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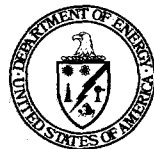
# Health & Environmental Research

## Summary of Accomplishments

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This report is a companion document to *Health and Environmental Research: Summary of Accomplishments*, DOE/ER-0194, published in May 1983. The information for both reports was gathered in 1982 and 1983. These reports are intended to foster an awareness of a publicly funded health and environmental research program chartered nearly 40 years ago, of its contributions toward the National goal of safe and environmentally acceptable energy development, and of applications of its findings toward the improvement of human health. This program, administered by the Office of Health and Environmental Research, is one of many research activities of the U.S. Department of Energy. Over the years, it has been a part of other Federal agencies responsible for the National energy mission. Its evolution has been a reflection of changes in time, public priorities, and public law. But throughout, there has remained a consistency of purpose: to seek a fundamental understanding of the health and environmental aspects of emerging energy technologies and to establish the body of knowledge necessary to their development and utilization consistent with the public health and safety.

The story of this research program can be told through its accomplishments. Several of the more significant accomplishments have been chosen here for illustrative purposes, including some whose value have far exceeded the cost of the research program itself. However, regardless of the measure of its economic benefit, the basic motivation for the program remains to *serve the public interest* through health and environmental research. In the pages that follow, the selected accomplishments are grouped and reviewed within each of several areas of research. It is useful, first, to recall the origins and development of the program.

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# Executive Summary

This is an account of some of the accomplishments of a 40-year-old health and environmental research program performed in National Laboratories, universities, and research institutes. Under the sponsorship of the Federal agencies that were consecutively responsible for the National energy mission, this research program has contributed to the understanding of the human health and environmental effects of emerging energy technologies.

Both direct and indirect societal benefits emerged from the new knowledge provided by the health and environmental research program. In many cases, the private sector took this knowledge and applied it well beyond the mission of supporting the defense and energy needs of the Nation. Industrial and medical applications, for example, have in several instances provided annual savings to society of \$100 million or more. Collectively, the diffusion of this knowledge has resulted in annual savings to the Government and to the public that are several times larger than the cumulative cost of the entire program itself.

The form of this presentation is, in fact, through "snapshots"—examples of significant, tangible accomplishments in each of the areas at certain times to illustrate the role and impact of the research program. The program's worth is not necessarily confined to such accomplishments; it extends, rather, to its ability to identify and help solve potential health and environmental problems before they become critical. This anticipatory mission has been pursued with an approach that combines applied problem solving with a commitment to fundamental research that is long-term and high-risk.

The narrative of this research program concludes with a perspective of its past and a prospectus on its future.



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1. The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that proper record-keeping is essential for the integrity of the financial system and for the ability to detect and prevent fraud.

2. The second part of the document outlines the specific procedures for recording transactions. It details the steps involved in the accounting cycle, from identifying the transaction to posting it to the appropriate ledger account.

3. The third part of the document discusses the importance of internal controls. It explains how internal controls help to ensure the accuracy and reliability of financial information by preventing and detecting errors and fraud.

4. The fourth part of the document discusses the importance of external audits. It explains how external audits provide an independent assessment of the financial statements and help to ensure that they are prepared in accordance with the applicable accounting standards.

5. The fifth part of the document discusses the importance of transparency and disclosure. It explains how transparency and disclosure help to build trust and confidence in the financial system by providing stakeholders with the information they need to make informed decisions.

6. The sixth part of the document discusses the importance of ongoing monitoring and evaluation. It explains how ongoing monitoring and evaluation help to ensure that the financial system remains effective and efficient over time and that any weaknesses are identified and addressed promptly.

# Origins of the Research Program

The origins of the Office of Health and Environmental Research (OHER) trace back to the outset of World War II and the establishment of nuclear research centers under the "Manhattan Project." The first formal program began in 1942 as a Health Division, established by Dr. Arthur Holly Compton, Director of the University of Chicago Metallurgical Laboratory. Already a Nobel laureate for his work on X-ray scattering, Dr. Compton recognized the unprecedented hazards posed by radiation to wartime workers at the laboratory. With the perspective of a half-century of earlier experience with X-rays and radium, he and his colleagues could well appreciate the dangers, as well as the possibilities, of atomic radiation. Biomedical programs were soon established at Oak Ridge, Tennessee, and in the Manhattan Project at large, and it is fortunate that these were able to attract the most competent physicians and medical researchers in the field of the biomedical effects of radiation.

Like the Curies and other pioneers in the field of radiation, those who sought to protect the health of their colleagues could understand, more than others, that the phenomenon that so concerned them was, at the same time, an opportunity. They grasped its significance and foresaw the promise of radiation and nuclear medicine as a new means for medical diagnosis and treatment. This promise has been fulfilled. Today, radiopharmaceuticals are produced and packaged in myriad forms and are in widespread use; for example, radiopharmaceuticals containing thallium-201 ions were administered for the diagnosis of heart disease to 370,000 patients in 1981.

In providing the first legislative basis for the health research program through the Atomic Energy Act of 1946, the Congress overlooked neither the opportunities nor the dangers presented by radiation. In the Act the Congress directed the Atomic Energy Commission (AEC) to

**. . . make contracts, agreements, arrangements, grants-in-aid, and loans . . . for the utilization of fissionable and radioactive materials for medicine and health purposes . . .**

and for

**. . . the protection of health during research and production activities . . .**

The need for a highly qualified group of research administrators was foreseen to fulfill this broad charter. Thus, the Division of Biology and Medicine was established, and Dr. Shields Warren, Professor of Pathology at Harvard University, was named its first Director. Under Dr. Warren, the Division laid down the outlines of a vigorous research effort of fundamental studies in the life sciences; in applied areas to ensure industrial hygiene in Commission facilities, as well as for the public health and safety; and in fostering the rapid growth of nuclear medicine.

The responsibility for administering this program was assigned to the Energy Research and Development Administration (ERDA), which succeeded the AEC through the Energy Reorganization Act of 1974. However, the oil embargo had underscored the need for developing a wide range of energy options and technologies in addition to nuclear, and this need was reflected in the new agency's mission. Therefore, this Act additionally charged the ERDA Administrator with the responsibility of

**. . . engaging in and supporting environmental, physical, and safety research related to the development of energy sources and utilization technologies.**

These responsibilities were assumed by the Agency's Division of Biomedical and Environmental Research, which initiated a significant program of non-nuclear



research, focusing on the development of fossil fuels and renewable energy sources. At the same time, a broad range of legislation\* strengthened and expanded the rationale for ERDA's program of health and environmental research by establishing a regulatory framework by which the results of this research could be integrated directly into the planning and development of energy technologies.

Although ERDA was relatively short-lived, these research functions were retained intact by the new Department of Energy (DOE), established in 1977. Within the Department today, these responsibilities have been carried on by OHER.

What, then, has been the net result of OHER's history of changing roles and mandates? A central mission has evolved, requiring the integration of three fundamental areas of study: (1) the "source," or potentially toxic agent of concern; (2) its "transport," or path from its point of release; and (3) the "effects" that it may produce upon populations and the environment.

The first of these areas of study involves the understanding and characterization of the material, pollutant, or agent of concern. Despite the seemingly limited scope of this phase of study, it can lead to unexpected rewards of a much broader nature. For example, the OHER mandate under the Atomic Energy Act required an understanding of radiations of various kinds and their interactions. This, in turn, created a need for the development of a host of radiation detection instruments, some of which became essential to the field of nuclear medicine, as noted later.

The second facet of the mission—source transport—began as an effort to understand the paths that

\*This legislation, beginning with the National Environmental Policy Act in 1969, included the Clean Air Act, Safe Drinking Water Act, Toxic Substances Control Act, and the Resource Conservation and Recovery Act.

might be taken by radioactive materials through the environment. But, as the range of energy options under development increased, the transport of materials from other technologies—coal fly ash, combustion gases, synthetic fuel components—also came under study.

The final segment of OHER's integrated mission is to detect the nature and extent of any possible danger to man and his environment from the potentially toxic source materials. Once again, initial research in this area was confined to radiation biology, the study of mechanisms and magnitudes of effects produced by radiation. These studies included the uptake and distribution of radioactive materials in animals and man to determine potential toxicity. This knowledge, when coupled with developments in nuclear instrumentation, provided the basis for the parallel development of nuclear medicine. The latter was but one of the new directions in research to receive its impetus from radiation biology. The quest for answers to the mysterious response of cellular deoxyribonucleic acid (DNA) to radiation spawned an unparalleled research program in basic genetics.

Thus, the objective of the OHER mission has been straightforward—to perform fundamental research on the energy-related triad of *source-transport-effect* and to integrate its basic findings toward the solution of practical questions.

The OHER Program employs a multidisciplinary "team" of nearly 1000 scientists in specialized facilities that have come to be regarded as National resources for biomedical and environmental research. (Table 1). For example, in FY 1985 other Federal, State, and local agencies, and private industry invested over \$115 million in DOE laboratories to conduct health and environmental research to help address their own mission needs. Additional research supported by the OHER Program is conducted at some 100 academic

Table 1. Health and Environmental Research Laboratories

1. Multiprogram Laboratories
  - Argonne National Laboratory (ANL)
  - Brookhaven National Laboratory (BNL)
  - Lawrence Berkeley Laboratory (LBL)
  - Lawrence Livermore National Laboratory (LLNL)
  - Los Alamos National Laboratory (Los Alamos)
  - Oak Ridge National Laboratory (ORNL)
  - Pacific Northwest Laboratory (PNL)
  - Savannah River Laboratory
2. OHER-Dedicated Laboratories
  - Environmental Measurements Laboratory
  - Inhalation Toxicology Research Institute
  - Oak Ridge Associated Universities
  - University of California, Davis Laboratory for Energy-Related Health Research
  - University of California, Los Angeles Laboratory of Biomedical and Environmental Sciences
  - University of California, San Francisco Laboratory of Radiobiology and Environmental Health
  - University of Georgia, Savannah River Ecology Laboratory
  - University of Rochester Biomedical Laboratory
  - University of Utah Radiobiology Laboratory

campuses, hospitals, and other research institutions. Hundreds of OHER-funded scientists hold academic appointments and serve as important resources in the formal education of the Nation's scientists, engineers, and physicians. Many of the research projects supported at the laboratories also serve as vehicles for training predoctoral students, as well as postdoctoral investigators. In addition, opportunities are provided for research collaboration with visiting scientists who stay for extended periods of time.

Throughout its history OHER's philosophy has been to encourage prompt dissemination of research results at scientific meetings and in the scientific literature. Scientists currently supported by the program make nearly 2000 presentations each year at technical meetings and document their work in more than 2000 journal articles that have been peer-reviewed prior to publication.

In addition to the intellectual and scientific resources which have made these advances in knowledge and technologies possible, the National Laboratories possess multiuser facilities that are having a major impact on the rate of progress in elucidating the structure of biological molecules. Such structural determinations are a prerequisite for solving molecular design problems; for example, the modification of proteins so that they have a specified type of activity. Moreover, the unparalleled computational resources available at the laboratories and the broad capability to exploit them fully also provide the environment necessary for major advances in predicting small molecule structure and activity, which are central to identifying mutagens and carcinogens and designing drugs and vaccines. Together, these structural biology activities will provide the firm foundation crucial to maintaining America's competitive advantage in private sector biotechnology during the coming decades.

The funding for the Biological and Environmental Research Program

is shown in Table 2, which also defines extensively the organizational structure of OHER. As in any large-scale research program, activities being conducted vary from year to year as existing projects are completed and new projects or lines of investigation open up. A synopsis of the principal research activities currently under way is presented in the Appendix.

The following descriptions of program accomplishments provide a glimpse of some of the more tangible products of the OHER research process. Having provided the background for the presentation of these products, some caveats are in order.

As in any other research enterprise, there is a continuum of effort, and a "snapshot" of selected OHER Program accomplishments can easily create a distorted view of the overall workings of the program. It has already been noted that while many of the accomplishments described have proved to be of considerable economic importance, that is not necessarily a measure of the effectiveness of the research within the context of the OHER mission, nor is it a factor in shaping its research agenda. The course of research is complex and can lead to a number of "dead ends," as well as to successes and breakthroughs. A seemingly fruitless effort can sometimes be useful by virtue of its indication of more productive pathways, and one of the accomplishments described, which eventually ended in a treatment for Parkinson's disease, provides a case in point. Basic research, a key part of the program, is long-term and often not immediately and measurably beneficial. Yet even in the event of no immediate product, the insights gained into the operation of biological processes improve our capability to anticipate or predict how the system will respond to new or untested events for which data are sparse or unavailable. The bone-marrow transplantation work undertaken early in the program is an example of basic research that ultimately provided much of the information that supports the

current state-of-the-art for organ transplantation work in medicine.

Thus, in summarizing the accomplishments of a research program designed for a mission as far-reaching as that of OHER, its worth should not be judged solely on the basis of economic benefit or immediate applicability. The result of research may be a tangible product (e.g., a nuclear scanner or radiopharmaceutical) of readily calculable value. But the "product" may also be the answer to the riddle of self-repair to cell injury, the mechanism by which a particle is transported, or the definition of the risk of bone cancer from radiostrontium. Thus, it is equally valid to judge the benefit of a research contribution in terms of its reduction of uncertainty or its description of a previously unknown mechanism. These criteria have been in consonance with the energy development missions of OHER's parent agencies (AEC, ERDA, and DOE), which, in an anticipatory manner, have made use of its research to prevent, modify, or mitigate potential health and environmental effects before an emerging technology reaches maturity. The contrast between the anticipatory nature of OHER research and that which is conducted by the regulatory agencies is readily apparent from the differing content and objectives of their respective research programs. The ultimate goal of the research program is, therefore, not so much to find effects as it is to aid in their prevention. The extent to which that goal is realized is the true measure of its benefit to the Nation.

The following sections contain descriptions of selected, definitive research contributions resulting from the program—accomplishments of the many individuals in National Laboratories, universities, and research institutes who conduct this work under contract to OHER. In some instances the research has been cofunded or is now pursued under auspices other than OHER.

**Table 2. Funding for Biological and Environmental Research  
(Dollars in Millions)**

Research	Appropriations	
	FY 1984	FY 1985
Human health research to quantify risks of late effects of acute and chronic exposures via epidemiological studies of workers and the general population and to develop methods to detect and measure latent disease induction or identify highly susceptible individuals	25.6	24.8
Health effects research in biological systems to define experimentally dose-response relationships and the factors influencing carcinogenic, mutagenic, and toxicological risks of energy-related exposures; and basic biological research to elucidate the mechanisms by which physical and chemical agents may cause their effects	57.0	59.5
Environmental research to determine the mechanisms that control and influence total ecosystems and the cycling of energy by-products through them	23.8	21.3
Physical and technological research to characterize energy-related emissions to which humans may be exposed and improve measurement and dosimetry instrumentation	27.6	35.4
Health and environmental risk analysis of emerging energy technologies	1.8	0.0
Nuclear medicine: research to develop new radioisotopes, labeled compounds, clinical procedures, and visualization devices for improved diagnosis, treatment, and study of human diseases	20.8	21.8
CO <sub>2</sub> <sup>a</sup>	12.4	13.3
Program direction	3.3	3.5
Total operating	173.3	179.6
Capital equipment and construction	10.7	10.9
Total	184.0	190.5

<sup>a</sup>CO<sub>2</sub> research is managed by the Basic Energy Sciences Program staff but is budgeted under the Biological and Environmental Research Program. CO<sub>2</sub> research is not discussed in this report.

# Emerging Energy Technologies

OBJECTIVE: Through Research, Examine the Potential for Adverse Effects on Human Health and the Environment from Emerging Energy Technologies.

*It is the purpose of this Act... to advance the goals of restoring, protecting, and enhancing environmental quality and assuring public health and safety...*

—Sec. 102, Public Law 95-91

*The functions which the Secretary shall assign...shall include...conducting a comprehensive program of research and development on the environmental effects of energy technologies and programs....*

—Sec. 203, Public Law 95-91

This new organization act identified, for the Department of Energy (DOE), responsibilities for public health and safety that were virtually identical to those of the AEC in its nuclear development and production programs and ERDA in its development of energy conservation and both nuclear and non-nuclear energy-supply technologies. In all three charters the intent of Congress was clear: to foster a better understanding of the potentially adverse effects on human health and the environment of emerging energy technologies. The dramatic dislocations following the oil embargoes of 1973 and 1979 gave impetus to the development of the emerging technologies—synthetic and renewable, as well as nuclear, fuels—and, thus, added to the urgency of these responsibilities.

## Identification of Human Health Effects

Early in the OHER Program, concerns centered around the responses of humans and animals exposed to radiation. Specific experiments to measure radiation effects were initiated and led very quickly to the realization that to recognize damage, scientists first had to understand the structure and functioning of healthy cells, tissues, animals, and, ultimately, humans. The resulting research program would make, and continues to make, major contributions to biology, medical diagnosis and

treatment, ecological science, genetics, biophysics, immunology, DNA repair, and the study of the causes of cancer, to mention only a few of the affected and enriched scientific areas.

The next decades could see a rising potential for new pollutants from such technologies as oil shale and synthetic oil from coal or from diesel emissions. The movement of these pollutants through the air, land, and water and possibly back to human beings would have to be evaluated. It is important to understand the ability of the environment to break down, detoxify, and absorb the residuals from these new chemicals. Testing their ability to cause cancer, mutagenic effects, or somatic damage is also needed to help minimize health and environmental effects. The time when guidance can be most helpful and least expensive is before billions of dollars are invested in new energy technologies.

Finally, should the unexpected occur, the OHER has developed capabilities to respond to emergency situations and realistically assess the potential public health hazards of toxic releases to the atmosphere. These systems were originally designed to predict fallout from atmospheric nuclear weapons testing but have evolved into an especially effective atmospheric-dispersion forecasting for chemical releases as well.

**Nuclear Technology** The biological and medical research program initiated during the World War II "Manhattan Project" has sponsored extensive research studies and measurements to determine the mechanisms and extent of radiation effects on human health through direct studies on exposed human populations and by experiments on animals, tissues, cells, and individual molecules of interest. Data on the health impacts of different types and levels of radiation exposure, the interaction of radiation with living tissue, and the manner in which radioisotopes are taken up into the body have been evaluated and used to determine the risks posed by radiation

to industrial workers and the general public. Such risk analyses have been used in the development of industrial hygiene practices, radiation exposure control guidelines, and regulatory criteria for the location, design, and operation of nuclear facilities. From the collective effort, a new scientific discipline, radiation biology, emerged and revolutionized the study of biological, ecological, and medical systems. Radiation biology has increased our understanding of fundamental processes by enabling greater quantification of results through new instruments and techniques and by applying the multidisciplinary skills of physical and biological scientists to vital questions of health, illness, and life.

**Overview** Major research and education programs to study radiation and its effects were first undertaken in the 1940's and 1950's. These programs provided systematic assessments of the immediate or genetic effects of various levels and types of radiation on both humans and animals. Most data on radiation risk before this time had been estimated from measures of effects in persons involved in diagnostic and medical X-ray irradiations or from special studies dealing with issues such as the effects of radium ingested by workers painting watch dials. The epidemiological study of the long-term effects on the survivors of Hiroshima and Nagasaki began with the establishment of the Atomic Bomb Casualty Commission, now called the Radiation Effects Research Foundation. Their studies provided initial information on a wide range of doses of ionizing radiation from many radioactive isotopes, including information on those common to the defense and nuclear power industries.

By the 1960's, comparative evaluations of health risks from radio-nuclides in defense and energy production included studies at each stage of these industries, from mining and production through storage and disposal of nuclear material. Insights gained from these studies permitted the

correlation of results from cells, animals, and humans to provide insight into the biological impacts of radiation. Moreover, they provide the scientific information required to establish realistic exposure limits for both nuclear industry workers and the general population.

The primary unresolved issue in human health-effects studies is the effect of long-term exposure to low levels of radiation. Over the next decade the study of health effects will benefit from its first direct information as many of the workers under study complete expected latency periods (time from exposure to possible cancer onset). Any variations from population norms will provide first-hand data for drawing conclusions about radiation effects. Without this confirming evidence, health effects from low-level exposures would continue to be based on indirect information of three kinds: (1) the lack of adverse effects in the workers under study, (2) estimates obtained from the use of animals as substitutes for humans, and (3) data from the studies of Japanese atomic bomb survivors exposed to medium-to-high levels in a single exposure event. Thus, although enough data for positive confirmation may be 10 or more years away, the fact that the estimates have held year after year for the last 35 years has allowed industries involved with radiation to gain increasing confidence in the standards by which they operate.

The next sections will outline the research areas undertaken by OHER in an attempt to gain a working understanding of the potential human health effects from nuclear technologies. The complementary research efforts of radiation biology, epidemiology, and animal studies support the evaluation of public and worker exposure standards. These sections are followed by a sample of the benefits that have accrued from OHER research in human health effects.

**Radiation Biology** Radiation biology is the study of the effects of radiation on biological systems.

The emergence of radiation biology as a major area of scientific research resulted from the establishment of the AEC and its Division of Biology and Medicine (later called the Office of Health and Environmental Research). Large-scale programs designed to examine the biological effects of atomic radiation were initiated at a number of the OHER-supported laboratories, including those at Oak Ridge, Brookhaven, Argonne, Los Alamos, and Hanford Pacific Northwest Laboratory (PNL), as well as within several nongovernment institutions, notably the Universities of California, Rochester, and Utah, and the Lovelace Foundation (Inhalation Toxicology Research Institute). A smaller program of university-based, contract-supported research was also instituted.

Undoubtedly, one of the major impacts on the expansion of biology in the 1950's and 1960's resulted from the close interaction among physicists, engineers, biologists, and physicians at the radiation biology laboratories. Interdisciplinary research and training with added emphasis on quantification were very effective in bringing about rapid advances in both basic and applied aspects of quantitative biology and medicine. The general trend towards quantitative biology can be seen in the increased emphasis placed on physics, chemistry, and physical chemistry content in biology courses taught at the university level. The value of a solid background in physical science to the biological or medical student is now well accepted.

Discoveries within the field of radiation biology have had a major impact in many areas of science: genetics, biophysics, immunology, nucleic acid structure and function, DNA repair, cell biology, and cancer research. Radiation biology research provided the basis for major advances achieved in research related to human health effects, environmental effects, and nuclear medicine, all discussed elsewhere in this report. Some additional examples will serve to illustrate the breadth of impact of

radiation biology on biomedical research: basic and applied investigations in molecular biology, cellular biology, genetics, and the mechanisms involved in the development of cancer.

The continuity and diversity of life forms depend upon the replication (duplication of genetic material), the recombination (the exchange of genetic material to yield genetic diversity), and the repair (the removal of damage resulting from environmental agents or from mistakes in replication) of DNA. When DNA repair mechanisms are functioning normally, cell survival increases while the mutation rate and the probability of cancer or other abnormal changes in tissues resulting from exposure to radiation or a toxic chemical decreases. The discovery of DNA repair, a landmark achievement, was a direct outcome of OHER-supported investigations in radiation biology—in this case, research on the genetic effects of ultraviolet light.

Cell cycle studies using agents such as radioactive thymidine ( $^3\text{H}$ -thymidine) and radioactive iodine (iodine-125) have led to increased understanding of DNA replication, DNA repair, and the genetics and biochemistry of specific phases of the cell life cycle. In addition, many effects of endogenous and exogenous environmental agents on these cellular functions have been determined. Drawing on this research, more rational and scientific uses of chemotherapy for the management of cancer and other proliferative diseases have been formulated and adopted.

The ability to perform many of the procedures in molecular biology now common in laboratories throughout the world clearly resulted from earlier work on radioactive precursors of DNA, as well as from the development of techniques for manipulating, isolating, and analyzing radiation-damaged DNA. Today, these techniques are being put into practical use in genetic engineering for the production of insulin, growth hormones, and other biological materials of great utility to mankind. Another

consequence of the early studies of DNA synthesis is the current interest in human genetic diseases associated with defects in the DNA repair mechanism or in the proteins that, along with DNA, form the genetic material of living cells, known as chromatin. Diseases of this type include xeroderma pigmentosa, ataxia telangiectasia, Bloom's syndrome, and Fanconi's anemia.

Knowledge of DNA repair and other cell cycle phenomena arose from attempts to understand radiobiological phenomena. The concepts and methodologies of DNA repair research have now been extended to two other important areas of biological research—the study of the chemical causes of cancer and aging. The connection between the chemical and radiological causes of cancer arises from the important discovery that the modes of repair of chemical damage in DNA of human cells mimic either ultraviolet damage and repair or radiation damage and repair. Hence, DNA repair is a general phenomenon, not one peculiar to radiation. Active repair of DNA in bacterial or mammalian cells treated with potential mutation or cancer-causing substances, mutagens or carcinogens, respectively, is taken as evidence of DNA damage and is the basis for several rapid tests for agents that cause harm or destroy genes. The use of bacteria that lack the ability to repair damage to DNA in such tests, for example, the Ames test, enhances by orders of magnitude their sensitivity for detecting cancer-causing chemicals.

In 1974 researchers at the Brookhaven National Laboratory (BNL) made the intriguing finding that the ability of cultured cells from different mammalian species to carry out the repair of ultraviolet-induced DNA damage increased as the life span of the species increased. Human cells are very good at excision repair; mouse cells are poor. The notion that there is a correlation between aging and DNA repair ability was derived from early experiments at Oak Ridge National Laboratory

(ORNL) on the accumulation of single-strand breaks in the DNA of tissues of old mice. This area of new and fruitful research was opened up by OHER support for radiation biology and DNA repair.

Radiation biology has had massive impacts on human medicine since the late 1940's, as discussed in the section entitled "Nuclear Medicine." We can get a glimpse of its significance in another important area of medicine from two summaries on the use of bone marrow transplantation in contemporary medical treatment. Bone marrow transplants were first used as a treatment for radiation-induced damage to blood-forming cells in bone marrow. R. A. Good writing in *The New England Journal of Medicine* in 1982 said, "Indeed more than 20 previously fatal diseases can now be successfully treated with bone marrow transplantation. These disorders range from genetically determined severe combined immunodeficiency diseases to acute leukemias." Similarly, E. Beutler of *The Journal of the American Medical Association* in 1981 pointed out, "Until recently, our mind-set was that leukemia was not curable." In selected leukemia patients and under appropriate circumstances,

*the vast majority (well over 90%) survive the transplantation procedure, and the extent of morbidity does not differ greatly from that associated with ordinary induction chemotherapy. Despite the occurrence of graft-vs-host disease and occasional relapses, the overall cure rate of this selected group of patients seems to be between 70% and 80%.*

**Epidemiology of Radiation Exposure** Quantitative data have been produced from epidemiologic studies of the genetic (on the germ or reproductive cells) and somatic (on the body as a whole or on cells other than germ or reproductive cells) effects observed in humans exposed to radiation. These data allow the establishment of upper-bound estimates of the genetic risk and numerical estimates of the somatic risk of such exposures.

At a more basic scientific level, research in molecular epidemiology on understanding the molecular basis of predisposition toward and resistance to damage by radiation and toxic chemicals now is extremely promising. The identification of populations that are particularly susceptible or resistant to certain types of insults is not only of the greatest significance to medical sciences, but it will have a major positive impact on Federal regulatory activities by providing data for setting health standards that take into account both variations in the population and the doses to which human populations are ordinarily exposed.

The study of atomic bomb survivors in Japan has provided the best available estimates of the risk of various types of cancer resulting from exposure to external low-energy radiation. Some of the characteristics that make this study particularly useful are as follows:

1. The survivors are the only large population with a wide range of whole-body exposures, or exposure over the entire body.
2. The population was comparatively random with respect to health and work history.
3. An elaborate dosimetry program has yielded individual dose estimates for major organs.
4. The family registration system of Japan ensures 100 percent followup on mortality.

Although intensive study has been under way for over 30 years, the past decade has seen the identification of new potential cancer sites and revisions of previous estimates of risk. Most recently, a reassessment of calculated gamma and neutron dose received by individuals has led to a major change in the carcinogenic, or cancer-producing, role assigned to neutrons and to a modest revision in estimates of gamma doses.

A series of epidemiological studies designed to detect genetic effects among the offspring of atomic bomb survivors has shown no statistically significant differ-

ence between them and the offspring of groups not exposed to the radiation. The genetic studies have provided valuable assurance that the use of animal data (see section on "Animal Studies") does not seriously underestimate the effect on human populations. The epidemiological results are consistent with the mouse data and also allow us to confidently place an upper bound on the level of somatic effects in irradiated humans.

Although the study of bomb survivors was the predominant factor in developing a quantitative estimate of the effects of various levels of exposure, i.e., a dose-response relationship for radiation-induced cancer, it has inherent limitations, notably that the data were compiled from a single exposure at a high dose rate and the population samples are not large enough to define with any confidence the risk of very low dose rates. These factors made questionable the extrapolation of the dose-response curve to lower, prolonged exposures without additional information. Moreover, animal studies had shown that the results of high doses of low energy-transfer radiation (low energy particles or gamma radiation) received over a short period of time are of far more consequence than the same dose received over a long period of time. As a result, studies of industrial workers were begun by the AEC as early as 1964. The initial studies of Hanford and other DOE-contractor employees have subsequently been expanded to include naval shipyard workers and soldiers present at nuclear weapons tests in Nevada. The results to date have reinforced the low risk that would be predicted for workplace external exposures.

The AEC initiated a study of radium-dial painters subjected to radiation from internal radium deposits accumulated in the era before the health effects of radiation exposure were generally known. Radium emits high energy alpha-particles and a gamma ray.

These epidemiological studies have provided the primary basis for setting all such standards for radium and for transuranic elements such as plutonium, which also emit alpha-particles and gamma rays. Epidemiological research on chronic internal exposure has more recently been expanded to include plutonium workers at several DOE facilities. Results of this ongoing work have corroborated the adequacy of current standards for these alpha emitters.

**Animal Studies** Important information about the risks from exposure to radiation has been derived from large-scale animal experiments. These studies determined the potential cancer or genetic effects from internally deposited radionuclides or from external radiation and revealed the importance of the rate with which the radiation is received, as well as the relative biological effectiveness of different types of radiation.

Because there was minimal human data on the effects of long-term exposure to low levels of radiation, animal data had to play a significant role in estimating guidelines for allowable human exposure to different types of radiation. Between 1956 and 1966, three large studies on mammals were conducted to determine (1) the latent effects of plutonium exposure in dogs and rodents, (2) the relative toxicity of strontium-90 and radium-226 deposited in the skeletons of humans and other mammals, and (3) the genetic effects of external radiation in mice. By 1974 ten major animal experiments were in place to determine the uptake, metabolism, dosimetry, and early and late effects of exposure to most major fission products of concern. There were also concerns about the importance of chemical forms of plutonium administered by different exposure routes and the importance of dose (quantity and rate) of external gamma ray or fission energy neutrons in the induction of late somatic or genetic effects.

Following are five examples of some of the studies developed to investigate these important issues:

1. *Relation of Human and Animal Effects of Bone-Seeking Radionuclides.* The radium-dial-painters study provided a quantitative epidemiological data base for humans exposed to, and carrying graded body burdens of, the natural bone-seeking radionuclide radium-226. By obtaining comparable data for radium-226 in a long-lived animal species (dog), a radiation effects ratio (RER) for radium-226 can be calculated as follows:

$$\text{RER} = \frac{{}^{226}\text{Ra-effects (man)}}{{}^{226}\text{Ra-effects (dog)}}$$

Assuming the same interspecies relation holds true for other bone-seeking radionuclides, such as plutonium-239, and using the following expression, the data from the dog studies can be used to estimate the potential hazards from these radionuclides to humans:

$$= \text{RER} \times {}^{239}\text{Pu-effects (dog)}$$

These studies provide vital data for predicting human risks of radiogenic bone cancer from important man-made radionuclides, which are already present in our biosphere. The data derived from these experiments have demonstrated that the present guidelines are scientifically defensible for radiation exposure by workers and the general population.

2. *Determination of Dose-Rate Effects of External Sources on Radiation Risks.* Most of the early data on radiation risk estimation were derived from studies of people involved in diagnostic and therapeutic medical X-ray exposure. Although there was strong evidence that low dose rates or protracted radiation exposure was less harmful than high-dose-rate single exposures, no systematic assessment and measurement of the magnitude of the dose-rate effectiveness factors had been made for

either heritable or genetic effects or for delayed toxicological effects and cancer induction. OHER-supported studies showed that genetically different mouse strains responded similarly to the varying dose rates. These findings prompted studies in which gamma and neutron irradiation would be compared as a function of dose rate.

3. *Potential Health Risks in Nuclear Research, Weapons Programs, and Power Production.* Multispecies animal experiments were initiated in several laboratories to validate the acceptability of standards and guidelines for radionuclides produced by nuclear fission. Priority among the fission products was established based on their relative fission yields, their half-lives, and their propensity, due to the metabolic characteristics of the exposed animal, to be deposited and retained in specific organs of the body. These studies showed that radiation responses could be altered by different routes of exposure, by differences in localized dose and dose rate, and by other variables such as the chemical characteristics of the radioactive compound and the type of radiation produced by its decay products. Development of nuclear power reactors led to expansion of the OHER effort to include evaluation of important radionuclides encountered at each significant stage of the nuclear fuel cycle, from uranium mining through storage and disposal of nuclear waste.

A major fraction of OHER's research has involved animal exposures by inhalation, one of the most significant routes of exposure for products of the fission process, especially plutonium. These animal studies were instrumental in developing models describing the distribution and fate of various soluble and insoluble aerosols in the lungs, including movement to remote critical organs at different times after exposure.

4. *Determination of the Genetic Effects of Radiation in Mice.* Until 1947 estimates of the genetic hazards of radiation were based entirely upon the data derived from the fruit fly (*Drosophila*). Because it was essential to obtain information on a mammalian species to provide a closer correlation with man and because a genetic study requires data over many generations, a long-term, very large-scale study of radiation-induced genetic effects in mice was begun. Pending definitive results from the epidemiological studies discussed earlier, the results of the mouse studies still provide the basis for our estimation of genetic risk to humans.

The large mouse study required the development of new techniques and methods for detecting radiation-induced mutation. One of these, the specific locus method, has found wide application in determining how mutation rate varies with changes in radiological and biological parameters such as dose rate, dose fractionation, total dose, radiation quality, sex, stage in the cell life cycle, and age at exposure. The specific locus method is also being applied to the study of the processes by which some chemicals cause mutations, called chemical mutagenesis, and to the possible effects of energy-related and other environmental pollutants.

It was found that the mouse was considerably more sensitive than the fruit fly to the induction of mutations by large, rapidly administered (acute) doses of radiation. This result was an important factor in the subsequent lowering of recommended permissible levels for human exposure to radiation. Additionally, it was discovered that the level of mutations produced in male and female mice was different over a range of dose rates. In males this was manifested by a one-third reduction in mutation rate when the same dose was absorbed at a low, as compared with a high,



rate of exposure. It was also found that the germ cell in the female mouse is so resistant to mutation induction by radiation that no significant increase over naturally occurring, spontaneous mutation rates has been detected in the irradiated animal.

These last two findings together suggested that genetic risk in man is only about one-sixth of what it was estimated to be when radiation exposure limits were based on high dose-rate results and on the assumption that females and males were equally sensitive. Although the findings did not lead to the raising of permissible levels of radiation exposure, they did provide a cogent argument for no further lowering of permissible levels.

5. *Supporting Animal Studies.* To interpret experimental results, it was necessary to understand the natural changes occurring in animals being studied, that is to study the role of aging and to gain a better understanding of the biological process of aging itself. Strong support was given to recording and analyzing specific biological parameters such as brain mass, metabolic rate, body temperature, and body mass—important parameters that correlate with and serve as actuarial predictors of longevity in animal species. The white-footed field mouse and the common laboratory mouse were particularly useful in this regard. Although these two species are similar in coloration, form, and size, the field mouse has a lifespan of nearly 8 years while the laboratory mouse seldom lives longer than 3 years. Additional aspects of aging and longevity are being explored and include immunologic factors and possible relationships between the aging process and cellular DNA repair.

**Evaluation of Exposure Potential to Workers and the Public** Detailed information on appropriate industrial hygiene practices was developed to ensure safe operation

of industries that use radiation sources and radioactive isotopes and to ensure public safety. This information was developed through major OHER-supported research and educational programs in the areas of radiation monitoring; dosimetry and toxicology; air, water, and soil analysis; bioassay; and health risk and analysis. These are now broadly included in the field of health physics.

To evaluate radiation exposures of workers in nuclear industries, health physicists needed devices to measure radiation from external sources and bioassay methods to determine the amounts of radioactivity that may have been taken into the body. Personal dosimeters were developed, first from radiation sensitive film and then from thermoluminescent crystals. Biological assay or bioassay techniques were developed that used radiation counters that measure radiation absorbed by the body, excretion assays, and biomathematical models of the metabolism of internally deposited radionuclides. These techniques have provided working lifetime records of external radiation exposures and the amounts of radioactivity that may have been taken into the body. Exposure records are available today for most workers in industries using radioactive processes or equipment and can be used to evaluate the potential for an individual developing a radiation-related injury.

Extensive research programs were initiated and expanded to develop models needed to project the dispersion of radioactivity in the environment and its uptake and retention by people. Models are currently available to predict transport of radioactivity through air, groundwater, and soil. Other biological research programs have produced models to project the transfer of radioactive isotopes through food pathways to man and their uptake from food, water, and air.

Large research and educational programs were established during the 1940's and 1950's to study

radiation concerns of the future. Graduate level training programs were begun at the University of Rochester, Harvard University, Vanderbilt University, and the University of California, among others. They were also coupled to research programs at several National Laboratories supported by the AEC. The majority of trained health physicists working in nuclear industries today are graduates of these programs.

The radiation monitoring instruments, measurement techniques, and models described above are the major tools used by health physicists in industry and Government safety programs to evaluate human radiation exposures at operating plants and facilities. They were mainly developed in DOE-supported research programs and have been used for many years to provide exposure records and risk evaluations for radiation workers and members of the general public. The nuclear industry is unique among industries that handle potentially toxic substances because of the state of development of its detailed methods to characterize or document human exposures.

Currently, about 200,000 people in the United States have occupations that involve handling radiation sources and radioactive isotopes. Their safety depends on proper application of radiation exposure standards and the abilities of health physicists to measure and record exposures. Thus, the most important uses of technology developed in radiation research programs supported by DOE and its predecessor agencies are in industrial hygiene and radiation safety.

**Benefits of Nuclear Technology Research** The bulk of worldwide regulatory and environmental assessment action regarding nuclear power is based largely on the body of knowledge acquired in the OHER Program.

A concrete example of a benefit of this information is to United States electric power consumers in a recent decision by Federal

regulators to maintain standards in the workplace at the same level as those maintained for the past 25 years. It can be estimated what a given reduction in the worker exposure limit would cost; and, thus, what value these studies have had for the consumer/taxpayer. For example, a reduction of the annual worker exposure limit from the current 5 rem\*/year to 0.5 rem/year would cost the Government and industry nearly \$2 billion/year. In both commercial and DOE facilities, moreover, the increase in number of work crews required to reduce exposure times would, in turn, increase cumulative exposure because each worker receives some fraction of his or her exposure during the non-productive time spent in removing contaminated protective gear. The greater the frequency of such changes, the greater cumulative exposure to perform the same amount of work. For a 0.5-rem/year limit, the Atomic Industrial Forum estimates an increase of 5400 man-rems/year for the power-reactor industry and an increase of 2300 man-rems/year for DOE's various programs. While there is substantial uncertainty in the financial evaluation of increased radiation exposure, the 7700 man-rems/year increase is certainly significant.

Because research supported by DOE and its predecessor agencies has put industrial radiation protection practices on a firmer scientific basis, these practices can readily be defended in legal actions taken against the United States Government and its contractors. OHER's research does not serve as part of Government advocacy but, rather, provides a scientific basis upon which claimants' injuries can be assessed and equitable decisions can be reached. One example involved a claim against the DOW Chemical Company, Rockwell International, and the United States Government for \$200 million in damages alleged to have been caused by

\*The amount of ionizing radiation required to produce the same biological effect as one Roentgen of high-penetration X-rays.

plutonium spilled at the Rocky Flats nuclear weapons facility between 1959 and 1965. Small amounts of plutonium were blown by the wind into neighboring lands. The claim, filed in 1975 in District Court in Denver, Colorado, was dismissed in May 1982 because the Government, and its contractors were able to demonstrate acceptably to all parties that the level of plutonium outside of the Rocky Flats facility did not represent a significant hazard.

Our understanding of the role of dose rate in risk estimation was significantly enhanced by the animal studies. Studies on mice, for example, demonstrated for the first time that for the same cumulative dose of radiation, fewer mutations and cancers are produced in animals receiving low dose rate exposures than in those receiving the same exposure at a high rate. Furthermore, it was shown that the same total amount of radiation delivered in smaller increments to mice was less damaging than when delivered as a single exposure. These data showed that mammals other than man are capable of repairing damage to cells involved in transmitting the genetic information from one generation to the next. A careful evaluation of the same endpoints from the radiation exposures of mice, dogs, and man has provided a model for the scaling of radiation effects between the species. Animal studies are also providing information on differences in radiation sensitivity as a function of the age when irradiated. The positive contribution is to provide sound scientific data that are essential for those charged with developing guidelines for the protection of human health.

The radiation biology research program and the applied studies in radiation effects continue to hold great promise of a better understanding of biological processes and of treatments and therapies for a number of human diseases. Research to date has led to a host of theories on the possible causes of genetic diseases, birth defects, aging, and cancer, as well as to

advances in immunology and treatment. Much of this research may eventually resolve the question of the existence of a threshold for radiation damage.

Simple discoveries, such as the use of tritium-labeled thymidine as a DNA precursor, were instrumental in helping characterize DNA replication and recombination in mammalian cells, as well as the properties of the different phases of the cell cycle. A knowledge of such phases is important not only in the estimation of mutagenic and carcinogenic risk, but also in radiation therapy as well.

**Synthetic Fuels** Human epidemiological studies provide the most direct information for developing relationships between levels of exposure and health risks. However, these studies are rarely available for industrial products not already on the market, as is the case for the products of such technologies as oil shale or synthetic oil from coal. Thus, laboratory studies are generally undertaken to provide the needed information. These usually begin with studies using bacteria and mammalian cells in cultures (see Fast Test for Cancer-causing Chemicals in "Detection and Measurement of Human Health Effects") and may progress to exposures of whole laboratory animals by skin painting, inhalation, or ingestion. Because costs of these studies increase markedly with the level of complexity, most elaborate life-span studies using laboratory animals are undertaken only when the less costly cell culture assays indicate a potentially important human health concern.

Mathematical methods are also being developed to combine the results of short-term bioassay tests, whole animal studies, and human epidemiology to predict the health risks associated with new chemical substances. With these methods the toxic potential of new substances is determined through comparison with other substances that act in similar ways and for which human health risks have been measured. Human health risks can thus be estimated per unit of exposure, providing the

information necessary to establish reasonable human exposure guidelines.

Research on the health risks associated with exposures to substances produced in coal conversion and oil shale recovery processes will also provide a firm basis for the development of exposure control guidelines for workers in these industries. It is important for the orderly development of safe working conditions that the health-effects research precede the large-scale deployment of fuel production facilities.

**Coal Gasification** Procedures have been developed and their validity demonstrated for (1) analyzing chemical toxicants in compound mixtures, (2) monitoring human and environmental exposures, and (3) mitigating exposures and their effects. These procedures have been proven effective in characterizing the toxic chemical species in the process and effluent streams of coal gasification pilot plants and process development units.

**History** Epidemiological information on workers in turn-of-the-century coal gasification plants (in England and Japan) and more recent experience in coking operations indicated that a coal gasification industry might present significant potential for adverse human health effects (e.g., increased incidence of lung and bladder cancer). Likewise, the tremendous amounts of coal that would be consumed in a gasification industry suggested that the entire conversion system had potential to create a number of adverse environmental impacts.

In the mid-1970's OHER initiated a broad program of health and environmental studies at operating coal gasification development units and pilot plant facilities to obtain definitive information on the potential health effects of modern coal gasification technology. These studies, which use state-of-the-art toxicological and ecological testing methods and procedures, are coordinated with and complementary to, studies

supporting the development of advanced high-Btu and low-Btu coal gasification technology.

Studies to identify and characterize the extent of toxins in gaseous products from coal focused on the potentially carcinogenic organic compounds in process streams and effluents. Ecological studies addressed the effects of air emissions, liquid effluents, and solid waste disposal. Industrial hygiene studies included workplace monitoring, medical surveillance, and evaluations of the adequacy of measures to limit exposures and effects. Finally, an initial risk assessment of coal gasification was performed.

**Benefits** As a direct result of the studies at pilot plants, toxicological evaluation of process streams and effluents from full-scale gasifiers can be limited to screening tests for most streams. Detailed analysis is necessary only for those streams or stream components with previously identified toxicity. This practical research has established that (1) the mutagenicity of organic compounds is limited principally to chemicals called the higher molecular weight polynuclear aromatic hydrocarbons, making it necessary to study and characterize the toxicity of less than 1 percent of the material found in most process streams, and (2) the more volatile hydrocarbons found in the process stream (e.g., naphtha with up to 1000 tons/day output) do not contain new toxins, need not come under Toxic Substances Control Act regulations, and thus will not require extensive toxicological study.

This means that it should be possible to design facilities to recover these commercially valuable chemicals rather than burn them as in-plant fuels or to dispose of them as waste materials. The evaluation of process streams for toxins has also been greatly simplified by the development of sophisticated procedures for separating the complex coal-derived products and isolating and identifying toxic chemicals. New instruments for vapors and liquids

have been developed and field-tested for monitoring contamination by polynuclear aromatic hydrocarbons in the workplace. These instruments provide a simple method for directly evaluating exposure and can monitor the effectiveness of mitigating procedures, which is almost impossible without such instrumentation.

Ecological studies have indicated that the effects of atmospheric emissions on vegetation decrease with decreasing humidity. Thus, judicious site selection criteria could yield economies in emission control requirements without sacrificing air quality.

Evaluation of environmental control technologies has provided information that will permit health and safety considerations to be incorporated in process design. In a low-Btu industrial gasifier, commercially available cleanup devices have been shown to be effective in removing materials of health and environmental concern. On the other hand, solvent extraction of wastewater from tar-producing gasifiers does not completely remove all products of potential concern; further treatment may be required before discharge to the environment. Similarly, leaching of the large amount of solid waste produced in a commercial-scale facility might in the long term have adverse environmental effects even though the concentration of toxins in the waste is low.

As a result of the knowledge gained through this program, the scope of health and environmental studies required at any future full-scale commercial facilities will be greatly reduced, information on toxic substances and their location in the product or waste stream is available, validated methodologies are available for obtaining meaningful data, sophisticated procedures for isolating and identifying toxins have been developed, and many of the problems that can be prevented by careful plant design are known.

**Coal Liquefaction** Less costly technologies can be used to control the toxic side effects of coal liquefaction processes while still meeting health standards likely to be established for the direct coal liquids industry. The carcinogenic and mutagenic activities of coal-derived liquids from numerous liquefaction processes occur only in a fraction of the liquid product and can be reduced through process modifications.

**History** In the early 1970's, interest in producing liquids from coal as a means of reducing United States dependence on foreign oil sources was heightened. However, the possibly deleterious effects (e.g., lung, skin, and scrotal cancers) of coal processing and, perhaps, products were known to both industry and Government agencies interested in developing coal liquefaction processes. Great care was taken in research and development (R&D) facilities to minimize the exposure of workers to process stream materials. In addition, careful medical surveillance programs were carried out to monitor the health of workers in pilot plants. Concern by industry and Government regulatory agencies led to preliminary commercial plant designs that would reduce the exposure of workers to all process stream materials and fugitive emissions. However, there were lingering concerns that excess costs were being incurred in safety systems and that equal or better worker safety could be obtained in a more cost-effective way.

To obtain the data necessary to evaluate the potential health impacts of coal liquefaction, a broad-based research program was undertaken to examine materials from a number of different coal liquefaction processes. Substantial effort was directed toward using simple tests to screen for possible carcinogens and mutagens. Other studies investigated the oral toxicity and teratogenic potential, or the ability to cause fetal malformations, of the materials.

**Benefits** The tests demonstrated that coal liquefaction products

with boiling points below approximately 650°F were not active biologically. This was true when the tests measured mutations in microbial changes in cells taken from mammals. Further examination showed that both the mutations and cancers observed resulted from fractions boiling above the 650°F to 700°F range. Moreover, the rates of occurrence increased markedly in fractions that boiled above 800°F.

It appeared, therefore, that mitigating procedures might be applied to a more limited set of materials than had been previously thought possible, with corresponding cost savings. For example, for a SRC-II (Solvent-Refined Coal) fuel oil blend (with boiling points ranging from 350°F to 900°F), materials boiling above 700°F represent about 25 percent of the total mass of material in the blend, and materials boiling over 800°F represent less than 10 percent. Thus, only the heaviest 10 to 20 percent of the product stream required treatment. It also appeared that hydrotreatment, a common petroleum-refining industrial process of hydrogenation using catalysts, might be effective in neutralizing the biologically active materials. Studies using the Ames assay or mammalian cell transformation assays indicate that hydrotreatment is effective in reducing the biological activity of coal-derived liquids. Skin-painting studies demonstrated that hydrotreatment dramatically reduces the potential for causing cancer.

This research also led to the definition of components acting as potential agents causing skin cancer. These are tentatively identified as compounds known as polyaromatic amines (PAA) and polynuclear aromatics (PNA). Although test data are incomplete, they provide a basis for more specific monitoring and the development of more reliable criteria for preventing worker exposure to potentially cancer-causing materials.

Research results also have an influence on the conceptual market-

ing strategy for coal liquids. An initial approach was to market the high-boiling materials as boiler fuels. As a result of the research, a second strategy has been identified, namely to market products with boiling points below 750°F for use without further treatment. Under this approach, the higher boiling materials would be considered for use as in-plant energy sources or as candidates for hydrotreatment to lower their boiling points.

The substantial difference between the capital and operating costs of hydrotreating all versus part of the material with high boiling points (heavy distillate) provides the basis for quantifying a portion of the potential benefits associated with OHER research. Four sets of capital and annual operating costs developed by the Chevron Research Company for the SRC-II process (a nominal 50,000-barrels/day plant) were studied, including hydrotreating the whole heavy distillate and hydrotreating only that fraction of the heavy distillate boiling above 750°F. For the Phase Zero design, SRC-II produces about 11,000 barrels/day of heavy distillate product. Material boiling above 750°F amounts to 2700 barrels/day. The estimated cost savings per year for a single SRC-II plant vary from \$98 to \$174 million for capital costs and from \$7 to \$14 million for annual operating costs. The projected cost savings per barrel of product produced are in the range of \$0.69 to \$1.14.

**Risk Analysis** Risk analysis is a system of principles, practices, and procedures that uses the information generated in scientific experiments to estimate the potential health and environmental consequences of man's activities. It is this measure, a probability or chance of an effect occurring, that is needed by policymakers, regulatory bodies, and insurance groups to formulate goals, criteria, and standards. Such estimates have proved particularly useful where atmospheric particles pose the principal concern, as in the exhausts of automotive diesels and

electric power plants. Moreover, what began as developing methods for estimating the health effects of particles and sulfates found application in a wide range of analyses of the risks of other pollutants.

**Evaluation of Health Risks from Atmospheric Particles** A comprehensive body of information is being developed to evaluate the health risks associated with the inhalation of atmospheric particles released from energy-related industries.

The human health risks associated with exposure to atmospheric pollution depend on many factors, including the physical and chemical composition of the pollutants, their transport and transformation in the environment, the amounts that may be inhaled or ingested by humans, and their toxicity. DOE-supported research is playing an important role in identifying the pollutants of greatest concern, the manner in which they can enter the body, and their potential for causing adverse health effects. The research provided methods for characterizing and evaluating emissions from different types of coal combustion plants, coal conversion processes, oil shale recovery, and the use of petroleum fuels in diesel and gasoline engines. In some cases, new instruments were invented, for example, a family of particle samplers for use under normal atmospheric conditions and at high temperatures and pressures. New techniques were also developed for chemical fractionation and identification of pollutants and for characterization of their toxicities.

**History** Work dealing mainly with radioactive aerosols began in the late 1950's at the University of Rochester, PNL, and the Lovelace Fission Product Inhalation Laboratory (now the Inhalation Toxicology Research Institute). This research was expanded after 1970 to include studies of aerosol particles originating from many different energy-producing, consuming, and conservation activities. These studies have examined the ranges of particle sizes that can be inhaled by

humans and test animals, to ascertain the fractions that deposit in the respiratory tract, and the potential mechanisms of their toxicity. Several such studies are now under way but will require several years to complete because lifetime observations of large groups of laboratory animals exposed to the toxic substances are necessary.

Each research project evaluates a single energy technology and estimates the risks resulting from human exposures to its products, by-products, and waste products. This research integrates diverse types of information, most of which has been developed in DOE-supported health and environmental research programs, on pollutant sources, characteristics, movement through the environment, human exposures, and health effects. These analyses are expected to provide the information necessary for cost-effective regulation of future energy industries, including models of exposure and risk from atmospheric particulates.

At present, the estimation of health risks from particles emitted by energy technologies is a complicated and uncertain process because of incomplete information regarding which components of atmospheric particulate matter are toxic and may cause illness or death in humans. As the toxicity of atmospheric particles becomes better understood, this information can be combined with knowledge of the atmospheric dispersion of particles to decrease the uncertainty involved in projecting the health risks that energy technologies might pose to the general population.

**Benefits** Two major benefits of research to evaluate the health risks associated with exposure to atmospheric particles follow.

1. **Development of the scientific information base.** The fossil fuels research program has focused mainly on characterizing emissions from electricity-generating power plants and light-duty vehicles used in road transportation.

These two categories of energy use account for nearly 50 percent of the emissions of regulated pollutants in the United States. The physical and chemical characteristics of these emissions are now well known.

The research program has also contributed greatly to an understanding of the deposition, retention, and health effects of atmospheric pollutants in general. It is now known that future regulations should be aimed at controlling respirable-size particles, that is, those with aerodynamic diameters below 10 microns. It is also known that sulfur dioxide emissions contribute greatly to the formation of sulfate particles, which are mostly in the small respirable particle-size range. Automobile emissions have also been shown to be respirable. This knowledge, along with the ranking of the toxicity of various respirable particles, is crucial to the development of cost-effective pollution control guidelines.

2. **Development of atmospheric dispersion models.** An important aspect of evaluating the health and environmental impacts of new pollution sources is projecting the atmospheric concentrations of pollutants in nearby populated areas. This must be accomplished before new industrial sources are permitted. Mathematical models have been developed for projecting the atmospheric dispersion of pollutants; an example of these efforts is the *Handbook on Atmospheric Diffusion* published in 1982 (Steven R. Hanna et al., DOE/Technical Information Center, DOE/TIC-11223). Although the value of these research programs lies in the development of new knowledge, it appears reasonable to assume that the enforcement of air quality standards would be on a "trial-and-error basis" if acceptable means of projecting environmental dispersion of pollutants were not available.

### **Evaluation of Public Health Risks from Diesel Engine Exhaust**

The public health risks associated with exposure to diesel engine exhaust were evaluated based on information on the physical and chemical characteristics of diesel engine exhaust, the transport of particles and gases in the atmosphere, and the potential health effects of diesel emissions. Health risks were stated in terms of the increased probability of persons living in congested urban areas developing chronic respiratory diseases or cancer. This risk evaluation is being used to focus related health effects research programs on areas where uncertainties remain about the effects of emissions from light-duty diesel vehicles.

**History** The attraction of diesels is largely that they achieve 10–25 percent higher fuel efficiencies than equivalent-sized gasoline engines and, thus, can make an important contribution to reducing U.S. dependence on foreign sources of oil. However, because current diesel engines emit more visible smoke and odors than gasoline engine vehicles, concern has been expressed that they may also involve new health risks. Indeed, particles emitted by diesel engines have been found to contain small amounts of known cancer-causing chemicals, which also have been shown to be mutagenic when tested in cell cultures. These particles are small enough to be inhaled by humans and deposited in the lungs. Although these are both signs of a potential health risk, epidemiological studies of workers who were exposed to high concentrations of emissions from diesel buses in garages showed no detectable increase in lung cancer incidence.

To understand this apparent anomaly, mathematical models were used to predict future air concentrations of diesel exhaust in congested urban areas. Relationships between exposure concentrations and health risks were developed by combining the results of short-term bioassay tests, whole-animal studies, and human epidemiological studies.

Because human epidemiological studies of workers exposed to diesel exhausts were not sensitive enough to detect changes in cancer rates of the general population, the mathematical models used results of human epidemiological studies of populations exposed to coke-oven emissions, cigarette smoke, and urban soot. All of these represent exposures to the combustion products of fossil fuels that are similar to diesel emissions in their physical and chemical characteristics.

Overall, the health risk evaluation concluded that future diesel light-duty vehicles are not likely to increase significantly the risks of developing respiratory diseases or cancer over those already present from atmospheric pollution. The projected risks were also much less than those associated with cigarette smoking or exposure to levels of cigarette smoke that are commonly found indoors. The potential reductions in health risk that could be achieved with pollution controls on diesel vehicles were also evaluated.

**Benefits** The analysis performed for OHER is being used to (1) guide the development of research programs aimed at directly measuring the relationships between levels of exposure and risk, (2) identify populations that may be at greatest risk from future diesel emissions, and (3) formulate cost-effective emission control standards for future light-duty diesel vehicles. The health risk analysis was incorporated into the Environmental Protection Agency's (EPA's) summary publication *Toxicological Effects of Emissions from Diesel Engines* [J. Lewtas, *Developments in Toxicological and Environmental Science* 10, 1982 (Elsevier Science Publishing Company)].

The health risk analysis indicated that if 20 percent of the light-duty vehicles in the United States were to use diesel engines, fewer than 400 lung cancers/year would likely occur as a result of exposures to diesel engine exhaust—even if no further emission controls were applied to reduce particulate exhaust. Fewer than 200 lung

cancers/year are projected if the proposed post-1985 emission standards reduce current particulate emissions by about 50 percent. This increased incidence would be a small fraction of the 100,000 lung cancers that already occur in the United States each year.

Thus, the research program developing risk analysis for the health effects of diesel engine exhaust has provided information that can serve as a basis for the cost-effective regulation of vehicle emissions.

### **Evaluation of Public Health Risks from Atmospheric Sulfates**

A probabilistic health-damage function that yielded a "best" estimate for increased mortality as a result of exposure to atmospheric sulfate particles, which included a confidence interval expressing the range of uncertainty of the estimate, was derived.

**History** Of the various pollutants produced in the combustion of fossil fuels, the chemically transformed products of sulfur dioxide and atmospheric sulfates have been of particular concern with respect to potential increases in human mortality. Numerous epidemiological studies have been conducted, generating a broad range of sometimes conflicting results. These studies were assessed for scientific validity and then aggregated into a single probabilistic function that expresses the uncertainty of the information available.

This probabilistic health-damage function has now become standard in the air pollution health impact literature, and the general methodology has been extended to a broad range of risk assessment and policy analysis applications. The function has served as an important tool in educating policymakers and the general public regarding the potential health impacts of future emissions. A recent state-of-the-art assessment of fossil fuel combustion stated that the probabilistic function might be regarded as the best available indication of the

magnitude of the effect of air pollution on health. In addition, the function was selected by the Office of Technology Assessment for use in estimating the health effects of sulfur dioxide emissions.

**Benefits** Concern about the health and environmental impacts of sulfur dioxide emissions has been evident in bills placed before the United States Senate. One such bill required a reduction of sulfur dioxide emissions from about 22.5 million to 12.5 million tons/year in the states bordering on and east of the Mississippi River (a reduction of about 45 percent of 1980 emissions), while another required a total emissions reduction of about 8.2 million tons annually in these states. Although these bills were aimed primarily at reducing the environmental damage caused by acid rain, they also have implications for human health. In response to these bills and hearings on revision of the Clean Air Act of 1970, the Office of Technology Assessment prepared a technical report for Congress on sulfur dioxide emissions. The health impacts portion of that report is based on the probabilistic sulfate/particle damage function. The cost of the emissions reductions specified in the first bill was estimated to range from \$3.9 billion to \$4.9 billion/year (1981 dollars) and the cost of the second bill to range from \$2.6 billion to \$3.1 billion/year. In a separate study the Congressional Budget Office estimated that simply maintaining current sulfur dioxide emissions standards would cost \$36.5 billion (1981 dollars) in capital costs and \$15.4 billion in annual operating costs.

To bring these numbers into perspective, the probabilistic sulfate damage function was used to estimate the health impacts of both bills. The reduction in excess deaths that might result from a reduced level of emissions was calculated along with the investment costs required to meet the reduced levels. The cost per death averted was found to vary in the 90 percent confidence range, from \$59,000 to infinity, with the median at \$180,000 to \$230,000.

With a method available to quantify potential sulfate health effects, both proponents and opponents of emissions-control legislation are able to generate widely varying, but defensible health-impact estimates to support their respective positions. General acceptance of the probabilistic damage function enables decision makers to place extreme estimates in perspective and provides them with a common basis for comparing alternate regulatory options and approaches.

#### **Responding to Hazardous Events**

Events in recent years, such as the reentry of Cosmos 942 and the atmospheric testing of nuclear weapons by foreign powers, have led to the development of a capability to react to such possible emergencies and evaluate their consequences. Two complementary systems that provide such a capability were developed under the OHER research program and are operational today. Both were initiated in the 1960s because of concern about fallout from atmospheric testing of nuclear-weapons.

#### **Atmospheric Release Advisory Capability**

The ARAC is a validated system for predicting the transport and dispersion of substances released into the atmosphere. ARAC provides real-time analysis and interpretation of the dispersal of atmospheric releases of potentially harmful substances that are used to support on-site decisions. Output containing position- and time-dependent concentrations is provided by telephone lines to user terminals, telecopiers, and computers.

ARAC can independently predict the dispersion of materials released simultaneously from several locations. The real-time estimation results from a prediction of the concentration of the toxic material in the atmosphere. ARAC includes (1) the ability to use a variety of dispersion models that range from complex to simple; (2) the capability to include terrain effects; (3) a centralized computer facility with access to

terrain data for any location in the United States; (4) the ability to use terrain information from outside the United States; and (5) access to real-time data on local weather conditions and winds aloft.

Inputs to ARAC are (1) the types of substances released, (2) the quantities of material released over time, and (3) the altitude of the release. If these factors are not known quantitatively, preselected approximations can be used in calculations. With these inputs, supplemented by current meteorological data and the internal terrain data base, ARAC can initiate its predictions. The ARAC system is activated through direct requests from ARAC sites and through DOE headquarters for non-ARAC sites.

Those users who are directly connected to the ARAC system are able to make faster and more accurate predictions. User costs vary according to equipment availability, software, and interface but generally range from \$10,000 to \$55,000 (not including manpower costs) for initial installation and 4 to 5 months of operation.

**History** The ARAC project was initiated as a result of AEC's concerns regarding the fate of radioactive debris from nuclear tests in the 1960's. Originally, the project focused on fallout and long-range transport and diffusion (thousands of kilometers) to ensure that the United States did not violate international agreements by nuclear debris from the Nevada Test Site crossing National boundaries. This capability was improved, verified by measurements, and expanded to include real-time predictions.

In 1972 the AEC decided to develop a real-time assessment capability for accidental radioactive releases from industry. The ARAC project was initiated by Lawrence Livermore National Laboratory (LLNL) in 1973. Currently, ARAC is being upgraded to state-of-the-art technology, and the staff is expanding to 24-hour coverage for Federal and state emergency response support.

**Benefits** ARAC is supported directly by subscribers who are concerned about both nuclear and non-nuclear releases. ARAC's subscribers include the following agencies:

1. **DOE.** Several DOE sites are tied directly to the ARAC system: Savannah River, Rocky Flats, Mound Laboratory, LLNL, and Sandia National Laboratories Livermore (SNLL).
2. **Department of Defense (DOD).** DOD was scheduled to have about 50 sites tied into ARAC by 1984.
3. **Federal Aviation Administration (FAA).** The FAA found ARAC to be very responsive in providing input for the development of air traffic advisories subsequent to foreign atmospheric nuclear tests.
4. **Federal Emergency Management Administration (FEMA).** FEMA provided support for New York and California and the commercial nuclear power plants at Rancho Seco and Indian Point to tie into ARAC. ARAC will be used to provide calculations of estimated dispersion for use in emergency planning.
5. **Environmental Protection Agency (EPA).** ARAC provided EPA with an independent (versus power company) source of information during the controlled krypton release at Three Mile Island (TMI) in July 1980.
6. **Nuclear Emergency Search Team (NEST).** DOE's NEST relies on ARAC for assessments associated with nuclear extortion threats.

ARAC provides analyzed information in circumstances where the paucity of data could lead decision makers to overrespond, resulting in an unnecessarily expensive emergency evacuation, or underrespond, leading to a compromise of public health and safety. To date almost all of the ARAC applications either indicated no threat to public health and safety, thereby avoiding unnecessary evacuations, or were used in managing the release to minimize overall risk.

An example of a major benefit of the use of ARAC was at the TMI nuclear power plant. Even though TMI was not tied into ARAC, DOE put the system into service. ARAC was operational during the first few days of the accident and provided dispersion calculations to the DOE Emergency Operations Center, the DOE emergency-response site commander, and Nuclear Regulatory Commission (NRC) representatives. The ARAC calculations indicated that an evacuation of the population around TMI was not necessary. This evaluation was consistent with other calculations and recommendations; and, therefore, no general evacuation was ordered. ARAC also supplied the FAA with dose calculations for the Harrisburg airport, which allowed officials to avoid closing the airport. In addition, ARAC was employed to help manage the controlled release of radioactive krypton in July 1980 by tracking the release and advising EPA regarding the best ground sites for portable monitors and routes to be flown by sampling aircraft. Good agreement was found between the model calculations and the observations. Fewer monitoring stations were required because of ARAC's use. ARAC was also used in a postaccident detailed analysis of population dose around TMI for the President's Commission on the accident.

Less tangible but very important benefits have been reported by DOE site users. Specifically, ARAC has been of great benefit in assuring local, state, and Federal officials responsible for protecting public health that they have an adequate capability to respond to accidental releases. Some of the DOE users have conducted public tours of their ARAC site facilities, receiving press and television coverage.

**Fallout Forecasting** Fallout forecasting is a system for collecting data on nuclear detonations, alerting users of nuclear events, and providing forecasts of the atmospheric spread of the radioactive debris. The National Oceanic and Atmospheric Administration

(NOAA) is responsible for providing the forecasts to users. To formulate these forecasts, NOAA uses meteorological input primarily from the Air Force and DOE.

The detonation of a foreign nuclear device during peacetime triggers a coordinated Federal response to ensure maintenance of public health and safety. Through a multiagency memorandum of understanding, the following responsibilities have been established:

1. NOAA collects data from the Air Force and DOE to develop the official fallout forecast; this serves as the basis for all public announcements on the movement of airborne radioactivity and areas of potential rain-out of nuclear debris.
2. The Air Force provides classified data to NOAA on nuclear debris samples, including the location, time, altitude, and concentration of airborne samples.
3. DOE gathers information on the nature of the nuclear detonation (such as location, time, yield, and height) and reports this information to NOAA for input to the fallout forecast. DOE also provides NOAA with advisories released by its ARAC center at Livermore, California. Data collected from radiation measurements at DOE facilities are made available to user agencies.

**History** OHER has sponsored fallout research at the NOAA Air Research Laboratory since 1952. The fallout forecasting system was developed in response to general public concern about the potential hazards of foreign nuclear detonations. It was a natural outgrowth of the Laboratory's research in atmospheric transport and dispersion, which became the focal point of the forecasting when the interagency fallout response team was formally established in 1976. Since that time the fallout forecasting element of the research program has cost approximately \$300,000. OHER currently provides funding as necessary to maintain its operational status.



**Benefits** The primary benefit of the fallout forecasting is its triggering of a network to alert officials in radiation-sensitive industries.

Once the news of a nuclear event is released, NOAA notifies the National Association of Photographic Manufacturers (NAPM), EPA (usually a joint announcement with DOE), FAA, NRC, the Food and Drug Administration (FDA), and FEMA.

Each organization responds according to the needs of its users. Generally, the actions taken are preventive in nature. The kinds of problems prevented and the actions taken as a result of the alert network and subsequent forecasts are user-specific.

1. The photographic industry is concerned about potential damage to sensitive materials during manufacture. The most sensitive are scientific plates and X-ray film. NOAA alerts NAPM, which in turn notifies 16 member-plant officials (DuPont, Kodak, 3M, and Polaroid, for example). If radiation levels rise sufficiently, filtered air and water may be recirculated to avoid contamination from external sources. Only in the early 1950's (from United States tests) has fallout been severe enough to damage materials and cause a production shutdown.
2. The EPA (a) disseminates to Federal agencies and the general public predictions from NOAA on pathways of contaminated air-mass movements over the United States and areas of possible rainout of radioactive materials and (b) activates the standby portions of the Environmental Radiation Ambient Monitoring System (ERAMS). EPA also recommends necessary radiation surveillance or protective actions to appropriate state agencies.
3. The FAA uses data from NOAA, the Air Force, and DOE to develop air traffic advisories for appropriate air traffic control centers, airman's information centers, and airlines regarding airspace that should be avoided because of potential or actual

radioactive contamination. These advisories depend most heavily on Air Force and ARAC information.

4. NRC is concerned about the possibility that fallout may trigger on- or off-site monitors at nuclear facilities. Local severe weather following a nuclear test can cause monitors to show significant increases in radiation levels that can be confused with a radiation leak from a reactor. NRC alerts all reactor facilities and has thereby avoided costly power plant shutdowns that might last from hours to weeks at a potential cost of \$500,000/day.
5. FDA receives information from NOAA regarding the probable location of fallout contamination and consults with EPA concerning radiation surveillance and protective actions. FDA then provides guidance to state and local Governments regarding appropriate responses for evaluating and preventing hazardous radioactive contamination of foods and animal feeds, as well as guidance on the control and use of such products should they become contaminated.

### **Detection and Measurement of Human Health Effects**

No area of science can develop very far without special tools, methods, and instruments. During the early stages of a science, observation with available instruments is usually sufficient. At some point, it becomes necessary to measure events that have not been measured before. A new technology often provides the means of developing new, more efficient or more cost-effective instruments that find applications outside the original thrust of the research.

The instruments developed in OHER programs have found specialized applications in hospitals and clinical laboratories, research laboratories, Government, and industry. They have brought true automation, as opposed to mechanization, to the areas of cell

counting and blood-chemistry analyses. The methods and procedures of short-term bioassays, fast tests for screening materials for potential cancer-causing agents, have revolutionized the field of testing new chemicals for potential hazards.

Instruments originally designed to measure radiation doses to biological systems are now found in operating power reactors and metal recovery plants, as well as in the delicate interior of electron microscopes. The concepts of personal badges and on-the-spot dosimeters are providing new ways to further increase employee safety in chemical processing facilities. The United States has a way to track and measure the path of dangerous substances released to the atmosphere should an accident or mishap occur.

In the 1960's the emphasis of environmental research shifted to the support of a civilian nuclear industry, and research efforts were directed toward perceived problems of nuclear power plants. Although all types of power plants release heat to the rivers used to supply their cooling water, the effect of the increased heat releases from the larger nuclear power plants needed to be understood. Plans to construct ocean-cooled, off-shore reactors focused research on the Continental Shelf and near-shore areas and provided valuable information for non-nuclear energy development, such as ocean thermal energy conversion (OTEC), and information necessary to evaluate ocean waste disposal. Research in the cycling of transuranic elements (man-made elements heavier than uranium, primarily plutonium) in the environment turned to the concern about their potential uptake by crops such as wheat, corn, soybean, and root crops.

Efforts to understand the impact of radioactive materials inadvertently introduced into the ecosystem by nuclear bomb tests led to a clearer understanding of how ecosystems operate. The controlled use of radioisotopes to further this understanding has

increased our knowledge of the fate of nonradioactive hazardous waste, the metabolism of plants, and many other subjects.

The extremely high detectability of radioactive atoms makes them easy to trace as they move through nature's cycles and migrate from one place to another. Their known decay rates, decay products, and ratios have led to greater understanding of physical, biological, and climatic processes over whole ecosystems and of biological and life processes at the microscopic level. This use of radioactive tracers enabled man to understand the process of photosynthesis vital to plant growth and food production.

In the 1970's health and environmental research in AEC and its successor agencies broadened to support all energy sources and uses. Basic research on toxic substances and cancer-causing agents focused on applying known methods to new substances. New, unique concerns, such as reclaiming of land affected by strip mining, were brought forward to be addressed and solutions identified.

### **Cell Sorting and Blood Analysis**

Two devices for biological analysis widely used in laboratories, hospitals, and clinics are the flow cytometer and the centrifugal fast analyzer. The flow cytometer was developed in 1965 to distinguish cells damaged by radiation from normal cells. Since then, the methods used for cell sorting and their applications have continued to increase. Today the flow cytometer is used routinely for performing complete blood counts (its greatest single application), detecting cancer and monitoring its treatment, detecting genetic abnormalities, and isolating specific chromosomes for analysis of their genetic composition.

The centrifugal fast analyzer also had its beginnings in the search for tools to measure radiation effects in humans. The analyzer, which exploits advances for processing uranium made in centrifuge technology in the 1960's, can

handle a large number of samples for automated analysis simultaneously. It is used principally to test blood and other body fluids for diagnostic purposes.

**Flow Cytometry** The flow cytometer characterizes and sorts individual cells, permitting the measurement of cellular properties and changes in those properties on an individual rather than on a population-average basis. The cells are suspended in a fluid droplet stream flowing past one or more optical or electronic sensors that measure cell characteristics. Typically, for characterization, a cell is stained with a fluorescent dye and passed through a focused laser beam. The fluorescent light emitted from the cell is analyzed and recorded. Cell sorting is a related procedure in which droplets with particular characteristics in the stream are charged electrostatically and then diverted. This separates relatively pure populations of the selected cells from the main sample.

The advantages of flow cytometry and cell sorting over other techniques include:

1. Rapid analysis of single cells and subcellular components (10,000/second versus about 100/minute with a microscope),
2. Statistical analysis of large numbers of individual cells,
3. Rare cell identification (one cell in 10 million can be detected),
4. Greatly enhanced resolution (the 9 percent difference in the DNA content of human male versus female cells can be measured),
5. Simultaneous analysis of many parameters of individual cells, and
6. Sorting of selected cells at rapid rates.

**History** The first device capable of separating biological cells was developed in 1965 by M. J. Fulwyler at Los Alamos National Laboratory (LLNL) as part of research into the effects of plutonium radiation. The flow cytometer was developed to provide a means of rapidly scanning for and separating cells damaged by radiation.

Further developments in the analysis of cell populations were based on optical phenomena such as absorption, light scattering, and fluorescence. The first sorter based on fluorescence analysis was developed in 1972. Almost simultaneously, a multiparameter cell/particle separator was developed. Recent developments in the field of flow cytometry and flow sorting have stressed the use of new or improved sensors for cell physical and chemical properties. Analytical capabilities such as the development of low-resolution morphological information (cell and nuclear size, chromosome length, and location of the chromosome constriction) offer the potential to detect important genetic defects and low-level background mutational events.

Since 1964 at Los Alamos and 1972 at LLNL, flow cytometry R&D has totaled about \$6.5 million (1982 dollars).

Four companies currently offer flow cytometry systems at an average cost of about \$100,000 per system. The number of instruments in place is estimated at 350. All companies contacted believe that there is a strong growth market for flow cytometers and are investing in new developments.

**Benefits** The flow cytometer cell sorter, originally intended to separate radiation damaged cells from normal cells, has been used extensively as both a biological and clinical research tool. Its major commercial potential, however, lies in its capability for automated diagnosis and economical population screening in the fields of hematology, immunology, cancer diagnosis, and genetics.

More recently, improvements in the method have permitted the creation of a chromosome-specific DNA library which scientists believe will advance the course of human genetics by a decade; an advance which will certainly be a major step forward in the diagnosis and treatment of genetic diseases.

1. **Hematology.** Complete blood counts, which are performed routinely in the clinical laboratory, represent the single largest current application of flow cytometry. Several dedicated, single-purpose commercial machines have been developed for this purpose. Reticulocyte and platelet counting are examples of two recent developments that are moving immediately into the clinical consulting laboratory. The efficacy of diagnosis and radiotherapeutic and chemotherapeutic treatment of leukemia is being assessed by flow cytometry.
2. **Immunology.** The clinical significance of circulating monoclonal B-lymphocytes in non-Hodgkin's lymphoma has recently been demonstrated. Accurate monitoring of new patients and those in remission is being performed, and definitive markers useful in determining the results of therapy and the prognosis for relapse have been developed.
3. **Oncology.** Considerable effort has been directed to modifying the basic flow cytometric instrument to allow automation of Pap smear analysis for detecting cervical cancer. The objectives are to reduce costs, increase the information content and statistical reliability of the tests, and increase the number of early detections.
4. **Genetics.** Several genetic abnormalities involve chromosome duplication beyond the normal human complement of 46 chromosomes. Flow cytometry is used not only to detect these gross changes in the number of chromosomes, which typically result in severe mental retardation, but also to detect more subtle polymorphic events that promise the first means of diagnosing several inheritable diseases.

**Centrifugal Fast Analyzers** The centrifugal fast analyzer is an instrument used for medical diagnostic purposes to perform routine and special blood chemistry tests in hospitals, clinics, and research laboratories.

The centrifugal fast analyzer tests multiple samples simultaneously. It is built around a flat rotor with numerous sets of wells arranged radially. Measured quantities of the samples and reagents are introduced into individual wells toward the center of the rotor. Centrifugal force mixes each sample and its reagent and moves them into transparent reaction cells at the periphery of the rotor. During each revolution a time-synchronized measurement is made of light transmittance, color, fluorescence, or other relevant property. The course of the chemical changes in each reaction cell is monitored by an on-line computer, and analytical results are developed simultaneously for all samples on the rotor. The resulting data are stored, interpreted, and provided to the laboratory technician very rapidly. One run of the analyzer performs the same analysis on from 1 to 42 samples.

**History** R&D of the centrifugal fast analyzer was an outgrowth of National Laboratory expertise in biological sciences and separations science. The original funding for the project was shared by the National Institute of General Medical Sciences and the AEC. The original name of the device, GeMSAEC, is an acronym of these two contributors. The National Aeronautics and Space Administration (NASA) provided support from 1974 to 1976 for a zero-gravity centrifugal fast analyzer. Invention of the centrifugal fast analyzer is attributed to Dr. Norman G. Anderson while he was Director of the Molecular Anatomy Program at ORNL in 1968.

The original GeMSAEC system received the Industrial Research Magazine IR-100 Award as 1 of the 100 most significant new technical products of 1969. A second IR-100 Award was awarded in 1977 for the portable, miniaturized, centrifugal fast analyzer developed at ORNL.

Transfer of the analyzer to industry occurred very rapidly. In late 1968 and early 1969, representatives of

Carbide Corporation, and the American Instrument Company applied for and were granted royalty-free licenses from AEC to commercially produce a centrifugal fast analyzer. Today, five domestic companies sell centrifugal analyzers. Both industry and DOE researchers have made major contributions to its continued development analyzer; for example, improved sample handling, miniaturization, and microchemistry techniques to save reagent costs and laboratory workspace and permit improved blood analyses in areas such as pediatrics and geriatrics, where only small samples are obtainable.

**Benefits** Major markets for the centrifugal fast analyzer are hospitals and laboratories with low-to-medium daily test volumes. These include small-to-moderate-sized hospitals, specialty laboratories in large hospitals, and commercial laboratories. Major advantages of the centrifugal fast analyzer are its throughput capacity, flexibility to perform any type of assay, concurrent ability to perform economically single tests and batches of tests, and ability to perform emergency tests. At the time of its introduction, the centrifugal fast analyzer represented a 25 to 50 percent cost savings over the discrete analyzers then available. The centrifugal fast analyzer also represented an 80 percent cost savings over the manual methods that predominated in small-to-medium-sized hospitals. Then, as now, existing continuous-flow analyzers perform a fixed battery of tests (a "profile") for less cost than a centrifugal analyzer, but this economy is only obtainable by a laboratory that has a high enough volume of tests to justify purchasing the larger, more expensive continuous-flow instrument.

The significant benefits arising from the development of centrifugal fast analyzers include:

1. Introduction of true automation to clinical chemistry (as differentiated from mechanization);
2. Improved precision for certain tests, thus eliminating the need to retest;

3. Availability of test techniques not readily available with other equipment;
4. Data reduction in "real time" using an on-line computer;
5. Flexibility to serve institutions having small-to-medium testing loads; and
6. Cost savings to users.

Sales of the centrifugal fast analyzer are estimated by industry sources to be at least 500 units/year, amounting to approximately \$25 million/year. Industry sources indicate that the current number of centrifugal fast analyzers in operation is about 4000 in the United States and as many as 10,000 worldwide at purchased prices ranging from \$20,000 to \$70,000. While there are no statistics on the number of tests performed with the analyzer, two estimates are available: (1) approximately 175,000 tests per year per analyzer and (2) 10 to 25 percent of the 2 to 4 billion clinical chemistry tests performed in a year, probably closer to 10 percent of the total tests.

Owners indicated that they save 10 to 30 cents/test performed on centrifugal fast analyzers, mostly in reagent costs. Applying these factors to 300 million tests/year yields the estimated savings of \$30 to \$90 million/year.

**Fast Test for Cancer-Causing Chemicals** Short-term cell bioassays are used as inexpensive, fast screens prior to more costly animal tests in screening chemicals for cancer-producing or cell-altering characteristics. A number of tests are included within the scope of short-term cell bioassays.

One of the most widely used is a test using special strains of the bacterium *Salmonella* developed by Dr. Bruce Ames of the University of California at Berkeley. The uniqueness of this test involves the use of a mutant strain of this bacterium that is unable to produce the amino acid histidine, which is necessary for its reproduction. If the chemical being screened causes the organism to undergo a genetic change that allows it to produce histidine and,

therefore, reproduce itself, then the chemical is considered a mutagen and potential cancer-causing agent. The mutational potency of the chemical under test is expressed in terms of the number of growing bacterial colonies that are observed after a period of incubation. The equipment required is minimal and a single technician can perform a number of tests in a day.

Because a negative Ames test does not absolutely ensure that a compound is inactive in humans, a "tiered" strategy in which the next levels of testing may include mammalian cells in tissue culture and acute animal studies is often employed. Although not quite as simple or inexpensive as the Ames test, such assays are still orders of magnitude quicker and cheaper than long-term, whole-animal testing.

Chromosomal aberration and sister chromatid exchange measurements are common bioassays performed with cultured mammalian cells. These assays are run either on cells grown in tissue cultures or on bone marrow cells, spermatogonia (a cell structure that precedes development of a sperm), or lymphocytes (a white blood cell formed in lymph nodes and several other organs) from experimental animals and human donors.

**History** Although short-term cell bioassays are most commonly used for measuring the response to chemical agents, the majority were developed from radiation studies sponsored by OHER. Their roots lie in two areas of investigation in radiation biology—chromosomal effects and genetic toxicology.

Scientists in the OHER-supported laboratories were the first to realize that the induction of chromosome aberrations—other than normal changes in genes manifested as mutations caused by the abnormal breaking and rejoining of chromosomes—could be used as a biological dosimeter. This was first demonstrated by exposing cells from a plant that is

extremely sensitive to radiation damage to radioactive clouds during the atomic bomb test, Operation Greenhouse, in 1951. Later it was found that chromosomal aberrations in lymphocytes could also be used to measure dose. Additional studies, combined with advances in the science of somatic cell genetics, were instrumental in developing the mammalian cell assays noted above.

Genetic toxicology—the study of the nature, effects, and detection of radiation and chemicals on genes and, thus, on the characteristics passed from one generation to another—is a new field of science that developed from the discovery of DNA repair. Studies by Rasmusson and Painter at the Radiobiological Laboratory, University of California at San Francisco, in the 1970's demonstrated that exposure to radiation (and other toxins) caused some DNA to undergo unscheduled DNA (repair) synthesis (UDS), and that this UDS is quite separate from the normal synthesis process in DNA. This observation forms the basis of the commonly used UDS assay. The ability to construct and characterize bacteria with deficient DNA-repair mechanisms was a crucial step on the path to the Ames test.

**Benefits** The testing of new products using short-term cell bioassays has resulted in reduced costs and increased productivity. Many different new substances have been created and introduced to the environment in recent years, some of which have the potential to cause genetic damage. Before the early 1970's, animal testing was the only accepted means of evaluating a substance for carcinogenic activity. With the advent of the Ames test and other short-term cell bioassays, however, it has become possible to test substances for mutagenic or carcinogenic potential far more rapidly and cheaply. The Ames test, for example, presently costs \$1000 to \$1500 and takes only 48 hours. These bioassays are used routinely by many drug and chemical firms to screen substances for potential mutagenic activity before

large expenditures are made to develop them into marketable products.

A measurable benefit of the Ames and similar tests is the amount of money manufacturers save by avoiding the development of potentially hazardous products. Because drug and chemical firms are the most active users of short-term bioassays, a very rough estimate of benefits can be developed based on calculating the amount of development money saved as a result of prescreening:

$$A = \left( \frac{D \times F_m}{1 - F_m} - T \right)$$

Where

- A = net annual benefits,
- D = annual R&D outlays by drug and chemical firms,
- F<sub>m</sub> = fraction of compounds shelved as potential mutagens, and
- T = annual cost of bioassays.

An estimate of the annual R&D outlays by drug and chemical firms is contained in the National Science Foundation publication *Research and Development in Industry, 1979*. The figure is \$1.99 billion in 1979, or about \$3.3 billion in 1982 dollars. Based on an informal survey of a number of firms, 5 percent appears to be a fair estimate for the fraction of compounds found to be potential mutagens. Dr. Ames estimated that over 3000 laboratories worldwide use his test routinely, resulting in an estimate of \$35 million to the annual cost of bioassays. This results in an estimated annual cost savings of some \$140 million/year in 1982 dollars.

Use of these low-cost tests to screen existing products that have never been examined for mutagenic potential represents a potential future benefit. Thousands of man-made compounds are currently in use. To date EPA has inventoried under the Toxic Substances Control Act over 60,000 such compounds that have never been tested for carcinogenic potential. Because the present capacity for animal testing in the United States is limited to a few hundred compounds

per year, short-term cell bioassays are the only feasible means of screening these substances.

### **Analyzing Complex Mixtures for Toxic Agents**

By the early 1960s, existing instruments were reaching limits that would adversely affect important areas of health and environmental research and progress in increasing industrial safety. Two such limits were the inability to determine the elemental composition of nonradioactive mixtures suspected of containing trace amounts of toxic materials and the inability to ascertain the isotopic composition of complex mixtures of radioactive elements such as those being encountered in nuclear reactors and laboratory analysis. Solutions to both of these problems emerged from the OHER research program. The first solution, a semiconductor X-ray spectrometer, has been widely applied to detect pollutants in the environment, identify unknown materials in the scrap metal and metal manufacturing industries, and to locate sites for examination by electron microscopes. The second solution, a high-resolution gamma-ray spectrometer, is commonly used for identifying the elements in the cooling water of nuclear power plants that cause radioactivity, logging oil wells, studying distant planets, and analyzing laboratory samples.

### **Semiconductor X-ray Spectrometer (SXRS)**

This instrument is widely used in industry, medicine, and scientific research to determine the elemental composition of nonradioactive materials. The SXRS is a member of the family of X-ray fluorescence spectrometers and is also known as the energy-dispersive X-ray spectrometer.

The SXRS has three primary components: a radiation source, a semiconductor detector, and a processor. The radiation source can be any material or device that emits X-rays; an isotope of iron that naturally emits X-rays is frequently used. X-rays from the source are directed at the sample to be analyzed, causing the sample to emit other X-rays. The semiconductor detector is made of

silicon with lithium added (lithium drifted into it) to obtain the desired detection capability. When X-rays enter the detector, the resulting interaction or ionization produces current pulses that are directly proportional to the energy of the X-rays from the sample. The processor, an electronic logic circuit, counts the number of pulses and records the pattern of X-rays, the distribution of measured energies. Because each element emits a unique pattern of X-rays, the elemental composition of the sample is identified. The typical output produced by the processor is a table showing the percentage composition of the sample.

**History** X-ray fluorescence spectrometers have been in use since the 1930's, when the wavelength-dispersive X-ray fluorescence (WDXRF) spectrometer was developed. However, the WDXRF spectrometer has limited resolution and can only analyze one element at a time. It is, thus, a very costly method, particularly when a large number of elements must be analyzed. Older methods of chemical analysis, particularly wet chemistry, which is very slow and destructive, were still predominant in 1960.

Research on alternative methods was undertaken on a large scale in the 1950's in the United States and other countries. The electronic properties of silicon and germanium were discovered during this period, and the first silicon detector was developed in 1960. The lithium-drifting process, which permitted construction of detectors thick enough to totally absorb the X-rays, was developed in 1960 and 1961.

These first semiconductor detectors provided improved resolution to distinguish elements, but the associated electronic processors were too poor to maintain the resolution. From 1963 to 1969, research to improve the associated electronics was undertaken. By 1965 a high-resolution SXRS was developed. During this period, improvements in the detectors and further development of the entire X-ray detector system also took

place. New applications were explored as scientists realized that the SXRS could potentially be used in industry and medicine in addition to laboratory analysis. Commercialization of the SXRS began in 1965, primarily to university, Government, and corporate laboratories. Between 1970 and 1973, trace-element analysis improvements were made at Lawrence Berkeley Laboratory (LBL). Improvements were also made in the speed of analysis such that a complete analysis of a typical sample now took less than 1 minute.

Approximately 8300 commercially manufactured SXRS units are presently in use in the United States. Of these, 2500 units are stand-alone analysis systems that include the radiation source, detector, and processor. The users of these systems fall into three categories: (1) industry; (2) commercial laboratories; and (3) Government, academic, and medical laboratories. The remaining 5800 SXRS units are attached to scanning electron microscopes.

About 350 of the 2500 stand-alone SXRS systems are used in the scrap metal, steel and metal manufacturing, and durable manufacturing industries. All of these units are located in the production area and are used as part of the production process. Approximately 1000 SXRS systems are used in commercial laboratories where they are typically one of many elemental analysis instruments used away from the actual production process.

The remaining 1150 of the stand-alone systems are used both for research and analysis of trace elements in patient specimens in National, university, and hospital laboratories.

The SXRSs attached to scanning electron microscopes assist the microscope in plotting a "map" of a surface; the elemental composition of each small area is determined separately, and the peaks and valleys are identified. These instruments are widely used in both commercial and Government/

university/medical laboratories. They are used frequently in quality control of ball bearings, airplane bodies, and machine parts, as well as in new materials research.

Eight factors are responsible for the large number of SXRS units in use and the wide variety of uses.

1. The SXRS analyzes all elements of a given sample simultaneously, thereby providing a complete elemental composition of the sample.
2. The SXRS's measurement accuracy is tenths of parts per million.
3. The SXRS provides information rapidly, typically in 10 to 30 seconds.
4. The SXRS is nondestructive.
5. The SXRS is flexible and can be programmed to analyze single elements in less than 5 seconds.
6. The SXRS can use portable detector attachments, and even the non-portable units require little floor space.
7. The SXRS system requires little additional maintenance.
8. The SXRS does not usually require skilled personnel.

**Benefits** The benefits of SXRS development are twofold: (1) reduction in the cost of analyzing materials compared with other elemental analysis techniques and (2) availability of information not otherwise obtainable.

The cost savings accumulated through 1982 by industrial and commercial users provide some indication of the benefits of SXRS development. SXRS users were contacted and asked to estimate the 1982 cost savings that could be attributed to the SXRS. Average annual savings for five user groups—scrap, steel/metals, manufacturing, commercial (non-research), and commercial (R&D)—were estimated to total \$88 million/year in 1982.

**High-resolution Gamma-ray Spectrometry** Gamma-ray spectrometry is a method of detecting, characterizing, and monitoring gamma radiation. The development of lithium-drifted germanium [Ge(Li)] and high-purity germanium

[Ge(HP)] solid-state semiconductor detectors and improvements in the associated electronics have revolutionized the field of gamma-ray spectrometry, particularly with respect to energy applications.

As a result of their much higher resolution (the ability to distinguish between gamma rays of different energies), germanium spectrometers have replaced other types of gamma-ray spectrometers in many uses. They are now commonly used in nuclear power plants, industry, and research institutions for identifying the elements in reactor cooling waters that cause radioactivity, logging oil wells, studying distant planets, and analyzing biological and laboratory samples.

**History** Until about 1970 the device most frequently used for gamma-ray spectrometry was the scintillation spectrometer. The most widely developed scintillator is a sodium iodide crystal that emits light when penetrated by gamma rays. The light is collected and converted to an electrical signal by a photomultiplier tube. The scintillation spectrometer is an efficient detector of gamma rays. However, the resolution of the scintillator is not fine enough to distinguish between isotopes emitting gamma rays of very similar energies. The need for a spectrometer with higher resolution in physical and biological basic research was the primary impetus for germanium spectrometer development.

The first germanium gamma-ray detector was developed in 1962 as a result of Federal (non-OHER), private, and foreign-sponsored research. The original instrument was inferior to the scintillator in both resolution and efficiency. Improved resolution was achieved in 1963 through OHER-sponsored research at LBL, BNL, and ORNL.

By 1971 the results of OHER research were twofold. First, the process of drifting the germanium crystal with lithium was improved, which considerably enhanced the resolution of the detector. Second, the associated signal processing

system was developed further so that the resolution of the detector was not degraded by the processor. During this period, the Ge(Li) detector surpassed the scintillator in resolution, and its use in research applications became widespread. These detectors, however, had to be manufactured and operated at very low (cryogenic) temperatures.

Research on the development of Ge(HP) detectors was initiated at LBL and General Electric (GE). The first high-purity germanium detectors were sold by GE in 1974. These detectors still needed to be cooled during operation but not during manufacture and storage. Manufacturing and operating costs fell as a result.

The ability to work with the germanium at room temperature also permitted the construction of multidetector systems. By connecting as many as ten detectors to a single processing unit, the efficiency of the germanium detector array can be increased without sacrificing resolution. These multidetector arrays are ideally suited to situations such as medical research and power plant environmental monitoring. Between 1975 and 1982, OHER funded development of these multidetector arrays at LBL.

**Benefits** Gamma-ray spectrometers are used primarily for gamma radiation monitoring and elemental analysis of radioactive or neutron-activated materials. Accordingly, gamma-ray spectrometer users fall into four main categories:

1. Nuclear power plants use gamma-ray spectrometers to monitor the content of gas and liquid effluents and the environment of the plant and to measure the condition of the reactor fuel elements.
2. Laboratories (National, university, and commercial) use spectrometers to monitor the environmental conditions of the laboratory and to perform elemental analyses.
3. Resource exploration companies use spectrometers in serial and ground surveillance

and mapping and in wellhole logging.

4. Environmental monitoring organizations (such as state and local environmental protection agencies) use spectrometers to monitor levels of radiation being emitted into the environment.

For users of gamma-ray detectors and spectrometers who require a high level of resolution, the only alternative in these applications is time-consuming chemical separations. The real choice to be made by users, therefore, regards the degree of resolution required. None of the competing detectors has the resolving power of a Ge(Li) or Ge(HP) detector.

Discussions with representatives of gamma-ray spectrometer systems and detectors indicated that the market is approximately \$7 to \$8 million annually. One major manufacturer offered a distribution of units by type of user:

User	Percent of units
Public utility	<10
Laboratories	75
Resource exploration	5
Environmental monitoring	10

The major manufacturers of Ge(Li) and Ge(HP) detectors are Canberra Industries, EG&G Ortec, and Princeton-Gamma Tech Inc.

The use of germanium detectors is most often justified by the need for fast, high-resolution measurements. Fairly short scan times are reported for Ge(Li) detectors, ranging from 100 to 1000 seconds. The time for radiochemical analysis to perform the same analyses ranges from one-half day to several days.

Cost savings associated with using germanium detectors were estimated based on discussions with the staff of approximately 20 utilities operating power reactors. Based on this survey, the annual cost saving in 1982 was estimated as \$21.2 million. Past savings were estimated as \$230 million (present value). Almost all of these benefits represent cost savings associated with measurements for which the alternative is radiochemistry.

It appears that other important, but difficult to quantify, benefits are being realized. For example, much of the scientific work in nuclear physics could not be performed without the germanium detector. Interestingly, a number of isotopes have been discovered by scientists using the Ge(Li) detector. The device is currently being used to determine whether the neutrino has mass. Also, the germanium spectrometer is now a primary method of gamma-ray spectrometry in astronomy.

**Industrial Hygiene Monitors** The expertise and methods in measurement sciences accumulated in the nuclear energy program served the Nation well in the 1970's when complex chemical mixtures became an area of vital concern in exploring the potential of synthetic fuels from coal. Lapel and pocket dosimeters for monitoring exposure to polycyclic aromatic hydrocarbons [(PAHs), known carcinogens] were developed to meet the needs of industrial hygiene. Sensitive instruments to measure skin contamination and spill spot- ters able to measure previously undetectable amounts of chemical contamination also emerged from the OHER Program. In addition to monitoring devices, scientific procedures such as biodirected chemical analysis were developed to measure the carcinogenic and mutagenic properties of complex mixtures of chemicals derived from coal liquefaction and gasification.

As part of the efforts aimed at detecting toxic chemicals, a survey of instrumentation for environmental monitoring was published, and an instrument for monitoring concentrations of PAH compounds, a hydrogen fluoride monitor, and a portable elemental survey meter were developed. The three monitors are in the prototype stage of development. A handbook *The Survey of Instrumentation for Environmental Monitoring\** has been in use for

\*LBL, Environmental Instrumentation Group, Vol. 1(4), 1972-1980, John Wiley and Sons.

several years and will soon be issued by a private publisher. This handbook provides baseline reference information to assist researchers and industrial hygienists in selecting the appropriate method for measuring energy-related toxins.

Instrumentation under development will provide simple and passive methods of monitoring worker exposure to hydrogen fluoride, more sensitive measurement of worker and skin contamination and work area surface contamination by PAHs, and a nondestructive method of measuring formaldehyde emissions. These monitoring techniques address the critical health-related measurement needs associated with these toxic chemicals.

**History** The Industrial Hygiene Measurement Science and Instrumentation Program was initiated to develop new or improved measurement tools and techniques to address a broad range of health protection problems. Since its inception in the late 1940's, the program has focused on concerns associated with chemical toxins related to atomic energy defense activities.

With the creation of ERDA, then DOE, and with broader missions to cover all energy and conservation measures, increased emphasis has been placed on chemicals related to energy development. These include PAHs, which are inherent in synthetic fuel production; hydrogen fluoride, an important chemical in DOE uranium enrichment activities; trace elements, which include respiratory and inhalable toxic metal particulates and vapors; and formaldehyde, a potential carcinogen found in materials used for building energy conservation.

**Benefits** The major benefit of this measurement science and instrumentation research is improved information aimed at protecting the health of industrial workers and the public. Advanced instruments are used to develop new and improved data to identify health hazards. The use of overly con-

servative and expensive health protection measures or, conversely, underestimation of the risks of human exposure to chemical pollutants is thereby avoided.

1. *The survey of instrumentation for environmental monitoring.* This handbook was compiled by LBL to assist users in efficiently selecting appropriate instrumentation. It is based on responses by over 4000 users, including state and Federal environmental agencies, analytical laboratories, instrument manufacturers, and technical libraries. Separate volumes have been published on air, water, and radiation monitoring methods, with each volume organized by pollutant. There are three major sections under each pollutant. The first section discusses the reasons for monitoring the properties of the pollutant, information on health and environmental effects, and regulatory standards and requirements. The second section describes, compares, and contrasts the principles used by the commercially available instrumentation methods. The third section presents a one-page summary for each of the commercially available instruments. The water volume, with a current circulation of 4000 copies, has been purchased by most of the water pollution control agencies in the United States. The volumes on radiation and water have been published and marketed by John Wiley and Sons.
2. *Monitoring of PAH compounds.* The Spill Spotter and the passive vapor dosimeter provide the capability to monitor routinely and cost-effectively PAHs in the workplace. The Spill Spotter is a device that illuminates PAHs with light of a specific color, causing them to fluoresce. The instrument then measures the fluorescent light emitted. The instrument is a hand-held optics unit similar in size to a small video camera and is connected to a small electronics module. Easily changed excitation and emission filters provide

selective detection of classes of organic compounds. This instrument also permits discrimination between organic and inorganic compounds. The Spill Spotter is simpler and safer to use and provides quantitative results comparable to existing methods. Its development was recognized by an IR-100 Award in 1980.

The vapor dosimeter is a passive air sampler that can be worn conveniently by the worker as a lapel badge or used as an area monitor. It is a unique device designed to measure the overall exposure to PAH compounds with three or more rings and can measure dosages as low as parts per billion. The dosage is read by placing the badge in an optical analyzer using the room temperature phosphorescence technique. The passive vapor dosimeter is faster, simpler to use, and less expensive than existing instrumentation. An IR-100 Award in 1981 recognized its invention.

3. *Hydrogen fluoride passive dosimeter.* A hydrogen fluoride passive dosimeter was developed by ABCOR, Inc., under contract to DOE. This monitor is used for industrial health monitoring at the ABCOR enrichment facility. Uranium hexafluoride breaks down into uranyl fluoride and hydrogen fluoride when it comes into contact with water vapor in the air. This dosimeter detects the hydrogen fluoride reaction product and has advantages over the existing methods for measuring hydrogen fluoride. It is small and simpler to use, and it can be worn on the lapel. In addition, it requires no pumps, impingers, sampling tubes, or calibration. The collection element can be analyzed quickly and easily with a fluoride-selective ion electrode. Further, it can be used either as a personal or an area monitor.
4. *Portable elemental survey meter.* The portable elemental survey meter was developed under a DOE contract by Columbia Scientific Instruments for rapid,



on-the-spot, elemental analysis of air particulates collected on filters (including respirable and inhalable particulates) and vapors collected on membranes by chemical adsorption. It was designed to meet the accuracy requirements for sampling in the workplace. The sampling method is nondestructive and can detect 23 elements. The survey meter provides immediate elemental analysis of air particulates and vapors present in the work environment; the alternative is to send the samples to an analytical laboratory. The meter can be used for rapid on-site checking of air contaminants in the case of accidental releases, as well as for routine monitoring purposes. For example, it can be used in the metallurgical and energy production industry to monitor welding fumes (which contain toxic metallic elements) or to measure air contaminants found in other workplace environments. The device is portable and is enclosed in a small compact carrying case. It uses a micro-processor-based, energy-dispersive, X-ray fluorescence technique to measure sequentially the concentrations of selected sample elements whose calibration parameters are stored in memory. Analysis time is on the order of 100 seconds/element.

**Predicting Pollution Pathways in the Atmosphere** Although great improvements have been made in our understanding of the processes that move pollutants through the atmosphere and deposit them in aquatic or terrestrial ecosystems, an even greater understanding is necessary to solve the problems presented by acid rain and the change in the heat budget of the earth caused by carbon dioxide increases. A step in this direction has been made by the production of stable, nontoxic tracer gas that can be released from source areas and detected at great distances.

Understanding and predicting pollutant transport are important

because it is a principal means by which health effects might be produced in the public by an emerging technology. The OHER research program pioneered the mathematical modeling, or prediction, of pollutant behavior in the atmosphere because of the early responsibility for understanding the possible effects of radioactive contamination. Models of the movement of materials through and chemicals reaction in the air and soil are crucial to rational decisions related to sitings of toxic waste dumps and to optimal decisions on mitigation to correct past mistakes. However, the validity of models and predictions must be tested, and OHER has also supported the development of the necessary tools for verification.

Although gas tracers have provided valuable information of this kind, it is also known that pollutant gases often interact with minute particle clouds (aerosols) from which the particles may be deposited on the ground or become resuspended in air. Pollutants themselves may even originate as aerosols. New instruments were needed to understand the transport and cycling of particles in streams, lakes, oceans, and the atmosphere. This need was met by developing aerosol and particle analyzers for both atmospheric and aquatic studies. Today these analyzers form a vital part of the Nation's ongoing research into the effects of airborne chemical pollutants, notably acid rain.

The major benefit of this research has been a sounder understanding of the relationships between pollutant releases and their concentrations in the human environment. Information of this nature is essential to regulation of pollutants in the general interest and for sound industrial planning.

**Atmospheric Tracers** Several nonradioactive, chemically inert systems have been developed to trace the dispersion of materials released into the atmosphere. These include tracers, samplers, and extremely sensitive analyzers

that can detect materials at concentrations as low as 2 parts per quadrillion ( $10^{-15}$ ). Such systems can be used to trace dispersions at ranges of over 100 kilometers.

Increased concern over the regional and international aspects of air pollution has created a need for reliable model calculations of concentrations as far as 1000 kilometers from pollutant sources. Experimental verification of these calculations, as well as environmental assessments based on model simulations, is essential to establish the credibility of models of dispersion processes. One way to verify the models is to trace the movement of actual materials in the atmosphere. This requires cost-effective, nonreactive and nondepositing tracers for local (less than 100 kilometers), intermediate (100 to 1000 kilometers), and long-range (greater than 1000 kilometers) dispersion of pollutants. The tracers must also be nonradioactive, nontoxic, and inexpensive and have low natural background to perform adequately.

Three sampling systems for perfluorocarbons have been developed. The BNL automatic tracer sampler was designed to be easily portable (15 pounds), automatic, and reliable. Each sampler can take a sequence of 23 samples of air. The start/stop time, flow rate, and total volume through the sampling tubes can be controlled. Each sampling tube contains 150 milligrams of Amborsorb, which traps all of the perfluorocarbon. The tracer is then recovered by thermal desorption from the sample tubes and separated by gas chromatography. An electron-capture detector provides measurement accuracy of 10 to 20 percent at concentrations as low as 2 parts per quadrillion (background concentration) with an 8-liter capacity air sample.

A second sampler, the prototype called the "dual-trap sampler," combines both sampling and analysis. Using two sampling tubes, it simultaneously traps a new sample as it analyzes the previous sample. This device can provide analysis of one air sample

containing perfluorocarbon tracers every 5 minutes. It can detect perfluorocarbon tracers at their ambient levels with 15 percent accuracy essentially in real time.

The third prototype sampler is a real-time continuous monitor intended primarily for use in aircraft sampling. Air is drawn through a catalytic reactor that removes the oxygen and other electron absorbers, leaving the perfluorocarbons and nitrogen in the remaining air. This air is passed directly to an electron-capture detector that provides continuous readout of perfluorocarbon concentration with only a 3-second delay. When completed, this sampler should yield accuracies of 0.1 parts/trillion in measuring perfluorocarbon traces.

**History** In the early 1970's, the only available atmospheric tracer with acceptable physical properties was SF<sub>6</sub>. The difficulty in measuring trace amounts of SF<sub>6</sub> against natural and man-made backgrounds limited its usefulness to a range of about 150 kilometers. Recognizing the need for longer-range tracers, OHER initiated research into two tracer types:

1. **Perfluorocarbon tracer.** Investigations reported by 1974 indicated that a perfluorocarbon tracer system could be developed that would be ideal for long-range dispersion studies. The NOAA Air Resources Laboratories contracted with Lovelock to develop the three different samplers as the first step in the development of the new tracer system. Prototype instruments were delivered by Lovelock in 1976. Since then the laboratory has been working closely with DOE's Environmental Measurements Laboratory (EML) and BNL in a cooperative effort to develop a practical perfluorocarbon system.
2. **Heavy methane tracer.** Following the observation that air contained an insignificant number of atoms with an atomic mass of 21, Los Alamos initiated work in 1973 to develop a tracer with that

atomic mass by synthesizing carbon-13 and deuterium into heavy methane, CD<sub>4</sub>. Both carbon-13 and deuterium are available from other Los Alamos programs. Concurrently, scintillation techniques for detecting single ions using mass spectrometry were being developed at the Atomic Weapons Research Establishment (AWRE), United Kingdom. After the initial tests of heavy methane tracers at AWRE were completed, OHER funded the development of a mass spectrometer analytical capability at Los Alamos to measure the tracer levels in ecological samples.

Several field experiments have been conducted to test the perfluorocarbon and heavy methane tracer systems. The most important of these were two demonstrations conducted in July 1980. In the first demonstration, SF<sub>6</sub> perfluorocarbons and heavy methane tracers were released and sampled at distances of 100 and 600 kilometers. The second trial used only perfluorocarbons and SF<sub>6</sub> with sampling only at 100 kilometers.

The key issue to be resolved by the experiments was whether the tracers and the analysis systems were similar; that is, if equal amounts of the two perfluorocarbons were released, would equal amounts be detected at every location? Even more crucial were the direct comparisons of different tracers, such as the perfluorocarbons and the heavy methanes.

The experiments proved that the perfluorocarbon and methane tracers behaved the same in the atmosphere, faithfully following the air motions and remaining in the air streams out to 600 kilometers from the source. Considering that the heavy methane and perfluorocarbon determinations are conducted by totally different analysis techniques (mass spectrometry for the methane and gas chromatography followed by electron-capture detection for the perfluorocarbons), these results inspired confidence in both tracer systems.

**Benefits** Atmospheric tracers are a recent development that may find applications in several research areas. These tracers allow the validation of computerized models to describe atmospheric transport and dispersion, as well as the investigation of fundamental aspects of dispersion or dynamic meteorology not accessible by other means.

These tracers will find applications in facility siting and empirical studies of specific situations where there is no adequate model of the dispersion of emissions or when existing models are inadequate because of the complexity of the terrain. For example, in a recent DOE study of drainage winds in complex terrain, the tracers were used to determine the capability of existing wind patterns to remove pollutants vented from geothermal wells.

**Aerosol Instrumentation, Dry Deposition, and Resuspension** In an effort to predict the fallout of minute particles of radioactive debris from weapons tests, research was undertaken in the science and technology of aerosols. Subjects studied include particle behavior in the stratospheric air, tropospheric interactions with rain and snow, and deposition in lungs from inhalation.

Dry deposition is the process by which particles and gases are transferred to the earth's surface from the air. Research into dry deposition has made possible the development of predictive models that relate deposition velocity to particle diameter. Although these models still contain considerable predictive error, the results are typically an order-of-magnitude improvement over earlier practice.

Resuspension is the process by which particles and gases become reintroduced into the air from the earth's surface. Research into particle resuspension has made possible the development of models to predict resuspension rates, which are used as boundary conditions in air transport models needed to reliably predict what will occur downwind.

**History** Research on dry deposition stems from attempts in the 1960s to measure worldwide fallout of radioactive debris from weapons testing. Dry deposition on grazing lands was of particular concern because it introduced radioiodine into the food chain. Researchers identified the phenomenon and developed a now widely used system that collects dry and wet deposition separately. The early monitoring efforts resulted in a body of data but also made clear the inadequate understanding of the underlying physics. The results of OHER-supported research into aerosol phenomena was combined in 1973 with other advances in aerosol research and with the emerging electronics technology to produce a new electrical aerosol analyzer for surface-level use. Compared with the preceding electrical analyzer, the prototype achieved an approximate sixfold reduction in size and weight. Recognizing its potential, TSI, Inc., an instrument manufacturer, completed the design and engineered a reliable electronics package for the unit. After its market introduction in 1974, the unit quickly became the standard method for measuring the number and size of submicron-sized particles or drops in aerosols.

**Benefits** Over 200 units of the electrical aerosol-size analyzer have been sold since its introduction in 1974; nearly one-half of these sales have been to overseas customers. TSI supplied the following approximate domestic sales by category:

Number of units	Applications
50-60	Air pollution monitoring and research
12-15	Diesel combustion research and health effects research
10-12	Military research on smokes, obscurants, and aircraft condensation trail suppression

Other applications include commercial smoke detector development and calibration, research on commercial air filters and

demisters, semiconductor clean rooms, and particle-size control of carbon black in tire manufacturing.

A number of health, safety, military, and industrial benefits are associated with the use of electrical aerosol-size analyzers. Air pollution monitoring and research benefits include accuracy in quantifying airborne pollutants, identifying particles small enough to be respirable, and improving the ability to enforce emission regulations for point sources. Benefits arising from diesel combustion and health-effects research include the ability to monitor more precisely the diesel combustion exhaust and to evaluate more effectively the effect of design changes on exhaust products. Research on smokes, obscurants, and aircraft condensation trail suppression enhances the survivability of military personnel and equipment. Industrial benefits include clean-room monitoring, leading to a lower rejection rate of electronic components and assemblies; particle-size control of carbon black used in tire manufacturing, resulting in greater tire treadwear; and miscellaneous applications, such as smoke detector development and calibration, information on the effects of pollutants on plant growth, and development of commercial air-cleaning filters and demisters.

A sound understanding of the complex relationships between pollutant emissions and pollutant concentrations in the environment is essential for promulgating sound environmental policy. In this regard, research on dry deposition and resuspension can benefit society in one of two ways: by providing basic data needed to demonstrate that human and environmental exposures to harmful aerosols are less than currently believed or by demonstrating that the threats are greater than currently believed. In the former case, society can benefit from this information by devoting fewer of its scarce resources to emission controls, and in the latter case, it benefits by taking actions to reduce emissions.

An additional benefit from research on resuspension relates to windblown soil erosion. The physical processes of resuspension and soil erosion are essentially the same. Hence, the results of research on resuspension can be applied directly to the study and prevention of windblown soil erosion.

## Identification and Evaluation of Environmental Effects

The concerns resulting from energy production and use have ranged from disturbance of natural systems by mining, deforestation, and drainage to offshore drilling, toxic waste disposal, thermal discharges, and the contamination or pollution of sources of food. Research initiated to gain an understanding of the effects of fallout from weapons tests, potential discharges from weapons production facilities, and pathways radioactive materials and other energy-related materials follow in moving from their source to the size of potential danger has been expanded to encompass pathways of substances through the food chain, underground migration of substances, as well as aspects of radioecology, geology, and many other fields.

**Riverine Ecology** "Riverine Ecology" is the title given to a group of studies and models developed to understand and describe the environmental impact resulting from industrial heating of river water.

**History** Beginning in the late 1940s, the environmental impacts of once-through cooling of reactors built for the United States nuclear weapons program at Savannah River and Hanford were the object of research on riverine ecology by the AEC. Later, environmental impacts resulting from once-through cooling of power reactors prompted a major research program at Oak Ridge on riverine ecology. The program focused on power reactors in an effort to anticipate problems the nuclear industry might face in complying

with the National Environmental Policy Act and other environmental laws. The problem of heating river waters is primarily nonradiological in nature and, thus, also germane to coal-fired plants, pumped-storage reservoirs, and other operations that have the potential to cause large-scale changes in river conditions.

By reviewing and analyzing worldwide experience and by conducting laboratory experiments, researchers were able to compile a data base on aquatic ecology impacts and establish criteria for altering water quality. From these data was developed a set of models of fish population dynamics, entrainment and impingement at plant intakes and discharges, and transport of water and entrained fish and larvae. The focus of this research was on the striped bass population of the Hudson River, site of the Indian Point Unit 2 nuclear plant. Later, the scope of the program was expanded, both in depth (to include more detailed studies of factors governing entrainment and impingement) and breadth (to include studies of other fish populations).

**Benefits** This basic research on riverine ecology led to the development of a body of knowledge that could be applied to a variety of problems arising in the design and construction of large electric power plants. The information was used specifically to evaluate the need for cooling towers planned for several power plants on the Hudson River.

Riverine ecology research was instrumental in the negotiated resolution of the longstanding dispute over the impacts of power plants at Indian Point (nuclear) and Bowline and Roseton (oil-fired) on the ecology of the Hudson River. At the time of the settlement (December 1980), EPA had entered its fifth year of administrative deliberations over whether the plants would be required to be retrofitted with cooling towers. Previous studies had alleged that the plant's emission of warm water and its huge withdrawals

of river water for once-through cooling would kill mature fish (through collision or impingement) and would draw in and injure or destroy (entrain) juveniles, larvae, and eggs and, thus, contribute to a serious depletion of the Hudson River population of striped bass.

The use of the models developed in the OHER research indicated that the impacts on striped bass were smaller than alleged but determinable. With the boundaries of the dispute settled, the parties were able to reach a compromise solution that served both their plan and the public interest. This is, perhaps, the major significance of the Hudson River case. Following its settlement, Russell Train, former EPA Administrator and mediator for the Hudson River case, stated, "the settlement demonstrates that acceptable accommodations can be reached which effectively balance the environmental and energy needs of the Nation . . . [through] mediation and negotiation, rather than by sole reliance on the more traditional adversarial legal procedures."

#### **Ecology of the Continental Shelf**

The continental shelf, which accounts for less than 10 percent of the total ocean surface area, produces most of our seafood. This shallow perimeter of water off our coast receives nearly all of the contaminants that wash off the land and flow downstream. Because it is the more productive, the coastal area is more susceptible to damage from pollution than are deeper parts of the ocean. Research on the continental shelf was initiated to determine the environmental impact of effluents from nuclear and fossil power plants on coastal areas and also to predict the effect of energy discharges over the coastal zone.

The sea, like the lowest region of the earth's atmosphere near the surface, is self-cleansing. Thus, it has a carrying capacity for contaminants. We need to know this carrying capacity to be sure that the sea is not used beyond its capabilities.

**History** The continental shelf program evolved from work that grew out of concern about nuclear fallout from weapons testing in the Pacific. Work began in the deep ocean, following the movement of the radionuclides from Eniwetok and Bikini in the Kuroshio Current toward Alaska. It soon became apparent, however, that the primary route of radioactivity to humans from the ocean was through seafood. Fallout on land was washed into the coastal zone, raising interest in the natural processes that move contaminants in this area.

The first integrated program dedicated to coastal transport was begun by DOE in 1975, using oceanographers from Skidaway Institute, the University of Georgia, the University of Miami, and North Carolina State University. The study began with an investigation of coastal currents that move dissolved contaminants, specifically the Gulf Stream that sends tongues of water twisting into the coastal zone, causing quantities of contaminant-laden water to move offshore. The scientists then moved inshore to study the mechanism driving freshwater runoff from rivers through the "dam" of saltwater offshore, carrying contaminated coastal water out to the deep ocean. Their research has shown that the coastal zone is regularly flushed and the buildup of contaminants is reduced periodically.

In the Northeast, oceanographers from the Woods Hole Oceanographic Institution, Yale University, the University of California at Los Angeles, North Carolina State University, Columbia University, and Brookhaven National Laboratory studied, and continue to study, the movement of natural particles and the manner in which they attract contaminants. The importance of this research was highlighted by the earlier discovery, in which DOE played an important role, that many, indeed most, pollutants tend to attach themselves to particles that gradually fall to the bottom of the sea. Also, since many of the particles involved are photoplankton cells

rich in carbon, this line of research is important in understanding how carbon dioxide is being removed from the atmosphere and stored as deposits of organic carbon in the ocean at the edge of the continental shelf.

Present research continues to study the processes that move contaminants in the coastal zone. The scope of studies has been expanded to include the Pacific Ocean off California. Special interest is in those processes that transport materials across the shelf and into deeper waters of the open ocean, where their direct impact with humans and natural coastal systems is minimized.

**Benefits** This continental-shelf dynamics program benefits many users, including:

- **DOE.** DOE is responsible for cleaning up several sites containing materials associated with earlier nuclear activities through the Formerly Utilized Sites Remedial Action Program. Data developed by the continental-shelf dynamics program are a key element in deciding whether sea disposal is safe. The program has also provided models to predict the fate of spilled materials, such as the oil from the Argo-Merchant. The information developed is also used by other agencies involved in modeling oil spills. Moreover, the modeling capability provides crucial information required to support the leasing of offshore tracts for oil development.
- **State and Federal regulatory agencies and utilities.** In Washington and Oregon, the program identified sites where industrial activities might harm the razor clam fisheries. Work at the Scripps Institution of Oceanography helped establish the chlorine release standard for the California coast. Studies at the University of Washington have shown that mercury is rapidly removed in coastal waters and could, therefore, be safely released at higher levels than previously anticipated. In the past, floatables in municipal wastes drifted onto the beaches

of Long Island, closing more than 100 kilometers of beaches and causing an estimated \$20-million (1976) loss in the tourist and related industries. The coastal-shelf model predicted the path of the wastes and showed that dumping farther off-shore or storing wastes for later dumping during favorable conditions could help avoid these damages.

- **Fishing Industry.** Based on a consideration of fronts, temperature, and upwelling, the coastal-shelf dynamics work helps determine where the fish are located. The impetus for fishery development was provided by a NOAA Sea Grant, and the information was provided by the coastal-shelf dynamics program. Dockside values of fin fish which landed in Georgia rose from less than \$38,000/year from 1969 to 1975 to over \$230,000/year from 1976 to 1979. The program has similarly benefited fin fisheries in South Carolina.

In 1976 there was a major kill of shellfish along the New Jersey coast with estimated damages of \$50 million. The coastal-dynamics program investigators identified the conditions and implemented an early-warning system in case similar conditions recur. Fisheries experts estimate this knowledge would enable them to save one-half of the shellfish. It is estimated that the peculiar oceanic conditions that lead to fish kills would occur about one year in ten.

**Tracing Pathways of Nuclear Wastes in the Life Cycle** Small amounts of transuranic elements produced by nuclear energy activities may move through the environment and back to humans or other biological organisms. (Transuranic elements are those with atomic numbers greater than uranium; they are radioactive and can be toxic to humans.)

Hundreds of tons of transuranic elements, mostly plutonium, have been produced since World War II as a part of nuclear weapons production. Small losses to the

environment from processing have occurred. Such losses have been studied at the Savannah River Laboratory and the Savannah River Ecology Laboratory. Plutonium emitted from a nuclear fuel separations plant is followed through the aquatic and terrestrial environments, and its dose to humans from ingestion is assessed.

Plutonium particles from the Savannah River nuclear fuel separations plant attach to dust particles. Concentrations of these particles in the air provide potential annual doses of less than 1 percent of the natural background at the plant boundary. Wheat, corn, soybeans, root crops, and tobacco grown in plutonium-containing soil—had the most plutonium on the surfaces, not in the edible part, of the plant. The potential dose from plutonium to humans eating these crops after more than 20 years of Savannah River operation is less than from naturally occurring radioactive potassium-40 in the same soil.

Measurements in sediments, biota, and water in estuarine systems near the Savannah River indicate that plutonium concentrations in this watershed are not different from those of watersheds with no nuclear facilities, even though the Savannah River is near one of the highest concentrations of nuclear facilities in the United States.

The results of all transuranic cycling research up to 1980 have been compiled in a book entitled *Transuranic Elements in the Environment: A Summary of Environmental Research on Transuranium Radionuclides Funded by the United States Department of Energy Through Calendar Year 1979*, [ed. by Wayne C. Hanson (DOE Technical Information Center), DOE/TIC-22800, 746p, 1980]. These research results, plus later scientific papers, form a valuable data base on transuranic cycling in the environment. Perhaps equally important is the evolution of a group of scientists who can answer questions about transuranic elements that arise from civilian and military applications of nuclear technology.

**History** Before 1973 environmental research into the behavior of the transuranium elements was conducted on an ad hoc basis, usually in response to an accident, such as the loss of nuclear material in military aircraft accidents, or to "hot spots" found in the environment, such as the discovery of plutonium concentrations that exceeded fallout levels (e.g., near the Nevada Test Site). Short studies were usually undertaken to describe the distribution of plutonium and assess the health hazard at the particular site. This information provided some basis for generalized observations about environmental movement, but most of the in-depth studies were only applicable to soils of high pH.

No concerted studies had been made of transuranic element movement through aquatic food chains or the marine environment. Early studies did not address whether biological modification of the transuranium elements might increase their mobilization in the environment, with more movement to humans. To remedy these deficiencies, OHER initiated basic research activities covering all aspects of environmental transport from soil processes to ecosystem cycling.

**Benefits** The major benefits of the information from OHER's transuranic environmental cycling research are utilized by:

1. **Nuclear Standard-setting Agencies, both National and International.** The results of research on transuranic cycling represent virtually the sole source of such data which is vital to standards writing bodies such as the National Council on Radiation Protection for the United States, the National Radiation Protection Board for the United Kingdom, the International Atomic Energy Authority, and the International Commission on Radiation Protection.
2. **Defendants in Personal Injury Litigation.** The United States and its contractors have been, and are being, sued by plaintiffs who claim damage caused by

transuranic elements and other radioactive substances to which the plaintiffs were allegedly exposed. The body of scientific knowledge on transuranic elements developed by OHER-sponsored research is being used in such litigation. The damages sought in these suits can be extremely large. In one such case, the punitive damages sought were \$4 billion.

3. **Hazardous Waste Managers.** The mathematical models developed and validated for chemicals containing transuranic elements can be applied to similar materials in the environment. Specifically, the modeling of surface erosion, surface water transport, and sediment transport in the canyons near Los Alamos has helped to determine remedial actions needed to deal with other forms of contamination in Los Alamos County.
4. **Future Plutonium Facility Design and Operation.** The transuranic cycling research at the Savannah River Laboratory and the Savannah River Ecology Laboratory has verified that technology exists for containing plutonium in operating nuclear facilities. The environmental assessment methodology and data can be applied to other nuclear facilities where plutonium is of concern.

**Radioisotope Tracers** Radioisotope tracers can be used to follow chemical reactions in biological and biomedical research. Radioactive isotopes, such as carbon-14 and hydrogen-3 (tritium), can be used to "tag" organic molecules. Because the tracer's radiation is easily detected, its movement can be followed through the diverse processes and changes occurring in the biological or physical system containing the radioactive tracer.

The following are examples of the successful application of radioisotope tracer techniques in the study of ecosystems and biological systems. The use of radioisotope tracers in medical diagnosis and treatment is discussed in the section on "Nuclear Medicine."

### **Linkages in Ecological Systems**

Use of radioisotopes as chemical tracers for food web (lateral food chain linkages) and related studies was developed to help understand and project the fate of radionuclides released to the atmosphere in weapons tests and by nuclear production facilities. These techniques soon played a key role in ecosystem investigations. In radionuclide studies, the tracers enabled researchers to distinguish the specific chains in an ecological food web. With this information they could trace the pathways and identify the processes that concentrated radionuclides as they moved from the environment to humans. More broadly, the successful use of radiotracers in this research area encouraged environmental scientists to use radiotracers for identifying and quantifying linkages in ecological systems that previously were difficult, if not impossible, to trace, thereby opening a whole new range of understanding ecology.

**History** A prime concern of the AEC and public health agencies was that radioactive materials might move and localize in the environment, thereby becoming concentrated before reaching humans. Recognizing that food webs were the major unknowns in understanding and predicting the fate of radionuclides in the environment and that radiotracers offer unusual possibilities for distinguishing specific pathways (food chains) in an ecological food web, AEC initiated a broad-based research effort on radionuclides and food webs. This research led to an understanding that organisms in ecosystems form feeding relationships and that these chains are usually limited to three or four links. A radioisotope of an element may be transferred up a food chain, concentrated, or discriminated against, at various levels, as it is passed to the next level through feeding and being fed upon.

As investigations yielded quantitative data on these processes, ecologists perceived the potential

to use mathematical models in addressing the complexity and dynamics of ecosystems. By the end of the 1960s, ecosystem modeling based on radiotracer techniques was recognized as useful in addressing the Nation's environmental pollution problems.

**Benefits** The analysis of food chains with radiotracers confirms the importance of food in passing radionuclides to humans. Consequently, calculations and estimations of the radiological dose to humans must take into account the behavior of radioisotopes in food chains. These data are critical because the standards for the release of radioisotopes to the environment have become more stringent. In contrast to the early days of nuclear energy when estimates of release were based on limited laboratory data, detailed quantitative information can now be provided on the rates of accumulation and residence times of radionuclides in a variety of organisms. This ability has proven extremely important in the preparation of environmental assessments of proposed nuclear facilities and has enabled radiation protection specialists to derive dose estimates.

#### **Dynamics of Biological Systems**

Carbon-14, which emits beta particles with a half-life of 5770 years, with slight toxicity, and hydrogen-3 (tritium), another beta emitter with a half-life of 12 years, are the two most widely used radioactive tracers in biomedical research. Ninety-five percent of the biomedical research reported in leading journals involves the use of these tracers. Research in biochemistry, physiology, and pharmacology relies on the continued use of these tracers.

Carbon-14 is the most popular isotope because of its favorable combination of properties. It emits beta particles strong enough to measure—but weak enough to make shielding unnecessary—and to give good definition in radiographs. Its long half-life makes it unnecessary to correct measurements for decay; and it is available in adequate quantities, with

suitable levels of radioactivity, and at low cost. Its toxicity is relatively slight and is not a problem in most applications. Tritium has been used mainly as an auxiliary tracer for carbon rather than as a hydrogen tracer; its shorter half-life offers some advantages.

Isotopes of other elements, such as hydrogen, nitrogen, oxygen, sulphur, and phosphorus, are of secondary interest but are valuable for certain uses.

**History** On June 14, 1946, in the journal *Science*, an announcement was made by Manhattan Project Headquarters, Washington, D.C., that:

*Production of tracer and therapeutic radioisotopes has been heralded as one of the great peacetime contributions of the uranium chain reacting pile. The use of the pile will unquestionably be rich in scientific, medical and technological applications.*

On August 2, 1946, the first shipment of reactor-produced radioisotopes left ORNL. The compound containing carbon-14 was sent to the Bernard Free Skin and Cancer Hospital in St. Louis. This signaled the beginning of widely available isotopes at reasonable costs for persons trained in their use. By 1962 ORNL had made over half a million shipments of radioisotopes. On July 31, 1964, there were 1085 physicians in the United States licensed to use radioisotopes in private practice and some 1201 medical institutions licensed to handle radioisotopes.

**Benefits** The use of carbon-14 in biochemical analysis is widespread.

1. Carbon-14 glucose has replaced the classic glucose tolerance test in measuring the absorption of glucose. Molecules "labeled" with carbon-14 are structurally identical to the nonlabeled molecules and behave exactly the same.
2. Carbon-14-labeled compounds have simplified the study of metabolic diseases in man because only the amount of carbon dioxide labeled with carbon-14 ( $^{14}\text{CO}_2$ ) in expiratory

air needs to be measured. This method is easily applied using carbon-14-labeled tripalmitate or trioleate to diagnose the malabsorption of fat. Problems associated with radiochemical purity are avoided when carbon-14 compounds are used.

One of the most important advances in medical diagnosis was made with the introduction of tissue biopsies, providing information that formerly could be obtained only at a postmortem examination. Usual chemical methods cannot be used because of the small amount of tissue involved. Use of carbon-14 provides a sensitive, specific, and technically easy measurement of biological reactions in these isolated tissues, by measuring  $^{14}\text{CO}_2$  liberated when tissues are incubated on surfaces containing carbon-14.

Carbon-14 is used mainly for in vitro, or test tube, studies of cells incubated on various carbon-14-labeled surfaces. One development at the Johns Hopkins University Hospital has been for rapid detection of bacterial contamination in various biological specimens. For example, blood or tissue suspected of harboring bacteria is placed in a reaction vessel in contact with an appropriate carbon-14-labeled material. The appearance of  $^{14}\text{CO}_2$  in the gas above the reaction vessel will indicate the presence of bacteria more quickly than routine bacteriological techniques.

Other advantages of carbon-14 and tritium are the long shelf-life of radioactive-labeled compounds; availability in relatively pure forms; the ease of attaching radioactive atoms to proteins; and broad applications in the production of complex molecules with living organisms, drug metabolism, cytology, and enzyme assays.

**Plant Metabolism** A complete mapping of the metabolic pathways of carbon in the photosynthesis process from the initial fixation of carbon dioxide from the atmosphere to the production of glucose by green plants was developed by Dr. Melvin Calvin and

associates at Berkeley from 1945 to the late 1950's. In 1961 Dr. Calvin received the Nobel Prize in Chemistry for this work.

**History** Once radioisotopes from reactors became available in quantities sufficient for research in the early 1950's, AEC encouraged the use of these isotopes and sponsored a variety of research relating to problems of fundamental significance. The association with the field of photosynthesis arose because the chemistry of metallic/organic compounds had been applied to the purification of plutonium and uranium during the Manhattan Project. Chlorophyll, the key molecule in photosynthesis, is one such metallic/organic compound and had been an area of research for Dr. Calvin prior to his work on the Manhattan Project. AEC subsequently provided both funding and isotopes to him for extensive fundamental research on tracing the complex physical and chemical processes involved in, or metabolism of, photosynthesis.

Other current directions of research, based upon understanding the physics and chemistry of photosynthesis, include the development of devices to convert solar energy directly into stable chemical forms and, on a longer-term basis, to reduce carbon dioxide in the atmosphere.

**Benefits** The scientific benefits of this work were twofold. First, understanding of the photosynthetic process was greatly enhanced. This understanding of the detailed biochemistry of the process laid the groundwork for further developments leading to an understanding of metabolic controls in plants. Such an understanding was a prerequisite to any genetically engineered plant modifications and led to commercial applications of chemicals specifically designed to accelerate plant growth and inhibit photorespiration.

The second early benefit was the demonstration of powerful research techniques that have since found extensive use in studies of both plant and animal metabolism.

These techniques include the use of radioactive carbon-14 as a tracer to provide detailed autoradiographs (pictures revealing the presence of radioactive material, the film being laid directly on the object to be tested) of the physical movement of carbon atoms through tissues or samples and the use of autoradiography combined with paper chromatography (the separation of mixtures into their constituents by preferential adsorption by a solid, as a strip of filter paper) to identify the intermediate chemical products and enzymes associated with the metabolic path.

Extensive research has continued at Berkeley and throughout the world to further define photosynthesis, not only in terms of carbon dioxide fixation, but also in terms of photochemistry, electron transport, and the metabolic mechanisms that regulate plant chemistry and structure subsequent to the formation of glucose. The development of further metabolic understanding, the codevelopment by other researchers of a spectrum of genetic engineering techniques that permits the insertion of gene fragments into single plant cells, and the ability to grow many types of plants from a single cell have made it possible to modify selectively plant characteristics.

A potential future benefit of research of this type is the transfer of the light-hydrocarbon manufacturing capability of certain tropical species into plants that could be grown in the United States. Another possibility is the genetic improvement of the efficiency of the photosynthetic process itself.

**Land Reclamation** The program in reclamation of surface-mined land was begun in 1975 and has demonstrated that reclamation of such land is feasible both in the arid West and in the Midwest.

**History** Two fundamental research efforts in soil science and plant ecology aim at understanding the processes leading to long-term changes in soils and plants. This information is needed to define

whether restoration following strip mining of coal is acceptably complete. OHER research focuses on plant competition, plant response to salt and water stress, soil biochemical processes, nutrient availability, and ecological processes of long-term significance affecting plant succession on disturbed landscapes.

The following examples of research efforts show that acceptable reclamation of surface-mined land is feasible.

Demonstration field plots at the Jim Bridger Mine in western Wyoming show that areas with unstored topsoil deposited directly on graded overburden can develop a stand of naturally occurring native plants 400 percent greater than that of a similar area covered with topsoil stored for 2 years prior to reapplication. Vegetation cover on the unstored topsoil plot almost equaled that on unmined areas after 5 years. With this information, the Bridger Coal Company now reapplies fresh topsoil whenever feasible. Because of weather and other factors, however, topsoil cannot always be deposited directly on graded overburden but, instead, must be stockpiled. How long can topsoil be stored before degrading? In 1981 DOE built an experimental topsoil stockpile, planted thousands of native plant seeds of known viability, and installed tubes for sampling gas and measuring soil density. With periodic testing of the viability of the seeds in the pile, the maximum period of storage for acceptable levels of seed germination is being determined. Periodic changes in soil microbial activity are observed in soil and gas samples from the pile. Results suggest that direct reapplication will enable operators to meet the 10-year revegetation period for arid sites mandated by the Office of Surface Mining, but use of stored topsoil may not.

A second, related project is the development of "super plants" adapted to mined-land reclamation in the arid West. The hybrid native shrubs are in the genus *Atriplex* (saltbush and shadscale) and,



planted in the dry saline/clay environment found on mined land at the Navajo Mine in the Four Corners region of New Mexico and the Jim Bridger Mine in Wyoming, have survived better than any existing native plants. Current efforts include the development of optimum cultural practices and machine-harvesting methods for Atriplex seed. Commercial production of large quantities of improved hybrid seed is possible in the near future. A similar project was conducted on prime farmland (rather than on arid desert) at the Burning Star Mine in southwestern Illinois.

**Benefits** Coal companies, under the exemptions to current regulations allowed in some states, are beginning to use these innovative land reclamation methods. Proposed changes in requirements by the Office of Surface Mining will make these new methods available to all United States' coal firms.

Current estimates indicate that as much as 45 percent of the stripable coal reserves in the midwestern United States lies beneath prime farmland used for crops, areas similar to the OHER test area in southern Illinois. The method prescribed under the Federal performance standards for returning surface-mined land to row crop production is to remove and stockpile the topsoil, segregated by soil horizon, and then replace the horizons in their original order once mining is completed and the overburden is regraded. Not only is this elaborate procedure very expensive, but research shows that it is counterproductive.

The experiments performed at the Burning Star Mine in southern Illinois have so far revealed no difference in crop yield between segregated and mixed soil materials: removing, storing, and replacing the soil horizons did not increase productivity any more than dumping newly dug and mixed soils from the bucket-wheel excavator ("wheelspoil") directly onto previously mined land in a single operation. The ANL land reclamation program has calculated the

cost of the latter procedure as \$22,700/hectare in 1979, compared to \$61,800/hectare for the practices mandated by the Office of Surface Mining.

If the above benefits are extrapolated for 20 years, the present value of the benefit would be \$2.3 billion.

The amount of surface-mined coal from western fields was about 200 million tons in 1980 (assume that western coal is mined at a rate of 58,800 tons/hectare). The actual cost of land reclamation at a typical western surface coal mine, the Jim Bridger Mine in Wyoming, is about \$54,400/hectare, of which earth-moving costs constitute about 75 percent. The direct-application method would save about one-half of this latter amount or \$20,400/hectare. The potential benefits summed over 20 years would have a present value of almost \$600 million.

Cheaper land reclamation offers at least two other types of social benefits of enormous significance: (1) the environmental damages avoided, such as habitat destruction, soil erosion, siltation of waterways, and visual degradation, and (2) the improved market position of an abundant domestic resource—coal—in relation to imported oil, and the associated favorable impact on the United States balance of payments and on National Security.

## **Detection and Measurement of Environmental Effects**

**Detecting Change Over the Ages** The quantitative ratio of one radioactive isotope of an element to another isotope (radioactive or stable) of the same element can be used to date or trace the movement of the material containing those isotopes. The source of the radioactive isotopes may be geologic, continually generated naturally through cosmic-ray activity, or man-made, originating from weapons-test fallout or accidental releases. Many questions can be addressed using isotope ratios; for

example, the age of volcanic ash on the ocean bottom, the rate of glacier building, the age of the Antarctic ice, the age and source of the water at the bottom of the ocean, groundwater age and motion, the speed of land erosion, the speed of winds traversing the atmosphere, and the exchange rate from the stratosphere of the Northern hemisphere to that of the Southern, to mention a few.

Two important applications of isotope ratios are the long-range tracing of effluents and establishing a historical baseline for assessing the impact on the world ecosystem of the recent buildup of radioactive and nonradioactive effluents.

**History** Beginning in the 1950's, the AEC undertook basic research using isotope ratio analysis techniques to understand the long-term dynamics of environmental processes. For example, W. S. Broecker and his colleagues used carbon-14/carbon-12 ( $^{14}\text{C}/^{12}\text{C}$ ) ratios to estimate that the mean residence time of carbon dioxide in the atmosphere is about 7 years. Bottom water in the Atlantic turns over once in about 500 years and in the Pacific once in about 1000 years.

In 1958 Goldberg suggested the use of ionium/thorium ratios ( $^{230}\text{Th}/^{232}\text{Th}$ ) to measure the accumulation of deep-sea sediments. A year later, he discovered silicon-32 in marine sponges and, with it, determined the rate of accumulation of silicious deposits. Perhaps his most important discovery, published in 1972, was the use of lead-210 for dating glaciers, currently the most widely used technique for dating recent (i.e., the past 100 years) lake and coastal marine sediments. In 1973 he and his colleagues published on the use of  $^{228}\text{Th}/^{232}\text{Th}$  to show that many, if not most, lake and marine sediments have mixed, indicating a greater than anticipated role of bottom-living organisms in stirring up the bottom. Other OHER contractors have since found "bomb plutonium" 5 to 15 centimeters below the surface of sediments laid down over many

centuries, indicating a more dynamic environment than previously believed. In 1976 Goldberg's associates showed that radon-226 could be used to help date sediments of biological origin deposited over the past 5000 years.

Scientists (Harley and H. L. Volchok) at the DOE Environmental Measurements Laboratory established the ratio of cesium-137 and strontium-90 in fallout and used this information to determine how quickly artificial radionuclides penetrated and moved in ocean waters and what factors (other than radioactive decay) changed the ratios. Oceanographers at Oregon State University measured Co-

lumbia River outflow to the sea by its chromium-51 content. Natural radon measurements were used to study the movement of underground water and the propensity of soil to retain introduced materials to judge the safety of waste disposal; PNL measured the natural interchange of materials between the air and seawater with beryllium-7.

Oceanographers at Hawaii and Livermore used fission products to measure the growth rate of corals. Woods Hole scientists used natural radionuclides to measure the absorption, desorption, and settling, that is, the processes that remove pollutants from the water and place them in the sediments.

**Benefits** Knowledge of how quickly the air is purged of pollutants, how pollutants are swept out of the ocean and into the sediments, how fast coastal waters flush, and where the materials in rivers are deposited provides important insights into the ability of the environment to accept human wastes. Thus, some basic issues can be addressed: the carrying capacity of nature's major sinks; the rate at which the land, air, and water can accept civilization's wastes; the time until cleansing mechanisms are operating; and the time and manner in which wastes break down into component parts.



# Nuclear Medicine

**OBJECTIVE:** Develop to Its Highest Potential the Application of Nuclear Science to the Diagnosis and Treatment of Human Disease.

The phenomenon of radiation was recognized by early investigators to provide an opportunity for both improved health care and decreased health risk. It was foreseen that radiation provided a unique tool that, through application of the combined skills of scientists from the fields of physics, chemistry, biology, and medicine, could be made available in forms convenient for use by the medical profession for the diagnosis, as well as for the treatment, of human diseases. Nuclear medicine would make it possible to monitor body functions, isolate the causes and extent of diseases, and to treat these with methods never before possible.

## Techniques that Aid in Diagnosis

Research programs sponsored by OHER have improved medical science's capacity to diagnose certain human illnesses. The use of radioactive elements that preferentially concentrate in certain body organs and that can be followed with very sensitive radiation detectors acts to make the body's internal organs visible to medical diagnosticians. This combination of selective radioisotopes and special instruments has decreased medical cost and simplified or made more effective some procedures. In general, radionuclides are injected into the circulatory system, the resulting gamma emissions are viewed with radiation detectors, and the detected signals are sent to a computer to be transformed into the images used in making the diagnosis.

The development of radioisotopes and their application to diagnosis, therapy, and monitoring of human health problems were accelerated dramatically by the formation of the AEC in 1947 and the establishment of a formal program to coordinate and expand efforts in this field. Nuclear reactors made it possible to generate enormous quantities of suitable radionuclides that could be incorporated into radiopharmaceuticals at moderate cost. In August 1946 the first reactor-produced isotopes

for civilian uses (carbon-14 for cancer research) were shipped from ORNL. At the same time, large quantities of radioiodine were shipped to experimenters and clinicians; and in late 1946 S. M. Seidlin, L. D. Marinelli, and E. O. Shory (*J. American Medical Association*, 1946), announced the first effective treatment of thyroid cancer using iodine-130 and iodine-131.

Three examples of radionuclides widely used in radiopharmaceuticals are thallium-201, technetium-99m, and gallium-67, whose use has resulted in improved and less costly diagnosis with lower risk to the patient. Other medically important radionuclides include iodine-123, ytterbium-169, xenon-127, and xenon-133.

**Thallium-201 for Diagnosis of Heart Disease** Thallium-201 ion is a radiopharmaceutical used primarily for detecting cellular damage and reduced blood flow to the heart (ischemia). The thallium ions that have been injected intravenously are taken up by various organs in proportion to the blood supply of the particular organ. Approximately 85 to 90 percent of the radionuclide passing through the heart or its blood vessels is extracted during each pass. Its use for heart imaging is based on the relationship between thallium uptake and blood flow to that region and the integrity of the cells themselves. Therefore, reduced thallium ion in the heart region indicates either reduced blood flow, cell damage, or both.

Thallium scans can be performed immediately after exercise or at rest. The combination of an abnormal exercise image in the presence of a normal resting image indicates reduced blood flow to the heart. An abnormal exercise image that does not differ from the image at rest indicates previous cell damage and scarring. An abnormal exercise image that is more abnormal than one noted at rest indicates both previous cell damage and reduced blood flow.

**History** Heart imaging with radioactive particles was performed in

dogs in 1966, and the feasibility of direct injection of radionuclide labeled particles into human hearts was demonstrated in 1970 using radioiodine. With the direct injection technique, virtually all radioactivity was localized in the heart and relative regional blood flow could be determined precisely. However, the inherent invasiveness and risks involved limited the application of direct injection to patients requiring cardiac catheterization.

Exercise-induced regional blood flow among patients with coronary artery disease using intravenously injected potassium-43 and rubidium-81 was demonstrated in the early 1970s. Thallium-199 and mixed thallium isotopes were used as imaging agents for heart muscle in the late 1960s under OHER support at the Franklin McLean Memorial Research Institute. Scientists at BNL developed the radiopharmaceutical production techniques for thallium-201 and demonstrated its use for heart imaging in the mid-1970s. This radionuclide is generated as the by-product of a process that starts with the bombardment by a particle accelerator of stable thallium-203 metal foils with protons.

The United States pharmaceutical industry invested between \$20 and \$25 million in developing the capacity to produce thallium-201. In 1981 about 370,000 thallium-201 scans were performed domestically. Thallium sales by the New England Nuclear Corporation alone increased from \$14 million in 1979 to approximately \$20 million in 1981. Worldwide thallium sales reached \$28 million in 1980, up from \$17 million in 1979.

**Benefits** The thallium-201 exercise testing has filled an important gap in the diagnosis of heart disease between electrocardiograph (EKG) exercise tests and the more invasive, risky, and expensive angiography using cardiac catheterization. This is especially true for females because false positive findings from exercise EKGs are much more frequent. Moreover, the inherent invasiveness, risk, complexity, and cost of angiography

using cardiac catheterization weigh against its use to provide the necessary diagnostic information in a disease that affects over 500,000 Americans each year. The thallium examination not only extends benefits to those patients who would not be able to withstand cardiac catheterization, but it also results in better selection of those patients who require cardiac catheterization.

The introduction of a new technology into an already well-developed process produces an altered set of benefits and costs. For example, at the Johns Hopkins University Hospital between 1975 and 1977, 57 percent of the women who had cardiac catheterization to investigate chest pain showed no evidence of suspected coronary heart disease. In these cases, coronary angiography and simultaneous catheterization were required to be certain that the women did not have coronary heart disease. Today, nuclear cardiology procedures, chiefly thallium-201 exercise testing, have decreased this to less than 20 percent. Data from Johns Hopkins also indicate the increasing linkage of cardiac catheterization to cardiac surgery, with nuclear examinations solving nonsurgical diagnostic problems. The total National benefit has been estimated at over \$70 million/year.

**Technetium-99m for Diagnostic Scanning** Technetium-99m is a radionuclide with a 6-hour half-life, favorable gamma-ray emissions, and no beta radiation. Depending on the chemical form, it concentrates in the liver and kidneys in a few minutes or in the skeleton in 2 to 3 hours after intravenous administration, thus allowing imaging with minimal patient radiation dose. Use of technetium-99m scans to examine prostate cancer patients identifies those—about 25 percent of the total—for whom expensive surgery or radiation therapy could be replaced by less expensive hormone therapies such as bilateral orchiectomy or exogenous estrogens.

Technetium-99m is considered to have the best overall properties of

currently available radionuclides for imaging with a scintillation camera (considering half-life of the radionuclide, patient radiation dose, gamma-ray energy, availability, and cost). Accordingly, it is used in over 80 percent of nuclear medicine examinations of the various body organs.

For routine diagnostic studies in adult patients, technetium-99m is administered intravenously in doses of 10 to 20 millicuries. Studies of the liver and kidney begin immediately. For the skeleton, imaging is usually performed 3 to 5 hours later.

It has been estimated that one in four patients hospitalized (out of 37 million admissions/year) in the United States received a technetium-99m-labeled compound as part of the diagnostic process. At least 6 million studies are performed annually. Industry is currently producing technetium-99m, with sales totaling \$26 million/year.

**History** Artificially produced technetium is usually obtained from activated molybdenum-98. Technetium was discovered by Emilio Segre and Glenn Seaborg in 1938 at Berkeley, California, in the laboratory of Ernest Lawrence. Molybdenum-99 and its daughter nuclide, technetium-99m, were obtained as a result of the fission process.

For many years the medical possibilities of the use of technetium-99m were overlooked because of its relatively short half-life (6 hours). However, L. G. Stang, Jr. and Richards (working at BNL) invented the radionuclide generator, in which the user could chemically separate the technetium-99 radionuclide from its longer lived radioactive parent, molybdenum-99. This made possible the availability of the short-lived radionuclide at those sites where a reactor was not available.

Stang and Richards advertised both molybdenum-99 and technetium-99m for sale on the cover of the Brookhaven catalog of 1960. In 1961 Beck published a theoretical study demonstrating

that the optimum gamma-ray energy for detecting brain tumors is below 200 kiloelectron volts, thus calling attention to materials such as technetium-99m. In 1963 Harper introduced a series of important compounds labeled with this nuclide. These compounds are used in medicine to diagnose disease, aid in planning treatment, monitor the response to treatment, and elucidate the cause of the disease. Technetium-99m-labeled compounds amenable to bone scanning were introduced in the early 1970s; labeled methylene disphosphonate and related compounds are now the primary agents used in bone scanning applications.

**Benefits** Technetium-99m currently has a broad range of diagnostic applications, as shown in Table 3. One important application of technetium-99m is its use in bone scanning to detect the presence of metastases associated with cancer of the prostate. Technetium-99m replaces isotopes of strontium that have high radiation levels, long half-lives, and poor physical properties, as well as isotopes of fluorine-18, which has high energy gamma radiation and must be produced in a cyclotron.

Table 3. Number of In Vivo Nuclear Medicine Examinations Performed by Organ System, 1982

Examination	Number of Millions
Brain	0.81
Bone	1.81
Liver	1.42
Lung	1.20
Thyroid	0.68
Kidney	0.24
Heart	0.95
Other	0.30
Total	7.41

Source: Mettler, F. A., et al., *J. Nuc. Med.* 26(2), 201-05, February 1985.

Cancer of the prostate is the most common cancer in men over the age of 50. The median age for the disease is 70. There are approximately 57,000 new cases and

25,000 deaths each year in the United States. Treatment for the disease varies with the severity and advancement of the cancer and ranges from surgical removal of the prostate (prostatectomy), or radiation therapy in less advanced or localized cases, to hormone treatment for relief from symptomatic pain in the more advanced or metastasized cases.

The use of technetium-99m bone scans enhances the diagnostic ability for early identification. Thus, costly radical prostatectomy surgery or radiation therapy can be avoided in patients with advanced cases where symptomatic relief is the appropriate treatment. Additionally, bone scans allow the physician to respond to various therapies or disease progression safely and noninvasively.

Prostatectomy has been used for decades by pioneering institutions such as the John Hopkins University Hospital as treatment for "curable" prostate cancer. Radiation therapy is an alternative treatment used by such major cancer treatment centers as Sloan Kettering Memorial Institute and is becoming more widespread.

A quantitative benefit of technetium-99m scanning was derived by computing (1) the net prostatectomy costs and (2) the net radiation therapy costs avoided. Averaging the net costs of the two treatments, assuming that one-half of the patients would have had prostatectomies and one-half would have had radiation therapy, yields an estimate of the cost benefit of about \$92 million/year.

**Gallium-67 for Diagnosis of Hodgkin's Disease** Intravenously administered radiopharmaceuticals containing gallium-67 emit highly penetrating gamma rays (with a half-life of 78 hours) and concentrate in tumors and abscesses. Gallium-67 was discovered at the Berkeley cyclotron in the late 1930s and was demonstrated clinically at Oak Ridge in the late 1960s. A two-dimensional image called a scintigraph is taken after 48 hours, using either a whole-

body rectilinear scanner, a large-view gamma-ray camera, or a scanning gamma-ray camera. Gallium-67 scintigraphy is of great value in diagnosing cancer of the lungs and peripheral lung tumors that are not accessible by bronchoscopy. It is a valuable tool for monitoring response to chemotherapy and radiation therapy. The use of gallium-67 for localizing abscesses is increasing and may soon exceed its use for localizing tumors. Early detection of bone inflammation (osteomyelitis) by gallium-67 scintigraphy enables physicians to begin antibiotic therapy before extensive bone destruction occurs. The early use of gallium-67 in investigating "fever of unknown origin" frequently allows the physician to embark on a more fruitful, cost-effective search.

Currently, approximately one-half of all gallium-67 studies are performed for abscess localization and one-half for tumor diagnosis. In 1979 approximately 250,000 gallium-67 scans were performed in the United States at a cost of \$5 million.

**History** The development of gallium-67 for use in detecting tumors and abscesses can be traced to the early 1950s, when H.C. Dudley at the Naval Research Laboratory (NRL) was conducting research on the toxicity of stable gallium-71. In the course of this research, it was noted that gallium-71 has an affinity for osteogenic (bone-related) activity. This led to investigation by ORNL, BNL, and NRL into applications of reactor formed gallium-72 embedded in stable gallium-71 for use in bone scanning. However, the short half-life (14 hours) and high energy of the gamma radiation (4 million electron volts) made this approach unacceptable.

In 1968 gallium-67 in gallium-71 was being evaluated as a new alternative for strontium-85 in bone scans. During this activity R. L. Hayes, C. L. Edwards, and others at the Oak Ridge Associated Universities observed that gallium-67 in its carrier-free form concentrates in tumors and

abscesses as well, permitting their detection via gamma-ray spectrography. This observation sparked the development and use of gallium-67 for detecting tumors (*J. Nuclear Medicine* 13:92-100, 1972).

**Benefits** A single application of gallium-67 scanning as part of a diagnostic package for detecting Hodgkin's disease demonstrates the range of potential economic benefits from the use of this radioisotope. In the diagnosis of Hodgkin's disease, patients are classified into four stages based on the number of lesions in the lymphatic system. In stage one, the disease usually involves only one lymph node region and is usually treated with radiotherapy. Stage two involves two or more adjacent lymph node regions above the diaphragm and is also usually treated with radiotherapy. Stage three involves lymph nodes above and below the diaphragm and is treated with radiotherapy, supplemented by chemotherapy in selected cases. Stage four, characterized by more diffuse and disseminated involvement of the lymph nodes and other organs, is usually treated only by chemotherapy, with only relief and no cure expected.

The benefit of gallium-67 scanning arises from the ability to discriminate between advanced stages three and four of this disease and can be estimated as the avoided cost, about \$10 million/year, of radiotherapy for individuals classified as stage four. Also important is the use of gallium-67 in follow-up treatment to evaluate remission or relapse, especially when confusing signs and symptoms appear. Symptomatic patients followed yearly, for example, can have recurrent disease that gallium-67 studies allow to be treated early and possibly more effectively. Conversely, many relapse symptoms are found to be falsely positive and not indicative of disease.

### **Instruments That Aid in Diagnosis**

A key to novel and increased uses

of radioisotopes in nuclear medicine has been improved instruments. Advances in imaging equipment that resulted from the post-World War II explosion in electronics and computer development had major impacts in improving detection sensitivity and the range of diagnostic studies that could be performed. The high-sensitivity Anger camera with sodium iodide (thallium) scintillators accentuated the significance of such radioisotopes as iodine-123 and technetium-99m, whose low particulate and gamma ray emissions are appropriate for camera use. Also, use of this modern imaging system allowed thallium-201 to be developed and utilized for diagnostic scanning of coronary artery disease.

The advanced imaging equipment allowed temporary concentrations of radioisotopes in various organs to be measured with good multi-dimensional spatial resolution. Thus, in addition to organ structural measurements, dynamic body functions such as circulation and organ metabolism could be measured. The Positron Emission Tomography (PET) scanner provides a good illustration of function-measuring capabilities.

When nuclear instruments were first developed by isolated groups of research scientists in different laboratories and institutions, the absence of standardization was not an important issue. However, as usefulness of these instruments increased, their use moved to other laboratories and the medical service industry. The demand grew accordingly, and the total investment became large. Therefore, plug-to-plug compatibility of instruments from various sources became both a scientific and an economic necessity. To address this problem, the Nuclear Instrument Module (NIM) system was developed under the OHER Program to provide a basis for replaceable plug-in instruments that form modules in power supply and instrument racks. The Computer Automated Measurement and Control (CAMAC)

system which was to provide compatibility at other electrical interfaces and in data formats followed later and is now an international standard.

**The Scintillation Camera** The Anger scintillation camera allows the image of a photon (gamma ray) source to be reconstructed. It is the most widely used imaging device in nuclear medicine worldwide, being used for 80 percent of the studies on patients in nuclear medicine. It was invented to replace mechanical scanning.

The Anger camera uses scintillation crystals and photomultipliers to obtain serial images of the distribution of a radioactive tracer within the body at various times after the tracer is injected intravenously. The data are analyzed and processed by a digital computer and displayed on a video screen to provide quantitative information about regional biochemistry and physiology within virtually every organ of the body.

The Anger camera consists of a lead, multihole, collimator, a 10- to 15-inch-diameter sodium iodide scintillation crystal, a two-dimensional photomultiplier tube array on the crystal face, and a positioning logic network. The lead collimator allows only those photons traveling in the preferred direction (i.e., those that can go through the holes without being absorbed by the lead) to strike the crystal and cause it to emit light. The photomultiplier tubes closest to the scintillation event (pulse of light) produce the longest signal. An energy discriminator allows only those photons associated with gamma rays of specified energy level to be detected. Thus, the camera produces a signal showing the position of every scintillation event with the appropriate photon energy. A collection of these signals over time produces an analog image of the organ being viewed in the form of a two-dimensional projection of the three-dimensional distribution of radioactivity within the patient.

**History** The scintillation camera was invented by Hal Anger in 1958 at the Donner Laboratory, an AEC-sponsored facility. A number of improved versions of the camera have been developed, building upon Anger's original invention. Paul Harper of the Franklin McLean Research Institute, developed in the 1960s the scanning camera concept that permitted the camera's field of view to be extended to make whole body scanning possible. A new version of the camera permits rotation around the long axis of a patient. Images acquired at a number of angles around the patient are used with a computer for highlighting three-dimensional characteristics of organs or structures of interest.

**Benefits** The nuclear cardiology procedures that use thallium-201 and technetium-99m are performed almost entirely with this camera. Thus, the numbers cited for patients diagnosed and the benefits associated with thallium-201 and technetium-99m apply to the Anger camera as well. About one in four patients in American hospitals has an examination with the scintillation camera as part of the process of medical diagnosis.

Anger cameras are now being interfaced with digital computers produced by specialized nuclear medicine manufacturers. By enhancing the images produced, such computers allow improved visual interpretation. More importantly, because the images are stored in the computer as a matrix of numbers, quantification is possible. Using mathematical models of physiological processes, the combination of Anger cameras and computers permits noninvasive measurements that were not previously possible.

In 1981, 6740 cameras were distributed among hospitals of all sizes in the United States.

**Scanning Instruments—PET** PET scanning is a technique used in nuclear medicine to provide virtually three dimensional images of body functions. The technique

measures the direction and intensity of gamma rays from a positron emitting radiopharmaceutical in the body.

Computer Assisted Tomography (CAT) scanning, which has been called the most important advance in medical diagnosis in a decade, uses X-rays and sophisticated computer technology to provide views of the body's interior, revealing in striking detail the anatomy and structure of various organs. PET scanning carries tomography one step further, depicting the active functioning of body organs, such as blood flow and glucose metabolism in the brain. Thus, PET represents "new" nuclear medicine.

A person undergoing a PET scan breathes or is injected with a small amount of a radiopharmaceutical labeled with a short lived radioactive isotope of some element that occurs naturally in the body (such as oxygen, nitrogen, or carbon). The radioisotope, produced in a cyclotron, emits positrons while undergoing radioactive decay. (Positrons are particles that have the same mass as an electron, but a positive charge.) The positrons are attracted to electrons associated with the normal matter in the body, and when the particles meet (and annihilate each other), two gamma rays (each with 511 kiloelectron volt of energy) are emitted in opposite directions (180 degrees from each other).

The gamma rays are detected using a ring of radiation sensitive crystals placed around the patient's head or body. When two gamma rays are detected by opposing crystals at the same time ("in coincidence"), the site of annihilation is assumed to be along the imaginary line joining the two crystals. The set of such lines detected over time from different pairs of crystals is fed to a computer, which reconstructs an image representing the internal distribution of the radioisotope. The image of body function or structure of interest is then displayed on a video terminal or recorded on film.

**History** The first imaging device to exploit the unique geometrical properties of the positron-electron annihilation reaction using scintillation detectors was constructed with OHER funding in 1953 by Gordon Brownell at Massachusetts General Hospital. The first PET scanner (PETT) was built by Michel Ter-Pogossian and colleagues at Washington University in St. Louis in 1974, with support from the National Institutes of Health (NIH). Scanners subsequently designed and built with support from NIH, DOE, and industry include:

1. PETT III, IV, V, and VI at Washington University;
2. Donner 280 crystal tomograph at the University of California at Berkeley;
3. Emission Computed Axial Tomograph (ECAT);
4. Neuro ECAT at the University of California at Los Angeles (UCLA);
5. Neuro PET at NIH; and
6. Other new tomographs at Massachusetts General Hospital, the University of Texas, and the University of Pennsylvania.

Several manufacturers, including Positron Corporation (Houston, Texas), CIT, Inc. (Knoxville, Tennessee), and Scanditronix (Sweden), now market PET scanners. The average cost of a unit is around \$1 million. Clinical applications of PET have included imaging of the cardiac blood pool and blood flow in the brain and heart by the Phelps (1976); imaging of the heart, lung, and brain by Ter Pogossian (1976) and Budinger (1979); and imaging of the cardiac blood pool and blood flow by Hoffman (1979).

**Benefits** Perhaps the most exciting use of the PET to date is to study brain metabolism quantitatively. In such studies, deoxyglucose, an analog of glucose that is taken up by metabolically active areas of the brain as glucose, is labeled with carbon-11 or fluorine-18 and then injected into a patient's blood stream. PET provides three-dimensional views of the brain that quantitatively reflect the rate



at which glucose is metabolized in different regions of the brain. Some remarkable findings have resulted from such studies:

1. Kuhl and colleagues at UCLA have scanned the brains of epilepsy patients, including some during seizures. The PET scans show that the brain cells that trigger a seizure are metabolically active during an attack. What surprised epilepsy specialists is that these same brain cells are less metabolically active between seizures than they are in normal people. The significance of this finding is as yet unknown.

The UCLA doctors also have used PET to locate precisely the trigger site of seizures in patients where it could not be determined by other means. This has led to successful surgery in some previously inoperable cases.

2. NIH researchers have confirmed a theory that rare but deadly brain cancers called *gliomas* increase their metabolism when the speed of their growth increases. Doctors may delay operating on such tumors in their early stages because the surgery itself can do serious damage to the brain. The problem is that no good way now exists to determine the growth rate of the cancers. PET could be the answer.

**Instrument Standardization** Two standard instrumentation systems, the NIM and the CAMAC systems, were developed and coordinated as a result of efforts to improve the effectiveness and efficiency of scientific instrumentation.

The NIM system provides mechanical and electrical power supply interchangeability of scientific instruments and encourages a considerable degree of electrical signal compatibility. Mechanical interchangeability means that any NIM module (e.g., an amplifier) will fit mechanically into any NIM bin (a frame for holding modules). Electrical power supply interchangeability means that any NIM module, when inserted into any

NIM bin, will be connected to the correct power supply. CAMAC includes these features plus the compatibility of digital signals and signal transfer processing, system interconnections, interfacing to computers and other processors, and associated software.

NIM and CAMAC are now the principal instrumentation systems used throughout the world in nuclear and radiation physics, nuclear chemistry, and nuclear medicine. Their use has also spread into other areas, including general laboratory and industrial research and industrial applications in process control and automated testing.

The CAMAC specifications are now industrial standards worldwide, having been promulgated by the American National Standards Institute (ANSI) and the Institute of Electrical and Electronics Engineers (IEEE), as well as by the International Electrotechnical Commission (IEC).

Approximately 80 firms supply NIM instruments and equipment. Over 50 firms manufacture CAMAC equipment. Major manufacturers of NIM and CAMAC instruments estimated United States sales for 1982 to be \$23 million for NIM and \$17 million for CAMAC. The United States market for NIM accounts for about 50 percent of the worldwide market, and the United States market for CAMAC accounts for about 60 percent of the worldwide market.

**History** Prior to the development of NIM and CAMAC, the users of solid-state nuclear instrumentation were severely limited in their ability to use the best available instrumentation. Instruments from different manufacturers often were neither electrically nor mechanically compatible. Consequently, the nuclear instrument user often had to choose to bypass the most appropriate instrument, to incur excessive costs by replacing all modules to obtain one new capability, or to design expensive ad hoc interface instruments.

In December 1963 the National Bureau of Standards, under contract to AEC's Division of Biology

and Medicine (now OHER), urged that the National Laboratories develop a module that could become standard in all of those laboratories. Representatives of the National Laboratories met on February 26, 1964, to establish the NIM Committee and assign responsibility for developing a standard module system. Prototype bins and modules were produced by ORNL, LBL, and LLNL. The specifications for the NIM system were published in July 1964.

As automated and computer-linked nuclear instrumentation systems came into use, however, new compatibility problems arose. In late 1964 the Harwell Laboratory in England took the initiative to organize the development of CAMAC. In 1967 responsibility for the system development passed to the European Standards or Nuclear Electronics (ESONE) Committee of European Laboratories, which initiated close collaboration with the United States NIM Committee (still under OHER sponsorship). The ESONE NIM collaboration continues.

**Benefits** The benefits identified with the NIM and CAMAC standards include:

1. Flexibility and interchangeability,
2. Optimization of systems,
3. Ease of restructuring,
4. Deferred obsolescence,
5. Reduction of interfaces,
6. Ready interchange between installations,
7. Reduction of inventories,
8. Increased utilization of instruments,
9. Ease of serviceability,
10. Reduction of design costs, and
11. Savings in software costs.

These advantages can be translated into producer surplus or cost savings resulting from the use of NIM and CAMAC equipment. Annual benefits for 1982 were estimated to be \$40 million. The present value of past and present cost savings associated with NIM and CAMAC between 1964 and 1982 totals \$1.9 billion. Major factors contributing to these benefits are:

1. Fifty-percent reduction in data transfer speeds;
2. Lower equipment costs (CAMAC users indicated that equipment cost for a CAMAC system can be 20 to 40 percent lower than the alternative); and
3. Reduced inventories (interviews with National Laboratory personnel indicate that for every NIM or CAMAC model in inventory, at least four of an alternative instrument would have to be in inventory).

## Treatment

Nuclear medicine has promoted new medical treatments directly and indirectly. Direct results have come through the use of radioisotopes that are specially produced and economically available. Treatment procedures have been modified by the involvement of a broadened range of scientific disciplines such as physics, radiation health physics, and electronic engineering. These disciplines brought a new dimension to medicine.

The direct use of radioisotopes includes cobalt-60 for the treatment of tumors, cesium to power implanted heart pacemakers, and the use of special radiation beams, as well as complementary instrumentation. Economic availability also greatly enhanced the use of radioiodine in thyroid treatment. Among the most recent experimental results is the treatment of tumors with radioactive monoclonal antibodies. Iodine-131 to treat hyperthyroidism and thyroid adenomas (benign or low malignancy tumors) typifies the use of radionuclides for medical treatment.

The use of radioisotopes in diagnosis allowed the tracing and understanding of body functions (especially the immune and blood systems) not previously possible. These new understandings promoted the indirect benefits of new nonnuclear treatments. For example, studies to develop specific inhibitors of protease enzymes resulted in the discovery of a compound that acts against thrombin, an enzyme that induces blood clotting. The compound has been

patented and is used as an anticoagulant. Another example is the development of L-dopa (levodopa) for the treatment of Parkinson's disease.

**Iodine-131 Therapy for Hyperthyroidism** Iodine-131 is a radioactive isotope that concentrates in the thyroid gland and, thus, can be used in the diagnosis and treatment of thyroid disorder. This isotope has an 8-day half-life and emits high-energy beta particles and gamma rays in the region of 360 kiloelectron volts and higher.

Hyperthyroidism is a hypermetabolic state, caused by excessive levels of circulating thyroid hormones, which contributes to a variety of clinical symptoms. The dose of iodine-131 that concentrates in the thyroid gland destroys abnormal, hyperactive thyroid tissue that is producing excess hormone. This treatment, therefore, allows the gland to return to normal activity without surgery, hospitalization, or adverse effects on other tissues.

**History** In late 1939, J. G. Hamilton and M. H. Soley (University of California-Berkeley) published a paper on the first use of iodine-131 in patients with benign thyroid disease. In early 1941 the first patient was administered a therapeutic dose of iodine-130 and iodine-131 at MIT, and in late 1941 iodine-131 was used therapeutically against toxic goiter disease at Berkeley. In mid-1946 iodine-131 from nuclear reactor fission products was being shipped from ORNL, and in late 1946 iodine-131 was used by Seidlin for successful treatment of metastasized thyroid cancer. Until the mid-1960's, iodine-131 was the main nuclide used for the diagnosis of many diseases. After the mid-1960's, many diagnostic uses of iodine-131 were supplanted by technetium-99m labeled compounds. Iodine-131 is still extremely important, however, in evaluating thyroid condition and thyroid cancer therapy, for studying thyroid uptakes, and for thyroid imaging.

**Benefits** Radioactive iodine-131 is used in about 12 percent of all

nuclear medicine procedures and is a good example of the use of radioactive therapy. Over the past 10 years at the Johns Hopkins University Hospital, surgery for hyperthyroidism has decreased drastically from 3000 to 4000 cases/year to a current level of 50/year. This reduction can be attributed to the use of nuclear medicine therapy with iodine-131.

In the United States, radioactive iodine is the preferred treatment for adults suffering from hyperthyroidism. Because peak occurrence of hyperthyroidism occurs between the ages of 30 to 50, approximately 85 percent of hyperthyroid patients are now treated with radioactive iodine. The alternative medical treatments for hyperthyroidism are surgical removal of the thyroid gland and drug therapy. Surgery is invasive, painful, and expensive and carries a significant risk of complications and, possibly, death. Drug treatment can be long term, can have serious side effects, and, in many cases, may still require subsequent surgery. The comparative costs (in 1982) of surgery and iodine-131 treatment reported for a medical teaching center were \$7400 and \$600, respectively. The reported overall incidence of hyperthyroidism in females and males is, respectively, 4.7/10,000 and 1.06/10,000. Thus, the total estimated savings in treatment cost because of the use of iodine 131 could be as high as \$280 million/year (based on the United States incidence of hyperthyroidism in 1980).

**L-Dopa Treatment for Parkinson's Disease** L-dopa [(*-*)-3(3,4-dihydroxyphenyl)-L-amine or levodopa] is an amino acid used in the treatment of Parkinson's disease. Oral administration of L dopa substantially slows the rate of progression of the disease, reduces symptoms, and decreases the mortality rate.

Parkinson's disease is a progressive neurological disease that produces tremors, inability to plan or initiate a movement, inability to control movements, rigidity, and disturbance of postural reflexes. The disease is characterized by a

marked deficiency of a chemical called dopamine in the brain, the cause of which is unknown in the majority of cases. Parkinson's disease mainly strikes the aged, with onset between the ages of 50 and 70 in two-thirds of the cases. However, a rare juvenile form also exists. The disease affects close to one million persons, and there are 50,000 new cases each year.

Following its clinical introduction, L-dopa quickly became the preferred treatment and remains so today in a number of derivative forms. Although it does not cure the disease, it retards progress toward complete debilitation so that patients remain functional for several additional years. Symptoms present at the initiation of L-dopa treatment are generally reduced dramatically but reappear gradually, along with other symptoms that may be associated with the therapy.

In a broader context, L-dopa represents a dramatic advance in the treatment of diseases of the brain. It has provided a rational approach to medical treatment based on brain biochemistry and has stimulated interest in research on neutral diseases based on similar biochemical principles.

**History** In the early 1950's, there was widespread interest in the biochemistry of trace metals, and the use of radiotracers was developing. Dr. George C. Cotzias of BNL was searching for a research area employing radioisotopes of trace metals to study the chemical effects of the metals in humans over long periods. Links between manganese poisoning and Parkinson's disease had been discussed in the literature. Dr. Cotzias investigated manganese-56 because it was easy to make and had an appropriate half-life.

Although it turned out that there was not a good connection between Parkinson's disease and manganese poisoning, several important new areas of research evolved from these studies. One stemmed from Dr. Cotzias's understanding, gained in his research, of how the chemical

Table 4. Life Expectancy for Pre-L-dopa and Post-L-dopa Treatment

Age at Onset of Disease (Years)	Normal Life Expectancy (Years)	Life Expectancy (Years)		
		Pre-L-dopa <sup>a</sup>	Post-L-dopa <sup>b</sup>	Post-L-dopa <sup>c</sup>
50	23	13	19	20
60	15	8	11	12

<sup>a</sup>Excess mortality rates calculated from Hoen and Yahr, "Neurology 17, 427-42 (1967).

<sup>b</sup>Excess mortality rates calculated by Macdowell, Papavasiliou and Sweet, 1979.

<sup>c</sup>Excess mortality rates calculated by Diamond and Markham, 1979

balance in the body gradually changed when a new substance was introduced.

The deficiency of the amino acid dopamine in the brains of persons suffering from Parkinson's disease had recently been discovered. Although it was not possible to introduce dopamine directly into the brain, it had been postulated that intravenous introduction of its metabolic precursor, levodopamine, might correct the brain dopamine level. Short-term clinical trials were unsuccessful; however, they were inconclusive and produced adverse reactions.

Dr. Cotzias recognized the need for very gradual L-dopa administration over long periods. The research hospital at BNL provided the capability for the necessary clinical trials, which proved successful. The first report of long-term L-dopa treatment was published by Dr. Cotzias in *The New England Journal of Medicine* in 1968, and a follow-up report on the results of a 2-year clinical study was published in the same journal in 1969. A February 1969 editorial described his work as "the most important contribution to medical therapy of a neurological disease in the past 50 years." Dr. Cotzias received the Albert and Mary Lasker Award for Experimental Medicine in 1969.

**Benefits** The two major benefits associated with the use of L-dopa in the treatment of Parkinson's disease are extension of life expectancy and delay of disability.

- 1. Extension of life expectancy.** Two studies provide a basis for measuring the effect of L-dopa treatment for increasing the life expectancy of a patient. The first study followed a group of 100 patients on L-dopa therapy for 10 years beginning in 1968. During that period, 56 died, leading to a calculated excess mortality ratio of 1.54 for untreated patients. The second study surveyed a random sample of 327 patients who were being treated with an L-dopa derivative over a 5-year period and found an excess mortality ratio of 1.42 for untreated patients. These figures can be translated into an individual life expectancy extension for treated patients with an assumed age of disease onset (see Table 4).
- 2. Delay of disability.** L-dopa therapy has also been found to produce moderate to marked improvement in 50 to 75 percent of Parkinson's disease patient's ability to function. Two studies demonstrate the initial improvement and subsequent decay of independent performances of patients treated with L-dopa. A disability index related to symptoms and ability to perform normal functions was calculated at various times during the 10-year period. For the 41 patients who remained in the study throughout the period, the average disability index improved initially, but at the end of 10 years, the index was the

same as that prior to treatment. However, although the indices had the same value and the impact on independence was similar, the specific disabilities at the end of 10 years were not primarily motor- and tremor-related as in the initial situation, but tended more toward instability and dementia.

In a private communication, Dr. Thomas Presiozi of the Johns Hopkins University Hospital Neurology Department confirmed that about 80 percent of the deaths of Parkinson's disease patients are actually due to causes unrelated to the disease or its effects.



# The Future

This account of selected accomplishments over the 40-year program of energy-related health and environmental research only partially illustrates its role in fulfilling an important National need. Use of this style of presentation makes it difficult to convey the program's most important characteristics: an evolutionary, integrated, and multidisciplinary research commitment; a synergism between fundamental science and applied problem solving; and an inevitable share of scientific setbacks, as well as achievements. Thus, in reality the accomplishments represent a continuum of scientific development from the basic unraveling of bio-environmental processes and the coupling of seemingly disparate facts to their application to specific problems.

These program characteristics, in turn, lend a distinct characteristic to the research itself; it draws continually upon an established base of knowledge, the rewards becoming increasingly apparent far downstream from the initial thought and investment. Thus, to a large extent, the program's future accomplishments are already embedded in its studies of the past and the present.

As a part of the evolving National energy mission, a responsive research program has developed the expertise and facilities required for its newer roles. The evolution continues, centered around a long term commitment to fundamental and basic research and aimed at addressing problems and issues of a high-risk nature with an anticipatory rather than a regulatory approach. Of particular

importance to the future is the fact that the program's multidisciplinary talent and capabilities in unique, dedicated facilities constitute a valuable National resource.

The research program is, therefore, as well equipped to meet future challenges as it was to meet past challenges. As our energy mission continues to evolve, with changing patterns of energy demand and the accompanying development of responsive new sources, it is reasonable to expect research contributions to assure safety, acceptability, and compatibility with the National goal.

The promise for the future, therefore, lies within the Program's traditionally interactive and interdisciplinary approach to complex problems. New biophysical and chemical tools and techniques in biomedical and environmental research now make it possible to attempt unprecedented studies on cells, molecules, and processes relevant to the triad. These technical advances, applied to basic studies, will continue to contribute answers to energy related questions, as well as to increase knowledge about causes and effects in biological systems. As in the search for radiation repair mechanisms that led to discoveries of DNA behavior and important theories of the nature of human disease and its treatment, the Program's research will continue to lead in making fundamental and practical contributions in reducing uncertainties about the health and environmental aspects of emerging energy technologies.



# Appendix The Health and Environmental Research Program

The Office of Health and Environmental Research (OHER) manages the Department's Biological and Environmental Research (BER) Program. The mission of OHER is to develop and sustain a high quality basic and applied research program at the frontiers of biomedical and environmental science consistent with the mission of the Department of Energy (DOE) and the objectives of the Office of Energy Research. More specifically, the OHER program objectives are based on the following considerations:

1. OHER is the principal organizational unit within DOE for conducting research on environmental and human health effects of energy strategies. The objective of these research programs is to develop principles and broadly generalizable knowledge that will be needed to address the wide range of questions that must inevitably be faced by future generations as well as by our own. OHER, therefore, is committed to using the most advanced scientific methods and technologies to explore the fundamental issues bearing on assuring safe energy operations, for example, the molecular and subcellular mechanisms which underlie human cellular, genetic, and environmental pathology and toxicology.
2. The Office recognizes that the unique facilities and computational capabilities, as well as interdisciplinary breadth and depth of skilled scientists at the National Laboratories, offer the Nation an important opportunity for addressing a wide range of important research and development problems. Programs in the area of nuclear medicine have contributed substantially to the health and economic well being of the Nation. OHER is committed to further development of these and other areas, such as biotechnology and related capital intensive long term projects in structural biology, which fully utilize the human and technological resources of the National Laboratories.

3. OHER views the National Laboratory system, research universities, and the private sector, as members of the same team working toward the solution of some of the Nation's most important problems. The Office is, therefore, dedicated to encouraging synergism between these three research sectors by various means, including stimulating access to advanced multiuser research facilities at the National Laboratories; the support of student fellowship and faculty sabbatical programs for collaborative research at National Laboratories; and the transfer of tools and technologies developed at the National Laboratories to the private sector and universities.

To attain these goals, a number of interdependent research objectives are addressed. The major objectives of the program are to:

1. Develop new concepts, procedures, and instrumentation for detecting and measuring energy related physical and chemical agents released into the occupational and general environment;
2. Characterize the long term atmospheric transport and chemical transformation processes of radionuclides and energy related chemical effluents to improve estimates of dispersion and potential human exposure;
3. Elucidate the mechanisms that control natural ecosystems and the processes that influence cycling of nutrients and energy related materials through terrestrial and aquatic ecosystems and to measure ecological effects resulting from energy related stresses to better predict environmental impacts and resiliency;
4. Quantify the late biological effects of exposure to ionizing radiation through long term human and experimental animal research;
5. Resolve the uncertainties associated with carcinogenic,



mutagenic, and toxic effects of energy related chemicals and complex mixtures of chemicals;

6. Define mechanisms involved in the induction of biological damage following exposure to low levels of energy-related pollutants by supporting research on biomolecular structure, gene function and control, genetic damage and repair, and cell transformation; and
7. Develop new approaches, instruments, and methodology for the improved diagnosis and therapy of human diseases, and in the study of human physiological processes, including the brain and heart.

The research is carried out in the following major program activities.

**Health Effects Research** This program is primarily concerned with evaluating the delayed types of health effects—tumors, heritable defects, developmental effects, and damage to body organs—that are caused by chronic low-level exposure to energy-related physical and chemical agents. The research utilizes molecular, cellular, and animal test systems to obtain quantitative data on dose response relationships and to develop an understanding of differences in species sensitivity. Because credible extrapolation of such data to man requires a knowledge of the mechanism underlying the induction of adverse effects in different species and because the production of delayed effects is not clearly understood, extensive use is made of generic and basic research to provide experimental systems, techniques, and insights having the broadest application to health-risk prediction. Included is the development of improved biological test systems and improved techniques for the extrapolation of experimental data to man.

Health effects research cuts across virtually all of the energy technologies. Areas of ongoing research include those that address health effects associated with the broad spectrum of ioniz-

ing radiation and a variety of energy-related chemicals, including indoor air pollutants, PAHs, and related compounds associated with synthetic fuels production. Extensive research is conducted to elucidate the mechanisms which cause cancers and mutations, metabolism of energy-related chemicals, and mechanisms of DNA repair. Categories of research include:

1. Carcinogenesis (the production of cancer)—Both established and developing energy technologies produce or involve physical and/or chemical agents that can cause human cancer. Carcinogenesis research emphasizes evaluation of the tumor-causing potential of such agents, detection and characterization of carcinogens, elucidation of pathways and ways to detect formation and growth indicators of tumor, investigations to correlate exposure conditions (carcinogen dose) with tumor incidence in animal populations, and elucidation of mechanisms of carcinogenesis.

Because the production of cancer is a complex process that may include discrete initiation and promotion steps, research into cancer induction often involves the study of complex interactions among different causative agents. Emphasis is also being given to researching free radicals and other oxidizing species that play a role in both chemical and radiation carcinogenesis.

2. Mutagenesis (the production of mutations)—Alteration of genetic material by physical and chemical agents may produce heritable defects as a result of mutations in reproductive, or germ, cells. Mutations in non-reproductive, or somatic, cells may result in cell modifications, leading to cancer or other health effects. The mutagenesis research program emphasizes investigations of the mutagenic potential of energy-related physical and chemical agents; metabolism of chemical agents in target cells; correlation of

mutation frequency with level of exposure to a mutagen; evaluation of health consequences that mutations may produce at the population level; measurement of chemical damage to DNA formation; and elucidation of mechanisms of mutagenesis, including the relationship of mutagenesis to tumor induction. Effects on germ cells (chromosomal modifications) are also studied in detail.

3. Systems damage—Many hazardous environmental agents manifest their toxic potential by impairing one of the body's functional systems. Such effects—particularly delayed impairment of the respiratory, immune, nervous, reproductive, and blood forming systems or the developing embryo/fetal system—may lead to chronic disease with attendant health costs. The major efforts in this research area include the identification of early indicators of biological damage, interspecies comparison of major functional systems and their sensitivity to environmental agents, the development of improved biological test systems, and the conduct of dose response studies that support risk estimates for man.
4. Basic research—This is a substantial research effort aimed at providing the mechanistic and conceptual foundation that is needed to understand how physical and chemical agents interfere with life processes. Emphasis is on molecular and cellular studies to elucidate the normal structure and function of key biological systems or processes. Included is research in biophysics (structure of macromolecules and organelles), genetics (including DNA damage and repair), and cell biology (cell growth, cell differentiation, and cell regulation).

**Human Health and Assessment** The Human Health and Assessment program supports research to provide information on the response of individuals and human populations to toxicants and the feasibility

of using nuclear technologies in biomedical applications.

1. Human health research—This program ascertains by epidemiologic studies the potential spectrum of human health problems associated with occupational and environmental exposures to radiation and chemicals in DOE operations and emerging energy technologies. Investigators also detect and measure genetic and significant subclinical changes in exposed humans that can serve as early indicators of latent disease induction or to identify particularly sensitive individuals.
2. Medical applications of nuclear technology—This program exploits the Department's interdisciplinary cadre of investigators and technological resources in physical, chemical, and computational sciences to develop and evaluate new approaches, instruments, and methodology for the improved diagnosis and therapy of human diseases and in the study of human physiological processes. Current emphasis is on the development, production, and evaluation of new radionuclides, labeled pharmaceuticals, radiation beams, imaging devices, and enriched stable isotopes.

**Physical and Technological Research** This is the physical sciences component of the health and environmental research program that addresses a broad range of fundamental and applied activities. Many of the projects interact with the biological and ecological components of the program. Other projects involve the development of experimental techniques or advanced measurement instrumentation. The major areas addressed are the physical and chemical characterization of products and effluents of new energy technologies, the transport and transformation of pollutants in the atmosphere, measurement science, health and safety, and the fundamental mechanisms of pollutant interaction with environmental and biological systems. Categories of research activity include:

1. Analytical Characterization—The distribution, concentration, and the physical, chemical, and radiological properties of emissions and effluents associated with energy-technology processes are determined. Field sampling and measurement and laboratory studies provide detailed information on the chemical and physical properties of collected materials.
2. Atmospheric Transport and Transformation—This category includes research to develop an improved understanding of meteorological, chemical, and physical processes that influence the transport, transformation, and fate of gaseous and particulate species emitted into the atmosphere. Improved atmospheric dispersion models are developed and validated through field experimentation.
3. Measurement Science—New concepts and improved measurement systems required to address environmental, health, and safety concerns related to energy production are investigated. Research covers a broad scope of activities ranging from the basic science of measurements to the construction and evaluation of prototype instrumentation systems.
4. Radiological Physics and Chemistry—This is a fundamental research program of radiological physics and chemistry directed toward understanding the entire chain of events from the initial radiation interaction process to the eventual biological effect. Both theoretical and experimental research investigate the mechanisms of radiation energy deposition and transfer in simple systems and extends this understanding to more complex and biologically relevant systems.

**Ecological Research** The ecological research program provides the scientific information base needed for appropriate siting, operation, and disposal of materials from energy activities. To obtain this information base, comprehensive basic research in terrestrial

and aquatic systems is conducted in different climatic regions of the United States and in off-shore regions along the eastern and western United States on mechanisms that influence and control total ecosystems. The research is carried out by integrating all aspects of the physical and biological sciences. This multidisciplinary program includes experts in soil science, plant science, animal biology, chemistry, geology, and freshwater and marine sciences.

Research describes how energy by-products move and are acted upon by plants and animals in terrestrial and marine systems and identifies the major routes and rates of transfer of these by-products back to humans. Natural and energy-related stresses are studied from the subcellular level to the community level of ecosystems to determine the rate and mechanisms by which populations and ecosystems disturbed by energy activities adapt or react to these stresses. Categories of research opportunity include:

1. Cycling of natural and energy materials that include mobilization and movement of trace elements and compounds through water bodies, soils, sediments, plants, and animals. Research into the cycling of energy introduced substances is coupled to research into the cycling of normally required nutrients to permit the most appropriate cost effective measures to be developed for redistribution and control of energy materials in the environment.
2. Biologic responses derived from community structure, population dynamics, and physiological ecology research. Knowledge of accommodation by plants and animals to natural stresses is used to allow energy-related activities to expand while taking into consideration limits of ecosystem stress. Processes of natural succession are studied to determine if disturbed land is best left to natural revegetation or whether revegetation can be accelerated or improved by

scientific means. Research is carried out on metabolic processes that accumulate exposure levels allowing ecosystems to exist without serious adverse impacts.

**Facilities** Facilities playing important roles for addressing radiation and energy-related chemical issues include the Radiological Research Accelerator Facility at Columbia University, the Health Physics Research Reactor at ORNL, and the Janus Reactor at ANL. These facilities provide a spectrum of relatively pure neutron beams over a wide range of doses and dose rates for studies in radiation biology, radiation dosimetry, and for training activities. The Environmental Measurements Laboratory (EML) develops improved techniques for radiolog-

ical and chemical measurements to characterize the chemical and radiological content of atmospheric, soil, and water samples and provides DOE with a rapid response capability for obtaining needed field data. For example, EML recently completed a re-assessment of population dose in Utah from weapons testing based upon their measurement of soil and water levels of cesium-137.

The National Environmental Research Parks (representing protected sites around five National Laboratories with a diversity of flora, fauna, and climate) have for two decades served as outdoor laboratories for quantifying ecosystem responses to a wide range of energy activities, including coal combustion, overhead transmission lines, reactor operations, and

burial of radioactive wastes.

A three-stage mass spectrometer, installed at the Savannah River Laboratory, provides accurate and precise analysis of isotope ratios for very low levels of environmental radionuclides, defining their source and time sequence of deposition in terrestrial and aquatic experiments under field conditions.

Advanced flow cytometers, developed at Los Alamos and LLNL, are also being used by DOE and other sponsors to identify and separate specific cell populations, and purify chromosomes for gene mapping studies to produce template material for making chromosome-specific human gene "libraries" for distribution to the scientific community.