chronic oral toxicity. Emesis in dogs and monkeys was caused by oral administration of large single doses. Lifetime exposure to 0.15 to 0.5 percent in the diet of rats caused renal damage; this was not apparent at 0.03 percent NTA in the diet. After oral administration NTA was rapidly and completely absorbed in the rat and dog. In the rat NTA was excreted fairly rapidly in the urine and was not metabolized. In rabbit, monkey, and man oral absorption was incomplete. This ranged from 5 to 12 percent in four clinical subjects. There appears to be no deleterious effects of NTA on bone composition or breaking strength. Although one study showed a very slight positive effect of high doses of NTA in the dominant lethal test for mutagenesis, other studies at high doses showed no effects. Under certain specialized experimental conditions NTA can be shown to increase maternal and fetal toxicity when given with cadmium, and can increase the extent of severe fetal edema and cleft palate in rats given NTA and methyl mercury. There are however other experimental situations in which NTA appears to protect against cadmium and methyl mercury toxicity.

DAVID P. RALL, M.D., Ph. D.,
Director, National Institute of Environmental Health Sciences.

STATISTICAL SUMMARY: TERATOLOGY OF ORAL ADMINISTRATION OF NTA TO RATS—
D. W. GAYLOR, M. D. HOGAN

BIOMETRY BRANCH, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES,
SEPTEMBER 8, 1971

1. (Tables 1 and 1a) The addition of the P. & G./IRDC study and switching of severely edematous (terminal) fetuses from abnormal to dead fetuses in the biotest studies, in order to be more consistent with the classifications used in other studies, result in fewer increases in anomalies than indicated earlier due to NTA. The biotest study in cysteine showed more severe edema among the NTA treated animals at the highest dose level (8 mg./kg. MeHgCl). There is no pattern for internal anomalies with the addition of NTA to MeHgCl (figure 1).
2. (Tables 1b and 1c) There is a consistent increase in the occurrence of cleft palates with NTA at the high dose level of 8 mg./kg. MeHgCl.
3. (Table 2) There is no consistent effect of NTA on fetal mortality with MeHgCl (Fig. 2).
4. (Table 3) With MeHgOH only one study was conducted. No patterns can be established but the data are suggestive of reduced maternal mortality with NTA.
5. (Table 4) With subcutaneous administration of $CdCl_2$, these data suggest the possibility of reduced maternal mortality with NTA.
6. (Table 4a) With administration of both $CdCl_2$ and NTA subcutaneously an increase of maternal and fetal mortality was observed with NTA.
7. (Tables 5 and 5a) No deleterious patterns appear for NTA with oral administration of $CdCl_2$ for fetal mortality or total anomalies. In the P. & G./IRDC study, there is an increase in bladder anomalies with 0.1 mg./kg. NTA added to 4 mg./kg. $CdCl_2$, but fewer bladder anomalies occurred with 20 mg./kg. NTA.
8. (Figures 3 and 4) There is no pattern for internal anomalies or mortality with the addition of NTA to $CdCl_2$.
9. (Table 6) These data indicate a tendency for NTA alone to result in fewer soft tissue anomalies. However, these reductions are offset by increases in soft tissue anomalies obtained in other studies (Tables 1a and 5) with NTA alone.

SUMMARY

While there are instances of increases in fetal anomalies or mortality associated with the addition of NTA in these studies, these are offset by decreases resulting in soft tissue anomalies obtained in other studies (Tables 1a and 5) with and feticidal effects of mercury and cadmium, although the addition of NTA does not appear to enhance their activity.

TABLE 1.—MeHgCl FETAL ANOMALIES (CD RATS TREATED DAYS 6 TO 13)

[In percent]

MeHgCl oral mg./kg.[1]	NTA oral mg./kg.	Biotest (6 to 24) cysteine			Biotest (6 to 24) BSA			NIEHS experiment I total	NIEHS experiment II total	P. & G.		P. & G. IRDC[3] soft
		External[2]	Skeletal[2]	Internal[2]	External[2]	Skeletal[2]	Internal[2]			Skeletal	Internal	
2	0	0	38	36	0	58	14	0				
4	0	1	64	18	0	81	16	0	5	82	78	82
6	0	6	79	38	22	99	46	30	26			
8	0	44	100	79	21	100	72		68			
2	10	0	30	11	0	55	24					
4	20	0	68	14	2	65	14	11	6	96	88	60
6	30	0	86	33	6	96	35	38	39			
8	40	33	100	72	52	97	78	60				

[1] Doses of Hg for P. & G. studies.
[2] External, skeletal, and internal anomalies.
[3] CD rats treated days 6 to 14.

TABLE 1a.—MeHgCl FETAL ANOMALIES AND MORTALITY (CD RATS TREATED DAYS 6 TO 14; P. & G./IRDC)

MeHgCl oral mg./kg.[1]	NTA oral mg./kg.	Soft tissue anomalies (percent)	Fetal mortality (percent)
0	0	22	12
0	.1	27	3
0	20.0	37	8
.02	0	16	4
.02	.1	26	9
.02	20.0	38	2
.20	0	34	6
.20	.1	34	7
.20	20.1	21	5
4.00	0	82	12
4.00	.1	43	3
4.00	20.1	60	7

[1] Dose of Hg.

TABLE 1b.—MeHgCl: PERCENT CLEFT PALATES (CD RATS TREATED DAYS 6 TO 13)

MeHgCl oral mg./kg.[1]	NTA oral mg./kg.	Biotest cysteine	Biotest BSA	NIEHS I	NIEHS II	P. & G.	P. & G./IRDC[2]
2	0	0(0/92)	0(0/97)	0(0/39)			
4	0	0(0/112)	0(0/102)	0(0/79)	0	3(5/153)	0(0/122)
6	0	0(0/110)	0(0/96)	1(1/82)	0		
8	0	0(0/57)	0(0/51)	0(0/9)	12(2/17)		
2	10	0(0/89)	0(0/114)				
4	20	0(0/99)	0(0/89)	0(0/44)	0(0/89)	0(0/100)	0(0/97)
6	30	0(0/112)	0(0/94)	17(5/29)	0(0/58)		
8	40	8(5/64)	12(5/41)	30(7/23)			

[1] Doses of Hg for P. & G. studies.
[2] Treated days 6 to 14.

Note: ( ) Proportion of fetuses with cleft palates.

TABLE 1c.—MeHgCl: PERCENT OF LITTERS WITH CLEFT PALATES (CD RATS TREATED DAYS 6 TO 13)

MeHgCl oral mg./kg.[1]	NTA oral mg./kg.	Biotest cysteine	Biotest BSA	NIEHS I	NIEHS II	P. & G.	P. & G./IRDC[2]
2	0	0(0/19)	0(0/19)	0(0/4)			
4	0	0(0/21)	0(0/20)	0(0/8)	0(0/6)	11(2/19)	0(0/14)
6	0	0(0/21)	0(0/20)	12(1/8)	0(0/8)		
8	0	0(0/13)	0(0/12)	0(0/1)	50(1/2)		
2	10	0(0/19)	0(0/20)				
4	20	0(0/17)	0(0/18)	0(0/4)	0(0/8)	0(0/13)	0(0/12)
6	30	0(0/20)	0(0/18)	33(1/3)	0(0/7)		
8	40	18(3/17)	25(3/12)	100(3/3)			

[1] Doses of Hg for P. & G. studies.
[2] Treated days 6 to 14.

Note: ( ) Proportion of litters with cleft palates.

TABLE 2.—MeHgCl FETAL MORTALITY (CD RATS TREATED DAYS 6 TO 13)

MeHgCl oral mg./kg.[1]	NTA oral mg./kg.	Biotest (6/24) cysteine[2] (percent)	Biotest (6/24) BSA[2] (percent)	NIEHS expr. I (percent)	NIEHS expr. II (percent)	Procter & Gamble (percent)	P. & G. IRDC[3] (percent)
2	0	3	4	2			
4	0	4	6	7	5	4	12
6	0	7	17	5	31		
8	0	48	66	89	88		
2	10	7	6				
4	20	6	2	5	3	6	7
6	30	4	6	53	35		
8	40	61	69	68	100		

[1] Doses of Hg for P. & G. studies.
[2] Includes severely edematous fetuses.
[3] CD rats treated days, 6 to 14.

TABLE 3.—MeHgOH (CD RATS TREATED DAYS 6 TO 19; BIOTEST 6/7)

MeHgOH oral mg./kg.	NTA oral mg./kg.	Maternal mortality (percent)	Fetal mortality[1] (percent)	Anomalies		
				External (percent)	Skeletal (percent)	Internal (#/fetus)
1.5	0	0	5	0	42	0
3.0	0	0	9	3	91	0.40
4.5	0	38	100			
6.0	0	57				
8.0	0	100				
1.5	9.4	0	6	1	51	.30
3.0	18.9	0	7	0	75	.26
4.5	28.4	19	48	16	94	.78
6.0	37.8	0	79	4	81	.60
8.0	50.3	100				

[1] Includes severely edematous fetuses.

TABLE 4.—$CdCl_2$ SUBCUTANEOUS (CD RATS TREATED DAYS 6 TO 19)

Biotest (6/24) NaCl							Biotest (6/24) cysteine					
$CdCl_2$ mg./kg.	NTA mg./kg.	Anomalies (in percent)			Fetal mortality	Maternal mortality	$CdCl_2$ mg./kg.	NTA mg./kg.	Anomalies (in percent)			Fetal mortality	Maternal mortality
		Skeletal	External	Internal					Skeletal	External	Internal		
2	0	34	0	25	4	0	4	0	28	0	27	15	0
4	0	46	6	34	5	11	4	0	59	1	33	13	0
6	0	92	2	40	56	28	6	0	79	0	32	65	6
8	0	83	0	35	64	39	6	0	82	4	10	51	42
2	10	47	1	16	8	0	4	50	55	0	12	7	0
4	20	70	1	12	14	0	4	125	51	0	20	22	0
6	30	85	0	5	60	6	6	75	66	13	35	35	0
8	40	62	0	5	74	17	6	188	100	0	14	54	5

TABLE 4a.—$CdCl_2$ AND NTA BOTH ADMINISTERED SUBCUTANEOUSLY

[Figures in parentheses indicate number of litters]

Compound	NIEHS			Biotest (7/5)		
	Dose mg./kg.	Percent maternal mortality	Percent fetal mortality	Dose mg./kg.	Percent maternal mortality	Percent fetal mortality
$CdCl_2$	2	0	4 (9)	2	0	6(14)
$CdCl_2$	4	0	5(11)	4	0	15(13)
$CdCl_2$	6	0	9(11)	6	7	32(14)
$CdCl_2$	8	0	55 (2)	8	80	100 (2)
$CdCl_2$+NTA	2+10	10	9 (7)	2+10	5	5(21)
$CdCl_2$+NTA	4+10	43	53 (7)	4+20	0	100 (1)
$CdCl_2$+NTA	6+10	100	----------	6+30	92	----------
$CdCl_2$+NTA	8+10	100	----------	8+40	100	----------

TABLE 5.—$CdCl_2$ ORAL (CD RATS)

$CdCl_2$ mg./kg.[1]	NTA mg./kg.	Procter & Gamble (days 6 to 13) (in percent)			Procter & Gamble/IRDC (days 6 to 14) (in percent)		
		Fetal mortality	Anomalies soft	Anomalies skeletal	Fetal mortality	Anomalies soft	Bladder anomalies
0	0	7	33	19	4	11	3
0	.1	----------	----------	----------	1	20	6
0	20.0	9	16	22	3	20	8
0.01	0	----------	----------	----------	7	27	7
0.01	.1	----------	----------	----------	4	14	9
0.01	20.0	----------	----------	----------	1	16	4
1	0	----------	----------	----------	6	24	16
1	.1	----------	----------	----------	2	20	11
1	20.0	----------	----------	----------	2	35	7
4	0	7	21	27	9	45	17
4	.1	----------	----------	----------	3	55	39
4	20.0	9	21	18	2	36	12

[1] Dose based on Cd.

TABLE 5a.—$CdCl_2$ ORAL (CD RATS DAYS 6 to 19, BIOTEST 7/5)

$CdCl_2$ mg./kg.	NTA mg./kg.	Maternal mortality (percent)	Fetal mortality (percent)	Anomalies (percent)		
				External	Skeletal	Internal
20	0	5	3	0	25	31
40	0	0	10	23	50	22
60	0	12	23	9	52	46
80	0	28	38	16	70	45
20	62	0	7	0	40	32
40	125	0	12	2	33	42
60	188	0	6	2	32	24
80	250	0	9	1	39	30

TABLE 6.—P. & G. MIAMI VALLEY LABS (CD RATS)

Na_3 NTA in diet (percent)	Generation	Fetal mortality (percent)	Soft tissue anomalies (percent)
0	F_1	7	25
0	F_2	3	16
Continuous:			
0.1	F_1	6	24
0.1	F_2	14	6
0.5	F_1	14	16
0.5	F_2	4	8
Days 6 to 15:			
0.1	F_1	4	19
0.1	F_2	3	13
0.5	F_1	1	12
0.5	F_2	3	9

Figure 1. MeHgCl Anomalies (internal)

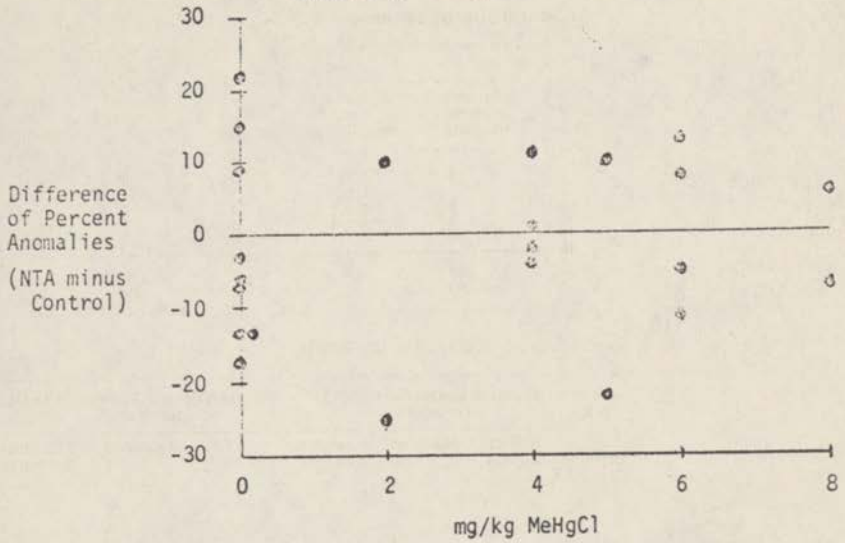


Figure 2. MeHgCl Fetal Mortality

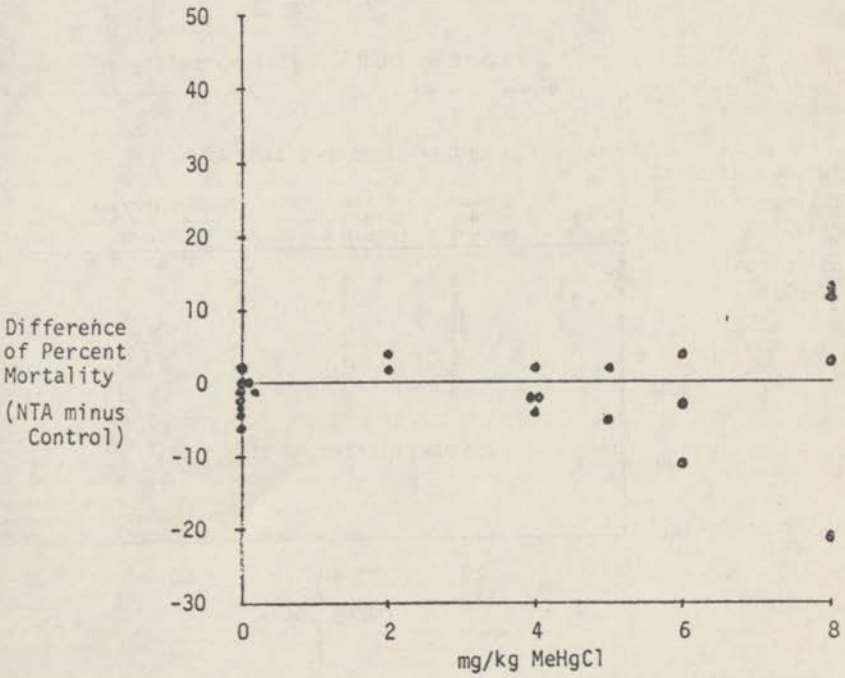


Figure 3. $CdCl_2$ Anomalies (soft)

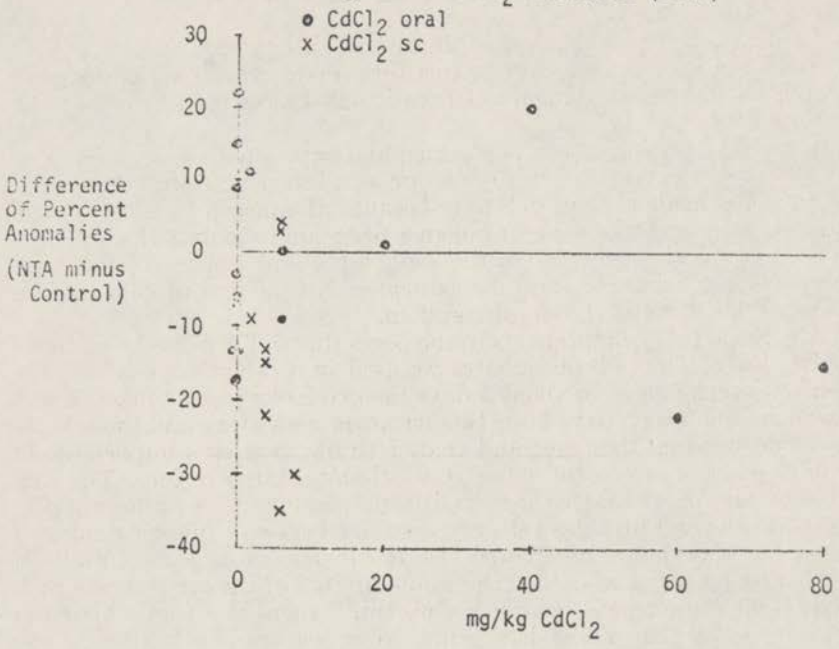
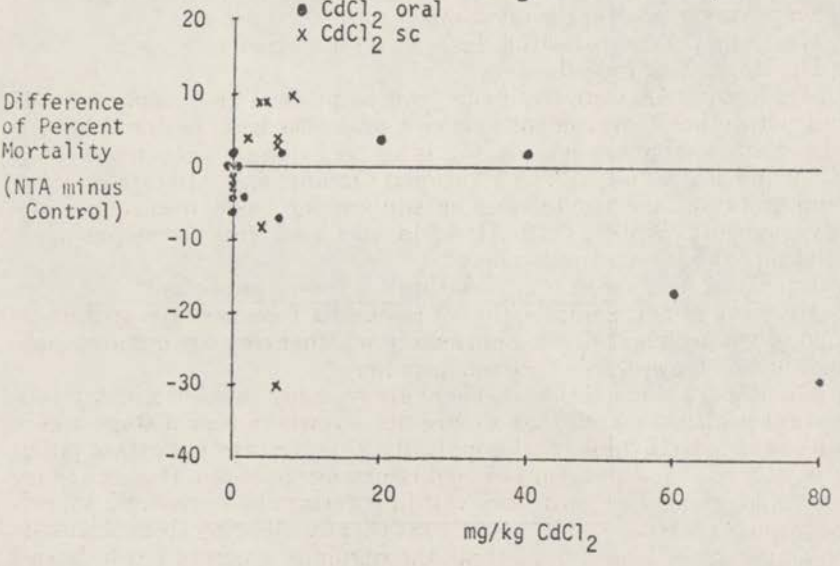


Figure 4. $CdCl_2$ Fetal Mortality



Mr. FUQUA. And you say studies are going on now with the National Cancer Institute?

Dr. RALL. With the National Cancer Institute; yes.

Mr. FUQUA. Is your agency or Institute conducting or supporting research on the health dangers of caustic substances used in household detergents?

Dr. RALL. We have both performed and supported research on this. We became concerned partially on our own internal feeling that there were problems here, and partially because of concern in general, and about the first of this year we began a program to look at the toxicity, primarily in the eye and in the esophagus and upper GI tract, of phosphates, carbonates, and metasilicates. Let me first discuss the eye because this is really the simpler system.

Mr. FUQUA. We had reports in the press that NTA caused blindness.

Dr. RALL. The polyphosphates we used in a rabbit's eye caused intense irritation, and in about 3 days the eye looks just awful. It's red, swollen; but 4 or 5 days later this irriation goes away and there is almost no residual damage; and that, I think, is what's important. If you've got a sore eye for a few days, that's not too serious. The carbonates and particularly the metasilicates produce a very different picture. At the end of 3 days the eye does not look any further damaged than the polyphosphate treated eye, but it goes on to cause blindness by making corneal opacities; the whole surface of the eye becomes such that light cannot get through. So we think there is a very important difference between these detergents. Now, we are just beginning the study of the effects on the pharynx and esophagus, and I don't think the experiments have gone along enough to discuss. In perhaps a year, perhaps we can answer the question.

Mr. FUQUA. You are testing this with animals then?

Dr. RALL. Yes, indeed.

Mr. FUQUA. In your testimony you mentioned the cooperation of and with other Government agencies, and also from personal knowledge that we have, some of the other regulatory agencies such as EPA and FDA and NOAA (National Oceanic and Atmospheric Administration), are conducting or supporting basic research in the environmental health field. How do you view this development in relation to your own mission here?

Dr. RALL. We welcome it. We think it's very important.

Mr. FUQUA. Is it a duplication of research? I am not saying duplication of research is bad, but I am asking whether they are not diminishing the mission and role that you have here?

Dr. RALL. I don't think so. There are so many problems in environmental health research that we are not anywhere near a stage where we ought to be. I think, philosophically, this is a very important point. I have considered problems of regulatory agencies too. It seems to me a regulatory agency must have within it certain basic research knowledge and expertise, and it can only get that by allowing those scientists to do research. Therefore, I think the regulatory agency has to have a basic research arm attached to it. On the other hand, I think it's vital that there be independent research, a basic research group, doing work along the same lines but not related to that regulatory agency. It's awfully easy for a regulatory agency, once it has made a decision, to be unenthusiastic about new research which would make that decision

in retrospect appear less than perfect. Let me say these are my personal opinions and nothing more.

Mr. FUQUA. I appreciate that, and I appreciate your candor about it. I am concerned, though, that you don't find empire building within the various agencies; that competition and a general sense of jealousy develops, and one agency—I am not accusing anyone of this, but I am saying in reality how these things develop—that each agency starts trying to get a little more in their budget, and, consequently, the amount of money we have to spend on research is being diffused to the point that you feel that you are being neglected.

Dr. RALL. Every once in a while we feel that way.

Mr. FUQUA. But I am concerned that this couldn't be done in a more centralized manner. I am very much impressed with the type of work you are doing, and I think it's the type of thing that we need more of, but I am afraid that we are diffusing this effort as these agencies proliferate as Congress creates them, and, consequently, maybe we are not getting as much effort in these areas as we should, and that we would get if they were concentrated in an institute such as you have.

Dr. RALL. I think that's one of the aspects that pleased me most, when Dr. David, the President's Science Advisor, asked us to pull together and chair this ad hoc committee on environmental health research. The primary members of this committee are representatives of the EPA, HEW, AEC, and NSF. These are really the four agencies primarily doing environmental health research and I am chairing this group.

Mr. FUQUA. You are coordinating this?

Dr. RALL. We first just surveyed what was going on, and that took quite a bit of time. I think we probably now have a very good view of environmental health research within the Federal Government. We are working up mechanisms whereby the various agencies actually will work together and will try to coordinate their efforts. Since this report will be presented to OST, presumably it would have an influence on the budgetmaking decisions of OMB. I think perhaps Dr. David had some of the same feelings you did.

Mr. FUQUA. You think this will be an effective monitor of what's going on?

Dr. RALL. We hope so very much.

Mr. FUQUA. Mr. Chairman, I don't want to take too much time, but I have one or two more questions. You mentioned about the mercury levels. I come from the gulf coast area, where the seafood industry is very important. There has been great concern about the levels of mercury in fish, which was found even in one fish in the Smithsonian caught 300 or 400 years ago. Have you reached any accurate measure of levels of mercury tolerances?

Dr. RALL. I think the answer to that has to be "No." There is still uncertainty. It is set now, I think, at a half part per million and that appears to be a reasonable tolerance.

Mr. FUQUA. That amount is allowed?

Dr. RALL. That's clearly a safe level, and I think the question is whether it could go up a little bit, and I think we just don't have the information to answer that. That's why I think the sort of basic research we are doing is important because if we can say that "No, one

part per million is safe," then this has enormous and beneficial impact. We don't know—is the answer.

Mr. FUQUA. The other question is, has the Institute done any work in connection with EPA or on your own on Mirex that has been used to control fire ants?

Dr. RALL. My recollection is that North Carolina just this last week decided to hold off on using that. We have done some research on Mirex. We are concerned for two reasons; one, it is possibly carcinogenic; and, second, it is incredibly persistent—if anything even more so than DDT or PCB's. We have studied with the Forestry Service, Department of Agriculture—the disappearance of Mirex in soils, and it doesn't disappear. Six months later there is still 100 percent of what was put there. It is not metabolized; rather, it is stored and very slowly excreted. We understand the fire ants are a very serious problem, but we would be very concerned about widespread use of large amounts of Mirex for long periods of time.

Mr. FUQUA. Now, the EPA has issued a regulation allowing one-quarter of a pound per acre or something like that.

Dr. RALL. Very low concentration.

Mr. FUQUA. For aerial spraying. Did you participate with them in arriving at this level?

Dr. RALL. Our scientists discussed with their pesticide people our findings and thoughts.

Mr. FUQUA. Do you feel as though this is a tolerable level, with limited use?

Dr. RALL. If it's a limited use and if it doesn't go on for years and years, I think it's tolerable. The important thing, I think, is that it can't just begin to be used the way DDT was. It's a potentially toxic compound.

Mr. FUQUA. You've got to use it with extreme care?

Dr. RALL. Extreme caution, and we've got to look and find better and safer substitutes.

Mr. ALEXANDER. Mr. Chairman, will you indulge me? Dr. Rall, what happens to your reports? Are they published? Are all of your reports published?

Dr. RALL. We are very concerned about this problem. We think we have developed over the course of the years some very good technical reviews in which we try to create a balanced story of what the problem is. We are establishing, and hopefully within the next few weeks, we will have the first issue of an experimental journal, Environmental Health Perspectives. We hope to publish this on an experimental basis to see whether in fact it will give the widespread distribution of these reports that we think they deserve.

Mr. ALEXANDER. In other words, you are saying that your reports are not published?

Dr. RALL. These technical reviews have not yet been. Some of them end up in journals as scientific reviews, but that's a very long process. We would like for it to occur more rapidly.

Mr. ALEXANDER. And what happens to your reports?

Dr. RALL. They are widely distributed to the scientists and Federal research and regulatory agencies that need them. I think they should have broader distribution.

Mr. ALEXANDER. One further question. Let's assume some congressional committee goes completely haywire in Washington—which is not an unheard of circumstance—in the area of scientific endeavor—questioning the use of some chemical or some chemical process in the use of food or food additive, or something of that nature, which is totally wrong. What action would your institution take to correct this activity?

Dr. RALL. I think we'd be put in a very difficult position.

Mr. ALEXANDER. Well, let me give you an example. A couple of years ago we had a scare in Washington on the use of cyclamates in soft drinks. I don't know the precise chemical situation on cyclamates, but I think a later report was that cyclamates were all right to use in soft drinks. Is that not correct?

Dr. RALL. The latest report is, I believe, that they are carcinogenic.

Mr. ALEXANDER. Let's use that as an example; that the press got hold of this, and that it was totally wrong. What initiative would your institution take to advise congressional committees or the National Institutes of Health, or someone in authority, that would be in a position to correct this wrong, before it wrecked an industry?

Dr. RALL. I think we probably would do what we could among those people we felt free to talk to. Our staff is called very frequently by science reporters to check out stories they are writing—"Is this really reasonable?"—and this would be one way we'd be able to say, "Hey, you know we don't believe the data supports that." What's being done? We have some contacts amongst the congressional staff, and I think we'd be very tempted to alert the DHEW and call them up and say we are concerned about this; that we don't think the science base of the decision is proper.

Mr. ALEXANDER. Thank you, sir.

Mr. FOUNTAIN. I believe you said you had found cyclamates to be carcinogens?

Dr. RALL. There is a report which reaffirms the original finding.

Mr. FOUNTAIN. I believe you also would admit that there are pressures on the regulatory agencies which you are not subject to?

Dr. RALL. That's right. There are intense pressures on the regulatory agencies that we do not have to withstand.

Mr. FOUNTAIN. All industrialized countries are polluting their environment, particularly the atmosphere and their waterways. Would you say that's true?

Dr. RALL. Yes, sir.

Mr. FOUNTAIN. To what extent does the air and water pollution, say of Japan or industrialized Europe, affect us here in the United States?

Dr. RALL. It certainly can. The specific example that I think is most interesting is this: Some countries south of the Mediterranean, rather than north, used an extensive DDT spraying program, and it was then discovered that the DDT floated in the trade winds across the Atlantic and ended up on some of the land in our State of Florida. So the planet has to be considered as one, and these pollutants move from country to country and don't respect national boundaries.

Mr. FOUNTAIN. We are mobilizing our forces to fight pollution of the environment. Congress is keenly aware, I think, of the potential

hazards of a polluted environment, as indicated by legislation we have passed and legislation still being considered, and has done and is doing something to counteract these hazards; but isn't it a problem that in the final analysis may have to be tackled in a concerted and coordinated way on a worldwide basis?

Dr. RALL. That would be the best way to do it, but there are very great problems, as I am sure you are aware, if I may just speak frankly. The underdeveloped nations feel very much that the way they can become industrialized nations and reap some of the benefits that industrialized nations have is to develop plants as rapidly and as inexpensively as possible, and these often are the worst polluters. Now, this is a subject that will be thoroughly aired in just a few weeks at the Stockholm Conference on the Environment, I am sure.

Mr. FOUNTAIN. That is interesting. How involved, if you know, is the United Nations in this problem?

Dr. RALL. They are involved in the sense of organizing this very large Conference. We hope there would be some continuing involvement after the Conference.

Mr. FOUNTAIN. What degree of international coordination of effort is there at the present time, if you know, to protect the environment? I recognize the problems you have mentioned.

Dr. RALL. Well, I think it's coming. I know that there are developing relationships between the Environmental Protection Agency in Japan, between the Environmental Protection Agency and the Economic Union in Western Europe. We have become involved in environmental research cooperative arrangements, first with Japan, more recently with the United Kingdom. We met not too long ago, with Sir George Godber, the medical officer of the United Kingdom, and are trying to develop an informal but very effective way of being sure that the United States and the United Kingdom research activities complement each other and we know what each other is doing. I guess it was 3 weeks ago, with Dr. Marston and some of the other Institute directors, we were in Moscow, Russia, for a week discussing the possibility of a much closer cooperation on environmental health research with the U.S.S.R.

Mr. FOUNTAIN. Is it your feeling that other industrialized countries are tackling their environmental problems and are as concerned about them as we are?

Dr. RALL. I think they are becoming very concerned about them.

Mr. FOUNTAIN. Doctor, on page 2 of your prepared statement you defined the study of the environmental health science as the study of the interaction of man with external noninfectious factors, both chemical and physical. Does this definition include our food supply as an external infectious factor?

Dr. RALL. Yes, sir.

Mr. FOUNTAIN. In other words, is our food supply included for your study?

Dr. RALL. Yes, it is. We are not concerned about the nutritiousness of foods, but as they contain potentially toxic compounds.

Mr. FOUNTAIN. By your use of "noninfectious factors," do you mean to exclude pathogens which may be in the environment?

Dr. RALL. Yes, in terms of their ability to cause disease.

Mr. FOUNTAIN. What about molds and other fungi which, under certain conditions may produce toxins; are they also excluded?

Dr. RALL. They are not excluded, and that is really the basic reason for the phraseology of "noninfectious factors." We are very concerned about the aflotoxins and the other mycotoxins which can affect our food. It's not as large a program as we would like it to be, but we've got a large program on toxins and toxicity.

Mr. FOUNTAIN. Mycotoxins affect peanuts, do they not?

Dr. RALL. Yes, sir.

Mr. FOUNTAIN. On page 3 you state that among your specific concerns is carcinogenesis, the production of cancer. Now, on April 22, 1970, a report was made to the Surgeon General of the U.S. Public Health Service by the Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens. Are you familiar with that report?

Dr. RALL. Yes, indeed.

Mr. FOUNTAIN. Do you agree with the substance and conclusions of that report?

Dr. RALL. Yes, I do.

Mr. FOUNTAIN. Dr. Falk, I note that you were a member of that at hoc committee, and I presume that you agree with and support the conclusions of the committee. Am I correct in assuming that?

Dr. FALK. Yes, sir.

Mr. FOUNTAIN. Dr. Falk, appendix II of the ad hoc committee report is entitled "Comments on 1969 Report of the Food Protection Committee." Are you familiar with this section of the report?

Dr. FALK. Yes.

Mr. FOUNTAIN. Do you agree with the comments?

Dr. FALK. Yes, I agreed with all the comments, as a matter of fact.

Mr. FOUNTAIN. I think appendix II is about one page long; you might care to read it and refresh your recollection.

Dr. FALK. Yes, I agree with the criticism that is made. Actually there were exchanges of information since that time between NCI and the people that were responsible for the statements, that is, the Food Protection Committee, and they actually agreed that certain statements made by them were not correct for carcinogens or to the best advantage of the public. So I believe that there are more experts now that are agreeing that you cannot make these statements with regard to carcinogenic chemicals; that is, regarding this safety just because they have been around—have been used without signs of toxicity, and, therefore, we can accept them without concern.

Dr. Rall says we need to review the data in light of the existing knowledge, other than on facts we had presented to us years ago. I believe that. I believe everybody now agrees, since the meeting of January 21, 1972.

Mr. FOUNTAIN. Do you have any comment, Dr. Rall?

Dr. RALL. I agree with Dr. Falk.

Mr. FOUNTAIN. The reason I am interested in getting your views on this section of the report is that the ad hoc committee recorded, and I quote, "its strong objections to the principles expressed" in the 1969 report of the Food Protection Committee of the NAS/NRC (National Academy of Sciences/National Research Council). Now, the specific

part of the NAS/NRC report, to which the ad hoc committee objected, is entitled, "Guidelines for Estimating Toxicological Insignificance of Chemicals in Food." The ad hoc committee comments on the NAS/NRC's guidelines end with this sentence, "Since the purpose of the report is to recommend guidelines and priorities for selecting chemicals for human use without direct experimental toxicological evaluation, the lack of consideration of irreversible long-term toxic effects (which would not be ruled out by the suggested criteria), makes the suggested approach practically inapplicable and potentially dangerous."

And in another section of the comments, the ad hoc committee states that certain assumptions in the NAS/NRC guidelines "display a lack of understanding and appreciation of factors involved in chronic toxicity, particularly of the irreversible and delayed toxic effects which occur in carcinogenesis."

I presume then, especially since you signed the report, that you do agree with the statement?

Dr. FALK. Yes, I can elaborate on it if you want to, to show or somehow explain some of the other factors involved in evaluation of carcinogenicity.

Mr. FOUNTAIN. Let me ask the next question and then give you a chance to elaborate. This is rather an anomalous situation since FDA's food additive regulation, 121.67, entitled "General principles for evaluating the safety of food additives" provides that the Food and Drug Administration Commissioner will be guided by the principles and procedures for establishing the safety of food additives stated in current publications of the National Academy of Sciences/National Research Council. Now, the NAS/NRC guidelines are found in current NAS/NRC publications and therefore fall within the scope of the regulation I quoted. If the ad hoc committee is justified in its statement that the NAS/NRC approach is potentially dangerous, I would think that this might represent a serious situation in view of the requirement that FDA be guided by the NAS/NRC guidelines. Would you not agree?

Dr. FALK. Yes, sir.

Mr. FOUNTAIN. Now, you may elaborate.

Dr. FALK: Your second point first. It is already clear that many compounds that we became very concerned about—some of which were referred to as GRAS (generally recognized as safe) compounds—are being reevaluated, and many of these compounds are given a second scrutiny. We would not accept the earlier decisions which were made by members of the NAS/NRC committee, but needed to reevaluate the safety of these compounds, and this is being done now, so there is no real discrepancy. Practically every compound has been reevaluated, if the basis for the decision was considered unsatisfactory, because it was not based on adequate experimental evidence. So there is complete agreement between the FDA and that ad hoc committee, as to what must be done.

With regard to the more complicated problem, I would like to make it clear that most of the chemicals that are hitting us in our daily lives reach us at very low concentrations, but that they are taken up in many exposures, over a long period of time, and that we deal with an ex-

posure not just to the same, single individual compound but to a whole variety of compounds at various doses. For the longest time it was already considered inadequate to evaluate one compound alone as the cause of a potential hazard, but we need to consider all of them together. The Russians have produced a formula that they published some years ago which suggests that one can consider all effects additive. This was already considered an advance, that is, to consider in this formula all the environmental hazards and give each one the same additive weighting.

We know, however, that in human cancer we are dealing with a much more complicated picture—cocarcinogenesis is not an experimental curiosity or something that may only apply to the skin of mice; no, it applies to all of us, and is really part of our problem, and let me state what it is. The exposure to a carcinogen at a very low level, which would not produce cancer in man or animal, during his lifetime can be modified or enhanced by compounds that are not carcinogens, that may not even be toxic, to produce cancer in man or animal, at this very low dose level. We have examples. Some apply to man and some apply to animals. We do not always have the same situations apply to both man and animal and this is one drawback, but we have examples on both sides. Dealing with skin cancer in man and mouse, there is frequently one chemical responsible for it: benzpyrene. This is one of the carcinogens present at low dose levels, and the cocarcinogen may be dodecane, which is present in many petroleum compounds, and it is not carcinogenic. A high concentration of dodecane will enhance the carcinogenicity of benzpyrene a thousandfold.

In other words, where you saw no tumors without the cocarcinogens, but with the cocarcinogens you will see cancer occurring in these animals at a high rate. In humans, the same type of chemicals are expected to produce cancer of the skin—workers have been exposed as long as a hundred years ago, to waxes, mineral oils, and other petroleum products, during their work in the oil industry, that have produced a rather high incidence of skin cancer at a time when the search for the carcinogen showed that it was not present at a high dose. So these contributors were put together in the human as well as in animal studies, as being very important factors, and we must therefore be aware of this aggravation of cancer induction and effectiveness of noncarcinogenic agents in changing the hazard produced by a carcinogenic agent. I want to say one more thing. Cigarette smoke is carcinogenic; so is tobacco. There is very little carcinogen present, and yet scientists know—and there is good evidence, that cigarette smoking produces lung cancer. The difference lies in the carcinogens in smoke. We haven't gotten so far in animal experiments as to identify the agents that are cocarcinogenic in smoke. This situation reflects on the Delaney amendment. We cannot change the letter of the Delaney clause if we have to worry about this synergistic effect, which may sometimes raise a dose of carcinogen which we consider entirely below the effective dose, a thousandfold in effect, in which case it becomes a carcinogenic dose.

Since that happens with a variety of compounds in a variety of ways, we are still at the same situation where Secretary Flemming was in 1958 when he answered that he could not determine where the safety threshold was for practically any of our carcinogens. That's why I

guess the amendment is still the way it was then because even with the knowledge we have gained we cannot determine this particular cutoff point of carcinogenicity.

On the other hand, there is such as cutoff point for carcinogenesis. That it is true can be seen from the many cocarcinogenesis experiments where dose levels of carcinogens can be given to animals and nothing happens in this lifetime. Absolutely nothing happens to the animals. They live their complete lifespan without adverse effect. In fact, these are the control studies. But the other ones also get the cocarcinogens and you see the effect. You must get an effect due to the chemical that can be hidden in man and animal and will not become apparent or be recognized as cancer unless you give some synergist. I mean that there was some crucial change. The changes have occurred in the subfractions of cell. These changed cells—they are called initiated—are ready to possibly show the effect if conditions are right but this is the situation that makes it so difficult to alter any judgment with regard to the safety level of any carcinogens.

Mr. FOUNTAIN. Shouldn't NAS/NRC publications be revised to reflect what you are saying?

Dr. FALK. I think they would if they had a chance to respond. They would show their change.

Mr. FOUNTAIN. Dr. Rall, on page 8 of your prepared statement, you discuss the principles of operation. In this connection you state, and I quote, "Maximum protection of the public health demands that the less we know about the health effects of a given product the more stringent and conservative must be the standards regulating its use." I don't think any reasonable and prudent person would take issue with that principle, unless we became involved in decisions with a lot of economics. But I'd like your views on the application of this principle to our efforts to regulate the use of diethylstilbestrol. As you know, this subcommittee has held hearings on the regulation of DES, both as a human drug and one which is used in medicated animal feeds to promote growth of animals and increase food utilization efficiency. I happen to have a lot of constituents in the animal business. DES is carcinogenic to a number of species of animals and has been linked to vaginal cancer of young women, where the mother took DES during pregnancy. At the time of the hearing in November of 1971, almost 70 cases of this rare form of vaginal cancer in young women had been associated with DES use by their mothers. This subcommittee's studies on DES revealed that it had produced cancer of the breast in female mice at the extremely low level of 6.25 parts per billion in their diet; it also revealed that its use in medicated feed resulted in residues in about one-half of 1 percent of the cattle and sheep livers marketed. The residues were on the order of 2 to 39 parts per billion. The benefits of DES lie in the saving of about $3.50 per person a year in the purchase of meat.

In view of these facts, what kind of a standard regulating the use of DES could or should, in your opinion, be applied? Is DES, in your opinion, one of those products about which our knowledge of its health effects when used in animal feeds is inadequate, therefore requiring more stringent and conservative standards regulating its use?

Dr. RALL. First, let me say that the problems of endocrine carcino-

genesis are particularly complex, that there are enormous differences in strains, and that species differ in response to various hormones. I am not an expert in this area. This is a very complex field. It seems to me, though, the whole DES story accentuates the need for a better understanding of long-term effects, of the compounds we are exposed to. We really need, I think, much better studies on the carcinogenicity; we should have a better feeling for the norm in experimental subjects, for instance, in the mouse. I am aware that 6.2 parts per billion caused mouse tumors; the question arises almost instantly, "Well, what about the normal estrogen levels in the mouse; has anybody looked at the normal amount of estrogen and compared it with the 6.2?" It seems to me these are questions we need answered and they should be supplied by the basic research we have been talking about.

Dr. FALK. I'd like to talk about it from a slightly different point of view; namely, are there any other compounds that could be used in feed for cattle that would have the same desirable characteristics, lack the undesired characteristics, and could be eliminated even faster than DES? This is the result of research that came out of the work on the fungal toxins. Pigs had eaten feed that was contaminated with molds and the chemical was isolated from the feed which was responsible for the estrogenic effect observed in these pigs. They give it an awful name; "Zearolanone." After the chemical structure of the compound was established, the chemists synthesized the compound and changed the structure; they changed it enough to get rid of the estrogenic activity but maintained the growth stimulating activity so that now it is on the market with a somewhat different name "Zearolanol," It is a food additive which has very little estrogenic activity, but is a growth stimulant for cattle and it is being used as such. I am not familiar with experiments that have been done to show the effectiveness of the addition or its estrogenic ineffectiveness on this, but this seems to be a possible answer. It is very simple to switch to this new compound that apparently can dissociate estrogenic activity and growth stimulation.

Mr. FOUNTAIN. Does FDA have access to this information?

Dr. FALK. Oh, yes, it is approved by them.

Mr. FOUNTAIN. Dr. Rall, on page 10, you mentioned that your agency has conducted an investigation of nitrite content of babyfood. I am familiar with your agency's Environmental Review No. 2 on Nitrates and Nitrites. On page 4 of that review, the following statement is made concerning the possible consequence of the use of nitrites in the diet, and curing in meat, and I quote, "The red color of cured meat is largely due to the formation of nitroso compounds of myoglobin and hemaglobin. It is entirely conceivable that a comparable reaction of nitrites with secondary amines would produce nitrosamine, a family of compounds which contain many known powerful carcinogens." In that connection, the U.S. Department of Agriculture and FDA issued a joint press release on February 5, 1972, which reported the finding of just such known powerful nitrosamine carcinogens in cooked sausage, dried beef, and cured pork, all of which had been treated with nitrite. In addition, the release reported that when bacon is fried—and I eat an awful lot of bacon and love it—a carcinogenic nitrosamine—that is not present in the uncooked bacon—is produced.

FDA reported that in four out of the four brands of bacon tested this carcinogen was produced, but the study was called "preliminary." That "preliminary" is in quotes. Dr. Rall, in your opinion, what standard should be used for regulating the addition of nitrite to foods; should it be conservative and stringent? Or just how would you handle it?

Dr. RALL. I think the whole problem of nitroso compounds in foods is going to be one of the problems that will probably attract the attention of the scientific and public community in the next year or two as much as any. And I think we are faced with a series of dilemmas. Nitrate and nitrite in food is a preservative. When I shop for hamburger, I shop for pink hamburger, not the brown. And now we are faced with the fact that there are low levels of nitrosamines and related compounds in many of the foods. I would be very concerned about this. I think we have probably not enough basis today to set any tolerances or limits, but I certainly hope we have very effective research programs going on to find out more about these very important compounds.

Mr. FOUNTAIN. Would you be willing to express an opinion as to how much exposure of the public to nitrites, and the carcinogenic nitrosamines they form, should be permitted?

Dr. RALL. I think the answer is—as little as possible.

Mr. FOUNTAIN. As little as possible?

Dr. RALL. Yes, sir.

Mr. FOUNTAIN. In your opinion, is our knowledge of the effect of nitrites on health, and the nitrosamines they produce, adequate so we can have less than a stringent or conservative regulatory standard?

Dr. RALL. Let's just be sure now—we are not talking about nitrates causing methemoglobinemia; not talking about the reports from Western Europe that, in fact, there were high concentrations. We are really talking about the problems of nitrosamines. I think we are in the stage where we have to have quite stringent controls and hope to get enough research data to see whether they are proper or not.

Mr. FOUNTAIN. Apparently, we are now in the process of obtaining data. FDA, and institutions under contract with FDA, are engaged in the process.

On page 16, you state that your staff frequently provides assistance in efforts directed toward the resolution of pressing environmental health problems, and you list a number of agencies and committees for whom you have rendered service. How were you brought into these activities; by invitation?

Dr. RALL. By a variety of mechanisms. There are formal governmental invitations where you are asked to send a representative. Another important way is that our staff, I am happy to say, are, by and large, distinguished scientists, and they get invited because they are experts in the field. Another mechanism is that I, and other members of our staff, are in really quite close contact with most of these regulatory agency people; and if they have a problem, we will often say, "Well, somebody on our staff is working on that and it would be worthwhile to talk to him." So there are really three mechanisms.

Mr. FOUNTAIN. I think Congress is always concerned that all who have access to information on a given subject be given a chance to

supply that information, so we will have the benefit of all of it. Quite often we find—in the Federal Government, at least—that the left hand doesn't know what the right hand is doing. Now, FDA and USDA organized a rather large interdepartmental committee to consider and to work on the problem of nitrites and nitrosamines. The committee includes members of FDA, USDA, NCI, Eppley Institute, and others who are representatives from industry and from several universities. Was your agency asked to participate in the work of this committee?

Dr. RALL. It was not, to my knowledge, but let me explain the groundrules. As I think you are aware, the National Cancer Institute appropriation is quite large and ours is not large, indeed, and I feel that when it is a problem of purely carcinogenesis or carcinogenicity of a compound, it seems the NCI had the resources to devote to that and we did not; although we are interested in problems of carcinogenesis, and we are doing some research in the area, we feel the prime area must be the Cancer Institute. In most instances it would not be necessary to have more than one NIH Institute represented.

Mr. FOUNTAIN. What I had in mind was participation, not funding. I realize, of course, some participation requires expenditures. Then, you were not asked to give the committee the benefit of your thinking?

Dr. RALL. No; we were not. We would have been delighted to participate if it didn't cost money.

Mr. FOUNTAIN. If it didn't involve money, do you feel that your agency could make a contribution to such a committee?

Dr. RALL. I would think so; yes.

Mr. FOUNTAIN. Also, on page 16, you state that your agency convened a conference on research into PCBs (polychlorbiphenyls). Did you invite FDA to participate?

Dr. RALL. Yes, sir.

Mr. FOUNTAIN. How about the Department of Agriculture?

Dr. RALL. Yes, sir.

Mr. FOUNTAIN. On April 13, 1972, FDA reported that final plans are being developed for long-range studies into the possible harmful effects of various chemicals on man. FDA further reported that a series of 2-week meetings with various representatives of Government, industry, and the academic community began on April 13, 1972—not very long ago—to establish experimental protocols for the National Center for Toxicological Research. To what extent, if any, did you participate in these meetings and programs?

Dr. RALL. We participated rather extensively in the whole series. Specifically, Dr. Payne represented the Institute at the meetings the 14th and 15th. Our senior statistician, the head of our statistics branch, last week, and presumably this week, is working with the FDA on their development of protocols. Our Chief of Pharmacology and Toxicology will be one of their senior advisers on development of this center. A pathologist, who is a visiting scientist with us this year, has served on another advisory committee. So we are very well involved in that particular development.

Mr. FOUNTAIN. That is fine. As I understand it, a great deal of environmental health research is carried on by the National Cancer Institute, the Environmental Protection Agency—which was created

after your Institute and its mission was established—and some other Federal agencies. What arrangements or understandings do you have with the Cancer Institute, for example, as to how you divide up the research responsibilities relating to cancer as an environmental problem? How do you prevent undesirable duplication and overlapping with these agencies?

Dr. RALL. The relationship with the Cancer Institute is perhaps unique because I spent many years there. Dr. Falk spent many years there. Dr. Payne did, too. We, in terms of our relationships with the NCI, operate on rather a more personal level than with the other agencies. We know the scientists involved very well indeed. We often discuss "is this a problem you want to take or is this a problem we should take"—and I think that works very well. Again, with the other agencies, I think the need for a more formal mechanism than had existed is what led to the development of the Ad Hoc Committee for Environmental Health Research. And one of the very nice things about this committee has been that the four major agency leaders have met together every two weeks, and this has provided a very great coordination by just meeting and talking together, and it is my expectation that this aspect will continue.

Mr. FOUNTAIN. Fine. I understand that your current appropriation is $26.4 million and you are asking for $28.8 million for the fiscal year 1973; is that right?

Dr. RALL. That's right.

Mr. FOUNTAIN. Now, your own laboratory and clinical operations are budgeted, I believe, at $7.1 and $7.6 million for 1972 and 1973 respectively, and that's roughly, 27 or 28 percent of your total appropriation; the rest is spent for research grants and contracts and training awards. Does that sound about right?

Dr. RALL. Yes, sir.

Mr. FOUNTAIN. Do you feel that you are doing enough of the work in your own facilities as compared with the supported research?

Dr. RALL. I think that our feeling is that we, in the best of all worlds, if there were not the restrictions on resources that there seem to be in the world we live in, would feel it would be enormously important to develop an effective intramural program that would be as immediately responsive to the needs when another methyl mercury or another NTA comes along. We would look forward to an intramural program perhaps four times its present size, which I think would give us the resources and facilities to really effectively handle environmental health problems.

Mr. FUQUA. You are asking for a budget of $28 million, an increase of $2 million; how much did you ask NIH for before they reduced it?

Mr. KINGMAN. Off the top of my head, about $38 million.

Mr. FUQUA. So they cut you about $10 million?

Mr. KINGMAN. In fairness to Dr. Marston, it was not the NIH that cut us. The difference occurred in a series of incremental cuts.

Mr. FUQUA. But you originally asked for $38 million?

Mr. KINGMAN. Yes, sir.

Mr. FUQUA. A loss of about $10 million from what you originally asked for?

Mr. KINGMAN. Yes, sir.

Mr. FOUNTAIN. Now, your Institute is the only NIH Institute located away from the Washington area. Does this geographical separation handicap your operations in any significant way?

Dr. RALL. Not at all, except I think my wife would prefer me home for dinner a little more often than when I'm flying to Washington. No; we found this really to be a superb place for a research institute. The association with the universities—it's delightful. Research Triangle Park, I think, is an ideal place; and, frankly, we like it down here very much indeed.

Mr. FOUNTAIN. Usually when these things come up, and particularly when there are battles between various sections of the country for institutions as valuable as yours, there are arguments about costs and overhead. I'd like to ask you, in your opinion, whether or not it increases your overhead costs significantly because of the need of your staff to travel frequently to Washington.

Dr. RALL. I would say it does not increase the cost significantly.

Mr. FOUNTAIN. In view of the magnitude of the task of identifying and studying for control purposes those environmental factors which endanger health, do you think we, as a Nation, are doing as much as we should to deal with the problem?

Dr. RALL. That's a very difficult question. I think the scientists, with the facilities existing, would like to do more than we are doing—but we are now talking about competing priorities within the other problems of the Nation. It has a fairly high tax rate. I think among my colleagues, we feel we are not doing enough; but the decision is basically that of the President and the Congress to allocate as much money as they feel, in the light of all the competing needs, can be allocated to environmental health.

Mr. FUQUA. What would you do if Congress gave you the other $10 million that has been reduced from your budget? How would you use it? What would you ask for?

Dr. RALL. One important aspect of this is that if we are to grow in our intramural research program, we need positions, ability to hire people to work.

Mr. FUQUA. More staff?

Dr. RALL. Yes.

Mr. FUQUA. About how many positions?

Mr. KINGMAN. An increase of about 137 budgeted positions.

Mr. FUQUA. Do you have any other specific areas? You said a hundred and some thousand for those?

Dr. RALL. 138 positions. We would have liked a modest amount of increase in contracts which allow us to go out and buy research and we would have liked a modest increase in grants because we are supporting some very excellent programs and there just isn't enough money to go around; but most of the money in that year's budget would have been for intramural research.

Mr. FUQUA. Did the cutback eliminate any of your objectives?

Dr. RALL. You just spread yourself thinner when that happens.

Mr. FUQUA. You didn't have to eliminate any projects, specific program areas that you had to reduce?

Dr. RALL. We had to reduce our plans for developing a much more effective pathology-physiology branch. We will still have a branch

but it will not be, you know, it won't have as many people—won't be able to do as much work. It will make it more difficult for our new mutagenic branch to develop what I think will be one of the most important research programs in the country. So, we spread ourselves thin and that's too bad.

Mr. FUQUA. Thank you.

Mr. FOUNTAIN. I think you may have already answered this in response to Congressman Fuqua, but if you were to expand operations, given greater resources, what specific programs or areas would you like most to expand? In other words, what things really need doing the most?

Dr. RALL. The two I mentioned. We need better facilities and resources for pathologic-physiology. We need to develop our mutagenesis branch. I think we've got two of the top people in that field in the world. We need to develop more than we have been doing. The means by which man and experimental animals get rid of and detoxify chemicals—that is just, I think, at the borderline and becoming one of the most important aspects we've got. If you administer a compound to an animal or a man, it can either be metabolized and secreted in a nontoxic way, and in many ways metabolism makes it more toxic. We are just beginning to get the necessary research done, and I think it would be a very important area. There is still another area I'd like to bring up. The ultimate objective of all this is protecting man's health, and we've got to find out, you know, what is the status of man's health, what is the status of a group of people exposed to DDT 30 years ago, heavily exposed; what is the state of people exposed to methyl mercury; this is human epidemiology.

This is very complicated, expensive, if you have hundreds of patients and take their whole lifetime to find out what they died of and what their diseases were. We have just a small program that could be called an epidemiology program, and we kept it small because of the very large amount of money that it would take to run it effectively. Now, the other thing I mentioned is we would like to develop in a more intensive way better methods of toxicity testing, because in the long run I think that's going to pay off as much as anything. So I think the pathology program growth, mutagenesis branch, human epidemiology, and better testing methods need the additional resources.

Mr. FOUNTAIN. I want to commend you for your comments on the subject of priorities. I realize you do have to operate within the budget as established by the Congress and the President, and those limitations concern me too; I hate to throw any cold water on environmental research at a time when we need to do more than we are doing to protect man's health. But in connection with these priorities, I think it isn't inappropriate to consider that we do have a $250 billion debt and the annual interest rate is about $23 billion a year, which, I am told, is more than we spent on our entire budget for the first 120 years of our Nation's history. These are things that have to be taken into account in establishing priorities although each of us would like to see more done in these areas.

Before we take a 5-minute recess: As we came in, I received a communication from Mrs. J. L. Cuddy—I don't believe I know her—addressed to the attention of House Intergovernmental Relations Sub-

committee. I will read you the letter—it's very short—and give you an opportunity to comment on it briefly. She says: "Please, in your hearings today on Environmental Health, consider the increasing hazards of indirect smoking (inhaling others' cigarette smoke). With our society turning more and more to urban jobs (indoors), more consideration must be given to whether air (indoors) is healthy. This will include air in restaurants, bowling lanes, buses, concert halls, basketball stadiums, theaters, classrooms, school lounges and other lounges, meeting rooms and halls, et cetera. And, of course, offices where millions spend at least 40 hours per week."

"All of us (particularly those of us with bronchial weaknesses—and there are more of us all the time—asthma, smoke allergy, emphysema, and other respiratory troubles) will appreciate your help, and consideration of this increasing 'Health Hazard.' "

Then, of course, enclosed with her letter are some other documents making reference to this with quotations from authorities. I would like to give you the benefit of commenting on this letter.

Dr. RALL. I am a cigarette smoker myself and I should disqualify myself.

Dr. FALK. I am not a cigarette smoker myself. I agree with what the lady says. There has been a document written by Dr. Daniel Horne on the problem of ill effects of nonsmokers being exposed to smoke. There seems to be some basis and some evidence for this effect. For instance, conference rooms in HEW carry big signs of "No Smoking." There has been the same move by some of the airlines to set up one area for smokers and one for nonsmokers. Not only the allergic person may suffer from cigarette smoke, but also those that are not allergic, and I must go along with the lady.

(A 5-minute recess was taken.)

Mr. FOUNTAIN. Let the committee come to order and the record show a quorum is present for the purpose of taking testimony. Our next witness is Dr. Daniel C. Tosteson, who has had a distinguished career in the field of physiology and pharmacology. Currently, I understand, he is professor and chairman of physiology and pharmacology at Duke University School of Medicine, the school with which he has been associated since 1961. Dr. Tosteson, we are pleased to have you with us this morning and we will be delighted to get the benefit of any statement you may have to make.

STATEMENT OF DR. DANIEL C. TOSTESON, CHAIRMAN OF PHYSIOLOGY AND PHARMACOLOGY, SCHOOL OF MEDICINE, DUKE UNIVERSITY

Dr. TOSTESON. Mr. Chairman, I'd like to begin with introducing Professor Narahashi, chairman, Division of Pharmacology at Duke University and pioneer in the study of toxic effects of nerve cells.

Mr. Fountain, members of the subcommittee: I am grateful for this opportunity to discuss with you the deepening crisis in the relationship between health and the environment. First, I propose to share with you some of my thoughts about the historical origins of this crisis. Next, I will treat in some more detail one specific and well known aspect of the crisis, namely, the use (or alleged misuse) of the

insecticide DDT. Finally, I will conclude with a few remarks about possible paths toward resolution or at least improvement of this crisis.

Sixty years ago, the distinguished American physiologist, Lawrence J. Henderson, wrote a monograph entitled "The Fitness of the Environment." Perhaps he'd have to find another title today. The book is a searching inquiry into the biological significance of the properties of matter. Henderson calls to our attention the remarkable suitability of the physical conditions on the surface of the planet Earth for the processes which we describe by the word life. He made a particularly careful study of the properties of water and carbon dioxide, two essential components of living things.

He delineated with great clarity the remarkable suitability of these molecules for participation in living processes as we know them. Henderson took particular pains to contrast his concept of the fitness of the environment to support life with the Darwinian idea of the fitness of living organisms to survive in the environment. An adequate synthesis of these two lines of thought has not yet been made and is indeed still a subject of active research. I do not bring the matter to your attention with a hope of resolving it here this morning. Rather, I want to point out that despite their disagreement on this issue, Darwin and Henderson shared an attitude about man and his environment which those of us who are privileged to live in 1972 must consider increasingly archaic. They both considered that the properties of the environment of man were determined by complex geological, biological, and cosmic events on which man had no significant influence. They did not seriously consider the possibility that the composition of the atmosphere or the sea could be changed significantly by the actions of man. Today, we know that that helpless, comfortable belief is wrong. The enormity of this fact becomes clearer and clearer to more and more of us every day.

Our situation can be seen more vividly, perhaps, in the context of geologic time. Richard Carrington's comparison shows rather strikingly how slow changes in ecological systems have been. "If the earth's history could be compressed into a single year, the first 8 months would be completely without life, the next two would see only the most primitive creatures; mammals would not appear until the second week in December, and no Homo sapiens until 11:45 p.m., on December 31. The entire period of man's written history would occupy the final 60 seconds before midnight." The modern scientific revolution began about 400 years ago with the work of Newton. The science of chemistry is little more than 200 years old. In that short time, less than one-one billionth of the total duration of life on earth, we human beings have managed to modify significantly the composition of the atmosphere, the soil, and the waters of the planet. We have become increasingly aware that many of these modifications threaten our health. Why do we behave in this self-destructive way? For several reasons. First, like Darwin and Henderson, we could not imagine that our actions could alter something so vast as the sea or the atmosphere. Secondly, we have been so intent to make our lives more comfortable in the short run, that we have paid little heed to the longrun consequences of technological progress. But mostly, we have done it because we didn't know better.

Let me illustrate the point with the story of DDT. Although this compound was first synthesized in 1874, its effectiveness as an insecticide was not discovered until 1939 by a scientist by the name of Muller in Switzerland. It soon became known as the miracle insecticide. The reasons for this reputation are not hard to find. It is exceedingly toxic to insects and extremely nontoxic to animals, including man. It is remarkably stable and not degraded by living organisms. It is easy and cheap to make and to distribute. As a result of these unusual properties, it soon came into mass use throughout the world in the control of insect infections in crops, as well as insect vectors involved in the transmission of such dangerous human diseases as malaria, trypanosomiasis, and yellow fever. A late as February of 1971 at a conference in Atlanta, sponsored by the World Health Organization on the use of insecticides, L. J. Bruce-Chwatt, professor of tropical hygiene at the London School of Hygiene and Tropical Medicine, said, "There is no doubt that a ban on the production of DDT, or even a large reduction, would cause a chain reaction that could result in the collapse of malaria eradication or control programs where they are most needed—that is, in countries inhabited by the underprivileged two-thirds of mankind now trying so hard to improve their level of existence." In the face of this fantastic success story, why does DDT have such a bad name among environmentalists today?

Ironically, the answer to this question involves the very characteristics of DDT which have made it so eminently useful as an insecticide. First, because it is not easily degraded by living organisms, it persists and is accumulated in the food chain. Thus, it is now present in relatively high concentrations in the fatty tissues of large animals of all kinds, particularly marine organisms and other aquatic animals. Second, the extremely low toxicity of DDT to animals other than insects made it very difficult at the outset to predict the ultimate consequences of its widespread use. There was simply no indication that the compound in high concentrations interferes with the process of calcification of bird eggs until the experiment of nature had been performed. It was with amazement as well as horror that we learned that pelagic birds nesting on islands in the mid-Atlantic were failing to reproduce because their eggs contained DDT which had been sprayed on the farmlands of America and thence washed into the sea. Even today we do not know in detail the mechanisms of toxic effects produced by DDT in high concentrations in higher animals, including man.

I tell the story in some detail because it seems to me to illustrate the very general problem that arises every time that we intervene in our environment. We live in a vast interacting universe, the complexities of which we only begin to understand. Each time we invent to solve an immediate problem, the possibility exists that we create new problems. When thalidomide was first developed as a drug, we did not know that it sometimes produces abnormalities in embryonic development. When the automobile became accepted as a means of transportation, we did not anticipate smog and lead poisoning. The problem confronting us now is to minimize the negative and maximize the positive benefits of invention.

In my experience, there is only one path toward wiser and more informed stewardship of our planet. It is the path of basic scientific re-

search. In order for us to anticipate the potential consequences of new chemicals and new machines and new sources of power, we must know more about their properties. In order for us to treat effectively diseases caused by agents which we have already introduced into the environment, we must understand better the mechanism of their toxicity. The only route to such understanding is through the hard mental work of careful experiments in the laboratory and in the field.

It is for this reason, Mr. Fountain, that I am particularly pleased to participate in this hearing with representatives from the National Institute of Environmental Health Sciences. This branch of the National Institutes of Health has already established itself as a leader in supporting basic research into the origins of environmental hazards to health. I very much hope that the Congress of the United States will see fit to continue to increase support for this essential component in our effort to improve the conditions of life for the citizens of the United States and for citizens throughout the world.

One aspect of the operations of NIEHS deserves special note. Unlike other components of NIH, this Institute is located not in Bethesda but in the Research Triangle Park of North Carolina. Because of this location, it has been possible for members of the Institute staff to interact closely with scholars in nearby universities. In my judgment, these interactions between members of the university community, both faculty and students, and scientists working in the laboratories of the Institute have been mutually productive. For example, it was not long ago that a graduate student at Duke University who has made some interesting new observations about the mechanism of toxicity of DDT had the opportunity to discuss his work with Dr. Rall and members of his staff. This kind of episode could well serve as a model for the proper relationship between agencies of the Federal Government and our citizens.

Mr. Fountain, members of the subcommittee, I hope that my remarks will encourage you in your work to strengthen Federal support for efforts to understand and control manmade health hazards. I have tried to convey the complexity of the problems and the essentiality of basic research to provide solutions. Thank you for your attention. I will be pleased to answer questions which you may have about these matters.

Mr. FOUNTAIN. Thank you very much for an extremely interesting statement. I think no one would disagree with the concluding remark emphasizing the essentiality of basic research to provide solutions.

In view of the fact that we are running a little later than we planned, I will withhold any questions and defer to other members for any questions they may wish to ask.

Mr. ALEXANDER. Doctor, one question—if I might ask. Do you in your studies have an interrelated exchange of information with those agencies which are concerned with the depletion of our earth's resources, or do you confine your research to the contamination of the environment?

Dr. TOSTESON. I think the answer to that would have to be the latter. We don't confine our research to environmental health hazards. We do research in fundamental physiology and pharmacology and all of its ramifications, but we do relatively little on research of the consequences of the depletion of the resources of the planet.

Mr. ALEXANDER. I wonder if one is related to the other?

Dr. TOSTESON. Certainly so.

Mr. ALEXANDER. And I wonder if an exchange would not be beneficial or helpful in the organizational structure that makes up the system that we have to police the planet?

Dr. TOSTESON. Well, I think one of the problems that living in the modern world is, is that everything is related to everything else and there is a limitation of the number of hours in the day. I think in principle it's a good idea, but as you well know, you can't do everything.

Mr. ALEXANDER. On that point, Doctor, I will yield to my colleagues.

Mr. FUQUA. I want to thank you for a very fine statement. I agree wholeheartedly and I appreciate your time spent to prepare this statement.

On page 4, you have made a great statement pertaining to basic research—that it applies to many of our social problems. You say, "Each time we invent to solve an immediate problem, the possibility exists that we create new problems." That's not just related to basic research; in dealing with many of our social problems we realize that we have created other problems. It's like putting your finger in a dike; plug one hole and you find another one. I think it sums up the big problem we have.

Mr. FOUNTAIN. I also think you have made a very self-explanatory statement, which will be a significant contribution to our hearing record. We thank you very much for being here.

Dr. TOSTESON. Thank you, gentlemen.

(Dr. Tosteson's curriculum vitae follows:)

CURRICULUM VITAE

Name: Daniel C. Tosteson.
Date and place of birth: February 5, 1925—Wauwatosa, Wis.
Marital status: Married, four children.

Education:

Harvard College, 1942–44
Harvard Medical School, M.D., 1949

Membership in societies:

AOA
American Physiological Society (Council, 1968–69, 1969–73) president-elect, 1972.
Society of General Physiologists (president, 1968–1969).
Biophysical Society
AAAS
AAMC
Council of Academic Societies (president, 1969–70)
Association of Chairmen of Departments of Physiology

Consultant and advisory positions:

Molecular Biology Panel, National Science Foundation, 1961–64.
Scientific Advisory Committee, NIH, Health Research Facilities, 1964–67.
National Advisory Council, NIH, Health Research Facilities, 1968–71.
Scientific Advisory Board, National Kidney Foundation, 1961–68.
Chairman, Grants and Fellowship Committee, National Kidney Foundation, 1965–68.

Positions held:

Professor and chairman, Department of Physiology and Pharmacology, Duke University School of Medicine, 1961–.
Associate professor, Department of Physiology, Washington University School of Medicine, St. Louis, 1958–61.

Research Fellow, Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, Bethesda, 1957.
Research Fellow, Physiological Laboratory, Cambridge, England, 1956–57.
Research Fellow, Department of Biological Isotope Research, Copenhagen, Denmark, 1955–56.
Research Fellow, Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, Bethesda, 1953–55.
Research Fellow, medical department, Brookhaven National Laboratory, New York, 1951–53.
Intern and assistant resident in medicine, Presbyterian Hospital, New York, 1950–51.
Fellow, Department of Physiology, Harvard Medical School, 1947–48.
Over 50 scientific publications.

Mr. FOUNTAIN. Another distinguished professor with us today is Dr. K. M. Brinkhous, the alumni distinguished professor of pathology, and chairman of the department of pathology at the University of North Carolina, Chapel Hill, who will testify concerning certain aspects of environmental health problems. Dr. Brinkhous, we are honored to have you here and we deeply appreciate your taking the time to appear and give us the benefit of your thinking this morning. You may proceed.

STATEMENT OF DR. KENNETH M. BRINKHOUS, PROFESSOR OF PATHOLOGY, UNIVERSITY OF NORTH CAROLINA

Dr. BRINKHOUS. Mr. Chairman, I am pleased to have this opportunity to comment upon the activities of the NIEHS in relation to certain environmental health problems facing us today. First I would like to say that those of you in the Congress who decided upon the location of this Institute in the Research Triangle, may look back upon this as having been a very wise decision. The Institute was quickly established and has been functioning in a very effective manner, considering its limitations in budget and personnel. It has been a good neighbor, and in the process has demonstrated that the Federal Government can carry out a research mission at the operational level jointly with adjacent universities. One of the greatest needs and one of the most difficult things to attain is that of essential new knowledge on which a sounder environmental health program can be based.

Manpower available for the development of new knowledge resides in good part in the major universities. The partnership that has been fostered between the Institute and the Research Triangle universities may well be a prototype in pursuing basic research essential to the Nation's needs that might be emulated in other research areas of the Federal Government. I could mention as an example of the success of this arrangement studies that have significantly advanced our knowledge of lead poisoning. These studies were carried out by pathologists and chemists at Chapel Hill in consultation with Institute scientists at the NIEHS. An addendum to this statement summarized what has been accomplished by this cooperation.

As a pathologist and hematologist, I am impressed that disease due to environmental agents as, for example, the heavy metals like lead, or halogenated hydrocarbons and organophosphates as in many of the pesticides, present challenging problems to us as a society in developing a rational and effective policy. It is perhaps easy enough

to identify some obvious toxic agents in the environment and to develop hastily a program for their control with arbitrary standards for tolerable contamination, whether it be in water, air, foodstuffs, or the occupational environment. And it is essential that this be done, as it is. But for long term policy, this is far from enough.

If one examines the scientific data on which practical decisions are made, all too often one finds it is sparse indeed. We are rather thoroughly exploiting the basic knowledge that is available. We are dealing with agents that are taken into the body in low levels over long periods of time, and whose effects, which eventually may be very damaging, are for years so subtle as to be undetectable by present methodologies. We have not yet developed our vision to the point where early damage can be seen. To make matters more complicated, as we live in our various environments, individuals are exposed to low levels of not just one but many potentially toxic agents over a long period of time. I personally would like to commend the Institute because they recognize the problem. The NIEHS has recognized this important problem and there is just beginning to be understood the effects of exposure to multiple agents at low levels from infancy to death. The end result is that one is dealing with chronic degenerative diseases that developed over the years, for which there is no curative treatment. So prevention appears to be the only feasible approach.

But in a highly technological society, which will undoubtedly become more technologic in the future, hazardous agents cannot be completely avoided. The potential magnitude of the problem becomes staggering when it is realized that chemists develop several thousand new chemical compounds each year. To determine realistic and relatively safe levels for all of these compounds appears impossible. Major effort should be given instead to developing principles as to how the body handles or fails to handle a group of compounds, both qualitatively and quantitatively. How are they stored and detoxified, and how can the body be aided in managing and getting rid of these toxic materials? Once one knows the exact pathways in the body and the microenvironment of the cell in which the toxic agent exerts its effect, drugs should be developed to help the body detoxify the environmental agents. An analogy is seen with phenobarbital which can increase the activity of enzymes in the liver responsible for detoxification of many drugs and chemicals. Thus, (1) we must work with the information currently available to develop realistic standards. A completely nonhazardous environment is only an ideal. And (2) we must support and protect the scientists who are developing the new knowledge that should eventually allow a completely rational environmental health policy.

One other aspect of research should be emphasized. A while back, a tobacco farmer from eastern North Carolina came to our hospital, hemorrhaging literally from all orifices. This bleeding state was due to the disappearance of one of the blood clotting factors, so-called Stuart factor, named after Mr. Stuart from the North Carolina mountains. This acquired hemophilia-like disorder developed following use of a common fungicide on the tobacco bed. He recovered in about 2 weeks. He delegated fumigation of his seed bed to his eldest son, and he had

no further trouble. No similar disorder could be produced in animals exposed to the fumigant. This and other experiences illustrate that some members of the population are more susceptible to a toxic agent than others—and this is not just a matter of dosage. Here we had a case of extreme hypersusceptibility. Many things may contribute to this varying susceptibility, as genetic factors, nutritional state, exposure to other agents, drugs, and even preexisting disease. Adaptation is one of the characteristics of the race. One needs to know the limits of individuals to adapt to noxious agents and thus to attain a protective mechanism. This spectrum of high susceptibility on the one hand and acquired resistance on the other needs to be better understood. Population or epidemiologic studies are in order here.

The population of North Carolina provides a good base for such studies, for several reasons. It has a relatively stable population, less mobile that many of the highly industrial States of the Union. Its population in many regards is well studied, and university medical center resources are available for specific investigations. It should be mentioned that there is a unique medical examiner system in this State, based at the university at Chapel Hill, which provides an important resource for analysis of the load of toxic agents as heavy metals, radioactive elements, and the like that the population carries.

The body of knowledge dealing with environmental health is relatively limited in comparison for example to the infectious diseases. Even the knowledge we do have has not been well collated for ready access by students and investigators. We badly need continuing up-to-date documentation of what is known, for the different disciplines contributing to environmental health. Certainly this is true of environmental pathology. The National Research Council and the NIEHS are exploring how this might be done effectively and soundly. For this, they should be commended, and I hope there will be evidence of results in this.

A corollary to all of this is need for the training of investigators of the future. Training grant support needs to be expanded. For example, there is only one training grant in the whole country in environmental pathology. And this is the area that should be determining how environmental toxins affect the human body.

A few specific suggestions of how the NIEHS could expand its efforts are contained in an appendix to this statement.

In summary, this statement has attempted to show the following:

(*a*) Special opportunities and resources are available to the NIEHS by reason of its location in the Research Triangle Park.

(*b*) The nature of the problems the biomedical community faces in dealing with the long term aspects of environmental health hazards requires intensified basic research studies of a special nature.

(*c*) A need exists for documentation and summation of the present state of the art.

(*d*) There is an urgent need for an expanded program for training professionals in the field.

With this statement, Mr. Fountain, I think I will conclude. There are addendum No. 1 and addendum No. 2 which I submit for the record.

(The documents referred to follow:)

Addendum No. 1 to Statement by K. M. Brinkhous, M.D.

Lead poisonings research program by Dr. Robert A. Goyer and associates, Department of Pathology, University of North Carolina

This program illustrates the type of basic knowledge which needs to be attained to better deal with environmental toxic agents. The program has been concerned with understanding the subcellular effects of lead, which is a near ubiquitous environmental contaminant. It is present in measurable amounts in the air we breathe and in practically all foods and water we ingest. Furthermore, there is no doubt that lead is toxic to man. It may produce irreversible brain injury to young children and even be fatal. On the other hand, adults in the general population carry in their various body stores one-half gram of lead without producing any apparent harm. The question, therefore, is whether these body stores of lead are in fact harmful in a way that we cannot yet detect, or whether the body has developed some compensatory mechanism to handle this metal.

It has been learned from studies conducted by this research program under the auspices of NIEHS that the earliest detectable structural and biochemical effect of lead ingestion by rats is the formation of a nondiffusable lead-protein complex in nuclei of liver and kidney cells. These two organs are important in the excretion of lead from the body. The lead containing bodies may be seen by microscopic techniques before the onset of any other detectable effect of lead, and more recently, we have shown that there is a particular fraction of nuclear protein bound to lead that is measurable even prior to formation of visible lead-protein complexes. In fact, this lead-protein complex is present in nuclei of kidney cells of rats with only the usual environmental exposure to lead, that is, the lead present in commercial animal chow and tap water.

It can be argued that such an effect of only trace amounts of lead is truly pathological or harmful. Or does it, in fact, represent a compensatory or adaptive mechanism? Such a discussion may become more philosophical than scientific, but it is important to know at what point such a mechanism influences overall health. How much does it cost the kidney cell to form these lead-protein complexes in terms of survival or ability to perform other functions? Study of this question is in progress.

Another question this program has addressed itself to is the matter of susceptibility to the toxic effects of lead. The medical writings regarding toxicity of lead go back more than 2,000 years and contain many suggestions regarding interaction with other environmental factors which either enhance or reduce the toxic effects of a particular dose of lead. These include age, season of the year, ingestion of other toxic metals such as cadmium and, in particular, various nutritional factors. Calcium metabolism influences the toxic effects of lead. Reduction of dietary calcium in the rat to 20 percent of the recommended nutritional requirement will decrease the minimally toxic dose of lead some 25 or 30 times. Translated into the clinical situation, this means that children who are calcium deficient are more susceptible to lead toxicity than children with adequate calcium ingestion. Similarly, iron deficient rats are more susceptible to the toxic effects of a low level of lead exposure but this is not nearly as dramatic as with calcium deficient animals.

Results of the research program to date indicate that the study of cellular effects of lead serves as a good model to define questions that must be entertained in the study of other environmental contaminants, particularly other metals. Such studies also point out the great depth of knowledge regarding the effects of toxic substances, particularly at the molecular level, that must be acquired before decisions regarding permissible or tolerable levels of a particular substance can be implemented in a meaningful way.

Addendum No. 2 to the Statement by K. M. Brinkhous, M.D.

Some examples of areas needing increased attention in environmental health

1. Training programs in universities in environmental pathology, including toxicology and biochemistry, with emphasis on applications of basic science background and tools to problems in environmental health, involving sophisticated approaches directed to the molecular level. Two- or three-year postdoctoral

programs with appropriate support for personnel already trained in the core science areas is suggested, rather than establishing predoctoral or technician training programs. Because of current trends in interest and in availability of students, a large pool of talent is available from which to draw candidates for these important fields.

2. Multidisciplinary centers directed toward solution of basic problems in environmental health should be established in universities. Each center should have a specialized focus with the aim of developing experience and knowledge in depth in a specific field.

3. Detection of early stages of disease: NIEHS should investigate the opportunities for interfacing with clinical pathology-laboratory medicine in the earlier detection of diseases induced by environmental agents.

Two aspects are of especial importance: (a) Development of routine screening tests of toxic agents suitable for use in clinical laboratories; (b) training programs for clinical pathologists and clinical chemists to include consideration of the health picture as regards heavy metal, pesticide, and industrial agent toxicology (that is, lead, mercury, cadmium, chlorinated pesticides, et cetera).

Mr. FOUNTAIN. Thank you very much, Doctor. I hope these statements will be carefully studied by the officials of the Institute.

You refer on page 4 to the need for more population studies to learn more about the limits of individuals to adapt to noxious agents. Have you given thought to who might best do those studies; where should that responsibility be placed? Where would it be most appropriate?

Dr. BRINKHOUS. It seems to me that studies of this type can best be based in a university environment, getting the cooperation of county health departments, the State medical examiner systems, and others. We mentioned scientists and others based in universities who could be involved. I believe that for the Federal Government to try to develop completely its own capabilities for something like this would be very expensive, and I am not certain how successful it would be.

Mr. FOUNTAIN. What agency would you suggest?

Dr. BRINKHOUS. The universities. I think the work should be done in the universities, supported by grants, contracts, and what other mechanisms that could be developed for an institute like we are talking about here to carry out these studies.

Mr. FOUNTAIN. Do you have an opinion as to what agencies the grants should come from?

Dr. BRINKHOUS. I think there ought to be enough funds available to the NIEHS to do this type of study. I don't think that the NIEHS should look to other groups to do it. They should do it themselves.

Mr. FOUNTAIN. Are there any other questions? Thank you very much, Doctor.

(Dr. Brinkhous' curriculum vitae follows:)

CURRICULUM VITAE

Name: Kenneth Merle Brinkhous.

Place and date of birth: Clayton County, Iowa, May 29, 1908.

Marital status: Married, two children.

Education and professional qualifications: Student, U.S. Military Academy, 1925; A.B., State University of Iowa, 1929; M.D., State University of Iowa, 1932; Diplomate, American Board of Pathology (Pathologic Anatomy & Clinical Pathology); D. Sc., University of Chicago, 1967, Honorary.

Military service: Army Medical Corps, 1941–1946, ranks from Captain to Colonel, South Pacific and U.S.A. areas; Colonel, Army Reserve, Commanding Officer, 3256th Research & Development Unit (Research Triangle) (1956–66).

Academic positions: Assistant in Pathology, State University of Iowa, 1932–33; Instructor in Pathology, State Univ. of Iowa and Intern, Univ. Hospitals, 1933–34; Instructor in Pathology, State Univ. of Iowa, 1934–35; Associate in Pathology, State Univ. of Iowa, 1935–37. Assistant Professor of Pathology, State Univ. of Iowa, 1937–45 (on Military Leave of Absence, 1941–45); Associate Professor of Pathology, State Univ. of Iowa, 1945–46; Professor of Pathology and Chairman, Department of Pathology, Univ. of North Carolina, 1946–61; Alumni Distinguished Professor of Pathology, and Chairman, Department of Pathology, Univ. of North Carolina, 1961—.

Society memberships: American Association of Pathologists and Bacteriologists (Secretary-Treasurer, 1968–71); American Medical Association; Durham-Orange County (N.C.) Medical Society (President, 1955–56); American Association for Advancement of Science; American Society of Clinical Pathologists (Chairman, Awards Committee, 1965); American Society of Experimental Pathology (Council 1959—; Sec'y-Treas. 1960–63; Vice President, 1964–65; President 1965–66).

American Society of Hematology (Exec. Committee, 1959–62; Advisory Committee, 1966–1970); Association of American Physicians; Central Society for Clinical Research; College of American Pathologists; Federation of American Societies for Experimental Biology (Vice-President, 1965–66; President, 1966–67); International Academy of Pathology; International Society of Hematology; Medical Society of North Carolina; North Carolina State Pathology Society (President, 1964–65); Society for Experimental Biology and Medicine (Council, 1969–73).

Committees, etc.: Member, 1948–52, Hematology Study Section, National Institutes of Health; Chairman, 1959–62; Chairman, Pathology Study Section, 1957–59, National Institutes of Health; Member, Panel & Subcommittee on Blood Coagulation, National Research Council, 1951–54; Chairman, 1954–62; Member, Subcommittee & Committee on Blood, National Research Council, 1954–64; Member. Cardiovascular Committee, National Research Council, 1957–62. Member Thrombosis Task Force, National Research Council, 1965—; Chairman Pathology Test Committee, and Member, National Board of Medical Examiners, 1956–59; Chairman, Medical Advisory Committee, National Hemophilia Foundation, 1954—; Member, International Committee on Haemostasis and Thrombosis, 1954—; Chairman, 1964–66; Secretary General, 1966—; Member, International Society on Thrombosis and Haemostasis, 1969—.

Consultant, Armed Forces Institutes of Pathology, 1956–64; Member, Scientific Advisory Committee 1957—; Chairman, 1964–65; Member, Committee on Coagulation Factors, Protein Foundation (Cambridge, Mass.), 1954—; Member, the Governor's Scientific Advisory Committee (North Carolina, 1961–65); Member, Program Project Committee, National Heart Institute, 1962–65; Member, Committee on Thrombolytic Agents, National Heart Institute, 1962–65; Member, National Research Council, Division of Medical Sciences, 1964—; (Member, Executive Committee, 1965–70); Member, Scientific and Advisory Committee, World Federation of Hemophilia, 1964—; Member, Council on Thrombosis, American Heart Association, 1970—; Member, Committee on Scientific Sessions Program, American Heart Association, 1971—; Member, Task Force on Arteriosclerosis, National Institutes of Health, 1970—; Trustee, Intersociety Committee for Research and Education in Pathology, Inc. 1964—; President, 1964; Member, Scientific Advisory Board, American National Red Cross, 1965—; Member, Scientific Advisory Council Hyland Laboratories, 1965—; Member, Editorial Board, Current Topics in Pathology; Board of Editors, Journal of Laboratory and Clinical Medicine, 1948–53; Proceedings of Society for Experimental Biology and Medicine, 1950–53.

Blood, Journal of Hematology, 1950–74. A.M.A. Archives of Pathology, 1961—; Thrombosis et Diathesis Haemorrhagica, Co-editor, 1960—; Member, Editorial Board, Human Pathology; Member, National Advisory Heart Council, National Institutes of Health; Member, Universities Associated for Research and Education in Pathology, Inc., 1964—; President, 1964–68; Chairman, Committee on Pathology, Division of Medical Sciences, National Research Council; Representative of American Society of Clinical Pathologists to the Intersociety Committee for Research Potential in Pathology, Inc.; Member, American Society Clinical Pathologists (Basic Science Research Symposium Comm.) Laboratory Investigation, 1963–71; Perspectives in Biology and Medicine, 1968—.

Other: Oliver Max Gardner Award, Board of Trustees, Consolidated University of North Carolina, 1961; Co-recipient, Ward-Burdick Award, American Society of Clinical Pathologists, 1941, for investigations on Vitamin K; Recipient, Ward-Burdick Award, 1963; North Carolina Award in Science, 1969; James F. Mitchell Foundation, International Award for Heart and Vascular Research, 1969; Phi Beta Kappa; Phi Lambda Upsilon Honorary Chemical Fraternity; Alpha Omega Alpha; Sigma Xi; Phi Chi.

Bibliography

(K. M. Brinkhous)

1. Smith, H. P., Warner, E. D., Brinkhous, K. M. Lung extract and blood clotting. Am. J. Physiol. 107: 63–69, Jan. 1934.
2. Warner, E. D., Brinkhous, K. M., Smith, H. P. The titration of prothrombin in certain plasmas. Arch. Path. 18: 587, Oct. 1934. (Abstract)
3. Smith, H. P., Warner, E. D., Brinkhous, K. M. Quantitative studies on blood coagulation. Arch. Path. 20: 163, July 1935. (Abstract)
4. Warner, E. D., Brinkhous, K. M., Smith, H. P. A quantitative study on blood clotting: prothrombin fluctuations under experimental conditions. Am. J. Physiol. 114: 667–675, Feb. 1936.
5. Hawkins, W. B., Brinkhous, K. M. Prothrombin deficiency the cause of bleeding in bile fistula dogs. J. Exp. Med. 63: 795–801, June 1936.
6. Brinkhous, K. M., Smith, H. P., Warner, E. D. Plasma prothrombin level in normal infancy and in hemorrhagic disease of the newborn. Am. J. Med. Sci. 193: 475–480, April 1937.
7. Smith, H. P., Warner, E. D., Brinkhous, K. M. Prothrombin deficiency and the bleeding tendency in liver injury (chloroform intoxication). J. Exp. Med. 66: 801–811, Dec., 1937.
8. Warner, E. D., Brinkhous, K. M., Smith, H. P. Bleeding tendency of obstructive jaundice: prothrombin deficiency and dietary factors. Proc. Soc. Exp. Biol. Med. 37: 628–630, Jan. 1938.
9. Seegers, W. H., Smith, H. P., Warner, E. D., Brinkhous, K. M. The purification of prothrombin. J. Biol. Chem. 123: 751–754, May 1938.
10. Smith, H. P., Warner, E. D., Brinkhous, K. M., Seegers, W. H. Bleeding tendency and prothrombin deficiency in biliary fistula dogs: effect of feeding bile and vitamin K. J. Exp. Med. 67: 911–920, June 1938.
11. Brinkhous, K. M., Smith, H. P., Warner, E. D. Prothrombin deficiency and the bleeding tendency in obstructive jaundice and in biliary fistula. (Effect of feeding bile and alfalfa—Vitamin K.) Am. J. Med. Sci. 196: 50–57, July 1938.
12. Seegers, W. H., Brinkhous, K. M., Smith, H. P., Warner, E. D. The purification of thrombin. J. Biol. Chem. 126: 91–95, Nov. 1938.
13. Seegers, W. H., Warner, E. D., Brinkhous, K. M., Smith, H. P. The use of purified thrombin as an hemostatic agent. Science 89: 86, Jan. 1939. (Abstract)
14. Warner, E. D., Brinkhous, K. M., Smith, H. P. Plasma prothrombin levels in various vertebrates. Am. J. Physiol. 125: 296–300, Feb. 1939.
15. Warner, E. D., Brinkhous, K. M., Smith, H. P. The prothrombin conversion rate in various species. Proc. Soc. Exp. Biol. Med. 40; 197–200, Feb. 1939.
16. Brinkhous, K. M., Smith, H. P., Warner, E. D., Seegers, W. H. The inhibition of blood clotting: an unidentified substance which acts in conjunction with heparin to prevent the conversion of prothrombin into thrombin. Am. J. Physiol. 125: 683–687, April 1939.
17. Scanlon, G. H., Brinkhous, K. M., Warner, E. D., Smith, H. P., Flynn, J. E. Plasma prothrombin and the bleeding tendency, with special reference to jaundiced patients and vitamin K therapy. J.A.M.A. 112: 1898–1901, May 1939.
18. Warner, E. D., Brinkhous, K. M., Seegers, W. H., Smith, H. P. Further experience with the use of thrombin as a hemostatic agent. Proc. Soc. Exp. Biol. Med. 41: 655–657, June 1939.
19. Knowlton, G. C., Hines, H. M., Brinkhous, K. M. Effect of wheat germ oil upon E-deficient muscular dystrophy. Proc. Soc. Exp. Biol. Med. 41: 453–456, June 1939.

20. Brinkhous, K. M. A study of the clotting defect in hemophilia: the delayed formation of thrombin. Am. J. Med. Sci. 198: 509–516, Oct. 1939.
21. Knowlton, G. C., Hines, H. M., Brinkhous, K. M. Cure and prevention of vitamin E-deficient muscular dystrophy with synthetic A-tocopherol acetate. Proc. Soc. Exp. Biol. Med. 42: 804–809, Dec. 1939.
22. Brinkhous, K. M., Smith, H. P., Warner, E. D., Seegers, W. H. Heparin and blood clotting. Science 90: 539, Dec. 1939. (Correspondence)
23. Brinkhous, K. M. Plasma prothrombin: vitamin K. Medicine 19: 329–416, Sept. 1940.
24. Brinkhous, K. M., Warner, E. D. Effect of vitamin K on hypoprothrombinemia of experimental liver injury. Proc. Soc. Exp. Biol. Med. 44: 609–610, 1940.
25. Brinkhous, K. M., Warner, E. D. Muscular dystrophy in biliary fistula dogs: possible relationship to vitamin E-deficiency. Am. J. Path. 17: 81–86, Jan. 1941.
26. Brinkhous, K. M., Walker, S. A. Prothrombin and fibrinogen in lymph. Am. J. Physiol. 132: 666–669, April 1941.
27. Seegers, W. H., Warner, E. D., Brinkhous, K. M., Smith, H. P. Heparin and the antithrombic activity of plasma. Science 96: 300–301, Sept. 1942.
28. Brinkhous, K. M. Clotting defect in hemophilia: deficiency in a plasma factor required for thromboplastin liberation from platelets. Fed. Proc. 6: 389–390, March 1947. (Abstract)
29. Brinkhous, K. M. Thrombin and its clinical applications. Southern Surgeon. 13: 397–402, June 1947.
30. Brinkhous, K. M. Clotting defect in hemophilia: deficiency in a plasma factor required for platelet utilization. Proc. Soc. Exp. Biol. Med. 66: 117–120, 1947.
31. Brinkhous, K. M. Initiation and acceleration factors in thrombosis. Blood Clotting and Allied Problems, Transactions of the First Conference. Josiah Macy, Jr. Foundation, New York, 1948, pp. 39–44.
32. Graham, J. B., Buckwalter, J. A., Hartley, L. J., Brinkhous, K. M. Canine hemophilia: the clotting anomaly and effectiveness of transfusions. Fed. Proc. 8: 356, March 1949. (Abstract)
33. Graham, J. B., Buckwalter, J. A., Hartley, L. J., Brinkhous, K. M. Canine hemophilia: observations on the course, the clotting anomaly and the effect of blood transfusions. J. Exp. Med. 90: 97–111, Aug. 1949.
34. Buckwalter, J. A., Blythe, W. B., Brinkhous, K. M. Effect of blood platelets on prothrombin utilization of dog and human plasmas. Am. J. Physiol. 159: 316–321, Nov. 1949.
35. Brinkhous, K. M., Graham, J. B. Occurrence of hemophilia in females. J. Lab. Clin. Med. 34: 1587, Nov. 1949. (Abstract)
36. Graham, J. B., Penick, G. D., Brinkhous, K. M. Studies on utilization of antihemophilic factor during clotting. Fed. Proc. 9: 330–331, March 1950. (Abstract)
37. Brinkhous, K. M., Graham, J. B. Hemophilia in the female dog. Science 111: 723–724, June 30, 1950.
38. Langdell, R. D., Graham, J. B., Brinkhous, K. M. Prothrombin utilization during clotting: comparison of results with the two-stage and one-stage methods. Proc. Soc. Exp. Biol. Med. 74: 424–427, 1950.
39. Graham, J. B., Collins, D. L., Jr., Godwin, I. D., Brinkhous, K. M. Antihemophilic factor: levels in canine and human plasmas, and following liver injury and dicumarol. Fed. Proc. 10: 355, March 1951. (Abstract)
40. Brinkhous, K. M. Canine hemophilia: studies on the inheritance of the disease and the clotting defect. Proc. 3rd Congress Internat. Soc. Hematol. New York, Grune and Stratton, 1951, pp. 439–440.
41. Graham, J. B., Penick, G. D., Brinkhous, K. M. Utilization of antihemophilic factor during clotting of canine blood and plasma. Am. J. Physiol. 164: 710–715, 1951.
42. Brinkhous, K. M., Graham, J. B., Penick, G. D., Langdell, R. D. Studies on canine hemophilia. Blood Clotting and Allied Problems, Transactions of the Fourth Conference. Josiah Macy, Jr. Foundation, New York, 1951, pp. 51–118 (with discussion).
43. Graham, J. B., Collins, D. L., Jr., Godwin, I. D., Brinkhous, K. M. Assay of plasma antihemophilic activity in normal heterozygous (hemophilia) and prothrombinopenic dogs. Proc. Soc. Exp. Biol. Med. 77: 294–296, 1951.

44. Penick, G. D., Cronkite, E. P., Godwin, I. D., Brinkhous, K. M. Plasma antihemophilic activity following total body irradiation. Proc. Soc. Exp. Biol. Med. 78: 732–734, 1951.
45. Brinkhous, K. M., Morrison, F. C., Jr., Muhrer, M. E. Comparative study of clotting defects in human, canine and porcine hemophilia. Fed. Proc. 11: 409, March 1952. (Abstract)
46. Langdell, R. D., Wagner, R. H., Brinkhous, K. M. Antihemophilic factor: its effect on one-stage clotting tests as basis for a simple AHF assay procedure. Fed. Proc. 11: 420, Mar. 1952. (Abstract)
47. Graham, J. B., McLendon, W. W., Brinkhous, K. M. Mild hemophilia: an allelic form of the disease. Am. J. Med. Sci. 225: 46–53, Jan. 1953.
48. Graham, J. B., Langdell, R. D., Morrison, F. C., Jr., Brinkhous, K. M. Influence of antihemophilic factor (AHF) and serum accelerator on prothrombin utilization in canine blood. Fed. Proc. 12: 388, March 1953. (Abstract)
49. Wagner, R. H., Brannan, W. M., Jr., Brinkhous, K. M. Antiaccelerator (anticonvertin) activity of canine plasma and serum fractions. Fed. Proc. 12: 405, March 1953. (Abstract)
50. Langdell, R. D., Wagner, R. H., Brinkhous, K. M. Effect of antihemophilic factor on one-stage clotting tests: a presumptive test for hemophilia and a simple one-stage antihemophilic factor assay procedure. J. Lab. Clin. Med. 41: 637–647, April 1953.
51. Graham, J. B., Brinkhous, K. M. Christmas disease. Brit. Med. J. II: 97, July 1953. (Correspondence)
52. Brinkhous, K. M. Head hunting of a less classical type; a word to freshmen. Bull. School of Med., Whitehead Soc., Med. Found., U.N.C. 1: 2–5, Oct. 1953.
53. Penick, G. D., Taylor, C. B., Huffines, W. D., Roberts, H. R., Wilson, S. G., Brinkhous, K. M. Comparative study of responses of normal and hemophilic dogs to local cold injury. U.S.A.F. School of Aviation Medicine, Project No. 21–1202–0001, Report No. 6, Dec. 1953.
54. Penick, G. D., Brinkhous, K. M. The purpuric states. Current Therapy 1953, H. F. Conn, Ed., Philadelphia, W. B. Saunders Co., 1953, pp. 238–243.
55. Brinkhous, K. M., Langdell, R. D., Penick, G. D., Graham, J. B., Wagner, R. H. Newer approaches to the study of hemophilia and hemophilioid states. J.A.M.A. 154: 481–486, Feb. 1954.
56. Langdell, R. D., Wagner, R. H., Brinkhous, K. M. Changes in levels of antihemophilic factor (AHF) of normal and hemophilic dogs after transfusion. Fed. Proc. 13: 436, March 1954. (Abstract)
57. Penick, G. D., Brinkhous, K. M. Influence of storage conditions on stability of antihemophilic factor (AHF) of canine and human blood and plasma. Fed. Proc. 13: 440, March 1954. (Abstract)
58. Wagner, R. H., Pate, D. H., Brinkhous, K. M. Further purification of antihemophilic factor (AHF) from dog plasma. Fed. Proc. 13: 445, March 1954. (Abstract)
59. Brinkhous, K. M., Graham, J. B. Hemophilia and the hemophilioid states. Blood 9: 254–257, March 1954.
60. Brinkhous, K. M. Hemophilia. Bull. New York Acad. Med. 3: 325–342, May 1954.
61. Brinkhous, K. M. Research training in pathology. Lab. Invest. 3: 395–401, Sept.–Oct. 1954.
62. Brinkhous, K. M. Pathology. Seventy-Five Years of Medical Progress, 1878–1953. Philadelphia, Lea & Febiger, 1954, pp. 133–142.
63. Brinkhous, K. M. Plasma antihemophilic factor, biological and clinical aspects. Sang 25: 738–741, 1954.
64. Graham, J. B., Langdell, R. D., Morrison, F. C., Jr., Brinkhous, K. M. Serum accelerator factors and antihemophilic factor (AHF) in early phases of clotting. Proc. Soc. Exp. Biol. Med. 87: 45–48, 1954.
65. Penick, G. D., Brinkhous, K. M. The purpuric states. Current Therapy 1954. H. F. Conn, Ed., Philadelphia, W. B. Saunders Co., 1954, pp. 267–272.
66. Penick, G. D., Wagner, R. H., Roberts, H. P., Brinkhous, K. M. Inactivation of plasma antihemophilic factor (AHF) Fed. Proc. 14: 415, March 1955. (Abstract)
67. Langdell, R. D., Wagner, R. H., Brinkhous, K. M. Antihemophilic factor (AHF) levels following transfusions of blood, plasma, and plasma fractions, Proc. Soc. Exp. Biol. Med. 88: 212–215, 1955.

68. Wagner, R. H., Brannan, W. M., Jr., Brinkhous, K. M. Antiaccelerator (Anticonvertin) activity of canine plasma and serum. Proc. Soc. Exp. Biol. Med. 89:266–270, 1955.
69. Brinkhous, K. M., Penick, G. D. Some systemic alterations in clotting factors following local tissue injury. Thrombosis and Embolism, First Internat. Conf., Basel 1954. Basel, Benno Schwabe & Co., 1955, pp. 428–433.
70. Langdell, R. D., Wagner, R. H., Brinkhous, K. M. Estimation of antihemophilic activity by the partial thromboplastin time technic. The Coagulation of Blood. L. M. Tocantins, Ed., New York, Grune & Stratton, 1955, pp. 72–76.
71. Graham, J. B., Penick, G. D., Brinkhous, K. M. Estimation of antihemophilic activity by the prothrombin utilization technic. The Coagulation of Blood. L. M. Tocantins, Ed., New York, Grune & Stratton, 1955, pp. 77–80.
72. Wagner, R. H., Graham, J. B., Penick, G. D., Brinkhous, K. M. Estimation of prothrombin by the two-stage method. The Coagulation of Blood. L. M. Tocantins, Ed., New York, Grune & Stratton, 1955, pp. 105–111.
73. Graham, J. B., Langdell, R. D., Brinkhous, K. M. Estimation of the rate of prothrombin utilization. The Coagulation of Blood. L. M. Tocantins, Ed., New York, Grune & Stratton, 1955, pp. 117–119.
74. Brinkhous, K. M., Penick, G. D., Langdell, R. D., Wagner, R. H., Graham, J. B. Physiologic basis of transfusion therapy in hemophilia. Arch. Path. 61: 6–10, Jan. 1956.
75. Wagner, R. H., McAllister, J. G., Brinkhous, K. M. Selective adsorption of antihemophilic factor (AHF) and fibrinogen from canine plasma. Fed. Proc. 15: 537, March 1956. (Abstract)
76. Brinkhous, K. M. The new medical examiner act of North Carolina. N. C. Med. J. 17: 253–259, June 1956.
77. Penick, G. D., Brinkhous, K. M. Relative stability of plasma antihemophilic factor (AHF) under different conditions of storage. Am. J. Med. Sci. 232: 434–441, Oct. 1956.
78. Wagner, R. H., Langdell, R. D., Richardson, B. A., Farrell, R. A., Brinkhous, K. M. Parenteral administration of antihemophilic factor (AHF) preparations in the dog. Fed. Proc. 16: 376, March 1957. (Abstract)
79. Wagner, R. H., Langdell, R. D., Richardson, B. A., Farrell, R. A., Brinkhous, K. M. Antihemophilic factor (AHF): plasma levels after administration of AHF preparations to hemophilic dogs. Proc. Soc. Exp. Biol. Med. 96: 152–155, Oct. 1957.
80. Wagner, R. H., Richardson, B. A., Brinkhous, K. M. A study of the separation of fibrinogen and antihemophilic factor (AHF) in canine, porcine, and human plasmas. Thromb. Diath. Haem. 1: 1–8, 1957.
81. Hemophilia and Hemophilioid Diseases. K. M. Brinkhous, Ed. Chapel Hill, University of North Carolina Press, 1957, 275 pp.
82. LeRoy, E. C., Hazlehurst, J. L., Vennart, G. P., Brinkhous, K. M. A factor in plasma and serum influencing platelet agglutination: use of a macroscopic test. Fed. Proc. 17: 445, March 1958. (Abstract)
83. Penick, G. D., Roberts, H. R., Webster, W. P., Brinkhous, K. M. Hemorrhagic states secondary to intravascular clotting. Arch. Path. 66: 708–714, Dec. 1958.
84. Brinkhous, K. M., Langdell, R. D., Wagner, R. H. Hemostatic disorders: hemophilia and the hemophilioid diseases. Ann. Rev. Med. 9: 159–190, 1958.
85. Brinkhous, K. M. Antihemophilic factor (AHF) of plasma and plasma fractions. Proc. 6th Congress of Internat. Soc. of Hematology, Boston, September 1956. New York, Grune & Stratton, 1958, pp. 463–467.
86. Brinkhous, K. M., LeRoy, E. C., Cornell, W. P., Brown, R. C., Hazlehurst, J. L., Vennart, G. P. Macroscopic studies of platelet agglutination: nature of thrombocyte agglutinating activity of plasma. Proc. Soc. Exp. Biol. Med. 98: 379–383, 1958.
87. Brinkhous, K. M. Physiopathology of hemophilia. Acta Haemat. 20: 125–130, 1958.
88. Penick, G. D., Averette, H. E., Jr., Peters, R. M., Brinkhous, K. M. The hemorrhagic syndrome complicating extracorporeal shunting of blood: an experimental study of its pathogenesis. Thromb. Diath. Haem. 2: 218–225, 1958.

89. Mason, R. G., LeRoy, E. C., Brinkhous, K. M. Cation specificity of thrombocyte agglutinating factor (TAg). Fed. Proc. 18: 492, March 1959. (Abstract)
90. Mason, R. G., LeRoy, E. C., Brinkhous, K. M. Cation specificity of thrombocyte agglutinating activity (TAg) of canine plasma. Proc. Soc. Exp. Biol. Med. 102: 253–255, 1959.
91. Brinkhous, K. M. Blood clotting: the plasma precoagulants. Am. Rev. Physiol. 21: 271–298, 1959.
92. Brinkhous, K. M., Wagner, R. H. Antihemophilic factor (AHF): some aspects of its biochemistry, Proc. of the IVth Congress of Biochemistry, Vienna, 1958, Blood Clotting Factors, Vol. 10. New York, Pergamon Press, 1959, pp. 1–12.
93. Hemophilia and Other Hemorrhagic States. K. M. Brinkhous, Ed. Chapel Hill, University of North Carolina Press, 1959, 266 pp.
94. Shermer, R. W., Mason R. G., Wagner, R. H., Brinkhous, K. M. Cation requirements of thrombin for platelet agglutination. Fed. Proc. 19: 64, March 1960. (Abstract)
95. Geratz, J. D., Editor, Brinkhous, K. M., Graham, J. B., Rodman, N. F., Ross, R. A., Talbert, L. M., Ferguson, J. H., Roberts, H. R. Coagulation problem conference: clotting defects with hydatidiform mole. Resident Physician 6: 91–100, April 1960.
96. LeRoy, E. C., Mason, R. G., Brinkhous, K. M. Species difference in platelet agglutination in man and in the dog, swine and rabbit. Am. J. Physiol. 199: 183–186, July 1960.
97. Langdell, R. D., Brinkhous, K. M. The hemorrhagic disorders. Current Therapy 1960. H. F. Conn, Ed., Philadelphia, W. B. Saunders Co., 1960, pp. 190–192.
98. Rodman, N. F., Brinkhous, K. M. Effect of surface activated clot promoting material on the assay of antihemophilic factor (AHF). Thromb. Diath. Haem., Suppl. 4, 142–144, 1960.
99. Brinkhous, K. M., Roberts, H. R. Thrombolysis and thrombolytic agents: a brief review. J.A.M.A. 175: 284–289, Jan. 28, 1961.
100. Rodman, N. F., Mason, R. G., McDevitt, N. B., Brinkhous, K. M. Thrombocyte alterations during coagulation: microscopic observations of thin sections. Fed. Proc. 20: 62, March 1961. (Abstract).
101. Shermer, R. W., Mason, R. G., Wagner, R. H., Brinkhous, K. M. Studies on thrombin-induced platelet agglutination. J. Exp. Med. 114: 905–920, Dec. 1961.
102. Brinkhous, K. M. Perspectives of fibrinolysis and thrombolysis. Throm. Diath. Haem. 6: Suppl. 1, 20–25, 1961.

Mr. FOUNTAIN. Our next witness is Dr. Daniel A. Okun, head of the Department of Environmental Sciences and Engineering in the School of Public Health of the University of North Carolina, Chapel Hill. Dr. Okun, also, is director of the Institute for Environmental Studies of the University of North Carolina. We are very happy for this opportunity to hear from you this morning, Doctor. It is, indeed, our pleasure, and we look forward to whatever you may have to say.

STATEMENT OF DR. DANIEL A. OKUN, HEAD OF THE DEPARTMENT OF ENVIRONMENTAL SCIENCES AND ENGINEERING, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA

Dr. OKUN. Thank you, Mr. Chairman, and gentlemen. I am quite honored to be invited here to testify. This opportunity is particularly pleasing to me because it was one of my colleagues, Prof. Emil Chanlett, and I who first brought to Gov. Terry Sanford's attention the prospect of the establishment of an Environmental Health Center by the Department of Health, Education, and Welfare. The mission conceived of at that time for such a center was that it be the environmental health resource for the Nation, with responsibilities in oper-

ations, regulation, training and education, and research, in all aspects of environmental health. Its location was in dispute. As we know, the Research Triangle was finally selected as the site for the Center.

Now, after years of Federal organization and reorganization, we have two Environmental Centers in the Research Triangle: the National Environmental Research Center of the Environmental Protection Agency, and the National Environmental Health Sciences Center of the National Institute of Environmental Health Sciences. Additionally, EPA has other environmental centers elsewhere in the country, and the Department of Health, Education, and Welfare has the Center for Disease Control in Atlanta. That the necessity for close cooperation between the National Environmental Health Sciences Center and the EPA Research Centers is obvious does not make it less necessary to emphasize the importance of such cooperation.

I am pleased to say that, except for adding to the congestion of the tortuously winding two-lane road between Research Triangle Park and Chapel Hill, the National Environmental Health Sciences Center and the National Environmental Research Center have been very good neighbors to the universities in the Research Triangle. They have enriched the area immeasurably. They have employed the universities' graduates, who were previously obliged to leave North Carolina upon completing their studies. They provide lecturers for our students, supplementing the faculty resources available. They address problems that require resources beyond those that can be justified at the universities. They turn to the universities for such research assistance as is appropriate to the role of universities in research. Their presence has also helped to attract other private research facilities to the Research Triangle and through these, manufacturing establishments elsewhere in North Carolina.

An example of this cooperation might be in order. Useful and mutually beneficial activities have been undertaken jointly by the Radiological Hygiene Program of the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill and the Biophysics Section at the National Environmental Health Sciences Center. This was readily initiated because two of the members of the Center scientific staff are graduates of our Radiological Hygiene Program. Center staff have been most generous in giving their time and making their facilities available for student instruction in the nonionizing radiations that are characteristic of microwave and laser devices.

Through Dr. Newton Underwood, the Radiological Hygiene Program of the Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina, has been on a joint project with the Biophysics and Instrumentation Section of the NIEHS through Dr. Phillip Walsh. A very significant development of great practical application for the detection of trace metallic toxicants and pollutants in environmental samples of air, water, and soil has been the object of intense work by Drs. Underwood and Walsh. These investigators have designed a low-cost instrument that utilizes the principle of X-ray energy spectrometry for the detection and analysis of trace metallic elements in environmental and biological samples. There has been joint work on the design of the instrument and the fabrication of a prototype in the instrument shop of the Depart-

ment of Environmental Sciences and Engineering. Experience has shown that quantities down to one millionth of a gram in the prepared sample can be detected with the present configuration. Metallic elements heavier than magnesium in the Periodic Table can be measured.

Graduate students in the Radiological Hygiene Program have carried on their own research with the Biophysics and Instrumentation Section. Dr. Robert Gastineau, an Army physician, made an important contribution to the analysis of radiation doses to uranium mine workers doing extensive work on the measurements of the thickness of the bronchial epithelium of the human respiratory tract. Prior to Dr. Gastineau's work that information was not known and was necessary to the calculation of radiation dose from radioactive material deposited in the lungs of uranium miners. Mr. Perry Wheless, who has a particular aptitude for the development of electronic instrumentation, worked with Dr. Walsh's group in the development of an instrument which greatly facilitates measurements from microwave, which is the energy form from radar units.

Center staff, furthermore, have participated in short courses for students and for those in professional practice in environmental protection in North Carolina and in surrounding States.

If committee members have not read the document "Man's Health and the Environment—Some Research Needs," I commend it to you. This volume, published 2 years ago, was prepared by a Task Force on Research Planning in Environmental Health Sciences, made up of 44 distinguished scientists including 39 from outside the Government service.

As stated in the foreword of this document, "the mission of the National Institute of Environmental Health Sciences was outlined during its organizational phases. The Institute is to concern itself with fundamental biomedical research on the health effects of a wide range of constituents in the environment of man. The NIEHS is particularly concerned with the deleterious effects on health resulting from long term exposures to low levels of chemical, physical, and biological substances, alone or in combination, in the environment."

The report goes on to state that, "The Institute will have failed in a major sense, however, if it does not deliberately devote a substantial part of its effort toward better means of anticipating future difficulties." Fortunately, the report does not limit itself to the narrowly defined mission of the Institute, but rather addresses itself to the comprehensive problems of environmental health. In order for the Institute to fulfill a broader mission and to assure that the recommendations of the task force will be addressed, the Institute must itself extend its limited charge or seek exceedingly close common enterprise with other agencies of Government, particularly the Environmental Protection Agency, and the universities. For example, the task force concluded that "* * * there is an urgent need to develop on the national scene a continuing forecasting system which will undertake to anticipate over an appropriate time scale future changes in the structure of the technology and of the community relevant to human hazard. While certain aspects of the existing methodology of technologic forecasting are applicable to environmental problems, there is need to develop a methodology specifically addressed to the environmental health field."

If we are to avoid "* * * fighting the last war rather than the one about to erupt" we must, *inter alia*, undertake research into the following problem areas to extend the mission of the Institute:

(1) We must investigate the assimilative capacity of the environment to accept wastes without impairment of the quality of water, air, and land, and without disturbing the natural life dependent on the level of environmental quality that existed before the wastes were discharged. As an example, engineers and scientists can predict adequately the assimilative capacity of a body of water for the carbohydrate and protein constituents of municipal wastewaters of human origin without deoxygenating the waters. Very much less is known of the assimilative capacity of water for heavy metals and complex organics, of air for gaseous and particulate discharges, or of land for the burial of solid or radioactive wastes over long periods of time.

(2) Closely related to the concept of assimilative capacity is the fate of particular contaminants and pollutants after their discharge into water, air, the soil, or upon the land. The chemistry, biology, and physics of the processes by which particular chemical and biological contaminants are changed, are known only in part. Some of these processes may mitigate the effects of these contaminants while others may render them more hazardous. For example, the fate of even so common a toxic gas as carbon monoxide is uncertain. The present hypothesis, most widely accepted, is that carbon monoxide migrates into the upper strata of our atmosphere where the incoming radiations from outer space transform it to carbon dioxide. Carbon monoxide does not persist and does not accumulate in our atmosphere over periods of months or years; but why this is so is uncertain.

(3) Related to the preceding issues is the need to study the features of particular geographical areas which greatly limit the extent and intensity to which a community may use the air, water, and land around it for the disposal of its wastes. The term "natural constraints" has been used to express these limitations. The meteorology, the hydrology, the geology, the topography, and the soil conditions in an area put limits on how much, when, and what kind of wastes may be discharged without deterioration of environmental quality and without, indeed, creating intense hazards to people of the area, hazards that exert their influence over long time periods by insidious and chronic impairment of health. For example, existing meteorological data for an area along the North Carolina-South Carolina border near Charlotte reveal meteorological phenomena that produce stagnation of vertical and horizontal air movement frequently and for several days at a time. These natural occurrences produce conditions that can result in damaging concentrations of air pollutants in that area. It is imperative that natural constraints of this type be identified to guide land-use planning so that human activity appropriate to particular regions can be encouraged, and inappropriate activities discouraged. Charlotte need not follow an unplanned path that would result in the extent and intensity of air pollution that characterize the Los Angeles basin. No agency in Government is now responsible for the systematic study of the natural constraints upon man's use of his air, water, and land resources with the objective of achieving their controlled and planned utilization for man's activities. We must clearly recognize

commitments which must be made to prevent a slow drift to severe and extensive deterioration of the environment.

I might interpolate one point. This variation of natural constraints points out that standards that are established need not be nationwide. Some standards seem to be far more appropriate in some areas, whereas in other areas these standards may not at all be appropriate. One example is the great controversy concerning the automobile and its exhaust controls. In certain urban areas this is extremely important, but in rural areas in North Carolina, Mr. Chairman, this will be of very little consequence; yet with a uniform standard each person will bear an equal burden. So I think identifying places in the Nation where constraints are important should have a high priority.

(4) All of the foregoing activities will be to no avail if we are not made continuously aware of the origin of materials that can reach the environment and how they are transformed in use, during manufacturing processes, and upon contact with other related materials in the environment. For example, more than a third of our total population draws its drinking waters from sources, portions of which only hours before had been discharged from some municipal or industrial sewer.

Some of the chemicals that are known to be discharged have been identified as being carcinogenic, mutagenic or teratogenic. For example, even small doses of polychlorinated biphenyls (PCB's), widely used industrial chemicals that were never intended for release into the environment even in a small dose can be toxic. Sewer outfalls are major sources of PCB's in the environment. Treatment plants, whether for wastewater or for water supply, are not now adequate to remove or even substantially reduce the concentration of most organic chemicals and their metabolites or the heavy metals that are likely to be of concern. Monitoring of these chemicals and determining their fate in wastewater treatment plants and in water supply systems is most difficult unless we have prior knowledge of their presence in these waters.

If we are not to be continually surprised by so-called "new" pollution problems, surprise that almost inevitably results in hasty, ill-considered legislative and regulatory responses, we must initiate programs of surveillance that anticipate problems. This must be handled from two disparate vantage points. First, we must improve our analytical capability in the sensitivity and simplicity of analytical determinations. Currently, many determinations are so costly that routine monitoring is not economically feasible. Second, because of the large number of chemicals that may be in a major river that serves as a water supply, it is virtually impossible to attack a water sample with any confidence that all contaminants of significance can be identified, unless we have prior knowledge of the materials that are discharged to the water in the first place. Without knowing what to look for, it is almost impossible to detect the presence of many troublesome constituents, much less design facilities for their removal. Such surveillance of materials that may reach the environment may threaten the heretofore confidential nature of industrial operations, but we have no alternative. Administrative protection can be given to industry in much the way that the Internal Revenue Service insures privacy of personal and corporate tax declarations.

80-012 O—72——5

(5) All of us, as individuals, in associations, in industry, and in public agencies are continually making environmental assessments with the avowed purpose of maintaining and improving the quality of the environment. Individual and societal decisions are being made based upon these assessments. When the investments in protecting the environment were small and the options limited, qualitative and subjective assessments may have been sufficient. Now, with major investments to be made, not only in resource development but also in the modification of our life styles, quantitative and objective assessments have become essential. In Executive Order 11514, the President specified among the duties of the Council for Environmental Quality: "Promote the development and use of indices and monitoring systems 1. to assess environmental conditions and trends; 2. to predict the environmental impact of proposed public and private actions; and 3. to determine the effectiveness of programs of protecting and enhancing environmental quality." While indices of environmental quality are difficult to conceive or to use, as John Fisher, President of Resources for the Future, points out, Americans want to know how things are going with their environment. While he recognizes that no single overall indicator of natural environmental quality is in sight ". . . indicators for environmental conditions must be found. The more rational they are the better, but, in any case, some kind of indicators will be used." The research that is conducted at the National Environmental Health Sciences Center can well provide the basis for the parameters that will help establish environmental indices. The development of indices that incorporate a wide variety of environmental parameters can, in turn, help identify the research problems that require attention.

Last, as an educator and as a consultant to many public and private environmental agencies, I am constrained to take this opportunity to identify and deplore an administration policy that threatens, if executed, to emasculate our ongoing and projected environmental research and control programs. I am speaking of the curtailment of graduate research and training programs at our educational institutions. The avowed reason for this position according to the White House is that "There are many trained scientists and engineers currently unemployed or underemployed who are available to enter environmental fields." Needless to say, aerospace engineers are not equipped to address themselves to the planning, design, operation, or surveillance of facilities for the removal of contaminants from our waters, for example, unless they undergo a rigorous and extensive program of retraining. And it is funds for just such training or retraining in environmental sciences and engineering that are now being threatened, just as our universities are beginning to meet the need for these professionals. The fund reductions are being made despite the recommendations of the task force that "* * * expanded and enriched programs are needed for educating and training greater numbers of scientists, administrators, and specialists * * * familiar with the needs and problems in environmental health."

The areas of study that have been commended to the committee for its attention and consideration are very difficult to attack. Were that not so, the work would have been done long ago and the situation would

be well in hand. The Research Triangle Area of North Carolina has a great wealth of scientific talent, institutional resources, and physical facilities. All of us at the universities in the Research Triangle Area are most willing and anxious to pledge our support and participation to joint efforts with the Federal research establishments in the elucidation and solution of the many problems of environmental health that face us.

Mr. FOUNTAIN. Thank you very much, Doctor, for an extremely informative and well thought out statement. I am extremely interested to hear that cooperation and working relations between the Institute and the Triangle universities is so good and mutually beneficial. I think this is one of the objectives which the Federal Government had in mind in locating some of its scientific activities outside of Washington, and we were delighted when the Research Triangle was selected for the Institute. But I might say that it was not selected on the basis of political pressures by people in high places. Actually, the Department of Health, Education, and Welfare had criteria which were thoroughly explored and this location was selected for the Institute on the basis of its actual merit. So I am proud of this choice.

You make reference on pages 8 and 9 to what you feel is an undesirable policy of the Federal Government in funding the training and retraining of unemployed aerospace engineers, while at the same time curtailing support for the training of graduate students in environmental science. I can appreciate your comment about graduate training. However, are you saying, or is it your thinking, that Federal funds are not well spent in retraining people from the aerospace industry, or are you saying you favor such programs and also more support at the same time for graduate students?

Dr. OKUN. Mr. Chairman, I didn't say the Government is training aerospace engineers now. The problem that we face is, with the curtailment of aerospace enterprises and with reduction in activity of the electronics and other similar industries, they claim that because employable scientists from these fields are available it is no longer necessary to provide training resources in the environmental field. Well, my feeling is that this situation makes training funds in the environmental field even more necessary; to have someone to come into such a complex field as the environment, and to have him make environmental decisions based on his experience in the aerospace industry, would be very costly to society. Much of the aerospace industry has been based on a psychology of cost-plus financing where there have been very few limits on expenditures that needed to be made.

The technology is quite different in the environmental field. In the environmental field we have first the necessity for knowing something of chemistry and biology, as well as engineering. Also, the moneys to be expended are often expended at the local level where it is in very short supply and the economy is very poor. Then, the method for spending is quite different. So the transfer of these people from aerospace to environment isn't too readily accomplished. Even more important, the areas of the country where these men and women are most available is not the area where the environmental problems may exist. Environmental problems are distributed throughout the country.

In aerospace, on the other hand, employed and unemployed are located in a few major centers, and most of these individuals are not prepared to move to where the problems are.

However, there are now opportunities for retraining in our department at the university. We have a young man who just left one of the aerospace companies in New York, and is retraining himself for the environmental field. This is going to take him 2 years and he will be a very welcome addition to our field. But in order for us to provide this retraining we have to have training funds. We have the funds now, but the administration policy is that as these training grants terminate, they will no longer be renewed. And it is this lack of concern for the very complex problems of the environment that is the heart of my testimony.

Mr. FOUNTAIN. Thank you very much.

Mr. FUQUA. Are you satisfied with the Rann program that the National Science Foundation has been operating?

Dr. OKUN. Yes; it's a very useful program and it is beginning to fill the breach somewhat in terms of providing resources for research which isn't the main goal for training; the grant program is just getting started and they are directing their attention to problems such as the fate of toxic substances in the environment. However, one of the other reasons the White House gives for curtailing training programs is that research funds being provided in other ways—through grants and contracts—are available. Well, the format of grants and contracts is not appropriate for training individuals in universities. Contracts have a fixed objective and termination date. If a contract is to be satisfied it must be done with full-time people rather than students. Industry and research institutes, such as the Research Triangle Institute are adapted to contracts, but not universities.

Mr. FUQUA. The other committee I serve on is Science and Astronautics, and we have jurisdiction over National Science Foundation. Dr. Stever, the new president of the Foundation, appearing before the committee, expressed a great deal of concern about what seemed to be the abandonment of basic research and more applied research through the Rann program, which is fine, and I have been assured by Dr. Stever that he is going to try to make a balanced program and not neglect the very basic research that we need of the type that you are doing here at the Institute. I appreciate your comments, and let me say that I share your concern about this.

(Dr. Okun's curriculum vitae follows:)

DANIEL A. OKUN, PROFESSOR OF ENVIRONMENTAL ENGINEERING, HEAD, DEPARTMENT OF ENVIRONMENTAL SCIENCES AND ENGINEERING, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA (BIRTH: NEW YORK, N.Y., JUNE 19, 1917)

EDUCATIONAL RECORD

School	Dates attended	Degree received	Field of specialization
Cooper Union Institute of Technology	1933–37	B.S.C.E.	Civil engineering.
California Institute of Technology	1937–38	M.S.C.E.	Do.
Harvard University	1946–48	Sc. D.	Sanitary engineering.

PROFESSIONAL POSITIONS

Institution	Address	Dates	Title
California Institute of Technology	Pasadena	1937 to 1938	Graduate assistant.
Illinois Institute of Technology	Chicago	1938 to 1940	Do.
U.S. Public Health Service	Washington, D.C., Ohio, New York.	1940 to 1942	Assistant sanitary engineer (res.).
U.S. Army	Newfoundland, Caribbean, Central America, Southwest Pacific, Philippines.	1942 to 1946	1st lieutenant to major, Sanitary Corps.
Harvard University	Cambridge, Mass	1946 to 1948	Teaching fellow.
Malcolm Pirnie Engineers	New York, N.Y. (Connecticut, Florida, Virginia, Venezuela).	1948 to 1952	Assistant to associate engineer.
Technological University	Delft, Netherlands	1960 to 1961	Visiting professor.
University College, London	London, England	1966 to 1967	Honorary research associate.
University of North Carolina	Chapel Hill, N.C	1952 to present	Associate professor to professor of environmental engineering.
		1955 to present	Head, department of environmental sciences and engineering.

UNC offices

Project Director, Sanitary Engineering Education in Peru 1954–59
Radioisotope Committee 1959–70
Project Director, International Program in Sanitary Engineering Design 1962–71
President, American Association of University Professors, UNC Chapter 1963–64
President, Sigma Xi, UNC Chapter 1968–69
President, Delta Omega, UNC Chapter 1964–65
Committee on Faculty Hearings, UNC 1964–69
Faculty Council 1965–67
Project Director, Sanitary Engineering Education at San Carlos University, Guatemala 1965–66
Director, Institute for Environmental (Health) Studies 1965–present
Member, Board of Directors, UNC Water Resources Research Institute 1965–present
Chairman of the Faculty, UNC 1970–73
Ex-officio:
Chancellor's Advisory Committee; Nominating Committee
Chancellor's Cabinet; Agenda Committee
UNC Consultative Forum
Chancellor's Selection Committee 1971

Professional societies

American Society of Civil Engineers, Fellow; Chairman, Executive Committee, Sanitary Engineering Division 1967–68
American Public Health Association, Fellow
American Water Works Association, Chairman, International Committee 1970–72
Water Pollution Control Federation: Director-at-Large 1969–72
Chairman, Research Committee 1961–66
American Water Resources Association
Environmental Engineering Inter-Society Board, Trustee 1967–71
American Academy of Environmental Engineers, Diplomate 1955–present
Society of Harvard Engineers and Scientists
American Public Works Association
Institute of Water Pollution Control (Britain)
Registered Professional Engineer: New York (24521), North Carolina (1965)

Honors and honorary positions

Kenneth Allen Memorial Award, New York Water Pollution Control Assn. ---- 1949
Harrison Prescott Eddy Medal, Water Pollution Control Federation--- 1950
Catedrático Honorario, Facultad de Ingeniería Sanitaría Universidad Nacional de Ingeniería, Lima, Peru---- 1957
Advisory Committee on Drinking Water Standards, Public Health Service ---- 1958–66
Senior Post-Doctoral Research Fellow, National Science Foundation--- 1960–61
Governor's Scientific Advisory Committee---- 1961–64
Member, National Academy of Science Research Council, Committee on Sanitary Engineering and Environment, and Chairman, Subcommittee on Waste Disposal---- 1962–65
On University of North Carolina Kenan Leave ---- 1966–67
Special Research Fellowship, Federal Water Pollution Control Adm--- 1966–67
Croll Memorial Lecturer, Institute Water Pollution Control, London-- 1967
Chairman, Scientific Group on Treatment and Disposal of Wastes, World Health Organization, Geneva---- 1966
Honorary member, Tau Beta Pi, National Engineering Honor Society--- 1969
Distinguished Alumnus Award, Cooper Union for the Advancement of Science and Art---- 1970
President, American Academy of Environmental Engineers---- 1969–70

Consultant assignments

Malcolm Pirnie Engineers, New York: miscellaneous assignments, Israel, U.S. ---- 1952–60
Public Works Publications, New Jersey---- 1954–67
Duke University, Visiting Lecturer---- 1958–60
Bowaters Carolina Corporation, South Carolina: water pollution control- 1959–62
Chicago Pump Company, Illinois: wastewater treatment---- 1961
Produce Processors, North Carolina: wastewater treatment---- 1962–64
Mead Corporation, North Carolina: wastewater treatment---- 1962–65
Member, Study Section, Environmental Sciences and Engineering, National Institutes of Health, Bethesda, Maryland: research evaluation- 1962–66
Robert A. Taft Sanitary Engineering Center; training---- 1963
Asian Institute of Technology, Bangkok: lecturer on water supply---- 1963
Rust Engineering Company, Alabama: industrial site location---- 1964
City of Savannah, Georgia: wastewater treatment---- 1964
Agency for International Development, Community Water Supply Program ---- 1964–present
Soap and Detergent Manufacturers Association: detergent studies---- 1965–68
Camp, Dresser, and McKee, Consulting Engineers: Bangkok: water supply and sewerage---- 1966, 1968
World Health Organization: water pollution, wastewater treatment 1967, 1969–70---- 1966
Bird Machine Company, South Walpole, Massachusetts: wastewater treatment ---- 1967–69
WED Enterprises: environmental planning, Disney World, Florida---- 1968
New York State Department of Health: research planning---- 1967
Academic Press, Editor, Environmental Sciences Series---- 1968–present
WAPORA, Inc., Director: water quality research and development- 1969–present
Secretary of Health, Education, and Welfare's Commission on Pesticides and Environmental Health---- 1969
Department of Commerce, Water Supply and Sanitation Seminar Director, Bangkok ---- 1969–70
Environmental Control Seminars Organizer, Rotterdam, Warsaw, Prague, Bucharest---- 1971
Asian Development Bank, Singapore water supply---- 1970
Environmental Protection Agency, Water Quality Office, Bureau of Water Hygiene, Consultant in Rio de Janeiro, Brazil---- 1971
Procter and Gamble, Cincinnati, Ohio, water pollution control---- 1971
Environmental Protection Agency; Water Supply Program Division, Washington, D.C.---- 1971–present
Camp, Dresser and McKee, Inc., Boston: water and wastewater engineering ---- 1971–present

Scientific Publications by Daniel A. Okun

Okun, D. A., E. Hurwitz and F. W. Mohlman, "Investigations of Methods for Determination of Grease in Sewage." Sewage Works Journal, 13: 485–491 (1941).

Moore, E. W., J. C. Morris and D. A. Okun, "Polarograph Determination of Dissolved Oxygen in Water and Sewage", Sewage Works Journal, 20: 1041–1053 (1948).

Okun, D. A., "Pure Oxygen in Bio-precipitation Process May Reduce Sewage Treatment Costs", Civil Engineering, 18: 288–289, 340 (May 1949).

———, ———. "System of Bio-precipitation of Organic Matter from Sewage", Sewage Works Journal, 21: 763–792 (Sept. 1949).

Mitchell, R. D., J. Cassanos and D. A. Okun, "Effect of Metal Wastes on Sewage Treatment Plant Design at Waterbury, Conn.", Sewage and Industrial Wastes, 23: 1001–1011 (August 1951).

——— ———, "Public Health Importance of Water Supply and Waste Disposal Works", Proceedings of the American Society of Civil Engineers, 79 (Aug. 1953).

——— ———, "Use of Tonnage Oxygen in Sewage Treatment", Water and Sewage Works, 100: 374–379 (Sept. 1953).

——— ———, "Financial Aspects of Sewer Service Charges", Proceedings of the N.C. Section, American Water Works Association, and N.C. Sewage and Industrial Wastes Association, 29: 69–77 (1953).

Arenander, C. and Okun, D. A., "High-type Sanitary Facilities Provided in Venezuelan Wilderness", Civil Engineering, 24: 220–223 (April 1954).

Lynn, W. and Okun, D. A., "The Use of the Rotating Platinum Electrode in the Determination of Dissolved Oxygen", Sewage and Industrial Wastes, 27: 4–7 (Jan. 1955).

Okun, D. A. and W. Lynn, "Preliminary Investigations into the Effect of Oxygen Tension on Biological Sewage Treatment", Biological Treatment of Sewage and Industrial Wastes, Reinhold Pub. Corp. Ch. 2–4: 192–207 (1956).

——— ———. "Discussion, 'High-Purity Oxygen in Biological Sewage Treatment' ", Sewage and Industrial Wastes, 29: 253–257 (March 1957).

——— ———. "Education for Sanitary Engineering", Proceedings of the American Society of Civil Engineers, Journal of Sanitary Engineering Division, 83: 1219, 1–9 (April 1957).

——— ———. "Recent Developments in the Aerobic Biologic Treatment of Waste by Aeration", Public Works, 90: 116–119, 161–162 (Jan. 1959).

Mancy, K. H. and Okun, D. A., "Automatic Recording of Dissolved Oxygen in Aqueous Systems Containing Surface Active Agents", Analytical Chemistry, 32: 108–114 (January 1960). ESE Pub. No. 16.

Mancy, K. H. and Okun, D. A., "Effects of Surface Active Agents on Bubble Aeration", Journal Water Pollution Control Federation, 32: 351–364 (April 1960).

Jenkins, John E., Charles E. Moak and D. A. Okun, "Sedimentation in Reservoirs in the Southeast", Transactions of American Society of Civil Engineers, 126: 68–82 (1961). ESE Pub. No. 20.

——— ———. "Sanitary Engineering Education in a Changing World", Journal of Sanitary Engineering Division, Proceedings of American Society of Civil Engineers, 87: 47–63 (July 1961). ESE Pub. No. 29.

——— ———. "Sanitary Engineering Education in a Changing World", De Ingenieur, 73: 41–50 (Nov. 1961). ESE Pub. No. 31.

Mancy, K. H., Okun, D. A. and C. N. Reilley, "A Galvanic Cell Oxygen Analyzer", Journal of Electroanalytical Chemistry, 4: 65–92 (1962). ESE Pub. No. 37.

Okun, D. A., "Aspects of European Water Management", Public Works, 111–113 (June 1962). ESE Pub. No. 43.

——— ———. "Water Supply and Treatment in Three European Countries", Journal American Water Works Association, 54: 650–656 (June 1962).

——— ———. "Wastewater Treatment in Europe", Journal Water Pollution Control Federation, 34: 704–722 (July 1962). ESE Pub. No. 42A.

——— ———. "Experience with Stabilization Ponds in the USA", Bull. World Health Org., 26: 550–553 (1962). ESE Pub. No. 23.

——— ——— and Charles M. Weiss, "U. of N.C.: Organic-Biological Relationships in Reservoirs", Water Works Engineering, 349–351 (May 1963). ESE Pub. No. 62.

——— ———, James C. Lamb III and C. C. Wells, Jr., "A Waste Control Program for a River with Highly Variable Flow", Journal Water Pollution Control Federation, 35: 1025–1043 (August 1963). ESE Pub. No. 39.

——— ———, "Planning for Water Supply Development", American Journal of Public Health, 54 : 900–907 (June 1964). ESE Pub. No. 47.
——— ———. "Sanitary Engineering Education in the United States", Selected Topics in Sanitary Engineering, Delft (1964), pp. 211–221. ESE Pub. No. 92.
Mancy, K. H. and D. A. Okun, "The Effect of Surface Active Agents on Aeration", Journal Water Pollution Control Federation. 37 :212–227 (Feb. 1965).
Okun, D. A., and J. K. Baars, "Experimental Work on Effects of Surface Active Agents on Bubble Formation", Proceedings of the Fourth International Congress on Surface Active Substances, Brussels, Vol. 2 : 1179–1188 (1967).
Westgarth, W. C., F. T. Sulzer and D. A. Okun, "Anaerobiosis in the Activated Sludge Process", Proceedings, 2nd Intl. Water Pollution Research Conference, Tokyo, August 1964, 43–61 (1965). ESE Pub. No. 82.
Brown, James C. and D. A. Okun, "An International Program in Sanitary Engineering Design", Ingenieria Sanitaria, 19 : 12–20 (1965). ESE Pub. No. 87.
Okun, D. A., The Community Water Supply Program of the Agency for International Development, Dept. of State, U.S.A., 45 pp. (Feb. 1965).
Segall, Burton A. and D. A. Okun, "Effect of Filtration Rate on Filtrate Quality", Journal American Water Works Association, 58 : 368–378 (1966).
Okun, D. A., "Water Pollution Research and Policy", Proceedings of the 1st Annual Meeting of the American Water Resources Assn., Urbana, Ill., 242–253 (1966).
——— ———. "The Changing Pattern of Environmental Health Problems", 21 pp. (Presented at the Virginia Public Health Association Meeting, Roanoke, Virginia, May 4, 1966). ESE Pub. No. 121.
——— ———, "Tomorrow's Methods to Provide Tomorrow's Services", Journal American Water Works Association, 58 : 938–952 (August 1966). ESE Pub. No. 123.
——— ——— and F. E. McJunkin, "Planning and Developing Water Supply Programs in Developing Countries", Proceedings, Intl. Conference on Water for Peace, Washington, D.C., Vol. 7 : 35–45 (1967). ESE Pub. No. 145.
Weiss, C. M. and D. A. Okun, "Water Quality Technology : Present Capabilities and Future Prospects", Proceedings, Intl. Conference of Water for Peace, Washington, D.C., Vol. 4 : 195–211 (1967). ESE Pub. No. 141.
Okun, D. A., "The Future of Water Quality Management", Journal, Institute of Water Pollution Control, 67, No. 2, 127–142, 1968. (1967 Croll Memorial Lecture at Torquay, England.) ESE Pub. No. 154.
——— ———. "Waste Water Treatment for Central America". (Symposium on Water Pollution at the University of San Carlos, Guatemala City, Guatemala) pp. 83–94 (1967). ESE Pub. No. 160.
——— ———. "Preparing Engineers for Community Water Supply Programs in Developing Countries", Aqua, International Water Supply Association, London, No. 1, 7–10 (1967). ESE Pub. No. 140.
——— ———. "Regrouping of Water Supplies in the United Kingdom", Public Works, 98, No. 6, 153–154, 206 (June 1967). ESE Pub. No. 165.
——— ———. "The Hierarchy of Water Quality", Environmental Science and Technology, 2, 672–675 (1968) ESE Pub. No. 176.
Brown, James C. and D. A. Okun, "Criteria for the Incorporation of Mechanization and Automation in Treatment Plant Design" (Environmental Engineering Conference of the American Society of Civil Engineers, Chattanooga, Tennessee, May 1968) ESE Pub. No. 183.
Okun, D. A., "Alternatives in Water Supply", Journal, American Water Works Association, 61, 5, 215–224 (1969). ESE Pub. No. 178.
Brown, James C. and D. A. Okun, "Economic Design of Water Supply and Sewerage Systems", Presented at XI Congress of AIDIS, Quito, Ecuador, July 21–26, 1968. ESE Pub. No. 193.
Okun, D. A., "Managing the Great Lakes Water Resource", Journal, Water Pollution Control Federation, 41, 11, 1859–1862 (1969). ESE Pub. No. 195.
McJunkin, F. E., James C. Brown and D. A. Okun, "Diseño de Sistemas de Alcantarillado para Centro América". Ingeniería Sanitaria. Vol. 22–3, 49–63 (Jan. 1969). ESE Pub. No. 200.
Okun, D. A., "Regional Planning and Management of Water and Sewer Systems", Proceedings, Symposium on Better Water and Sewer Services for Small Communities in North Carolina, UNC Water Resources Research Institute, Raleigh (1968), 94–98. ESE Pub. No. 206.

Okun, D. A., and Stanley J. Weidenkopf, "Man and His Urban Environment", Improving the Physical Environment of the South, The Agricultural Policy Institute, N.C. State University, 25–42 (1969). ESE Pub. No. 207; Agricultural Policy Review, N. C. State Univ., 9, 189 (1969).

——— ———. "A Water-Quality Hierarchy for Arid Lands", Arid Lands in Perspective, The University of Arizona Press, Tucson, 291–296 (1969). ESE Pub. No. 223.

——— ———. "Community Water Management in Asia", Presented at Annual Meeting, American Chemical Society, New York, Sept. 8, 1969. ESE Pub. No. 228.

——— ———. "The Engineer's Role in Environmental Management", Presented at the National Capital Section, American Society of Civil Engineers, Washington, D.C., Nov. 12, 1969. ESE Pub. No. 229.

——— ———. "Advanced Treatment of Wastewater: Research Needs", Problems in Community Wastes Management, World Health Organization Public Health Papers No. 38, Geneva, 61–75 (1969).

——— ———. "New Development of Urban Water Supply", J. Japan Water Works Assn., No. 414, 54–57 (March, 1969).

——— ———. "Education for Environmental Health Services", The Encyclopedia of Education, The MacMillan Co., New York (in press).

——— ———. "Wastewater", Encyclopedia Americana, New York (in press).

——— ———. "New Directions for Water Supply", Water Pollution and Health, Proceedings, Fifth International Water Quality Symposium, Water Quality Res. Council, 22 (1970).

——— ———. "Phosphates in Detergents—a Bane or a Boon", ESE Pub. No. 269, 6 pp. (1971).

——— ———. "New Directions in Wastewater Collection and Disposal", J. Water Poll. Control Fed. 43, 2171–2180 (1971); also in Clean Water for Our Future Environment, Am. Soc. Civil Eng. 157–178 (1971); ESE Pub. No. 260.

——— ——— and F. E. McJunkin, "Feasibility of Dual Water Supply Systems", Seventh American Water Resources Conference, Washington, D.C., Oct. 25, 1971.

Books

Manual on Sewage Treatment Plant Design, Chairman of Committee, Am. Soc. Civil Eng. and Water Pollution Control Fed., ASCE Manual No. 36, N.Y.; WPCF Manual No. 8, Washington, D.C., 375 pages (1959).

Okun, Daniel A., ed., *Proceedings, VIII Congress Inter-American Assn. of Sanitary Engineering*, June 10–15, 1962, Washington, D.C., 705 pages (1963).

Fair, Gordon M., John C. Geyer and Daniel A. Okun, *Water and Wastewater Engineering, Volume I Water Supply and Wastewater Removal*, John Wiley and Sons, Inc., New York, 489 pp. (1966).

Fair, Gordon M., John C. Geyer and Daniel A. Okun, *Water and Wastewater Engineering, Volume II Water Purification and Wastewater Treatment and Disposal*, John Wiley and Sons, Inc., New York, 664 pp. (1968).

Pescod, M. B. and D. A. Okun, ed. *Water Supply and Wastewater Disposal in Developing Countries*, Proceedings of Bangkok Seminar, Asian Institute of Technology, Bangkok, 309 pp. (1971).

Fair, Gordon, M., John C. Geyer and Daniel A. Okun, *Elements of Water and Wastewater Engineering*, John Wiley and Sons, Inc., New York, 752 pp. (1971).

Okun, Daniel A. *Wastewater Collection and Disposal for Communities in Developing Countries*, World Health Organization, Geneva (in press).

Environmental Control Seminar Proceedings, Rotterdam, Warsaw, and Bucharest, May 25–June 4, 1971, Daniel A. Okun and Arthur C. Stern, eds. U.S. Dept. of Commerce, Washington, D.C., 297 pages, September, 1971.

Book Reviews

Review of Arthur Maass, Maynard M. Hufschmidt, Robert Dorfman, Harold A. Thomas, Jr., Steven A. Marglin, and Gordon Maskew Fair, *Design of Water Resource Systems* (Cambridge: Harvard University Press, 1962), in *Amer. Inst. of Planners Journal*, 55–56 (January, 1966).

Review of *Water, Health and Society*, Selected Papers by Abel Wolman, edited by Gilbert F. White (Indiana University Press, 1969) in *The American Journal of Tropical Medicine and Hygiene, 20*, 1, 165–6, Jan. 1971.

Mr. FOUNTAIN. Thank you, Dr. Okun.

Our last witness is Prof. Frank E. Guthrie, director, Program in Molecular and Environmental Toxicology, North Carolina State University in Raleigh. Dr. Guthrie will discuss aspects of pesticide environmental problems.

I might say, Dr. Guthrie, I hope you don't mind our scheduling you as cleanup witness. We arranged it this way because the other witnesses have a longer distance to travel and you indicated you had no serious time pressure this morning. We appreciate your cooperation. You may proceed with your statement at this time.

STATEMENT OF DR. FRANK E. GUTHRIE, PROFESSOR, MOLECULAR AND ENVIRONMENTAL TOXICOLOGY, NORTH CAROLINA STATE UNIVERSITY

Dr. GUTHRIE. In the way of brief credentials, I am the director of Research and Training Grants (ES–00044, ES–00083) funded by the National Institute of Environmental Health Sciences. This interdisciplinary program involves the participation of seven other faculty members (W. C. Dauterman, D. S. Grosch, E. Hodgson, A. R. Main, R. J. Monroe, D. E. Moreland, and J. F. Roberts) from a number of departments and faculties (biochemistry, botany, cell biology, entomology, genetics, physiology, statistics, and toxicology) and supports seven postdoctoral trainees, 15 graduate students, and seven technicians who work with some 20 organisms to evaluate environmental effects of chemicals.

I have been asked to address this subcommittee about the environmental dangers to health which concern me most in my professional work.

The problems in environmental health are legion, and all concern me as an environmental scientist and as a citizen. The overwhelming causes of environmental health hazard are the interrelated problems of population explosion and a technology committed to industrial expansion—too many people wanting too many things. In the not-too-distant future, governmental task forces must address themselves seriously to plans which will stabilize a population commensurate with our ability to maintain an agreeable environment requiring concomitant stabilization of the economy. We are rapidly approaching critical restraints within this solar system. Although I feel compelled to draw your attention to these as the overriding causes and ultimate issues, I recognize that your interest at this hearing concerns problems of a more specific nature.

For the purposes of this discussion I would like to break down the environmental problems into two categories—contaminants accidentally added to the environment (mercury, automotive emissions, smog, PCB's, et cetera) and contaminants purposefully added to the environment (pesticides, food additives, cosmetics, alcohol, drugs, et cetera). I am, of course, interested and concerned with accidental contamination but as our program and my own limited expertise has been concerned with contaminants purposefully added, I will limit my formal presentation to parts of that latter problem.

The group at North Carolina State University has long felt that contaminants tend to merge in a common basis for detrimental action at the biochemical level, and an explanation of the molecular events caused by one group of pollutants would provide information essential to an explanation of the action of somewhat unrelated xenobiotics. Thus, we should be able to establish principles for predictive models relating to contamination as a unit.

Our work has primarily dealt with establishment of biochemical principles concerning the action of pesticides. We feel that these principles can be used to more quickly solve the problems that arise with pesticides but also feel that the same biochemical parameters can be transferred to other pollutants for all ultimately act at a common level. Although such work is primarily of the basic type, it often has direct application as will be repeatedly pointed out in this discussion.

Our major concern would then be on the lack of information concerning the basic biochemical mechanisms related to pesticide action and interaction. Lack of information was the problem that got us into the trouble with DDT. We knew a lot about its gross effects and it certainly appeared to be among the safer insecticides. But the fact is, we still don't know how it poisons. This ignorance of its fundamental mode of action is at the root of the controversy concerning whether we should continue to use DDT. Suddenly after 25 years of use we find it "might" alter drug and hormone metabolism (through induction of oxidative enzymes), it "might" be a carcinogen, it "might" cause reproductive changes in birds (thin-egg shelling effect), and it certainly has become a common component of human tissues (appearing in the fat of adults, the new born and even in mother's milk). We would hope that a more thorough comprehension of the biochemistry of other insecticides will enable us to predict such effects within a few years instead of a few decades.

Elucidation of biochemical events leading to an explanation of action at the molecular level will require increased knowledge in a number of areas some of which are presently under investigation at this university. Among these are purification of target enzymes (Main et al., 1972), kinetics of the enzymic reactions mediating both toxicity and detoxication (Main, manuscript) (Dauterman and Main, 1966), studies with chemical analogs (Abernathy et al., 1971), spectral studies on isolated enzyme systems (Philpot and Hodgson, 1971), and effects on synthesis of nucleic acids (Moreland et al., 1969) and oxidative phosphorylation (Blackman and Moreland, 1971). An appropriate motto for this sort of endeavor might be "Safety in Knowledge."

Another concern we have is the possibility of accidental introduction of a chemical into the environment which has subtle, latent reproductive effects. We all recall the tragic thalidomide episode. Classical toxicology normally delineates the toxicity of a chemical—the end points being reduction in the life span of the treated animal or its immediate death. Attention to reproductive capacity has received less attention—both with regard to reduced fecundity of offspring as a result of subtle change in the parent and effects on the ability to reproduce at all. Relatively little attention has been given to production of gametes and subsequent events of fertilization so necessary to maintenance of the human germ plasma.

In our work a unique biological system is used which can detect both reproductive and somatic effects in living organisms far below those which can be shown in other laboratory animals. Following Miss Carson's "Silent Spring" and her charges that DDT was a mutagen, work was initiated with a number of pesticides. We were unable to detect any adverse effects on reproductive capacity with the pesticides tested in these preliminary experiments (Grosch, 1967; Guthrie et al., 1971). It is unfortunate that the emotional outcry and nonexisting effects of DDT on DNA detracted scientists from more important research. More recently we have investigated the biological action of aromatic rings of certain "biodegradable" insecticides (Grosch, unpublished manuscript) as well as some of the more degradable detergents (Moffett and Grosch, 1967, 1968) with some surprising results. Both tests showed that obvious solutions may introduce new problems. Although none of the results to date would be cause for alarm, they do prove the point that a constant monitoring program is an absolute requirement for this concern.

Development of safer insecticides and more effective therapeutic measures is a third concern. Although a large number of reasonably informed persons are involved in extensive occupational use of insecticides (pest control operators, aerial applicators, formulators, et cetera), a more important part of the population from the standpoint of pesticide safety is the homeowner. There are over 45 million single occupancy homes in the United States (1970 Census of Housing, U.S. Bureau of the Census), most of which have occasion for pesticide use in and around the premises several times each year. As one example of the problem, the common household aerosol bomb also contains a compound called piperonyl butoxide, a powerful inhibitor of oxidative enzymes (Philpot and Hodgson, 1971). When aerosol bombs were introduced during the war years no one would have thought that their use would be commonplace in today's environment. What sorts of problems are being created as these unskilled, pesticide-ignorant, applicators treat the closed environment of their homes, their children, and their sick and aged parents? Obviously the advent of much safer insecticides whose effects are easily predictable would give us considerable assurance in this matter. One important approach to such an investigation would be to correlate the biochemical action of the chemical with changes in structure, picking out those analogs which killed insects while sparing mammals (Hastings and Dauterman, 1971).

Another approach involves learning more about the differences in the basic physiology and biochemistry between and among organisms. One approach to this problem has been to determine the differences among a class of chemicals common to all cellular membranes, the phospholipids. Important differences in these lipids have been found between the target organism (insects) and mammals (Hodgson et al., 1969). Probably the most important factor holding back a rational approach to discovery of less toxic chemicals has been our relative ignorance about cholinesterase, the enzyme which serves as the target for the phosphate and carbamate insecticides in use today. Only when this enzyme, cholinesterase, has been adequately purified from target and nontarget organisms will we be able to devise chemicals on a

rational basis. Within the last year an enzyme preparation some 200-fold more pure than any reported has been prepared (Main et al., 1972), a giant step toward intelligent design of insecticides.

Another health problem that requires attention concerns the dermal hazard to agricultural workers caused by substitution of "safer" insecticides for the chlorinated hydrocarbons. Although phasing out of the chlorinated materials caused less total environmental problems, many substitutes are appreciably more dangerous to workers because of their appreciable dermal toxicity. Persons entering treated fields a few days after application to harvest fruit or engage in other cultural operations, may undergo some risk, particularly if they work in such fields for several weeks or months. Even in local situations such as tobacco farms, it may be necessary to monitor the accumulative effects of pesticides; an expensive program requiring voluntary contribution of blood samples (Guthrie et al., manuscript). Increased use of these more dermally toxic substitutes has aso caused a direct conflict in pest management programs designed for more sophisticated insect control. In these programs, "scouts" must enter recently treated cotton or tobacco fields to determine insect infestations weekly, advising the farmer to treat only when populations of insects are out of balance with their natural control factors. Some sort of monitoring program must be made available to this agriculturally exposed population to assure them of minimal occupational hazards. A Federal task force has been assigned to establish some priorities to this problem.

I should be remiss in my testimony if I did not mention the impact that establishment of the Environmental Health Sciences Center has had on the program at North Carolina State University. The funds granted by the Institute have provided us with the support for our entire program. However, I feel that the associations we have had with the personnel from the Center have been equally important. Their mission-oriented research program complements our research and training functions. A number of well-known scientists from the Center serve in our training program, providing our students with frequent opportunities to discuss problem-solving situations that are not possible in most university settings. Soon after the Center started, a very important seminar group was organized in the Triangle area to discuss problems of environmental health throughout the Triangle area and the Nation. This has served as a very valuable person-to-person method of informally coordinating the activities of this critical mass of environmental scientists. Such activities prevent duplication of effort. For example, as a result of a large governmental program involving large scale use of Mirex to control fire ants, it became obvious that some of the toxicological aspects of this chemical were lacking. Following discussions at several of our seminars, three subprojects on this problem were initiated. The Center worked out the persistence of this compound in mammals, a second group in the Triangle studied degradation by micro-organisms, and the group at North Carolina State conducted the work on induction of microsomal enzymes (Hodgson et al., manuscript).

This critically needed information was presented to our State pesticide board and will enable them to arrive at a decision relative to use of this pesticide. This work will also be useful to the entire south-

80-012 O—72——6

eastern region as similar programs have been proposed from Texas to Florida. I am confident that many other such timely complementary activities will be commonplace in the Triangle as we cooperate in this nationwide effort to protect our citizens from environmental pollutants.

Mr. FOUNTAIN. Thank you very much, Doctor. You made reference on page 4 of your statement to the problems created when unskilled, pesticide-ignorant, applicators treat the closed environment of their homes. I think this may well raise two kinds of questions: (1) do pesticide products bear adequate directions for use; and (2) are these directions clear enough and understandable enough and so labeled that homeowners, and also agricultural and other workers, can safely follow them?

Dr. GUTHRIE. Yes, I think, speaking of the immediate effects, not the chronic effects, that they do bear adequate explanation, if the people would read them. I think the information is there. It's the question, if people read them. I doubt that most people do. Teaching people to read the label is one important part of the problem.

Mr. FOUNTAIN. I might say in connection with the first question, the subcommittee held hearings and issued a report in 1969 on "Deficiencies in Administration of the Federal Insecticide, Fungicide, and Rodenticide Act."

Among the committee's findings was that some pesticide labeling is confusing and contradictory. In one instance, the subcommittee investigation disclosed that a concentrated fly and roach spray, whose labeling had been approved in May 1969, cautioned the user to "use in well-ventilated rooms or areas only," while the directions for use began by instructing the user to "close all doors, windows, and transoms." Obviously, they can't have it both ways.

Dr. Guthrie, what has your experience been with respect to the adequacy of labeling and the capability of the consumers to follow the directions for toxic pesticides in order to use them safely?

Dr. GUTHRIE. Well, of course, the information on the label is very minimal. A large part of the problem, of course, is the general education of the people. I think that many of the problems about labeling have been cleared up in the last couple of years and they are getting labels that are more explanatory. I don't think we ever get to the standpoint where we can explain everything on a label. It's impossible. But the information we have on these labels, within the constraints of what we have, is probably minimally satisfactory.

Mr. FOUNTAIN. Do you find instances where labels might recommend using greater quantities than are needed?

Dr. GUTHRIE. This has not been my experience. I don't recall. There may be some, but I don't recall any.

(Dr. Guthrie's curriculum vitae follows:)

CURRICULUM VITAE

Name: Frank E. Guthrie.

Education: University of Kentucky, B.S. agriculture, 1947; University of Illinois, M.S. entomology, 1949; University of Illinois, Ph. D. entomology, 1952.

Experience: Teaching assistant, University of Kentucky, 1946–47; research assistant, University of Illinois, 1947–51; infantry officer, U.S. Marine Corps, Korea, 1951–52; assistant professor, North Florida Experiment. Station, 1952–54; assistant to full professor, North Carolina State University, 1954 to present;

director, research and training program in molecular and environmental toxicology, North Carolina State University, 1964 to present.

Consultant: U.S.P.H.S., 1965 to present; E.P.A., 1972; F.A.O., 1971; National Association on Standard Medical Vocabulary.

Societies: American Chemical Society, Entomological Society of America, Sigma Xi, North Carolina Academy of Sciences.

Travel: F.A.O. consultant to Bangalore, India, 1971; CORESTA plenary lecture at Stockholm, Sweden, September 1968.

Publications (five most recent from a list of 60 total scientific journal articles):

Guthrie, F. E., W. B. Tappan, M. D. Jackson, F. D. Smith, H. G. Krieger, and A. L. Chasson. 1972. Cholinesterase levels of cigar-wrapper tobacco workers exposed to parathion, Arch. Env. Hlth. (June issue).

C. O. Abernathy, E. Hodgson, and F. E. Guthrie, 1971. Structure-activity relationship in the induction of hepatic microsomal enzymes in the mouse by DDT analogs. Biochem. Pharmacol. 20:2385–2343.

Guthrie, F. E., R. J. Monroe, and C. O. Abernathy. 1971. Response of the laboratory mouse to selection for resistance to insecticides. Toxicol. Appl. Pharm. 18:92–101.

Guthrie, F. E., and W. E. Donaldson. 1970. Distribution of DDT and dieldrin in the avian embryo. Toxicology and Applied Pharmacol. 16:475–481.

Guthrie, F. E., 1968. The nature and significance of pesticide residues on tobacco and in tobacco smoke. Beitr. Tabakforschung 4:229–246.

Mr. FUQUA. Thank you for your fine statement.

Mr. FOUNTAIN. Thank you very much, Doctor. We appreciate your coming. I'd like to say before we recess that the subcommittee will spend time this afternoon at the Research Triangle visiting the laboratories and other facilities of the National Institute of Environmental Health Sciences. I understand the Institute scientists will brief the subcommittee on the very important research work which is being conducted there at the present time, and I am hopeful we will have time to see some other areas of the Research Triangle. Are there any other questions, observations, or comments? If not, the subcommittee stands adjourned, to reconvene subject to the call of the Chair.

(Whereupon, at 1 p.m., the subcommittee adjourned, to reconvene subject to the call of the Chair.)

(Following adjournment of the hearing, the subcommittee toured the facilities of the National Institutes of Environmental Health Sciences at Research Triangle Park, N.C. The tour was conducted by Dr. Rall through the laboratories of the Institute, where scientific personnel explained their work and answered subcommittee questions.)

APPENDIX

Subcommittee Tour of Facilities of NIEHS at Triangle Research Park, N.C.

Summary Description of Interim and Permanent Facilities of the National Institute of Environmental Health Sciences Given During the April 24, 1972 Visit to NIEHS by Members and Staff of the Intergovernmental Relations Subcommittee of the House Committee on Government Operations

(By W. W. Payne, Sc. D., Deputy Director)

Following the selection of Research Triangle Park as the location of the National Environmental Health Sciences Center, the Research Triangle Foundation and the State of North Carolina donated a 509 acre tract in the park to the Public Health Service for the site of the center. (See figure 1.) Because the Secretary of HEW had determined that no temporary structures should be erected on the permanent site, the Research Triangle Foundation constructed and leased to HEW interim facilities immediately adjacent to the permanent site. (See figure 1a.)

When the responsibility for developing the center was transferred in November 1966 from the former Bureau of State Services to NIH, these interim buildings had just been completed and were ready for occupancy. These interim facilities, which are constructed of brick and steel, consisted of an administration building, three laboratory buildings, one animal building, a service building, and a powerplant to provide steam and chilled water for heating and air conditioning. An additional building in the complex was occupied by a data processing activity of the National Center for Health Statistics.

The first additions to the interim facilities were a preengineered warehouse and two temporary office buildings. At about the same time that these additions were completed, the National Center for Health Statistics moved to larger, leased facilities in the park and that building became available for conversion to laboratories. This was the first addition to our laboratories and provided urgently needed space for the installation of an electron microscope and for expansion of histro-pathology services. (See figure 2.)

The next expansion of the interim site was the completion of 30,000 square feet of additional specialized laboratory facilities known as phase II. This complex of three buildings and powerplant was constructed by a private investor in accordance with plans and specifications developed by a firm of architects for NIEHS and upon completion in May 1971 was leased to the Institute. This addition to our facilities was important not only because it doubled our available laboratory space but enabled important program expansion that could not take place until these specialized facilities were available. The aerosol toxicology program could not be initiated until exposure chambers were available and long-term animal experiments were limited by the lack of a barrier type animal building that would assure the long-term survival of the animals that is essential in chronic studies at low levels of exposure. At about the same time the interim facilities were completed, another temporary office building was added adjacent to the laboratory buildings to provide office space for the branch chiefs and for the biometry branch which would be convenient to the laboratories without using specialized laboratory space for office functions.

In the meantime, a firm of architects and engineers was retained to develop a master site plan for the 509 acre permanent site. The design was to include a facility for NIEHS that would accommodate 1,000 to 1,200 persons with pos-

sible expansion to three times that size. The National Air Pollution Control Administration, then a part of HEW, was also to be located on the site in a facility approximately the same size as the NIEHS Center. The designers were asked to determine whether the site would accommodate additional centers together with the support services that would be required for operation. The site planning was completed in March 1971. (See figure 3.) The focal point of the site plan is provided by the construction of an earthen dam across a natural ravine to create a lake around which four centers could be located—one for NIEHS, one for Air Pollution (now Environmental Protection Agency), and two unidentified centers. In addition the master site plan includes a community center for meeting rooms and other facilities that would be shared by the four centers as well as a service center which includes the powerplant, warehousing, maintenance, and the like.

Funds have been appropriated for the planning of the first unit of the NIEHS permanent buildings. The program of requirements for this first unit has been prepared and the request for apportionment of the planning funds is now at the Office of Management and Budget. It is hoped that an architect can be retained in the next few months to prepare plans and specifications for the first buildings with necessary utilities and roads to accommodate a staff of approximately 400. Because of the need to expand our intramural research program, the emphasis in the plans will be on laboratories and animal facilities. Additional animal space of a more flexible design than our present ones will be included in the first unit.

Because of the specialized nature of our interim facilities, the plan of development is to use the first unit on the permanent site and the interim facility concurrently.

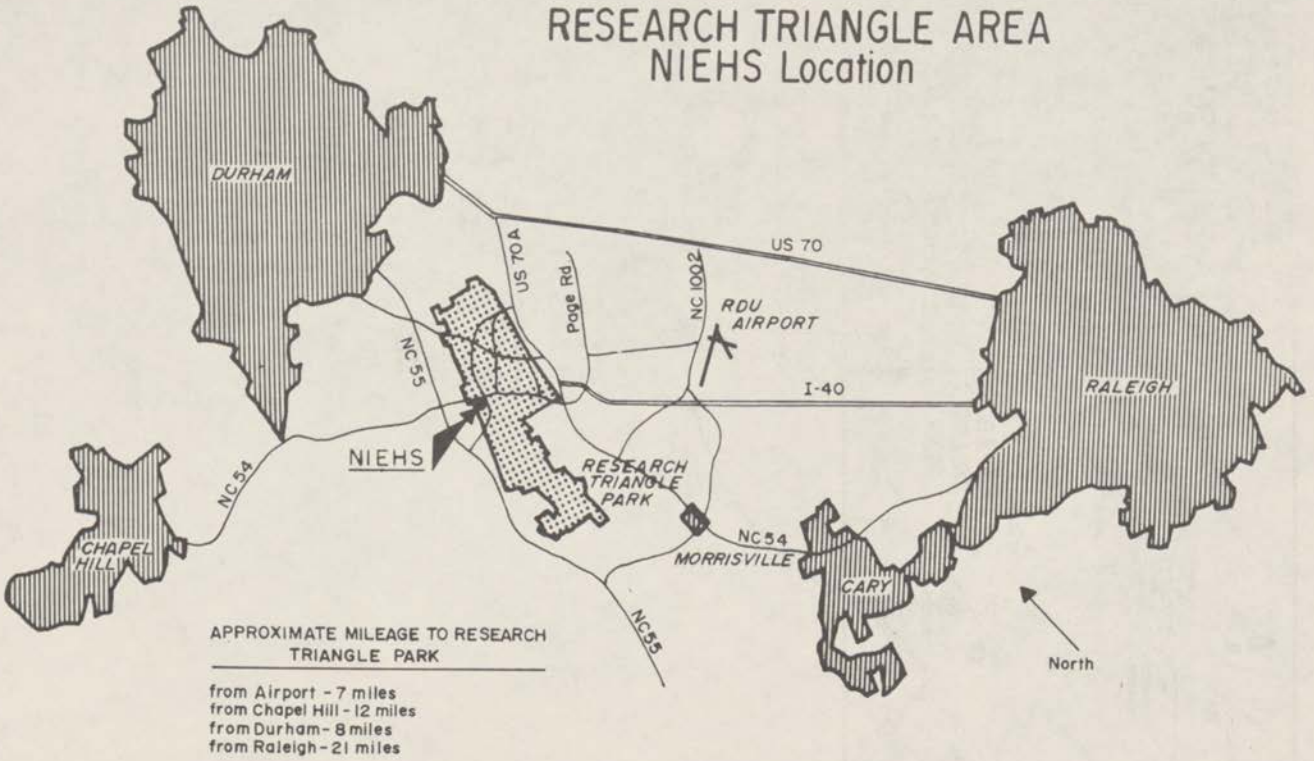

RESEARCH TRIANGLE AREA
NIEHS Location
DURHAM
US 70
US 70A
Page Rd
NC 1002
RDU AIRPORT
NC 55
I-40
RALEIGH
NIEHS
RESEARCH TRIANGLE PARK
NC 54
CHAPEL HILL
MORRISVILLE
CARY
NC55
North
APPROXIMATE MILEAGE TO RESEARCH TRIANGLE PARK
from Airport - 7 miles
from Chapel Hill - 12 miles
from Durham - 8 miles
from Raleigh - 21 miles

FIGURE 1

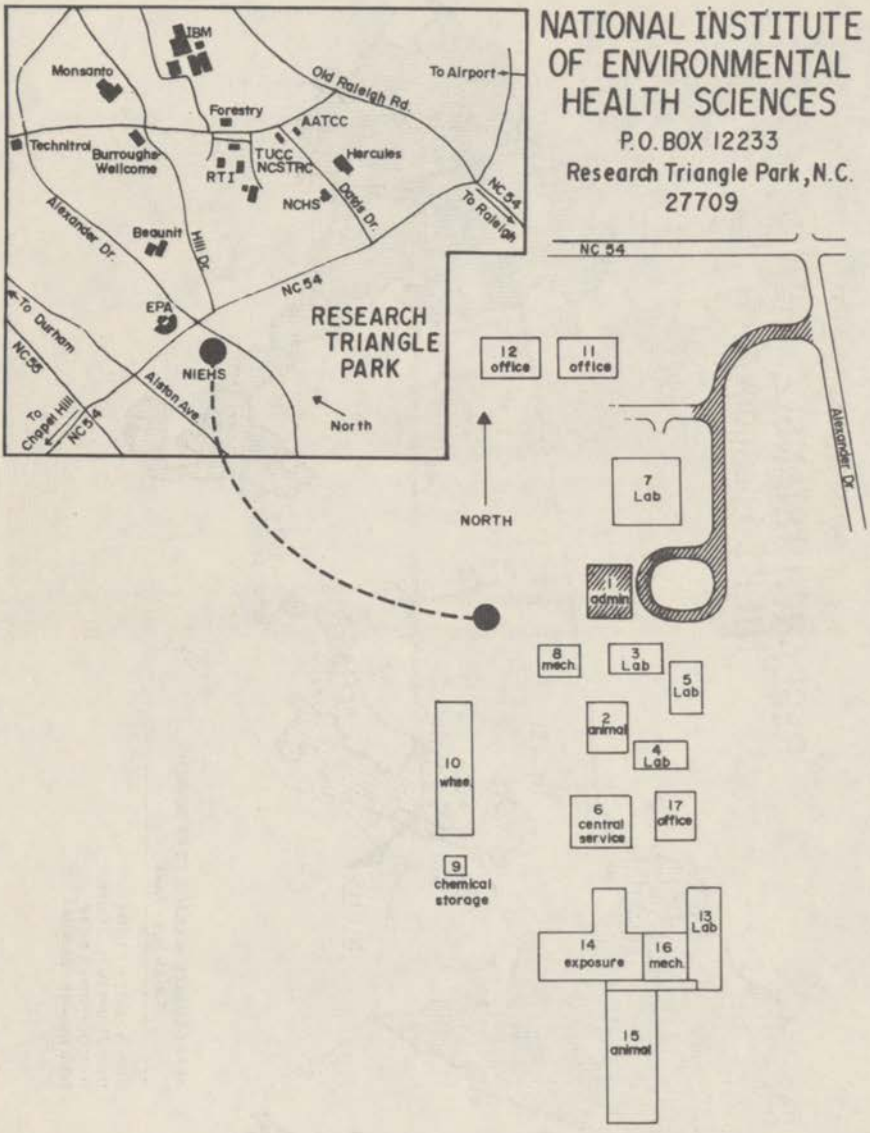

NATIONAL INSTITUTE
OF ENVIRONMENTAL
HEALTH SCIENCES
P.O. BOX 12233
Research Triangle Park, N.C.
27709
IBM
Monsanto
Forestry
Old Raleigh Rd.
To Airport
AATCC
Technitrol
Burroughs Wellcome
TUCC
NCSTRC
RTI
Hercules
NCHS
Davis Dr.
NC 54
To Raleigh
Alexander Dr.
Beaunit
Hill Dr.
NC 54
EPA
To Durham
NC 55
NIEHS
RESEARCH
TRIANGLE
PARK
Alston Ave.
To Chapel Hill
NC 54
North
NC 54
12 office
11 office
Alexander Dr.
NORTH
7 Lab
1 admin.
8 mech.
3 Lab
5 Lab
2 animal
4 Lab
10 whse.
6 central service
17 office
9 chemical storage
13 Lab
14 exposure
16 mech.
15 animal

FIGURE 1a

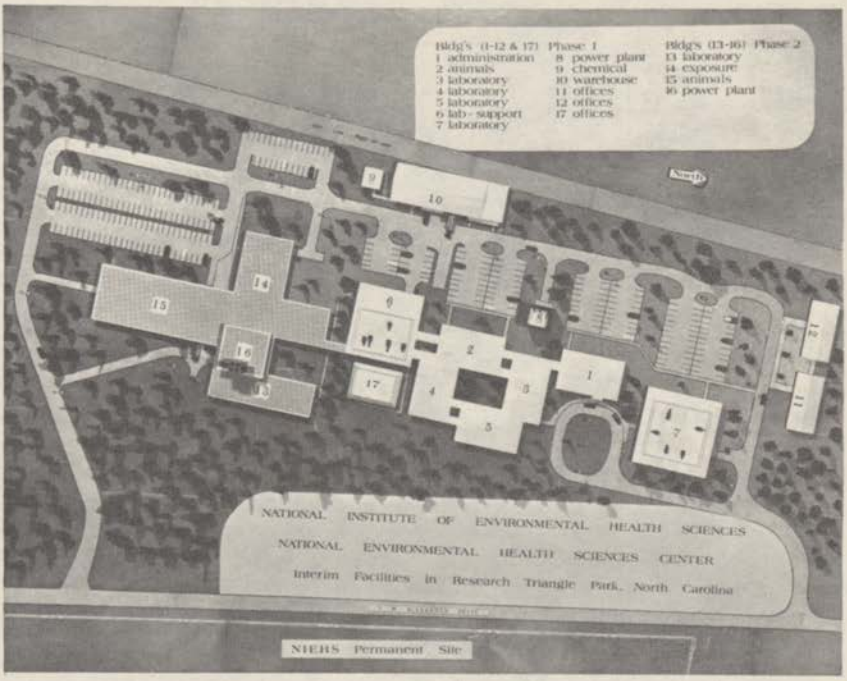

Bldg's (1-12 & 17) Phase 1
1 administration
2 animals
3 laboratory
4 laboratory
5 laboratory
6 lab - support
7 laboratory
8 power plant
9 chemical
10 warehouse
11 offices
12 offices
17 offices
Bldg's (13-16) Phase 2
13 laboratory
14 exposure
15 animals
16 power plant
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
NATIONAL ENVIRONMENTAL HEALTH SCIENCES CENTER
Interim Facilities in Research Triangle Park, North Carolina
NIEHS Permanent Site

FIGURE 2

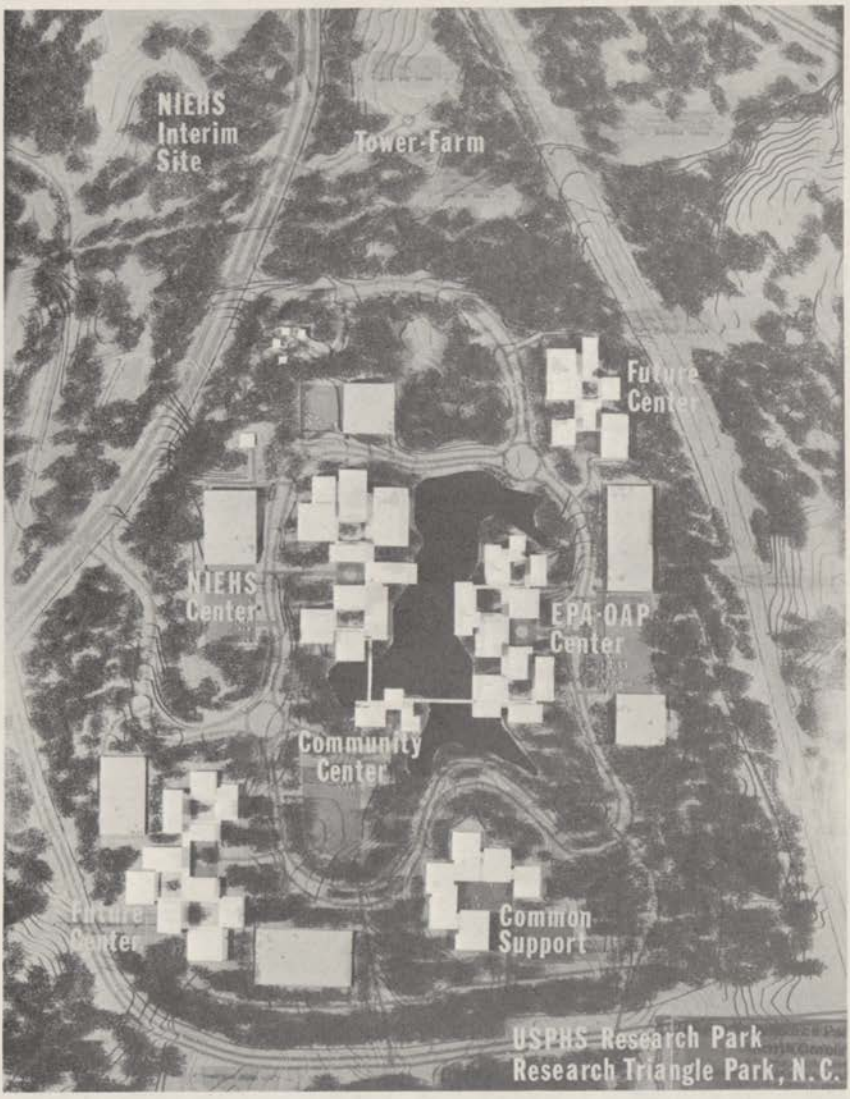


FIGURE 3

SUMMARY DESCRIPTION OF PROPOSED MUTAGENESIS PROGRAM GIVEN DURING THE APRIL 24, 1972, VISIT TO NIEHS BY MEMBERS AND STAFF OF THE INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE OF THE HOUSE COMMITTEE ON GOVERNMENT OPERATIONS

(By Frederick J. de Serres, Ph. D., Chief-designate, Mutagenesis Branch)

(Dr. Serres' curriculum vitae follows:)

CURRICULUM VITAE OF FREDERICK J. DE SERRES

Born: September 24, 1929, Dobbs Ferry, N.Y.
Education: Tufts University, 1947–1951, B.S. biology; Yale University, 1951–1955, M.S. botany, Ph. D. botany.

Fellowships: Predoctoral fellowship of the National Cancer Institute Public Health Service, 1952–54; Wadsworth fellow, Yale University, 1954–55; research associate, Biology Division, Oak Ridge National Laboratory, 1955–57.

Present position: Senior staff biologist, Biology Division, Oak Ridge National Laboratory, 1957 to present; coordinator, Environmental mutagenesis program, Biology Division, Oak Ridge National Laboratory, 1969 to present; lecturer, the University of Tennessee, Oak Ridge Graduate School of Biomedical Sciences, 1971 to present.

Professional activities: Consultant, DDT Advisory Committee, Environmental Protection Agency (1971); member, Committee on Assessment of Nitrate Accumulation in the Environment, Agricultural Board, Division of Biology and Agriculture, National Research Council (1970–72); member, Advisory Committee, Environmental Mutagen Society Information Center; editor-in-chief, Environmental Mutagen Society Newsletter; member, Council, Environmental Mutagen Society; member, Editorial Board, Mutation Research; member, committee for RBE of Neutrons, ICRP task group (1969–1970); member, Honorary Editorial Advisory Board, Radiation Botany; representative, Genetics Society of America on the Division of Biology and Agriculture of the National Research Council (1970–1973); member, Panel on Non-Psychiatric Hazards of Drugs of Abuse, National Institute of Mental Health, DHEW (1969); Consultant, Joint FAO/IAEA/WHO Expert Committee on Irradiated Food (1969); consultant. NASA biosciences experiment survey (1968); consultant, Genetics Study Section, Division of Research Grants, NIH, 1967; chairman, local committee, Neurospora Information Conference (1966); experimenters representative, NASA biosatellite program (1964–1968); chairman, Neurospora Information Conference (1961).

Societies: Sigma Xi, Botanical Society of America, Genetics Society of America, Radiation Research Society, Society of General Physiologists, American Association for the Advancement of Science, Environmental Mutagen Society, New York Academy of Sciences.

Field of research: Microbial genetics, radiation, chemical and environmental mutagenesis, space biology, mutagenicity of carcinogens.

The genetic basis for many human diseases is now well established; they can result from abnormal numbers of chromosomes, chromosome rearrangements or gene mutations. Well known examples of such diseases include mongolism, sickle cell anemia, cystic fibrosis, muscular dystrophy and Tay-Sachs disease.

It has been estimated that from 13 to 36 percent of the hospital beds of this Nation are occupied by patients suffering from diseases of genetic origin. In addition, we know that there are genetic disorders that predispose carriers to particular types of disease, such as the susceptibility to different types of carcinomas.

The load of genetic damage in the human population is responsible for the present levels of those human genetic diseases which have been identified. Any increase in the genetic load would result in an increase in the numbers of individuals with these diseases.

Many patients suffering from human genetic disease have to be institutionalized either for many years or their entire lifetime—often at public expense. The cost of such care has been estimated to be on the average between $100,000 to $275,000 per patient for his lifetime. Human genetic disease is not only a personal tragedy but when patients have to be institutionalized at public expense the expenditure of our national resources on their care becomes an additional consideration.

Many chemicals already in widespread distribution are known to be mutagenic on experimental organisms. Since most chemicals in use have not been tested for mutagenicity we need to know which ones are mutagenic and whether any of these provide a hazard to human health.

The primary emphasis in the new mutagenesis branch will be to develop better methodology to detect mutagenic activity and to determine whether environmental chemicals will cause undesirable genetic effects in man. In addition, methods will be developed to monitor the population to determine whether the genetic load is increasing.

The mutagenesis branch will work closely with other Government agencies and the national laboratories to establish priorities and to determine how best to utilize the resources of each institution to provide a coordinated research program on this important health problem.

SUMMARY OF THE TOUR OF THE PHARMACOLOGY AND TOXICOLOGY BRANCH DURING THE APRIL 24, 1972, VISIT TO NIEHS BY MEMBERS AND STAFF OF THE INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE OF THE HOUSE COMMITTEE ON GOVERNMENT OPERATIONS

(By J. R. Fouts, Ph. D., Chief, Pharmacology and Toxicology Branch)

(Dr. Fouts' curriculum vitae follows:)

CURRICULUM VITAE

Name: Dr. James Ralph Fouts.
Date and place of birth: August 8, 1929, Macomb, Ill.
Citizenship: United States.
Education: June 1947—graduated, South Denver High School, valedictorian; June 1951—B.S. (chemistry), with highest honors, Northwestern University; August 1954—Ph.D. (biochemistry, pharmacology), Northwestern University (Thesis: "On the Specificity and Mechanism of the Diamine-Diamine Oxidase Reaction").

Brief Chronology of Employment: 1951-1954—Tutorial fellow. Biochemistry Department, Northwestern University Medical School, Chicago, Ill.; 1952–1954—laboratory assistant, University College, Northwestern University (Chicago campus); 1952–1954—laboratory instructor, University College, Northwestern University (Chicago campus); 1953–1954—instructor, nurses' course in chemistry, Wesley and Passavant Memorial Hospitals, Chicago, Ill.; 1952–1954—Research Associate, Biochemistry department, Northwestern University Medical School; 1954–1956—U.S. Public Health Service, Laboratory Chemical Pharmacology, National Heart Institute, NIH Bethesda, Md.; 1956–1957—senior research biochemist, Burroughs Wellcome & Co., Wellcome Research Laboratories, Tuckahoe, N.Y.; 1957–1959—Assistant professor, Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, Iowa; 1959–1965—Associate professor, Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, Iowa; 1965–1970—Professor, Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, Iowa; 1968–1970—Director, Oakdale Toxicology Center, Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, Iowa; and 1970 to present—Chief, pharmacology and toxicology branch, NIEHS, Research Triangle Park, N.C.

Military service: Commissioned officer, U.S. Public Health Service (Assistant scientist and senior assistant scientist), 1954–1956.

Societies: American Society for Pharmacology and Experimental Therapeutics; Society of Toxicology; Society for Experimental Biology and Medicine; American Association for the Advancement of Science; and Sigma Xi.

Honors and Awards:

1. Winner by competitive exam, Merit Scholarship, State of Colorado. To any State university or college, 1947.
2. Marple Schweitzer Award in Chemistry—1950—Given to a senior student majoring in chemistry. Recognition for best scholarship in chemistry courses, Northwestern University.
3. Phi Lambda Upsilon (chemistry honorary society)—1950—Northwestern University.
4. Phi Beta Kappa—1950—Northwestern University.
5. Tuition Scholarships—Northwestern University 1947–1950—undergraduate school.
6. B. Sc. with highest honors—1951—Northwestern University.
7. Tuition plus stipend fellowships—Northwestern University 1950–1954—graduate school.
8. Abel Award in Pharmacology, from American Society for Pharmacology and Experimental Therapeutics, 1964.
9. Claude Bernard Professor (Claude Bernard Medal), Institut de Medicine et de Chirurgie Experimentales, University de Montreal, Montreal, Quebec, April 1970.

Editorial Activities

Editorial Board, Journal of Pharmacology and Experimental Therapeutics, 1960–65.

Editorial Board, Molecular Pharmacology, 1964–68.
Editorial Board, Biochemical Pharmacology, 1966–69.
Editorial Board, Chemico-Biological Interactions, 1969– .
Editorial Board, Xenobiotica, 1970.

University of Iowa Activities

Research Council, University of Iowa, 1966–69—chairman, Subcommittee on Conflict of Interest, 1966–67; chairman, Subcommittee on Classified Research, 1967–68; member, Subcommittee on Role of the University in Public Affairs, 1968–69.

Hospital Board, Oakdale Hospital, University of Iowa, 1967–1970.

Protocol Review Committee, General Clinical Research Center, University of Iowa College of Medicine, 1967–70.

College of Medicine Lecture Committee, University of Iowa, 1969–1970.

Consultant in pharmacology and toxicology, Poison Control Center, University of Iowa Hospitals, 1968–1970.

University of North Carolina Activities

Adjunct professor of pharmacology, Department of Pharmacology, School of Medicine, September 1970 to present.

Member, Scientific Review Committee, Dental Research Center, School of Dentistry, September 1970 to present.

Chairman, Subcommittee for Review of Dental Materials Program of the Dental Research Center.

National and International Committees

Pharmacology and Experimental Therapeutics Study Section, Division of Research Grants NIH, Bethesda, Maryland, 1962–66 (PET SS became PET SS–A in 1966).

Pharmacology-Toxicology *Ad Hoc* Advisory Committee, Nat'l. Inst. General Med. Sciences NIH, DRG, 1964–65. Advisory to Dr. Shannon on Pharmacology-Toxicology Centers.

Scientific Group on Principles of Pre-Clinical Testing for Drug Safety, World Health Organization, Geneva, Switzerland, 1966.

Committee on Comparative Pharmacology. Program Planning Group, Nat'l. Inst. General Med. Sciences and Nat'l. Cancer Inst., Nov. 1965–Feb. 1967.

Pharmacology-Toxicology Review Committee, Nat'l. Inst. General Med. Sciences, NIH, 1967–68.

Abel Award Committee of the American Society for Pharmacology and Experimental Therapeutics, 1967–68.

Environmental Health Sciences National Advisory Committee (Council), National Institute of Environmental Health Sciences, NIH, 1968–70—member, Subcommittee on University-based Centers, 1968–70.

Program Committee, National Institute of General Medical Sciences, Symposium on Microsomes and Drug Oxidations, Bethesda, Maryland, 1968.

Member, Task Force on Research Planning in Environmental Health Sciences, NIEHS, NIH, 1968–69—chairman, Subcommittee on Toxicology.

Ad Hoc committee on Anticonvulsant Drugs, National Institute of Neurological Diseases and Stroke, NIH, Bethesda, Maryland, 1969 to present.

Education Committee, Society of Toxicology, 1970 to present (Elected Office).

Committee for Environmental Pharmacology, American Society for Pharmacology and Experimental Therapeutics, October 1970 to present.

Public Information Committee, Fifth International Congress on Pharmacology, American Society for Pharmacology and Experimental Therapeutics, March 1971 to present.

Consultantships

Consultant in Pharmacology, Salsbury Laboratories, Charles City, Iowa, 1960–66.

Consultant in Pharmacology, Smith Kline and French Laboratories, Philadelphia, Pennsylvania, 1964–70.

Special Consultant in Developmental Pharmacology, Nat'l. Inst. Child Health and Human Development, 1965–66.

Consultant in Pharmacology, Hoffman-La Roche, Inc., Nutley, New Jersey, 1966–70.

Invited Speaker—Conferences and Symposia:

(Seminars and talks at other universities, government or industrial laboratories are not listed.)

1. First International Pharmacological Meeting, Stockholm, Sweden, August, 1961, Symposium on "Metabolic Factors Controlling the Duration of Drug Action."

2. Forty-first Ross Conference on Pediatric Research No. 1961, San Francisco, California. Symposium on "Perinatal Pharmacology."

3. Federation Symposium, Atlantic City, N.J., April, 1962, Symposium on "The Action of Drugs on Subcellular Particles."

4. Gordon Research Conference on Toxicology and Safety Evaluation, Meriden, N.H., August, 1962.

5. New York Academy of Sciences Conference, October 1962, New York, N.Y. Conference on "Hepatotoxicity of Therapeutic Agents."

6. International Symposium on "Regulation of Liver Enzyme Activity and Synthesis." Indianapolis, Indiana, October, 1962.

7. Gordon Research Conference on Medicinal Chemistry, New London, N.H., July, 1963.

8. Second International Pharmacological Meeting, Prague, Czechoslovakia, August, 1963. Symposium on "Drugs and Enzymes III. Biochemical Mechanisms of Drug Toxicity I."

9. Conference at New York Academy of Sciences—"Evaluation and Mechanism of Drug Toxicity." Session on "Drugs and the Mammalian Embryo." Held March, 1964, New York City. Sponsored by the Interstudy Section Group of the National Institutes of Health.

10. Second International Workshop in Brain Research, sponsored by International Brain Research Organization and UNESCO. Held in New Delhi, India, Oct. 4–23, 1964.

11. Symposium on "Developments in the Safety Evaluation of Pesticides and Food Chemicals." Sponsored by the Food Protection Committee of the National Academy of Sciences—National Research Council. Washington, D.C., December 2–3, 1964.

12. Symposium on "The Embryopathic Activity of Drugs." Sponsored by Biological Council Coordinating Committee for Symposia on Drug Action. University College, London, England, March 29–30, 1965.

13. Conference on Developmental Pharmacology. Sponsored by Nat'l. Inst. of Child Health and Human Development, Niagara Falls, N.Y. Oct. 10–12, 1965. Also served as Conference Chairman.

14. Scientific Group on Pre-Clinical Testing for Drug Safety. Sponsored by World Health Organization, Geneva, Switzerland, March 21–26, 1966.

15. Meeting of Drug Research Board, National Academy of Sciences, National Research Council. Fourth Meeting of the Committee on Applications of Biochemical Studies in Evaluating Drug Toxicity. November 22, 1966.

16. Symposium on Comparative Pharmacology. Sponsored by Nat'l. Inst. General Med. Sciences. Held in Washington, D.C., Jan. 24–27, 1967. Co-chairman of Session on "Mechanisms of Detoxification and Transformation in Living Organisms."

17. Guest Faculty, Workshop on Biochemical Approaches to Clinical Pharmacology, June 12–16, 1967, Vanderbilt University, Nashville, Tenn. Sponsored by The Drug Research Board of the National Academy of Sciences and the Pharmaceutical Manufacturers Association Foundation.

18. Food and Drug Administration conference on "Experimental Design for the Evaluation of Anticonvulsant Drugs"—section on Toxicology. August 24–25, 1967, Arlington, Virginia.

19. NIH Conference on "Diagnosis and Treatment of Disorders Affecting the Intrauteine Patient." Dorado, Puerto Rico, Oct. 29–Nov. 1, 1967. Sponsored by the Nat'l Institute of Child Health and Human Development.

20. NIH Conference on "Microsomes and Drug Oxidations." Bethesda, Md. Feb. 16–17, 1968. Sponsored by Nat'l Institute of General Medical Sciences and the Drug Research Board of the National Academy of Sciences. Also served as chairman of one of the sessions.

21. Gordon Research Conference on Toxicology and Safety Evaluations. Meriden, New Hampshire, July, 1969.

22. Claude Bernard Professor, Institute de Medicine et de Chirurgie Experimentales, University de Montreal, Montreal, Quebec, April 29–May 1, 1970.

23. Gordon Research Conference on Drug Metabolism, Tilton, N.H., July 26–30, 1971.
24. Thirteenth International Congress of Pediatrics, Vienna, Austria, Aug. 29–Sept. 4, 1971.
25. Symposium on Pharmacology of Anticonvulsant Drugs, Phoenix, Arizona, Sept. 7–10, 1971. Also *member*, organizing committee for symposium and editorial committee for symposium publication (June 1970-present).

Research Interests:

Mammalian drug metabolizing enzyme systems; factors affecting these enzymes (age, disease, induction and inhibition by pesticides); correlation of cell ultrastructure and function of these enzyme systems; intracellular localization of these enzyme systems; comparative pharmacology and drug metabolism; the metabolism of drugs by tumors; the pharmacology of antimetabolites and antibiotics.

Three parts of the pharmacology and toxicology branch's research program were described for the visitors: (1) cell culture and teratology, (2) uptake and release of chemicals by the lung, and (3) aerotoxicology. These were chosen since they at least partly represent the scope of research of the branch and, like many of the branch's programs, are unique—combining facilities and techniques applied in few if any other laboratories engaged in studies of environmental effects on mammals.

Cell culture and teratology.—We have set up techniques under the direction of Dr. Robert Staples and his colleagues, Drs. Donald Elliott, Laila Moustafa, and Ralph Maurer, for the culture of fertilized eggs and embryos from several animal species. During this period of living outside the mother's body, the embryo can be exposed to known chemicals, in precisely known amounts, for exact periods of time and at selected stages of development. It is our hypothesis that a major reason for the fact that a chemical will produce birth defects in one animal species, but not in another is that the mother of the resistant animal prevents the chemical from reaching her fetus at the right time or in an active form. We propose that an understanding of the direct effects of environmental pollutants and other chemicals on the fertilized egg (uncomplicated by species-specific maternal actions on the pollutant) will help us identify those chemicals, et cetera, most likely to cause birth defects in man, and to devise ways to protect against these effects. Eggs and embryos treated in culture with chemicals can be transferred back into the mother and allowed to mature for varying periods or even be born before further examination for defects which have resulted from exposure to such chemicals. The culture-transfer process is illustrated in figure 1.

We are also able to expose only certain parts of the fertilized egg to suspected toxins and teratogens. Using micromanipulators, Dr. Moustafa and colleagues can inject the chemicals into only certain cells of the embryo or selected areas of a single cell. One or more cells so treated can also be transferred to a recipient embryo and be incorporated there. Parts of a treated cell, such as a nucleus, can be transferred to an untreated cell or group of cells. Such studies help localize even more precisely the critical cells of an embryo or the most sensitive part of the critical cell that is affected by the chemical or pollutant. These techniques are illustrated in figure 2.

To our knowledge such techniques of cell culture and microsurgery have not been applied by anyone else to a study of birth defects produced by any environmental agent, or to such defects produced by any drug. We believe these new approaches can give us much better predictions of chemicals and pollutants with liabilities as teratogens, as well as a start on changing, minimizing, or even preventing such effects by chemicals and pollutants that we have no hope of avoiding, even with the most active cleanup programs.

The perfused lung.—Dr. Thomas Eling and his collaborators, Drs. Terry Orton and Marshall Anderson (Dr. Anderson is a member of the biometry branch) are investigating the lung as a storage site of chemicals and pollutants. They have been studying the uptake and release of chemicals by the isolated perfused rabbit lung. The perfused lung system that we use (fig. 3) allows us to vary blood flow and rate of respiration, and to apply the pollutant either by adding it to the blood or by adding it to the air supply being "breathed" by the lung. This isolated lung system seems to be very close to the situation in the living animal, but lets us exclude complications from the rest of the body which can account for

wide variations in chemical toxicities between species and even from one animal to another, for example, fear, difference in respiratory rates, and breath-holding.

At present we are studying the uptake of basic chemicals by the lung. Among the wide variety of such chemicals are many common herbicides such as the triazines and the paraquat-diquat family, and widely used drugs such as the analgesics (morphine), tranquilizers (phenothiazines), and stimulants (amphetamines, imipramine). We are most concerned with the rate of uptake of these compounds (extremely fast in most cases), their duration of stay in the lung (often very long), and whether one such chemical can compete with others for either uptake and storage, or release. This latter is of great, but at present only theoretical concern. We hope to see if such competition (which we have already seen with a few pairs of chemicals) results in more or less storage of chemical by the lung, and storage for different periods of time. Also whether a chemical stored (and thereby rendered relatively inert or inactive) can be released from the lung by another chemical or drug breathed or ingested later. Such interactions might result in sudden, and unexplainable toxicities by otherwise "safe" chemicals—the safe chemical or drug producing toxicity because it released a pesticide or pollutant all at once from its storage site. This kind of study can be done with several organs, but the lung system is chosen because it is an organ exposed continuously to the environment, is an organ with large but relatively unknown chemical storage capacity, and is an organ where such storage interactions are rarely studied or understood.

Aerotoxicology: Dr. Drew and his colleagues (Drs. Roland Roth and Ray Lo) are conducting several studies of effects of chemicals and mixtures of chemicals when inhaled by various animal species for short or prolonged periods of time. Such studies are conducted in a facility having chambers of varying size and complexity to provide for maximum flexibility. Dr. Drew's tour of the facility included a look at animals inhaling vapors from a commonly used room deodorizer, and single components of aerosol spray deodorants. Several specialized isolation units were described (see fig. 4). Such units will allow us to expose animals to highly toxic or suspected carcinogenic materials such as the ubiquitous air pollutant benzpyrene, or very dangerous pesticides like paraoxon.

A major part of Dr. Drew's efforts interdigitate with those of other scientists in this and other branches who study the animals after exposure to gases, vapors, particles, and mixtures of these. Thus the effects of deodorant sprays on lung systems for metabolizing chemicals were studied by Dr. Drew working together with scientists from the Animal Science and Technology branch and with Drs. Bend and Hook of his own branch. The combination of specialized types of exposure chambers (for example, isolation units) and collaboration with scientists able to measure so many different kinds of effects of such exposure on the body makes this research program unique.

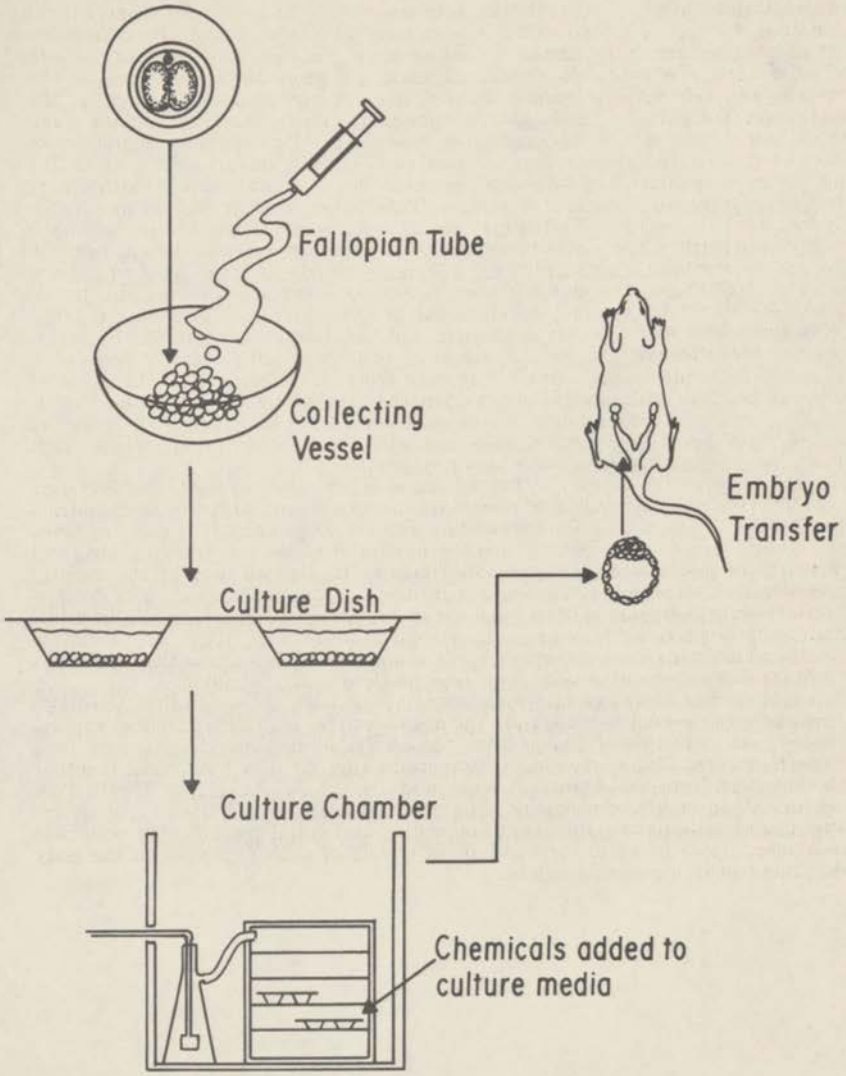


FIGURE 1.—Schematic drawing showing how fertilized eggs are collected, grown in culture dishes outside mother's body, exposed to chemicals being tested, and reimplanted back in mother's body for further growth or even birth.

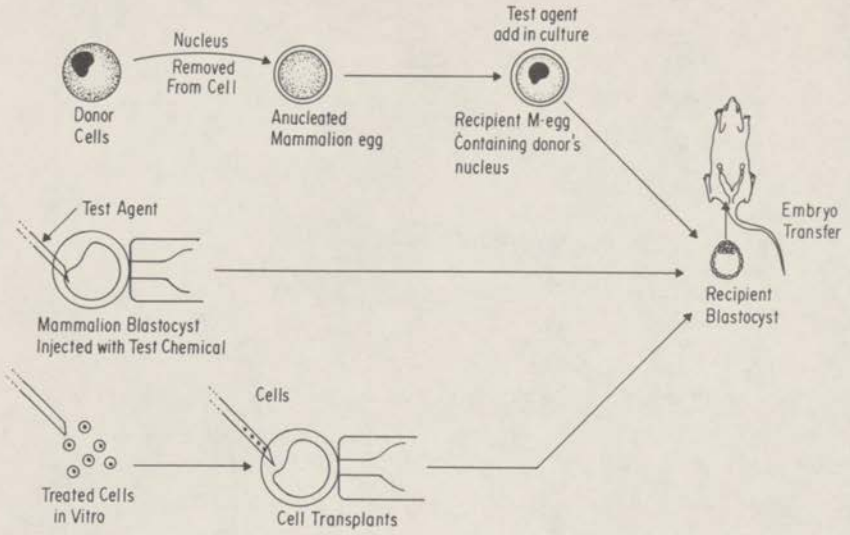


FIGURE 2.—Schematic drawing showing how various parts of cell or embryo can be selectively exposed to chemicals. At top, one cell can be exposed to a chemical, the nucleus from this treated cell can be removed and transferred to normal cell in place of normal nucleus (transfer to anucleated egg). Then this half-treated, half-normal cell can be grown in culture or even further treated in culture before transfer back into mother for further development of embryo. In middle, chemical can be injected into fertilized egg; this blastocyst can be grown in culture or immediately transferred back into mother for further development. At bottom, chemically treated single cells from embryo can be "grafted" into otherwise normal embryos (blastocyst) and then this "mixed embryo" placed into mother for further development. Treatment of single cells prior to grafting can occur in culture or by direct injections into cells held against a micropipet as shown (seen as though under microscope).

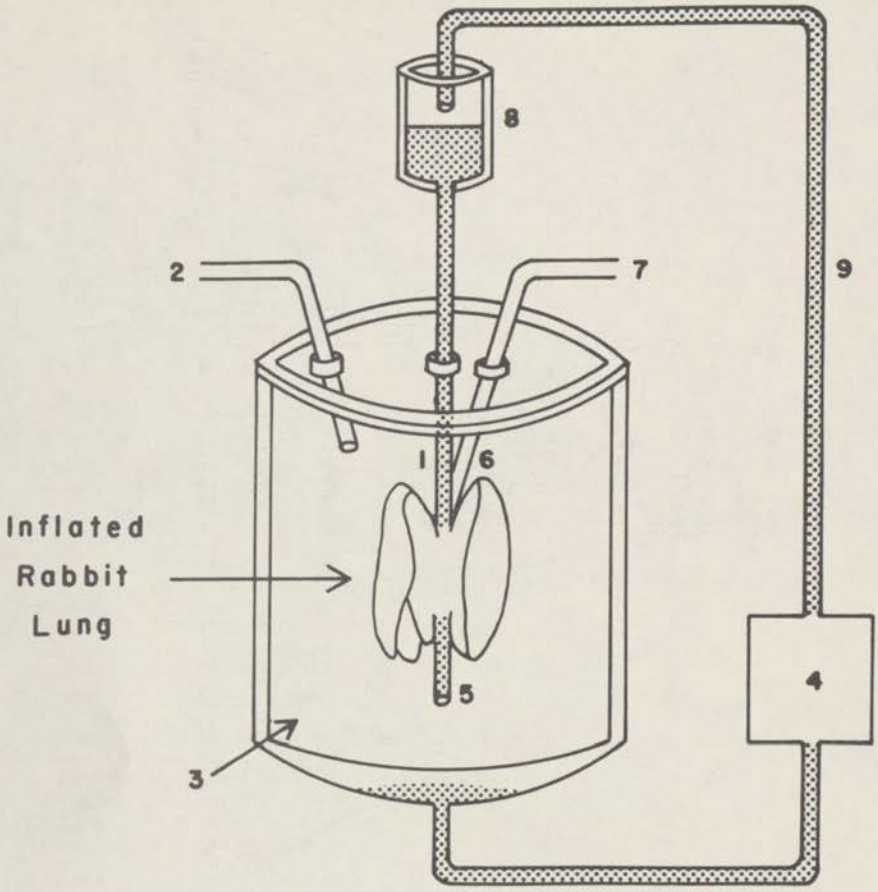


FIGURE 3.—This is a simplified drawing of the isolated perfused lung system shown to the visitors. The numbers identify key parts of the system: (1) artery-blood enters lung here; (2) to vacuum and respirator—lung expands by negative pressure as in living animal; (3) artificial thorax; (4) artificial heart (pump); (5) vein—blood leaves lung here; (6) trachea or windpipe; (7) air enters here—pollutants as mist or vapor can be added here; (8) blood reservoir—pollutants in solution can be added to blood here; and (9) blood in circulation system.

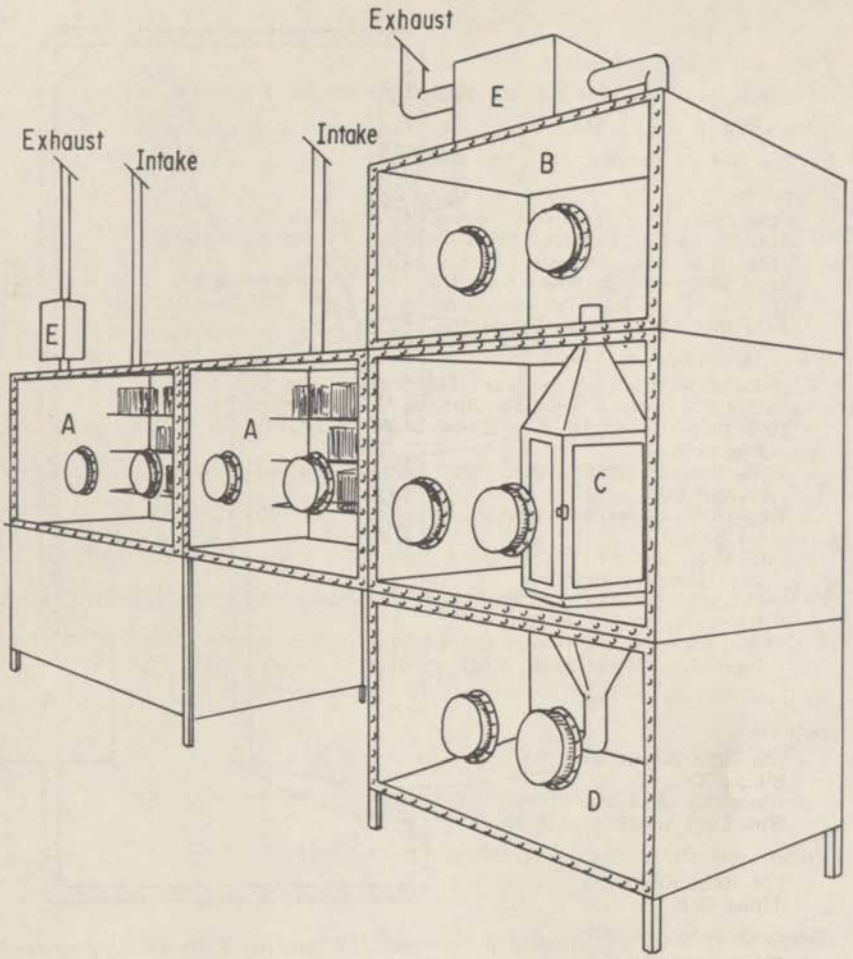


FIGURE 4.—This is a simplified drawing of the isolation chambers used for exposing animals to highly toxic materials. Letters refer to key areas of the exposure chambers: (A) Living quarters where animals can be observed continuously and can also be exposed to relatively nontoxic gaseous pollutants or clean air; (B) aerosols (suspensions of particles, dusts) of nongaseous pollutants can be generated here; (C) doubly isolated exposure chamber—where animals can be exposed to highly noxious materials; (D) cleanup area; and (E) absolute filters on exhaust lines to remove all pollutants before discharge to outside air.

SUMMARY OF PROJECT TO DEVELOP OPOSSUM AS AN ENVIRONMENTAL RESEARCH TOOL GIVEN DURING THE APRIL 24, 1972, VISIT TO NIEHS BY MEMBERS AND STAFF OF THE INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE OF THE COMMITTEE ON GOVERNMENT OPERATIONS

(By William Jurgelsky, Jr., Ph. D., M.D., Head, Cellular Control and Morphogenesis Section, Pathologic Physiology Branch)

(Dr. Jurgelsky's curriculum vitae follows:)

CURRICULUM VITAE

Name: Dr. William Jurgelsky, Jr.

Date and place of birth: May 25, 1931, Englishtown, N.J.

Citizenship: United States.

Martial status: Married, 1954, two children.

Education:

June 1949—Graduated from Jamesburg High School.
June 1953—B.S. (Agriculture) cum laude, Rutgers University.
June 1955—M.S. (Genetics), Rutgers University.
June 1958—Ph. D. (Genetics), Rutgers University (Thesis: The variation, interrelationship and inheritance of nitrogen, carotene and zanthophyll).
June 1967—M.D., Duke University.

Brief Chronology of Employment:

1953–1955—Research Assistant, Rutgers University.
1955–1957—Research Fellow, Rutgers University.
1957–1960—Geneticist, Territorial Experiment Station, USDA, Mayaguez, Puerto Rico.
1960–1963—Pharmacologist, Food and Drug Administration, HEW, Washington, D.C.
1963–1967—Research Associate, Dept. of Pathology, Duke University Medical School.
1967–1968—Intern (Pathology) and Fellow (Neuropathology), Duke University Medical School.
1968–1970—Acting Chief, Pathologic Physiology Branch and Medical Officer, Research, NIH, NIEHS.
1970–Date—Head, Cellular Control and Morphogenesis Section, Pathologic Physiology Branch and Medical Officer, Research, NIH, NIEHS.

Military Service: None.

Societies:

Phi Beta Kappa.
Sigma Xi.
American Association for the Advancement of Science.
New York Academy of Sciences.

Honors and Other Special Scientific Recognition:

Phi Beta Kappa.
Alpha Zeta.

Research Interests:

Carcinogenesis.
Embryogenesis of thyroid brain.
Experimental epilepsy.
Demyelination.
Experimental thyroiditis.
The Marsupial as a biomedical model.

A major concern of the National Institute of Environmental Health Sciences is the identification and better understanding of agents in the environment which may be detrimental to the human fetus and neonate. The standard laboratory approach to this problem is to expose laboratory animals at different stages of pregnancy to the suspect materials and to observe the young at birth for adverse effects. While this technique has great scientific validity and is unlikely to be improved on for routine screening purposes, our understanding of how the developing fetus responds to harmful agents would be increased if a method could be found which would permit the growth and development of fetuses outside the uterus where they could be directly manipulated and observed. Such a system did in fact evolve in nature eighty million years ago in the form of the opossum; the problem has been to adopt this "experiment of nature" to the laboratory.

The newborn opossum is semi-embryonic; it weighs about 5/1000 ounce, is less than 7/10 of an inch in length, and is at a stage of development roughly equivalent to a two-month-old fetus. (Fig. 1.) The brain is only half formed, and many other organs are just beginning to grow. In comparison to the full grown animal, the neonate is minute. (Figure 2) At birth "this abortion which has learned to survive outside the womb" uses its front legs (the hind legs are undeveloped embryonic stubs) (Figure 1) to crawl from the birth canal to the mother's pouch, a moist envelope of skin which protects the young animals during their first three months of life. Inside the pouch, the neonate finds and attaches to a nipple by an as yet unknown mechanism; within a few days, its jaws fuse so that it cannot release the nipple. In this state, the infant animal completes, over a period of 2½ months, much of the growth which in other animals takes place in the womb. While still in part developing fetal tissue, the young opossum is in fact independent of its mother except for the milk it drinks and the protection of the pouch. By comparison, a rat or mouse equivalent in maturity to the newborn opossum is only half way through gestation and is still in the mother's uterus.

To experiment on a rodent fetus, the investigator must either feed or inject the test material to the pregnant animal, risking both damage to her and alteration of the material by her system and by the placenta, or he must remove the embyro surgically, a highly unnatural procedure which obviously cannot be repeated in the same animal. By contrast, in the opossum growing embryonic tissue may be directly and repeatedly exposed to test materials with a minimum of maternal influence simply by opening the pouch and any experimental changes may be observed as they occur.

The great laboratory potential of the newborn opossum has been recognized by scientists ever since the animal was first studied in the laboratory some eighty years ago. No progress was made in exploiting this potential for toxicological and pharmacological studies because, despite many attempts over the years, no one was able to breed the opossum under laboratory conditions sufficiently to make adequate numbers of young available for meaningful investigations. Four years ago, the Institute began seeking a solution to this problem. Experiments which involved observation of the reproductive response of the animal under different methods of care and housing, have led to the development of methods which permit, for the first time, the production of large numbers of young opossums of known age. Key to this success is a semi-outdoor facility (Figure 3) which is designed to minimize or eliminate the problems of waste disposal, insect and rodent control, animal monitoring and exposure of personnel to weather while retaining some semblance of the natural environment which we found the animals required if they were to reproduce in captivity.

In this building, 100 females and 50 males are housed in individual cages featuring a flip-top nest box and walk-through shelf. (Fig. 4.) Breeding is controlled by monitoring individual females. In the breeding season from January to June, a technique similar to the "Pap" smear is used on each female every other day to determine the optimal time to breed her. Only when the female is in heat and for a few days thereafter is she allowed access to the male's cage. Unless the breeding is controlled in this fashion, many males are killed by non-receptive females and reproduction is reduced. Under the conditions described, our conception rate (the number of females bred which actually deliver young) has reached 90 percent, with a yield of over 100 litters (1000+ young) per year. This reproductive efficiency, which compares favorably with that of many laboratory and domestic animals, has made it feasible to explore the usefulness of the newborn and young animal as a model system for carcinogenic (cancer), teratologic (birth defects), and toxicologic studies.

However, first it was necessary to develop special techniques for working with the minute newborn animals and for exposing them quantitatively to the toxic materials to be tested. Because of the neonate's miniscule size and its firm attachment to the nipple, standard techniques of injection or intubation are not feasible methods for introducing test material into the young opossum's body. In one new method we have taken advantage of the young opossum's powerful sucking activity as it nurses. In this procedure a fine polyethylene tube is filled with the test material and gently placed a fraction of an inch into the young animal's mouth; as the animal nurses, it also drinks the contents of the tube. (Fig. 5.)

Our first attempts to use the opossum in the laboratory have centered around an evaluation of the usefulness of the animal as a model for studies of environ-

mental causes of cancer. In these experiments, groups of opossums bred in our facility and representing 11 different age levels have been exposed to ethyl nitrosourea, a cancer-producing chemical which has been shown to be formed in the animal (and probably human) stomach from chemicals present in foods. This experiment is only half complete. Plans are to allow the animals to live 1 more year to complete the 2-year average life span of the opossum. However, results to date are encouraging in several ways:

1. The time for tumor development appears to be short compared to other species, a great advantage in carcinogenic studies.

2. The opossum appears highly susceptible to tumor induction. One hundred percent of opossums exposed have developed one or more tumors within 1 year following exposure.

3. A large variety of malignant tumors is induced. They range from skin tumors (melanoma—fig. 6) to tumors of the kidney (figs. 7 and 8), liver (fig. 9), stomach (fig. 10), eye (fig. 11), gum and jaws (figs. 12 and 13), lungs (fig. 14), and tongue (fig. 15).

4. Many of the tumors are types common to childhood which have been heretofore difficult to produce in laboratory animals. For example, the tumor of the eye (fig. 11) has never before been experimentally induced in a laboratory animal. If it can be reproduced in larger numbers of opossums in experiments presently underway, it may become a valuable tool in the study of tumors such as the retinoblastoma, a highly malignant childhood tumor whose understanding has been handicapped by the lack of a laboratory animal model.

5. There is an association between developmental defects (fig. 7) and cancer in the opossums exposed to the cancer inducing agent. A possible relationship between cancer and congenital defects has been postulated but direct study of this postulated relationship, which might yield clues to cancer mechanisms, has not been possible because of the difficulty of inducing both cancer and growth defects simultaneously in standard laboratory species. The opossum may provide a useful model for the study of this intriguing relationship.

These findings imply that the young opossum may have special advantages in the study of the causes and the mechanisms of cancer common to childhood.

Experiments to further develop the animal as a biomedical model will continue. Attempts to develop a domestic opossum have now reached the second generation of animals produced in captivity. In addition we are especially interested in the possibility of further improving the efficiency of our animal production and experimental procedures. In this connection, we are exploring the feasibility of developing a special chamber in which young opossums might be grown outside the pouch in a kind of "assembly line" arrangement.

At present, our opossum population numbers over one thousand animals and represents the largest colony of its kind ever established.

In summary, a program to develop the opossum as a laboratory model for the study of environmental hazards has been successful in developing methods which permit, for the first time, the production of large numbers of young under controlled conditions. Preliminary experiments indicate that the young opossum may have special advantages in cancer research and may be a powerful biomedical tool in studies of environmental hazards.

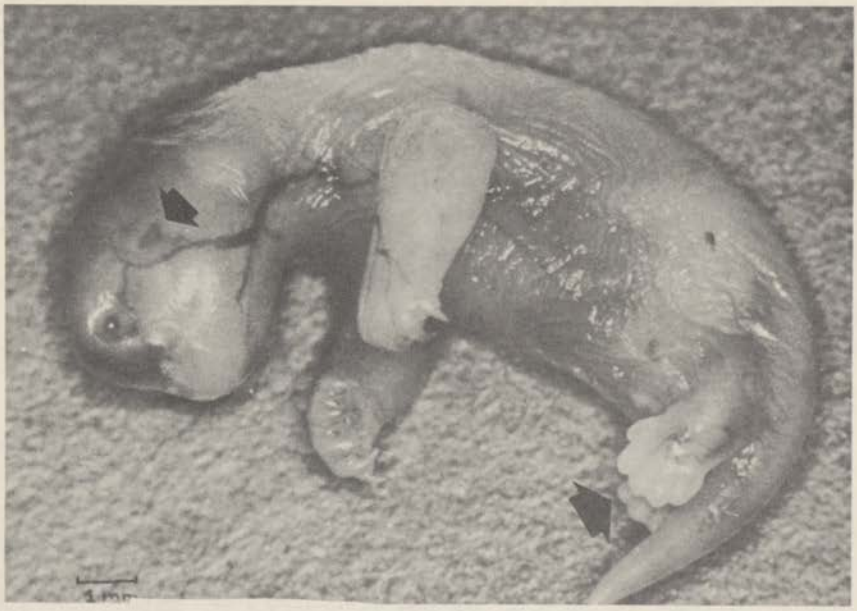


FIGURE 1.—Newborn American Opossum. Note undeveloped hind legs and rudimentary eye (arrows).

FIGURE 2.—Newborn Opossum (arrow) compared to adult opossum.

FIGURE 3.—Opossum breeding facility designed on the basis of research at NIEHS.

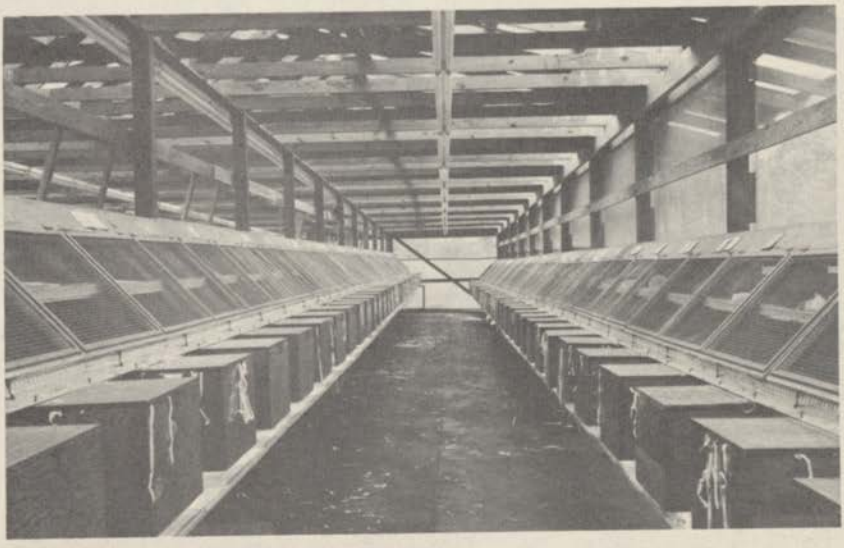


FIGURE 4.—Indoor view of opossum breeding facility showing cage arrangement.

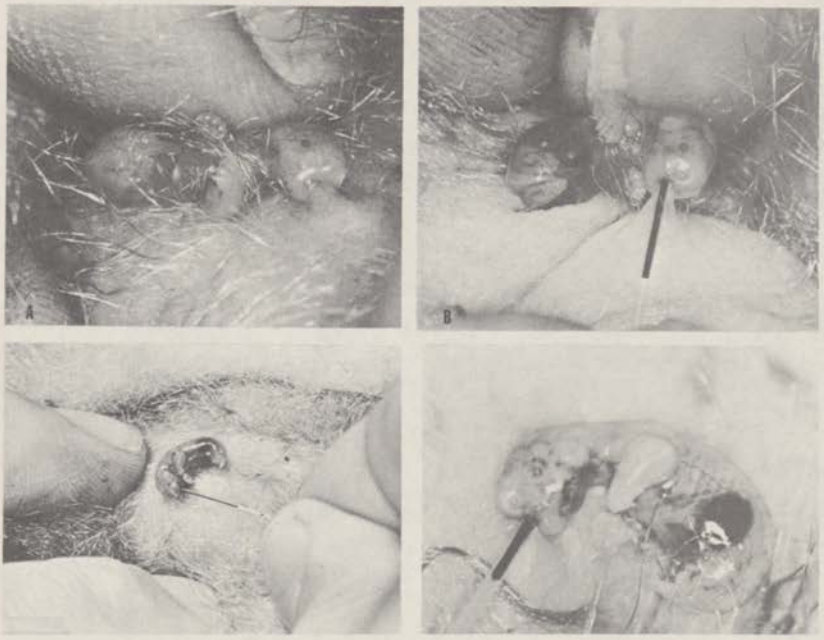


FIGURE 5.—Sequence showing a special technique developed for administering test materials to the newborn opossum by mouth.

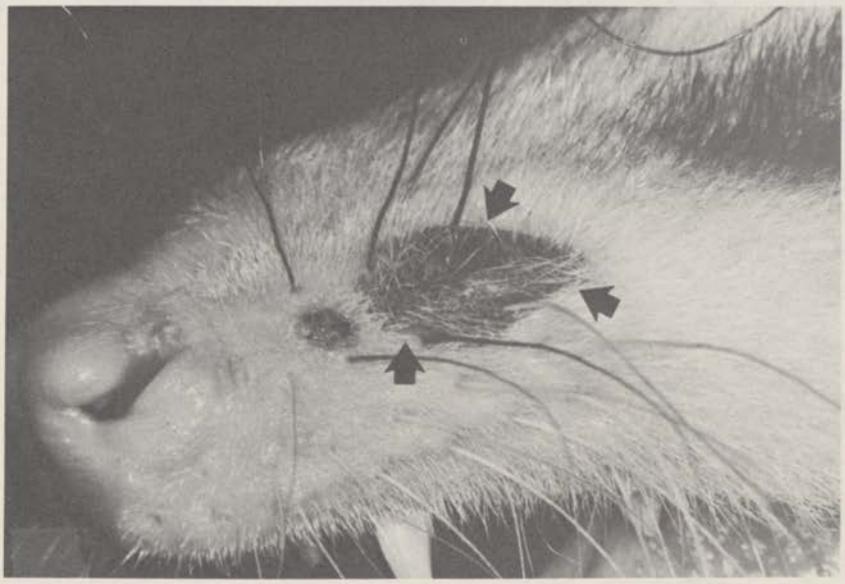


FIGURE 6.—Malignant tumor of the skin of the snout of an adult opossum exposed to the carcinogen ethyl nitrosourea (ENU) as a baby.

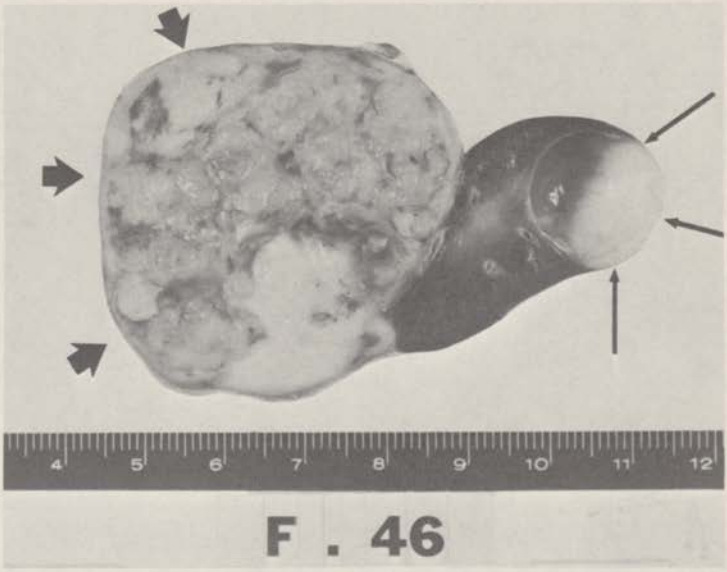


FIGURE 7.—Massive cancer (large arrow) in the kidney of a year-old opossum which received a single dose of ENU as a baby. Note large cyst or growth defect (small arrows) in the same kidney.

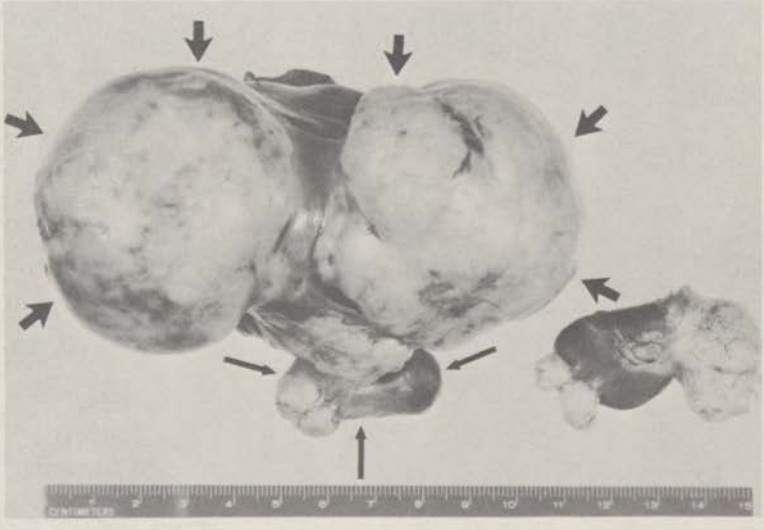


FIGURE 8.—Massive cancer (large arrows) of right kidney (small arrows) in a 1-year-old opossum exposed to ENU as a baby. The left kidney, which contains a similar but smaller tumor, is to the left of the photograph.

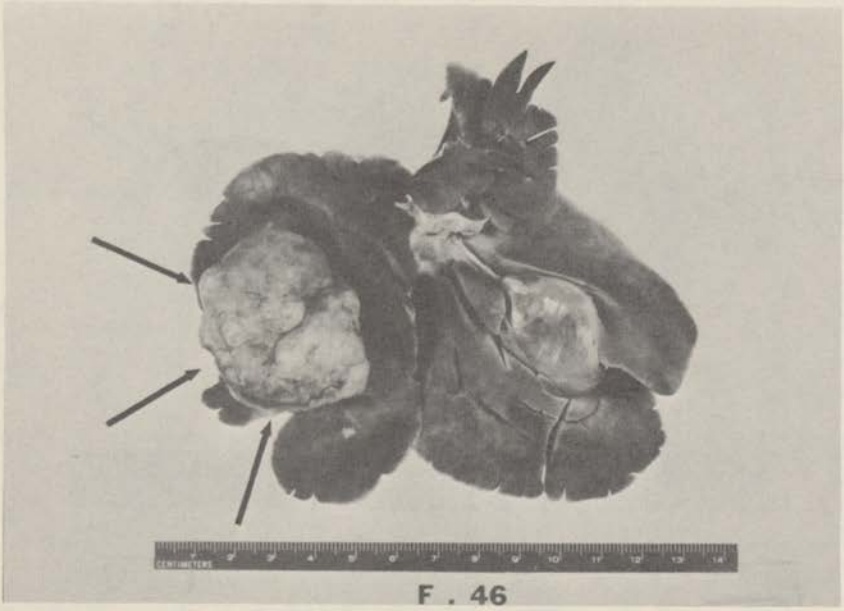


FIGURE 9.—Embryonic tumor of the liver in a 1½-year-old opossum given ENU when still in the pouch.

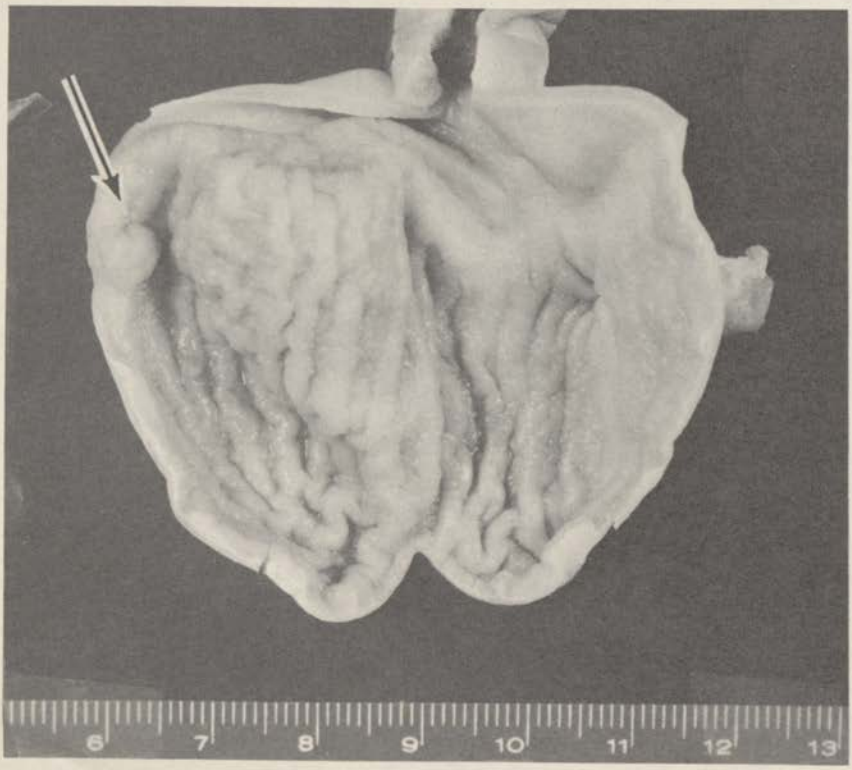


FIGURE 10.—Tumor (arrow) of the stomach in an 8-month-old opossum which was given ENU by mouth as a baby.

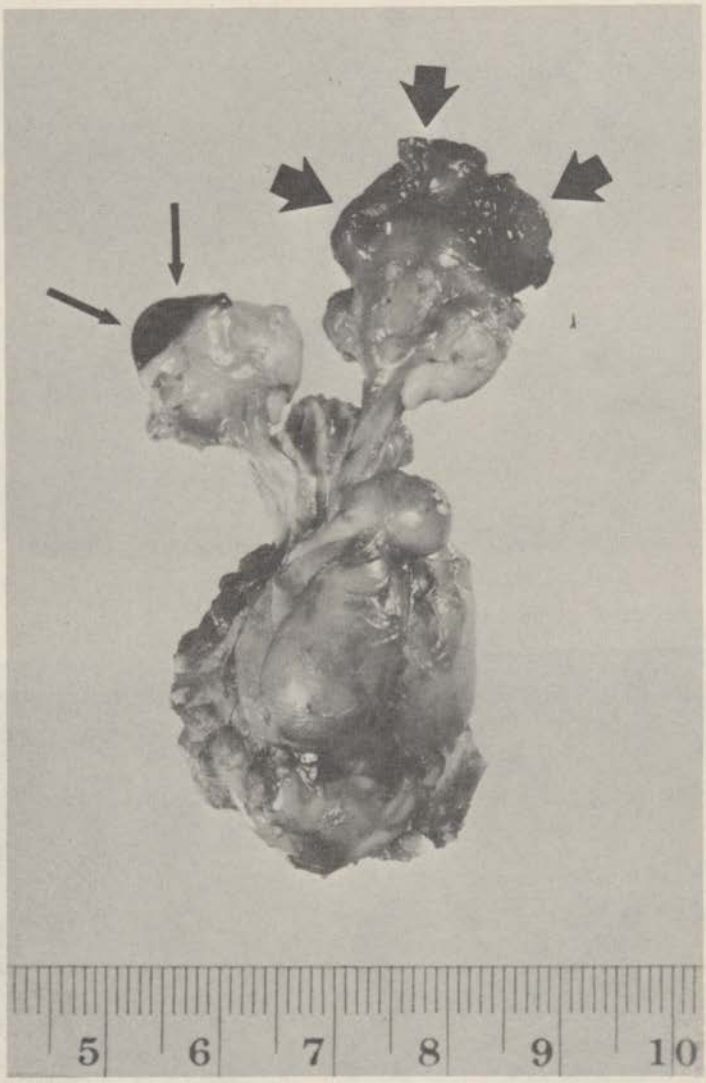


FIGURE 11.—Malignant tumor of the right eye (large arrows) of a 6-month-old opossum exposed as a baby to ENU. This tumor has never before been produced in the laboratory. Normal eye of the same animal (small arrows) is on the left.

FIGURE 12.—ENU induced cancer (arrow) of the gum in a 1-year-old opossum.

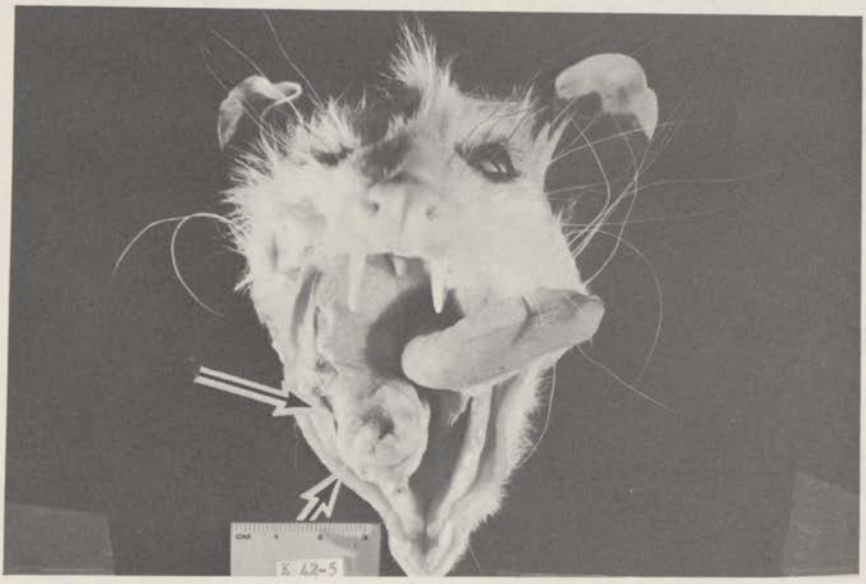


FIGURE 13.—Massive malignant tumor (arrow) of the opossum jaw induced by ENU.

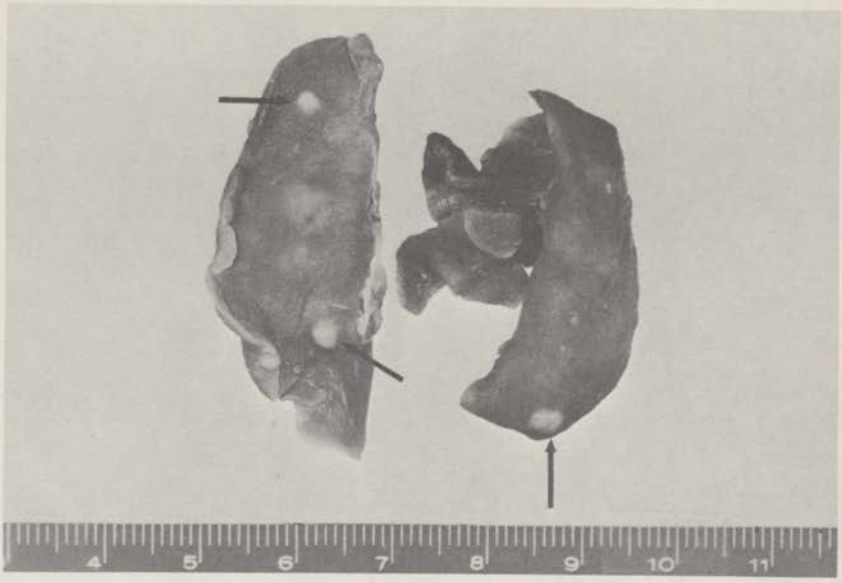


FIGURE 14.—Multiple cancers (arrows) of the lungs in a 1-year-old opossum exposed to ENU at birth.

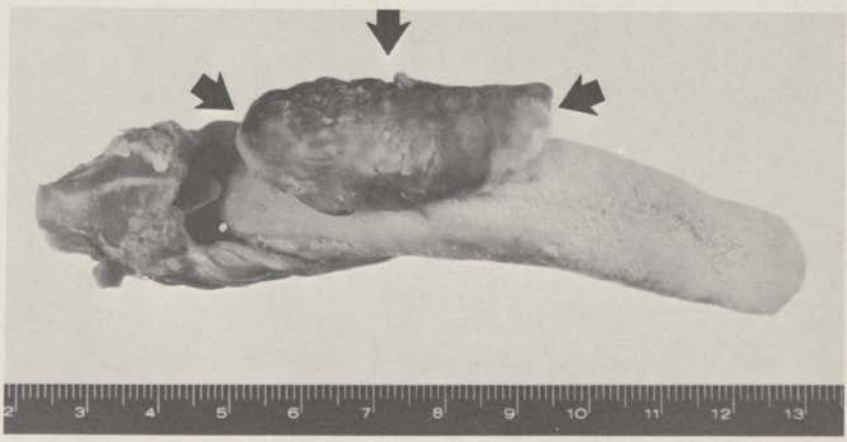


FIGURE 15.—Malignant tumor (arrows) of the tongue induced by ENU in an opossum exposed to the cancer agent at birth.