A VITAL LEGACY

Biological and Environmental Research in the Atomic Age

September 1997

To the tens of thousands of scientists, engineers, technicians, postdoctoral research associates, and graduate students who produced the rich record of achievement from which this account was drawn. And to the nearly one thousand principal scientists addressing current Biological and Environmental Research program priorities at more than 200 universities, government laboratories, and private facilities.

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FOREWORD

In 1946 the Congress passed the Atomic Energy Act and with it created the Atomic Energy Commission. For the ensuing half-century, the AEC and its successors have pursued biological and environmental research (BER) with an unwavering mandate to exploit the use of fissionable and radioactive material for medical purposes and, at the same time, to ensure the health of the public and the environment during energy technology development and use. The following pages are testimony to the success of this undeviating vision. But more than a clear and consistent charge underlies this success, and it is important, I think, not to lose sight of these other ingredients of achievement—especially as we seek to extend our record of accomplishment into the next millennium.

■ *In pursuing its charge, the BER program has consistently emphasized basic research. It has addressed long-term generic issues, rather than the near-term questions that are the focus of the regulatory community and industry. This consistency of focus has been essential to the program's half-century of success.*

■ *Equally important has been the scientific diversity of the energy agencies' biomedical and environment program. Cooperation among physicists and physicians, ecologists and engineers has been one of the program's hallmarks. In the future, cross-fertilization will become even more important, as science advances at the interfaces between such disciplines as biology and information science.*

■ *From the early days of the AEC, cooperation has also linked researchers from the national laboratories, the academic community, and the private sector. Coordinating these diverse performers has been crucial to the unique teaming that has made many of the BER successes possible. And this teaming will continue to be a paramount objective of BER management, as we pursue both our stewardship of the national laboratories and our commitment to academic research and education.*

■ *The success of the BER program has often been shared with other federal agencies. The future will demand even stronger and more substantive intraagency, interagency, and international collaborations. The BER program is thus committed to the continuation and enhancement of the interagency collaborations that have been integral to the success of such programs as the Human Genome Project and the U.S. Global Change Research Program. The BER program is also committed to strengthening collaborations with other offices within the Office of Energy Research, such as Basic Energy Sciences and Computational and Technology Research.*

The year 1997 marks the fiftieth anniversary of biological and environmental research within the DOE and its predecessor agencies.

To mark the occasion, and to look ahead to the future, the DOE and the National Research Council of the National Academy of Sciences cosponsored a symposium in May. Entitled "Serving Science and Society into the New Millennium: The Legacy and the Promise of DOE's Biological and Environmental Program," it both celebrated the past and looked optimistically to the future. This booklet likewise commemorates five decades of contributions to science and society—and concludes with a view to the years ahead. But the following pages merely hint at the wealth of achievements that have emerged from the BER program. An exhaustive chronicle of those achievements would, in fact, exhaust any reader. Therefore, despite the lurking risk of omitting even some of the most important accomplishments, our intent has been to offer a representative selection, telling in the process a coherent story of evolution and progress.

A*t the doorstep of the 21st century, the BER program is now poised to continue this tradition of scientific advancement. We invite you to follow our progress at* www.er.doe.gov/production/ober/.

Ari Patrinos

Associate Director of Energy Research for the Office of Biological and Environmental Research

In the Beginning

An Introduction

The earliest glimmering of radioactivity's promise long predated any sense that ours would be the Atomic Age. By the time of the Manhattan Project, physicists had almost a half-century of experience with radioactive elements and their radiation, and several such elements, most notably radium, had been used since the turn of the century in efforts to treat human disease. By the 1930s, radioactive isotopes were being produced artificially in Berkeley's cyclotrons, and the pace of medical use and biological experimentation increased dramatically. At the same time, even the earliest pioneers saw that radioactivity was not a benign blessing; protection standards, albeit far from adequate, were published as early as 1915. Nonetheless, it was World War II that firmly thrust the nuclear genie onto the public stage. At first, the spotlight was on the awesome power of the atom, then on the emerging promise of nuclear energy, but splitting the atom would also herald a vital new era for biology, medicine, and environmental research.

Even during the war years, biological research was a priority. A Medical Advisory Committee chaired by Stafford Warren developed health and safety policy for the Manhattan Project and inaugurated research programs to assure adequate protection for Project workers. Teams of physicians, biologists, chemists, and physicists worked to learn how radiation affected the body, what protective measures were most effective, and in the event of mishap, what methods of diagnosis and treatment were best.

At the war's conclusion, recognizing the opportunities of atomic energy—and acknowledging, too, an obligation for public safety—the Congress passed the Atomic Energy Act of 1946, which would transfer responsibility for atomic energy research and development from the War Department to an independent civilian agency, the Atomic Energy Commission. On January 1, 1947, the AEC thus took charge of research programs in health measures and radiation biology conducted in government facilities at the Clinton Laboratories (now Oak Ridge National Laboratory), Hanford, and Los Alamos; at the Metallurgical Laboratory at the University of Chicago (now Argonne National Laboratory); and at many university laboratories, large and small. Among the ongoing efforts were health physics research for "improving our knowledge of the potential dangers presented by fissionable materials, reactors, and fission products and for proposing methods of elucidating or circumscribing such dangers"; research aimed at extending our "fundamental knowledge of the interaction of nuclear radiation and living matter"; and radioisotope distribution programs to "provide indirect aid to

research in many fields of biological and medical research." The Commission budget for fiscal 1947 was $342 million.

Early in its first year, the AEC moved to provide a solid foundation for its biomedical research and education efforts by asking the President of the National Academy of Sciences to nominate a panel of experts as a Medical Board of Review to advise the Commission. The Board was promptly established, and by June it had issued its initial recommendations, broadly supporting biomedical research and training efforts and proposing a permanent Advisory Committee for Biology and Medicine (ACBM). In September 1947, the chairman of the AEC appointed seven distinguished physicians and biologists to the ACBM.

Immediately upon its creation, the ACBM recommended that a Division of Biology and Medicine be established to "coordinate medical, biological, and biophysical (health physics) research programs related to atomic energy" and to "direct for the Commission its health physics works and industrial hygiene activities." The recommendation was quickly adopted. Thus was forged a commitment that has endured for a half-century—a commitment to vigorous research aimed both at nurturing the fruitful use of a new technology in the life sciences and at ensuring public health and safety in the face of that technology's perils.

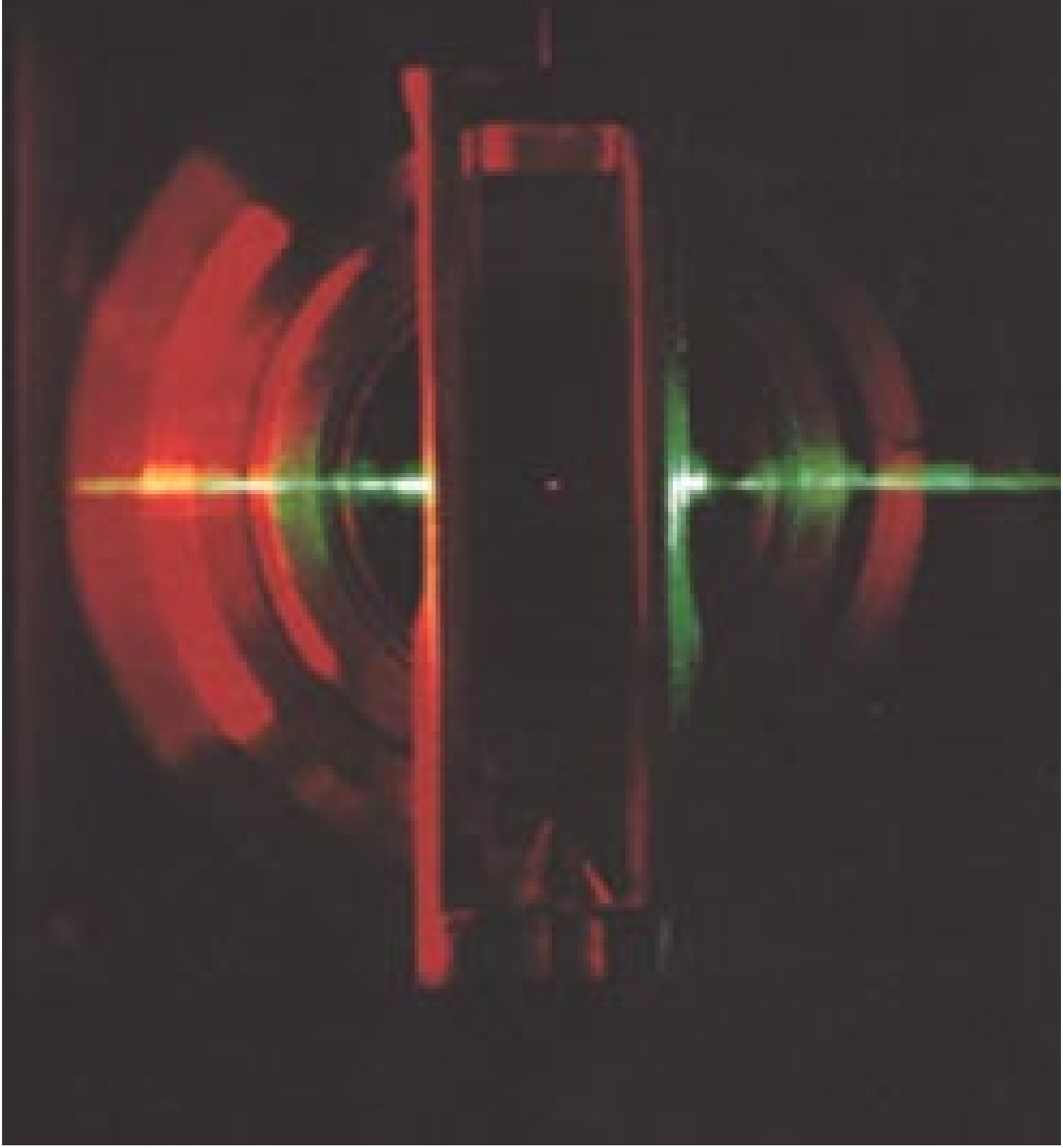
Almost thirty years later, the mandate broadened. On the heels of the 1973 oil embargo, the nation's awareness of energy issues took a new turn: An unlimited flow of oil was no longer a given. Other options must be explored. And nuclear energy was only one of several alternatives whose prospects and consequences called for thoughtful examination. Accordingly, the Energy Reorganization Act of 1974 created the Energy Research and Development Administration, which assumed, and greatly enlarged on, the AEC's research responsibilities. In the words of the Congress, ERDA was to engage in and support "environmental, physical, and safety research related to the development of energy sources and utilization technologies." The new agency's Division of Biomedical and Environmental Research thus launched significant new programs of research, widening its scope beyond the environmental and health consequences of nuclear energy to encompass conventional and synthetic fossil fuels and renewable energy sources.

Three years later, with the creation of the Department of Energy, energy concerns achieved Cabinet rank. Today, the DOE's Office of Biological and Environmental Research carries forward the mandate of its predecessors. Born in the shadow of the atomic bomb, biomedical and environmental research continues to shed light on the consequences of energy technologies—and to exploit their boundless promise. The Human Genome Project, for example, is a surprising but logical offspring of long-standing research on health issues and genetic effects, research that is the underpinning of today's radiation protection standards. Medical research that has produced life-saving radiopharmaceuticals and diagnostic technologies now pursues molecular-level insights into human physiology and disease. And studies of global climate change continue a tradition of environmental research that includes ground-breaking work in modern ecology, pioneering studies of oceanic processes, and one of the nation's first environmental impact assessments.

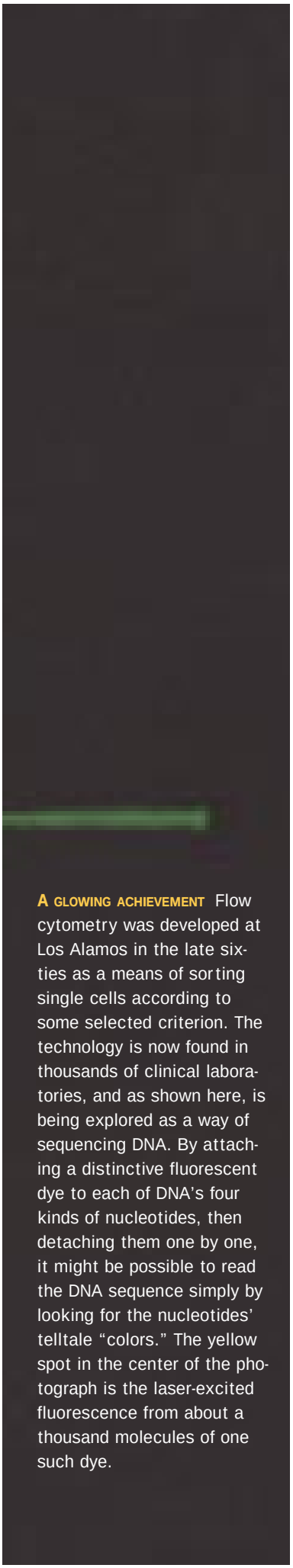
The concerns and aspirations that launched the AEC's Division of Biology and Medicine gave rise to a continuing tradition of research that is as logical—but, in its details, just as unpredictable—as the course of progress itself. The following pages chronicle only a few of the highlights.

Safety First

In the Shadow of a New Technology



For the freshly chartered AEC, perhaps the most fundamental health research issue was the risk posed by the newly unleashed power of the atom. World War II had added tragic testimony to the short-term effects of intense radiation. But a more abiding concern was the less visible, long-term consequences of much lower radiation doses. Leukemia had already claimed the life of Marie Curie, and in the twenties, working with fruit flies, Hermann Joseph Muller had shown x-rays to be powerful agents of mutation. A new era of radioactive isotopes, nuclear reactors, and atomic bombs demanded the most thoroughgoing stewardship. Today, rigorous standards born of research launched by the AEC safeguard radiation workers and the common citizen alike: Regulations guide the medical use of x-rays and radionuclides, set limits on radioactivity in consumer products, and define permissible doses for everyone touched by radiation. But the road to such regulations has been a long one; it stretches back to the early days of the century, and it is sure to take us even further in the quest to fully understand the health effects of radiation.



A GLOWING ACHIEVEMENT Flow cytometry was developed at Los Alamos in the late sixties as a means of sorting single cells according to some selected criterion. The technology is now found in thousands of clinical laboratories, and as shown here, is being explored as a way of sequencing DNA. By attaching a distinctive fluorescent dye to each of DNA's four kinds of nucleotides, then detaching them one by one, it might be possible to read the DNA sequence simply by looking for the nucleotides' telltale "colors." The yellow spot in the center of the photograph is the laser-excited fluorescence from about a thousand molecules of one such dye.

THE PROPER STUDY OF MANKIND

One of the giant steps on this road was creation of the Atomic Bomb Casualty Commission, established in 1946 to follow the long-term consequences of radiation on the survivors of the Hiroshima and Nagasaki bombs. Today, the work continues within the renamed Radiation Effects Research Foundation, jointly funded by the U.S. and Japan. This definitive effort has, for a half-century, traced the medical histories of more than 86,000 survivors and tens of thousands of their descendants. It remains the most ambitious study ever carried out on the effects of a toxic agent on human beings. From it we have learned that the major long-term effect of radiation is an increased risk of leukemia and solid cancers. Between 1950 and 1990, bomb survivors suffered 7827 cancer deaths, about 420 more than would be expected in an unexposed population. Attempts have also been made to identify genetic effects in the survivors' children, so far without success—an outcome that prompted early thinking about today's Human Genome Project (see page 15).

Other early epidemiological studies were likewise products of circumstance, in a time of routine above-ground nuclear weapons tests. South Pacific Islanders exposed to fallout from a 1954 atmospheric test and, decades later, residents returning to face residual radioactivity on Bikini and Eniwetok were carefully monitored for many years, both to provide for their own health and to enhance what we know about radiation and its effects.

Today, with atmospheric nuclear tests largely a relic of the past, concerns about radiation have different sources—but the concerns endure. Furthermore, such studies as that of the atomic bomb survivors can tell us little about the potential effects of prolonged exposure to very low doses. For more than thirty years, then, OHER and its predecessors continued long-term health studies of naval shipyard workers,

1895 German physicist Wilhelm Conrad Röntgen discovered an invisible form of radiation, which he called "x-rays." Röntgen would win the first Nobel Prize for Physics in 1901.

1896 French physicist Antoine-Henri Becquerel found that uranium salts emit an invisible penetrating radiation—the first observation of radioactivity.

1901 Becquerel observed one of the biological effects of radioactivity when he carried some radium in a vest pocket, reddening the skin beneath. In 1903 Becquerel and his French colleagues Pierre and Marie Curie (pictured) would receive the Nobel Prize for Physics. Both Marie Curie and her daughter Irène Joliot-Curie would later die of leukemia, probably caused by their long-term exposure to radioactivity in the laboratory.

ANNUAL CHECKUPS For several decades, doctors and health physicists made annual trips to the Marshall Islands to check the health of islanders accidentally exposed to radioactive fallout during a 1954 U.S. bomb test in the Pacific.

employees at weapons design and production sites, uranium miners, and soldiers present during weapons tests in Nevada. Another effort, stretching from 1947 to 1993, extended prewar studies of instrument-dial painters exposed since 1912 to radium-laced paint. Taken together, these and other epidemiological studies form the core of what we know today of radiation exposure risks—both the risks of long-term, low-level exposure and the dangers of a single high dose. They are likewise the foundation of the laws and standards that protect those who work with radiation every day, as well as the citizen on the street.

Public perception of the risks of radiation continues to cloud the future of nuclear energy in the U.S., but we know

A SUBJECT OF CONCERN

■ Using human beings as experimental subjects in radiation research is no longer countenanced by the federal government. But this has not always been the case. In years past, humans were the subjects of therapeutic studies and of inquiries into how radionuclides get processed and distributed in the body. In fact, rudimentary studies date back at least to 1926, and after the invention of the cyclotron, the pace of such experimentation quickened considerably. In the late thirties, for example, Joseph Hamilton, at the University of California's Radiation Laboratory, conducted a series of human metabolism studies with sodium-24, in hopes of developing a short-lived replacement for the long-lived radium isotopes then used to treat leukemia and other diseases. Then, between 1945 and 1947, in four hospitals around the country, eighteen subjects were injected with plutonium. The aim was to develop a diagnostic tool, based on the amount of the element excreted, that could be used to quantify industrial exposures to plutonium. Despite the studies' laudable goals—namely, to establish protective standards for industrial workers—these experiments were recently the focus of a national controversy. None of the subjects suffered any apparent harm from the plutonium injections, but neither had they been fully informed of what was being done. And many of the scientific results were kept secret for years. ■ When details of these experiments were revealed in 1993, the public was indignant at the appearance of scientific arrogance. Fortunately, times—and ethical standards—have changed. Well before this story hit the press, strong federal regulatory measures were in place to protect subjects of research. Since 1976 DOE regulations have protected human research subjects, and in 1991 the DOE was the first agency to sign the Federal Policy on Protection of Human Research Subjects. Further, following the deliberations of the White House Advisory Committee on Human Radiation Experiments, even greater federal attention is now focused on the need for subjects to be fully informed regarding experimental procedures or treatments. Research using human subjects, including clinical trials to assure the safety and efficacy of new pharmaceuticals, is an important part of modern biology and medicine, but today it is performed openly and in strict accordance with ethical and humanitarian principles. ■

now that no energy source is entirely free of untoward consequences. Since the seventies, the DOE has thus extended its epidemiological studies to gauge the health effects of the energy choices we must make. Subjects have included turn-of-the-century laborers in coal-gasification plants in Japan and England, present-day workers exposed to diesel bus exhaust, and even residents living near high-voltage power lines.

ENTER THE ANIMALS

Notwithstanding their undeniable value, retrospective epidemiological studies amount to unintended experiments—experiments that often emerge from historical naiveté, the tragedy of war or accident, or natural forces. Better to know the likely effects of toxic agents before humans suffer the consequences. To get at a deeper understanding of radiation's effects, therefore, the AEC supported animal studies in its very first years—studies that were, in fact, a logical continuation of research carried out during the Manhattan Project to protect workers confronting an utterly unexplored frontier of science.

Perhaps the most comprehensive of these investigations was the "internal emitters" program. Using beagles as their subjects, scientists at many universities and national labs sought to understand the health effects of ingested or inhaled radioactive fallout and of radioactivity associated with nuclear power generation and weapons production. For a variety of elements, in a variety of chemical forms, researchers asked, Where does the radioactivity go? How long does it persist in the body? What organs are affected? What are the health consequences? The answers became a landmark database for the establishment of national and international safety standards.

Another tack was taken by William and Liane Russell at the Clinton Laboratories (now Oak Ridge National Laboratory), where they established a mammalian genetics program in 1947. It was there in the early fifties that Liane Russell observed the exquisite vulnerability of the mammalian embryo to radiation, leading to new radiation safety guidelines for women of child-bearing age, and especially for pregnant women. In the sixties and seventies, the Oak Ridge mice were pioneers again, as mouse genetics studies were extended to the chemicals in our daily lives: the components of pharmaceuticals and pesticides, fuels, airborne pollutants, and cigarette smoke. In 1991, in a commemorative volume, the international journal *Mutation Research* lauded William Russell by saying that "no single person has contributed more to the field of mammalian mutagenesis, and thus to genetic risk assessment in man."

A FAMILY AFFAIR At the Clinton Laboratories in 1947, Liane and William Russell established a program that would make notable contributions to mammalian genetics for the next half-century. An assay they developed for quantifying heritable gene mutations in mice remains a standard today for assessing the human risks posed by radiation and toxic chemicals.

1915 Protection standards describing "safe practices" for handling radium and x-ray machines were published in Germany and Sweden.

1927 American geneticist Hermann Joseph Muller found that x-rays greatly increase mutation rates in fruit flies. His work would be rewarded in 1946 with the Nobel Prize for Physiology or Medicine.

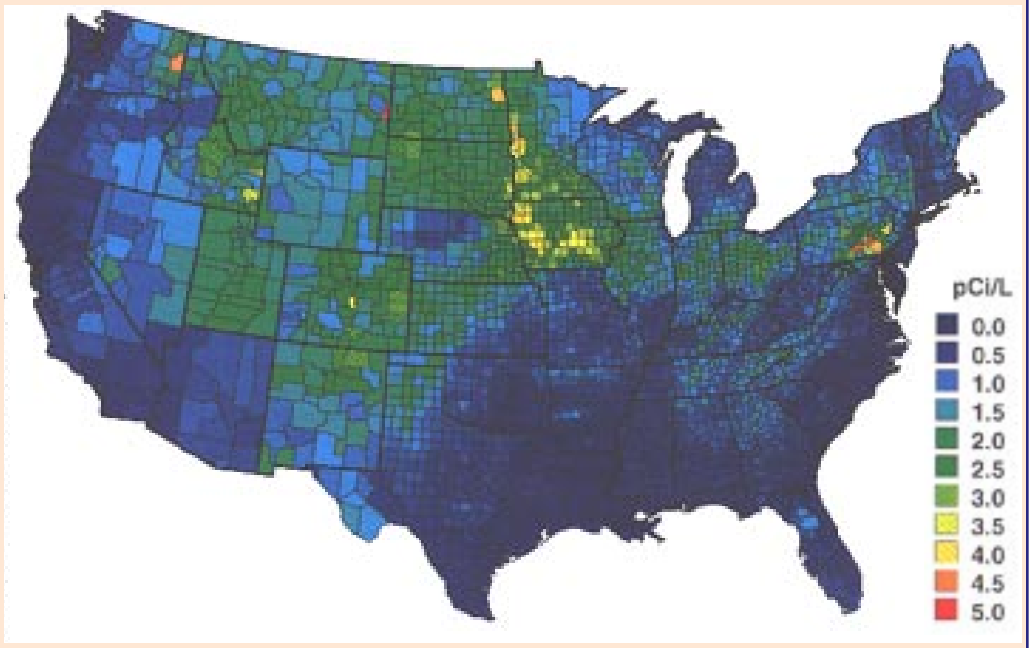
1928 An international congress adopted the first widely accepted x-ray protection standard, a monthly dose limit equal to 1/100 of the amount that burns skin.

1946 President Truman directed the National Academy of Sciences to study the long-term effects of radiation on survivors of the atomic bombs. The Atomic Bomb Casualty Commission was created to pursue this effort, supported by funds from the AEC's Division of Biology and Medicine; its work would continue after 1975 within the Radiation Effects Research Foundation.

1947 Argonne undertook a long-term study of instrument-dial painters to assess the effects of occupational exposure to radium. As a group, the painters had high rates of bone disease and anemia; below a threshold dose, however, no ill-effects were observed.

1947 Alexander Hollaender created the Biology Division at the Clinton Laboratories. In 1983 Hollaender would receive the DOE's prestigious Enrico Fermi Award, and in 1986 OHER would establish the Alexander Hollaender Distinguished Postdoctoral Fellowships. To date, some eighty-five young investigators of outstanding promise have received fellowships to conduct research in BER-supported programs.

INSIDE THREAT: RADON IN THE HOME



■ In 1984 an employee of a nuclear power plant triggered the facility's radiation detectors when he arrived at work. The cause was a level of radioactive radon gas in the worker's home much higher than allowed in a uranium mine. This incident rekindled smoldering concern about radon in homes and led to a Congressional mandate to study the extent of the risk. Epidemiological data were available for uranium miners exposed to radon, so the key challenge was to define the distribution of radon in American homes and then to relate household exposures to workplace experience. Over the next twelve years, the DOE played a central role in providing the data needed to rationally assess this household risk. The map above, for example, shows median indoor radon concentrations across the country, as estimated by a predictive model based on available monitoring data, together with information on soil types, climatology, and home construction standards. ■ In addition, animal studies at Pacific Northwest uncovered a synergy between radon and cigarette smoke in heightening the risk of lung cancer. The bottom line? We now know that under some circumstances household exposure to radon and its decay products can be a significant health risk, but we also have guidelines that suggest when consumers should take action to reduce exposures—and that point to effective actions they can take. ■

Other animal studies, many with a heritage that predated the AEC, focused on the risks of ingested strontium and transuranics, inhaled plutonium, inhaled fission products, inhaled radon, and later, diesel exhaust and other products of fossil fuel combustion and conversion. At Hanford, site of the nation's first major reactor complex, some early experiments were part exposure study and part ecological research. In both field and laboratory studies, University of Washington scientists looked at the effects of waste effluents on Columbia River biota and cooperated in similar early studies on the fisheries of the Pacific Northwest. Such efforts were "animal studies" in a broader sense and pointed to a whole suite of ecosystem studies that will be one of the subjects of this booklet's third chapter.

Later, between 1975 and 1985, chemists and biologists from Argonne, Oak Ridge, Pacific Northwest, and the Inhalation Toxicology Research Institute (now the Lovelace Respiratory Research Institute) extended their studies to other energy tech-

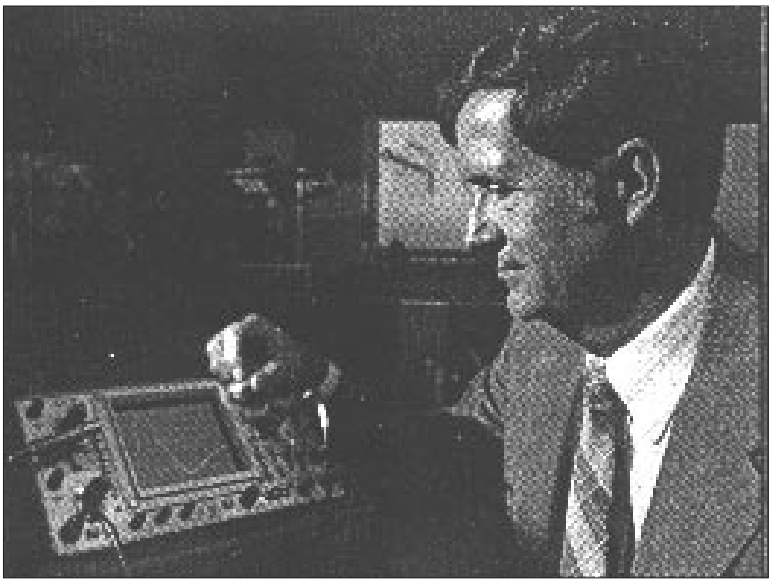
nologies. Together with industrial engineers, and using model systems such as laboratory animals, cultured cells, and bacteria, they worked to define the health risks posed by the manufacture of synfuels from oil shale and coal, and by several advanced fossil fuel combustion technologies. The resulting database remains one of the most extensive bodies of information available on the short- and long-term toxicity of the complex chemical mixtures that emerge from the production and use of fossil fuels.

The aim of all this, of course, the epidemiological studies, the controlled animal experiments, and the toxicological studies, is to understand the nature of the risks posed by our society's activities. This kind of "risk assessment," born of AEC, ERDA, and DOE research, led to guidelines for the use of diagnostic x-rays, to confidence in the safety of countless radiopharmaceuticals, and to safety standards for the presence of radionuclides in the air, in food, and in drinking water. It is also one of the underpinnings of our ability to assess the likely consequences of such incidents as the reactor accidents at Three Mile Island and Chernobyl.

Constant Vigilance

Well before the years of the AEC, standards prescribing safe practices in dealing with radiation had grown increasingly strict. But safety would become a preoccupation with the energy agencies. Among the earliest apostles of radiation safety was Herbert Parker, a British-born medical physicist who became chief health physicist and eventually director at Hanford. Among his contributions, Parker's concept of the *rem*, still a standard measure of biological dose, is perhaps the most obvious. But more than that, the vigilance of the earliest pioneers and those who followed them has been a driving force behind today's safety consciousness. In that same postwar era, increasing attention to radiation health protection led the AEC's Division of Biology and Medicine to establish graduate-level programs at the University of Rochester, the University of Washington, and Vanderbilt, all linked to field training programs at nearby national laboratories. Fifteen other universities added similar programs later. All told, these programs have produced about a thousand professionals with postgraduate degrees in health physics, industrial hygiene, and radiation biology.

Support also extended to the development of techniques to assess individual radiation exposure. Film-badge dosimetry was the early standard, followed in the sixties by thermoluminescence dosimetry, developed largely at the University of Wisconsin. This is the method now used by radiation workers worldwide. Research also took an entirely new turn in the sixties, focusing on ways to quantify the dose



One atom at a time Samuel Hurst at Oak Ridge developed resonance ionization spectroscopy, a laser-based technique that succeeded for the first time in counting individual atoms. The earliest success was the detection of a single cesium atom among 10^{19} argon atoms.

1951 Using an ion-exchange technique originally developed to separate fission products, Oak Ridge researchers devised a simple method for isolating the components of DNA and RNA, a discovery that would significantly accelerate biochemical studies of these materials around the world.

1956 At Oak Ridge Larry Astrachan and Elliot Volkin (pictured) discovered a previously unrecognized form of RNA, which they called "DNA-like RNA." Four years later, this species would become known as messenger RNA, the essential courier of genetic instructions to the sites of protein synthesis in the cell.

1956 At Brookhaven W. L. (Pete) Hughes synthesized a radiolabeled version of thymidine, whose uptake by cells signals the synthesis of DNA.

1959 At Columbia University, Harald Rossi introduced the concept of measuring energy deposition by ionizing radiation in small volumes, thus launching the field of microdosimetry. This concept would lead to significant advances in our understanding of the risks of exposure to low-level radiation.

1961 In a joint effort with the NIH, a team headed by Norman Anderson developed a high-speed zonal centrifuge at Oak Ridge. By the late sixties, commercial descendants of this machine were producing highly purified vaccines for humans and animals.

1962 Richard Setlow at Oak Ridge pinpointed the damage caused in bacteria by ultraviolet light. Two years later, he would discover the role of genetic repair mechanisms in mending such damage.

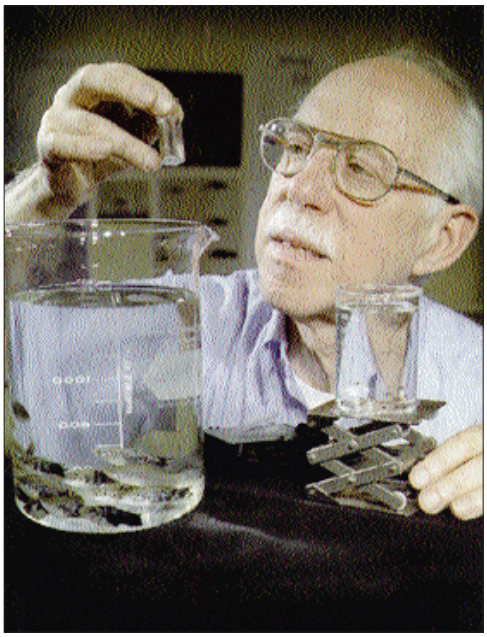
of potentially toxic agents—chemicals as well as radiation—and to reckon their effects by looking for biological change in human tissues. New cell-culture techniques and sensitive methods for assessing chromosome damage in cultured human cells led Oak Ridge researchers to the concept of biological dosimetry or *biomarkers*. In one extension of this concept, Richard Albertini at the University of Vermont quantified mutations to a specific "reporter" gene, known as HPRT, as a means for gauging human exposures to radiation and to hazardous materials. Since their introduction, biomarkers have been used successfully to estimate radiation doses to astronauts, radiotherapy patients, and radiation accident victims. They were widely used, for example, in the wake of the reactor accident at Chernobyl.

Along similar lines, engineers and physicists have directed consistent effort since the forties toward improving instrumentation for measuring radioactivity in medical, biological, and environmental samples. Early research centered around photomultiplier tubes and scintillation detectors, but a crucial breakthrough came in the sixties with the development of solid-state silicon and germanium detectors. Properly prepared, these materials produced electrical signals precisely matched to the energy of the detected x-rays—and thus pinned down the identity of the radioactive isotopes present. Now successfully commercialized by several manufacturers, many of the underlying practical discoveries arose from AEC-supported research, especially by Fred Goulding and his colleagues at Berkeley.

Then, in the seventies, with the broadening scope of ERDA, and then the DOE, concern extended to the chemical by-products of all energy production and use. Techniques have thus been developed to monitor known cancer-causing chemicals, to measure skin contamination, and to detect trace amounts of environmental contaminants. An especially notable tool is resonance ionization spectroscopy (RIS), an Oak Ridge–developed technique so sensitive that in 1977 it allowed single atoms to be detected for the first time. Spin-offs have included several RIS-based analytical techniques for studying trace materials in the environment. And in 1990, at Los Alamos, similar concepts led to another milestone, the first detection of a single molecule.

RADIATION EFFECTS: A CLOSER LOOK

A shortcoming of epidemiological studies—and most animal studies, too, for that matter—is that they offer little insight into Why. Why does radiation cause mutations? Why are low levels of radiation often harmless? Why do the consequences of more severe exposures often appear as cancers decades later? These and similar questions fall within the province of radiation biology, which looks beyond mice and fruit flies, to uncover the underlying effects of radiation on cells and their components. One of the ground-breaking discoveries came at Oak Ridge in the early sixties, when Richard Setlow pinpointed the damage caused by ultraviolet light in the genetic material of bacterial cells, and fur-



DAMAGE CONTROL In the early sixties at Oak Ridge, Richard Setlow elucidated the mechanism of DNA repair, thus opening the door to a field of inquiry that is at the center of cancer research today. Now at Brookhaven, he is shown here with fish used to study the induction of melanoma by ultraviolet light.

ther discovered that the bacteria survive the insult by repairing the damage—snipping the damaged regions from one strand of their double-stranded DNA. Then, in 1968 at the University of California, San Francisco, James Cleaver found that a genetically impaired DNA repair apparatus underlies xeroderma pigmentosum, a human disease that predisposes affected individuals to skin cancer. A link was thus solidly forged between unrepaired DNA damage and human cancer.

The legacy of these landmark discoveries is striking. The role played in hereditary cancers by defective repair genes—the genes that direct the production of the enzymes responsible for the actual repair work—is now a focus of research around the world. And OBER-supported scientists continue to be leading players. At Livermore and Los Alamos, for example, researchers have isolated and cloned several repair genes, including the very one whose defects lead to xeroderma pigmentosum. But the clear picture that unrepaired DNA damage was the insidious culprit in the long-term consequences of radiation exposure had far deeper ramifications. It was now seen that x-rays, ultraviolet light, and cancer-causing chemicals worked in similar ways, subverting or overwhelming the natural DNA repair mechanisms that our health relies upon. So central is the role of DNA repair, and so active is today's research community in seeking to understand it better, that in 1994 the prestigious journal *Science* designated the entire class of DNA repair enzymes as its "Molecule of the Year."

Another upshot of the earliest research on DNA repair was the development of new screening tests for possible cancer-causing chemicals. If unrepaired DNA damage was at the source of most cancer, then detectable cellular mutations were danger signs to be heeded. In short order, then, the seventies produced a number of new tests for cancer-causing potential, the best known of which is the Ames test, developed with AEC support in 1973 by Bruce Ames at the University of California, Berkeley. Some strains of bacteria, hobbled by an inability to produce an essential molecular building block, can reproduce only if something alters them genetically. Thus, any chemical that produces a flourishing colony of these bacteria is a potential human mutagen. Today, around the world, the Ames test is one of the first hurdles a new chemical or pharmaceutical must clear on its way to regulatory and public acceptance.

DNA SNAPSHOTS

■ Another window into the workings of the cell opened in 1956 at Brookhaven, when W. L. (Pete) Hughes synthesized tritium-labeled thymidine, a highly specific precursor of DNA. (Tritium is a radioactive isotope of hydrogen.) Cells take up thymidine in preparation for cell division, build it into their DNA, and then hand it down to their daughter cells. The tritiated version emits low-energy electrons, which can be made to expose photographic film and thus to produce microscopic pictures showing where DNA synthesis has taken place. By observing the fate of tritiated thymidine in living cells, Brookhaven scientists were able to confirm the Watson-Crick hypothesis for DNA replication at the chromosomal level—and to "watch" chromosomes exchange genetic material during the process of cell division. Their careful experiments also elucidated many of the details of the cell cycle, the sequence of observable stages a cell passes through between cell divisions. Today, tritiated thymidine is a standard tool around the world in studies of how cells proliferate and how cancer develops and responds to treatment. ■

A Logical Consequence: The Human Genome Project

A surprising but cogent thread links the atomic bombs that ended World War II with today's most ambitious health research effort, the Human Genome Project. One of the unanswered questions of radiation research is the extent to which the descendants of bomb survivors harbor DNA mutations as a legacy of their par-

1966 Argonne radiation biologist Miriam Finkel isolated the murine osteosarcoma virus, the source of a gene that would be widely used in subsequent research. The *fos* gene plays a prominent role in the regulation of cell proliferation.

1967 At Los Alamos Mack Fulwyler and Marvin Van Dilla developed the fluorescence-activated flow cytometer.

1968 James Cleaver at the University of California, San Francisco, showed for the first time that a human disease (xeroderma pigmentosum) associated with a susceptibility to cancer is caused by a genetically impaired ability to repair damaged DNA.

1972 Peter Mazur and Stanley Leibo pioneered cryopreservation of mammalian embryos. At Oak Ridge they succeeded in freezing, thawing, and implanting mouse embryos, thus spurring a revolution in the livestock industry.

1973 Bruce Ames at the University of California, Berkeley, devised a screening test, now known as the Ames test, for identifying potential cancer-causing chemicals and pharmaceuticals.

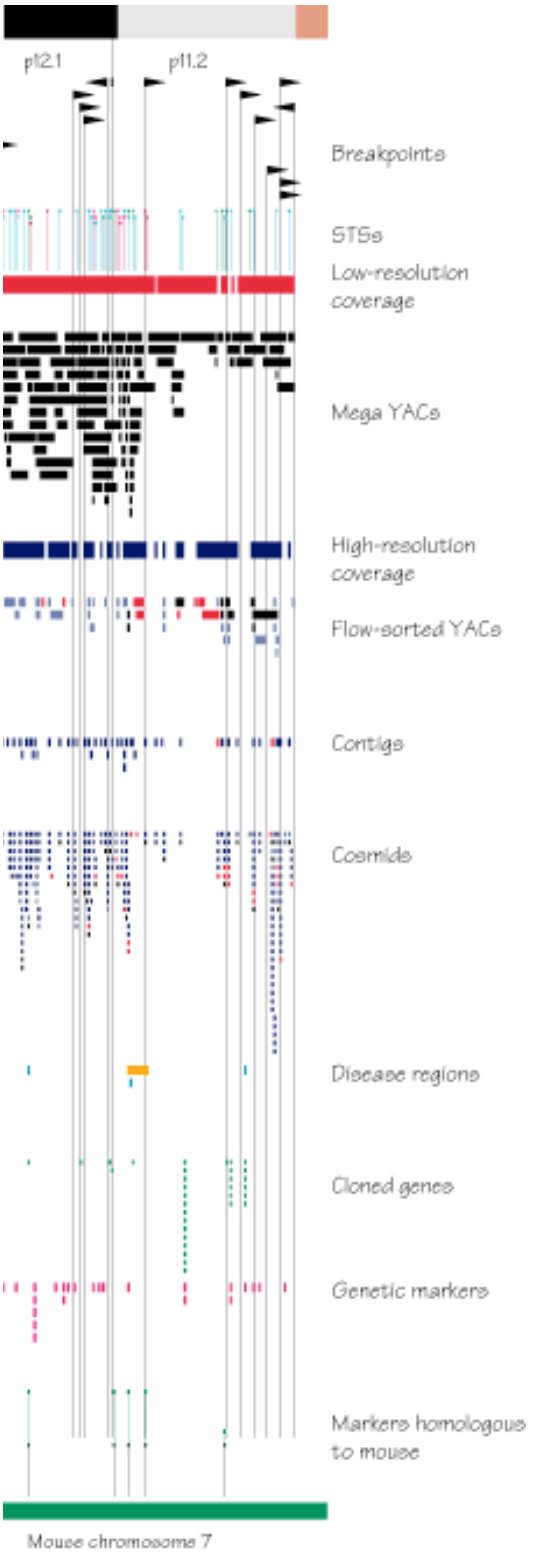
1974 Brookhaven biologists demonstrated that ultraviolet-produced pyrimidine dimers in cells induce the formation of tumors. They would later succeed for the first time in using UV light to transform normal human cells in culture to premalignant cells.

ents' exposure to radiation. Indeed, the Radiation Effects Research Foundation maintains a precious resource of frozen white-blood cells from almost a thousand families of survivors and children, awaiting the day when their DNA can be analyzed for telltale mutations. But that day awaits new tools for genetic analysis and a far more detailed knowledge of the human genetic makeup. Thus the tie to the genome project.

In 1986 the DOE boldly announced its Human Genome Initiative, both to develop these needed tools and, far more broadly, to provide a comprehensive picture of the human genetic script. For the genome project is no less than this, to read in detail the sequence of three billion letters (or *base pairs*) that makes up the genetic recipe of our species. The ultimate payoffs stretch the imagination: Molecular medicine will turn from treating symptoms to addressing the deepest causes of disease; new pharmaceuticals will attack diseases at their molecular foundations. More sensitive diagnostic tests will uncover ailments in their earliest stages. New preventive therapies targeting individuals with genetic susceptibilities—either to heritable disease or to environmental carcinogens—will thwart some diseases altogether. Even gene therapy will become possible, actually "fixing" genetic errors.

By the mid-eighties, the foundations for this formidable project were already firmly established. GenBank, a DNA sequence repository, was in place at Los Alamos, backed up by DOE computer and data-management expertise. Chromosome-sorting capabilities, essential to the genome initiative, existed at both Livermore and Los Alamos. And these same labs had recently launched the National Laboratory Gene Library Project. Nonetheless, the idea of sequencing the entire genome was greeted at first by skepticism. Today, though, the DOE's prescient initiative has been embraced nationally and internationally, and the genome project is making steady progress toward reaching its goal in the year 2005.

Together with investigators supported by the National Institutes of Health, DOE-funded laboratories and university scien-



MAPPING THE TERRAIN A much-simplified map covering some 20 million base pairs of chromosome 16 hints at the complexity of chromosomal mapping. Most of the different symbols indicate a different kind of well-characterized chromosomal fragment or marker; collectively, these genomic signposts provide a sound basis for detailed sequencing efforts.

tists continue to lead the U.S. effort. Although "production sequencing" of the human genome is just beginning around the world, the project has already produced newsworthy results. Los Alamos and Livermore have published high-resolution maps of chromosomes 16 and 19, the first efforts to provide a sufficient number of chromosomal signposts to support large-scale sequencing projects. In the process of this and later work, mappers uncovered genes implicated in many human ailments, including adult-onset diabetes, pathologically high cholesterol levels, the most common form of muscular dystrophy (a success shared by an international team of researchers), and very recently, Down's syndrome. Livermore also shares credit for founding the I.M.A.G.E. (Integrated Molecular Analysis of Genomes and their Expression) Consortium, which coordinates the world's largest public collection of cloned gene fragments, an invaluable resource for the international biological community. Berkeley, meantime, has focused on automating a large-scale sequencing technology, which has been adopted by private companies and by two major NIH sequencing efforts.

Another part of the task is genome "informatics," the full range of computational support the project demands. At Oak Ridge, for example, researchers in 1991 developed GRAIL (Gene Recognition and Analysis Internet Link), an on-line computer program that uses the principles of artificial intelligence to sort out genes from the much longer stretches of noncoding DNA in the genome. In 1995 alone, the international community used GRAIL to search for genes among 180 million base pairs of human DNA—a volume of DNA equal to six percent of the entire genome. OBER also manages the world's central repository of mapping information, the Genome Data Base at the Johns Hopkins University.

The OBER genome program also broaches ethical, legal, and social issues. For example, one effort has led to high school curriculum units on human genetics and on the ethical management of genomic information. In addition, a model privacy act developed at Boston University's School of Public Health has become the basis for pending state and federal legislation aimed at safeguarding individual rights. And yet another effort, headed by the nonprofit Einstein Institute for Science, Health and the Courts, led to educational workshops for state and federal judges who must deal with increasingly sophisticated genetic evidence.

THE THREADS OF LIFE

■ In the fifties and sixties, the details of the genetic apparatus were still being filled in: the double helix discovered, the genetic code deciphered, and the intricate process of protein synthesis sorted out. In 1956 Oak Ridge scientists Larry Astrachan and Elliot Volkin isolated a form of RNA that they called "DNA-like RNA." Four years later, this molecule would become known as messenger RNA (mRNA), the molecular courier that carries the instructions contained in DNA to sites where the encoded information is used to produce enzymes, antibodies, and the rest of the body's proteins. Among the visual landmarks of this period were early images from Brookhaven showing RNA to be made in the nucleus of the animal cell and then the first photo (below) of mRNA actually being transcribed from chromosomal DNA. This picture, a high-resolution electron microscope image, was produced at Oak Ridge in 1970. ■

1979 High levels of naturally occurring radon were observed by Argonne researchers in homes in the Midwest, a consequence of soil porosity beneath the houses, rather than the concentration of radium (the parent of radon) in the soil. Public awareness of radon would be heightened in the mid-eighties, leading to an intensive national research program.

1982 Brookhaven scientists William Studier and John Dunn completed the first DNA sequence of a double-stranded virus, the bacteriophage T7. At 39,936 base pairs, it was the longest sequence then known.

1984 The National Laboratory Gene Library Project was established jointly between Livermore and Los Alamos to create chromosome-specific gene libraries from each of the human chromosomes and to distribute them to the worldwide scientific community.

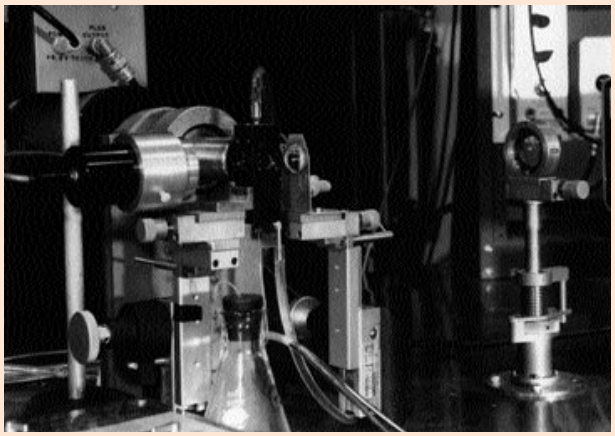
1984 OHER and the International Commission on Protection against Environmental Mutagens and Carcinogens co-sponsored a conference in Alta, Utah, highlighting the growing role of recombinant DNA technologies. The Congressional Office of Technology Assessment would subsequently incorporate the Alta proceedings into a report acknowledging the value of a human genome reference sequence. The following year, Charles DeLisi and David Smith would outline plans for a DOE Human Genome Initiative.

1986 OHER announced its Human Genome Initiative after organizing a meeting in Santa Fe to explore the project's feasibility.

1988 The DOE and the NIH sign a memorandum of understanding for coordination of the U.S. Human Genome Project. Two years later, the agencies would jointly announce the project's first set of five-year goals.

SORTING CELLS

■ Often unsung in the march of scientific progress are the achievements in instrumentation that make modern research possible. One such instrumental foundation stone was laid between 1965 and 1972 when Mack Fulwyler and Marvin Van Dilla developed the flow cytometer at Los Alamos. For the first time, this device made it possible to rapidly sort single cells and subcellular components according to some chosen criterion (the amount of DNA in a cell, for example, or the size of a chromosome). An entire industry subsequently arose to put this device to clinical use—most routinely for performing blood counts—and it now plays a leading role in a host of research areas, from AIDS to toxicology. Adapted for chromosome sorting and purification, it is a staple of the Human Genome Project. ■

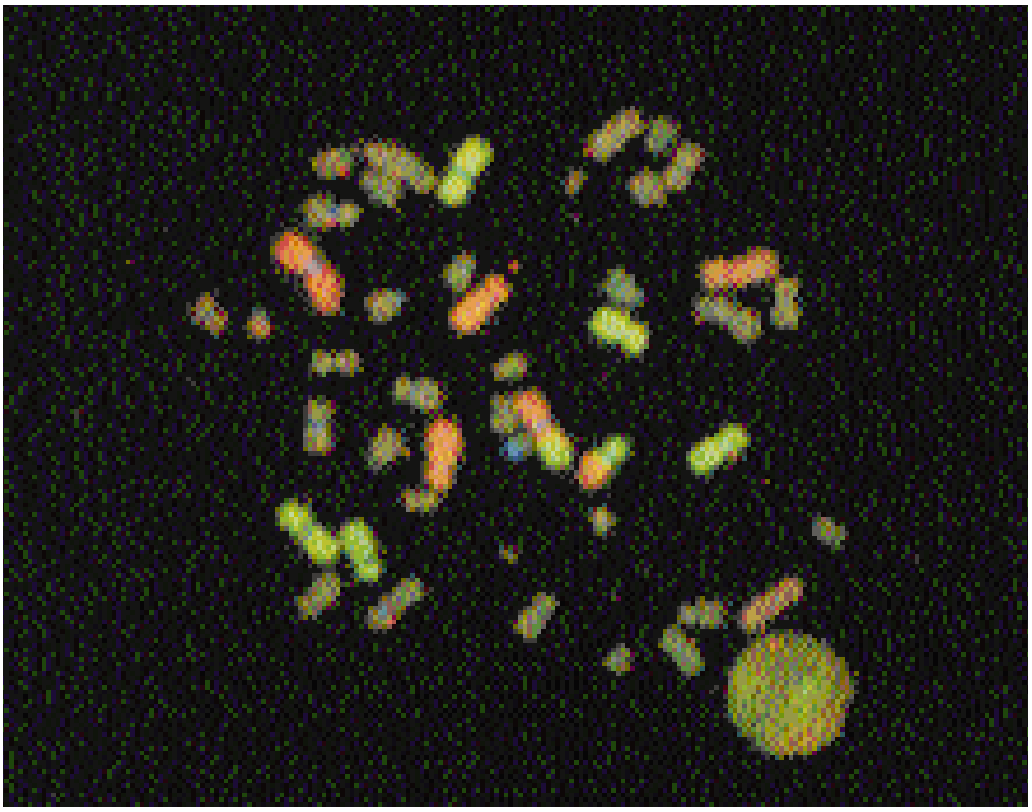


A HERITAGE OF GENETICS RESEARCH

But DOE's interest in genetics research is both older and broader than today's genome project. One of the historic efforts, for example, was two decades of research at Brookhaven, culminating in 1982 with the longest DNA sequence then known, the complete genome for the "bacteria-eating" virus T7. Furthermore, the work produced more than just sequence; it provided a profound insight into how the genetic program is translated into action—the molecular mechanisms by which T7 takes over and exploits the reproductive machinery of its host bacterium. As a direct consequence, T7 has now been genetically engineered by the biotechnology industry to serve as cellular "factories" for producing selected proteins.

Oak Ridge scientists also played an early role, owing in large part to their celebrated "mouse house." Years of mutagenesis studies there helped shape the foundation for today's molecular genetics research. Mutant strains of Oak Ridge mice express heritable disorders that model human birth defects, metabolic maladies such as obesity and diabetes, and human cancer. Over the past decade, many of the genes responsible for these disorders have been identified, and often the corresponding human genes have been characterized as well. Further, whereas many of these strains arose from random genetic alterations, modern biotechnology has now largely supplanted such reliance on chance. Today, at Oak Ridge, Berkeley, Livermore, and many other labs around the world, *transgenic* mice carry "designer mutations" that allow scientists to study specific genetic defects

A COLOR-CODED GENE The different coat colors of these Oak Ridge mice arise from mutations in the "agouti" gene, which affects a number of functions, including pigmentation. The mouse in the rear has the normal grizzled agouti coat.



MIX AND MATCH Developed at Livermore in 1986, chromosome painting allows many genetic events, natural and otherwise, to be readily observed. In this image, human chromosomes 1, 2, and 4 (two of each) have been stained orange, chromosomes 3, 5, and 6 green. Along with the normal chromosomes, two can be seen that are part orange, part green, a result of chromosomal exchange.

that mimic those found in human patients, thus paving the way to new diagnostic and therapeutic techniques. Diseases being studied in such mice include sickle-cell disease, polycystic kidney disease, and leukemia.

Also recent are breakthroughs in a field called molecular cytogenetics. In 1986, as part of the biodosimetry effort at Livermore, Joe Gray developed a technique for "chromosome painting" whereby the different human chromosomes can be uniformly tagged with fluorescent dyes of diagnostic colors. Major genetic changes—the swapping of pieces of chromosome, for example—are thus easily seen, whether the product of natural mutational events or exposure to mutagenic agents. Thus the obvious application to biodosimetry (see page 14). Chromosome painting has also been used to illuminate the incremental genetic changes that accompany the transformation of normal to malignant cells in a number of human cancers, including those of the breast, colon, and prostate.

Efforts launched in the immediate postwar years to ensure the public safety thus produced not only today's radiation safety standards, short-term assays such as the Ames test, and advances in dosimetry, but also the bright prospects of the Human Genome Project. Another thrust, though, had medical advances as its goal from the start—not the protection of human health, but its dramatic enhancement through nuclear medicine—the theme of the next chapter in the history of biological research in the Atomic Age.

1989 Los Alamos scientists isolated and characterized the ends (or telomeres) of human chromosomes. The telomeres are involved in cell maintenance and longevity, since they are shortened during normal cell replication. "Immortal" cancer cells somehow escape the restraint of telomeric shortening.

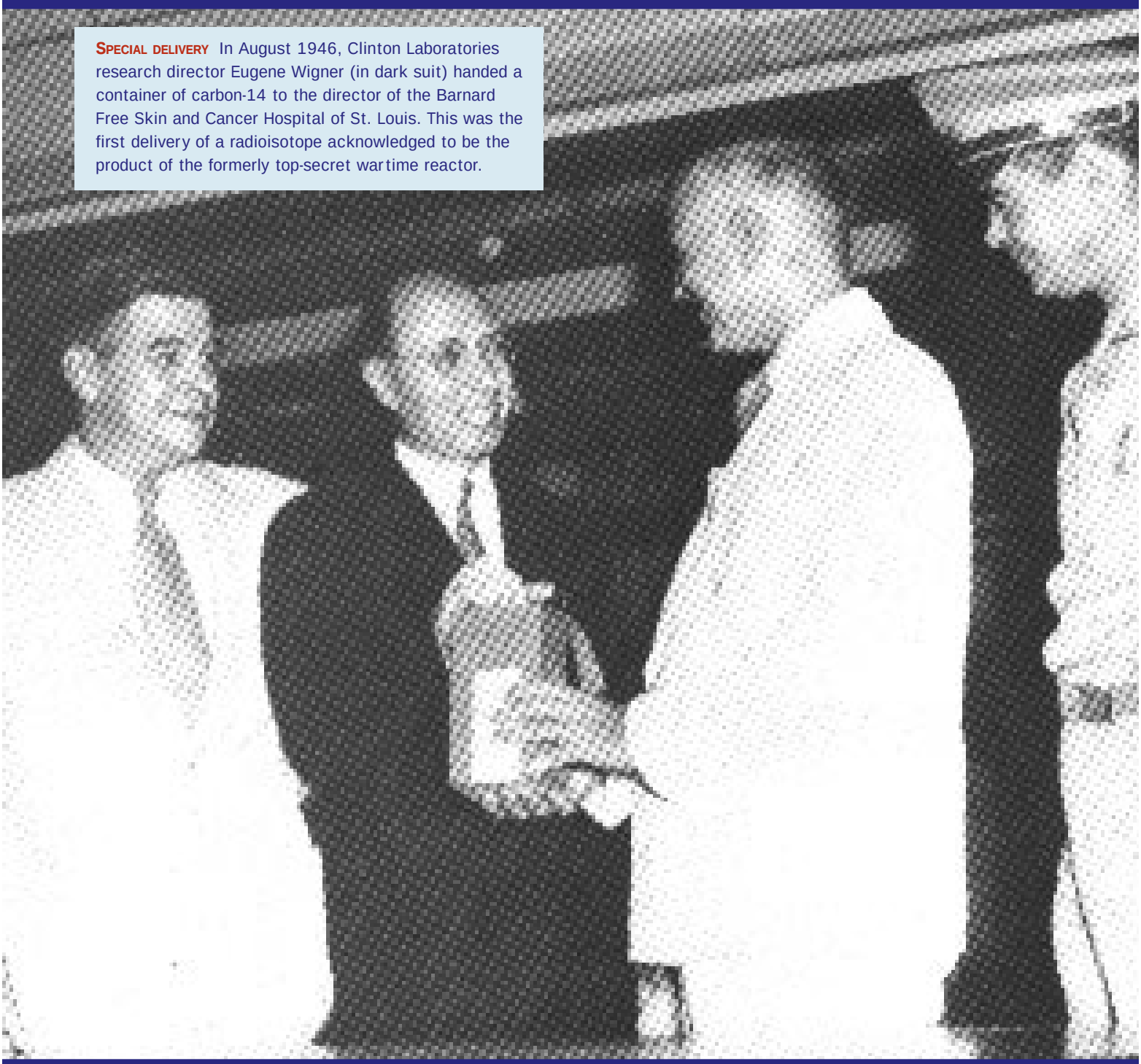
1992 The gene for myotonic dystrophy was discovered by a consortium that included Livermore scientists, leading to a diagnostic tool for a late-onset disease that affects one out of every eight thousand people.

1993 Using hybrid fish as their model systems, Brookhaven scientists showed that UVA wavelengths are more important than UVB wavelengths in the induction of malignant melanoma.

1994 Livermore and Los Alamos announced high-resolution physical maps of human chromosomes 19 and 16, respectively.

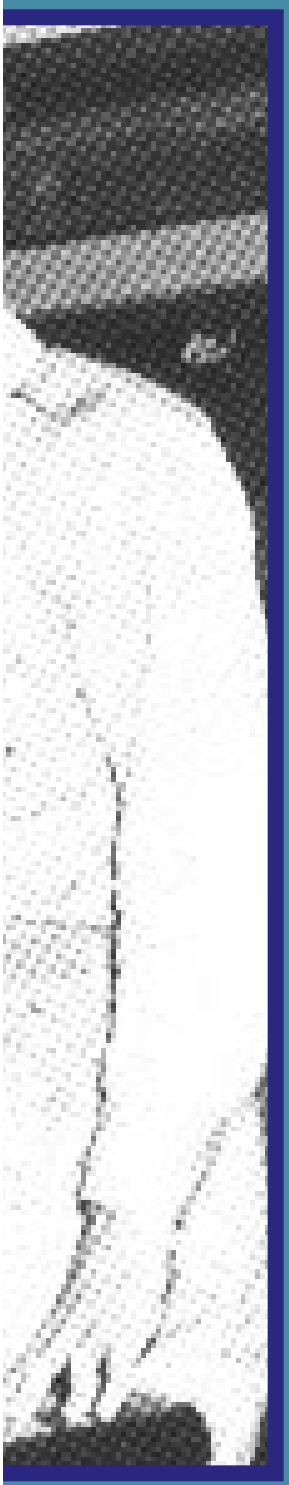
1997 OBER formed the Joint Genome Institute to integrate the high-throughput production efforts of the genome centers at Berkeley, Livermore, and Los Alamos.

A Healthy Citizenry



Special delivery In August 1946, Clinton Laboratories research director Eugene Wigner (in dark suit) handed a container of carbon-14 to the director of the Barnard Free Skin and Cancer Hospital of St. Louis. This was the first delivery of a radioisotope acknowledged to be the product of the formerly top-secret wartime reactor.

Gifts of the New Era

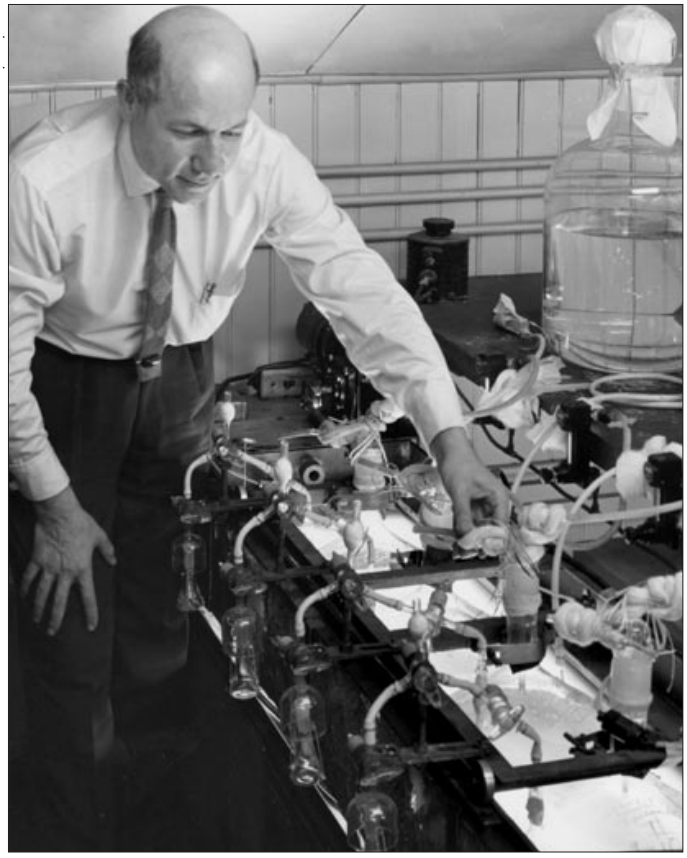


Modern nuclear medicine has a pedigree that stretches almost a hundred years. As early as the first years of the twentieth century, radium was used in several hopeful experiments to treat conditions for which no effective therapies were known: tuberculous skin lesions, goiter, tumors, and chronic infections. Two decades later, George de Hevesy was the first to explore the use of radioactive tracers, following the course of radioactive lead in plants. Over the next few years, minute quantities of radioactive elements were injected into humans and animals to study metabolic processes and to trace the circulation of blood. Then, in the thirties, at the University of California's Radiation Laboratory in Berkeley, Ernest O. Lawrence produced radioactive isotopes under controlled conditions for the first time. In a few short years, Lawrence's cyclotrons produced iodine-131, technetium-99m, carbon-14, thallium-201, and gallium-67, all of which would play pivotal roles in the future of nuclear medicine and biology. At the same time, the therapeutic use of radionuclides and their application to physiological studies increased in proportion to the sudden availability of these new "artificial" substances.

Atoms for Health

The AEC thus inherited a field not yet mature, but brimming with potential. In 1946 the veil of wartime secrecy was lifted from the nuclear reactor at the Clinton Laboratories, which had for three years been the clandestine origin of phosphorus-32 being produced for medical purposes. A prolific new source of radioisotopes was thus revealed, and before production ceased in 1963 at the original reactor, Oak Ridge had filled over a half-million orders for radioactive tracers and pharmaceuticals.

Nor did the AEC limit itself to supplying the biomedical community with isotopes already well characterized. In the late sixties, for example, under AEC sponsorship, Paul Harper, at the University of Chicago's Franklin McLean Memorial Research Institute, developed radioactive thallium as an imaging agent and proposed it as a potassium analog for visualizing the living heart. Subsequently, in the mid-seventies, Brookhaven scientists developed the first practical techniques for producing thallium-201 and then used the isotope successfully in obtaining cardiac images from goats. Today, thallium-201 exercise testing is among the standard noninvasive methods of scanning for reduced blood flow or tissue damage to the heart. In 1995 about one million thallium-201 scans were performed in the U.S. alone, most of them heart scans. The underlying idea is common to the use of all diagnostic radioisotopes. The isotopes themselves, or biochemicals containing them, are taken up preferentially by one organ or another, whereby the emitted radiation can be measured or used to produce pictures not unlike conventional x-ray images. The results reveal not so much the structure of



KEYS TO THE PLANT KINGDOM Melvin Calvin's early use of carbon-14 tracers uncovered many of the mysteries of photosynthesis and led to the 1961 Nobel Prize for Chemistry. The central metabolic cycle by which plants transform carbon dioxide and water to sugar is now known as the Calvin cycle.

1903 Alexander Graham Bell proposed using radium to treat tumors.

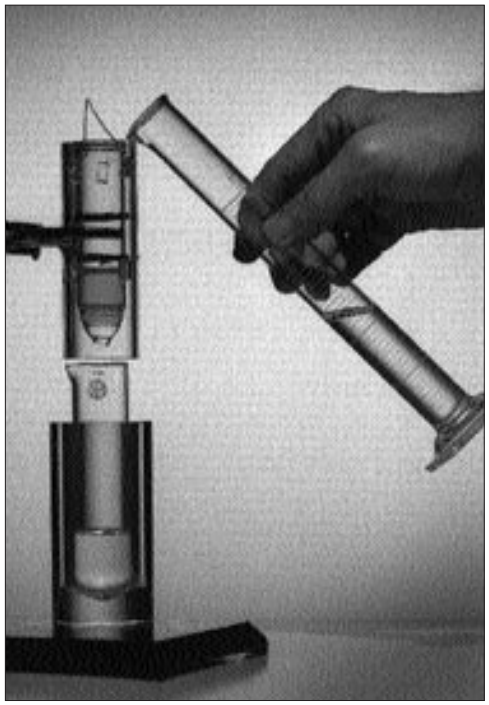
1923 Hungarian chemist George de Hevesy used a natural radioisotope of lead to investigate the metabolism of lead in plants. His realization that radioactivity had no effect on the biochemical properties of the lead laid the groundwork for all subsequent biological uses of radiotracers. Hevesy would receive the Nobel Prize for Chemistry in 1943.

1929 Ernest O. Lawrence invented the cyclotron, which would become a major tool for the production of radionuclides. Lawrence would win the Nobel Prize for Physics in 1939.

1936 At Berkeley's Radiation Laboratory, John H. Lawrence made the first clinical use of an "artificial" radionuclide, treating a leukemia patient with phosphorus-32.

the body, but rather the details of function and dysfunction.

Even more widespread than thallium heart scans is the use of technetium-99m for diagnosing diseases of the thyroid, kidney, liver, heart, brain, and bones. About thirteen million patients per year, roughly one-quarter of all U.S. inpatients, receive technetium-99m scans as one of their diagnostic tests. As a radiotracer, its properties are nearly ideal: It exposes the patient to minimal radiation, while sending out a clear beacon to the camera. And its activity then diminishes in a matter of hours. On the other hand, owing to its short, six-hour half-life (the period during which half of the material undergoes radioactive decay), technetium-99m was long overlooked as a practical tool for widespread use; in effect, it had no "shelf life." But in the late fifties, Walter Tucker, Powell Richards, and others at Brookhaven discovered a way by which hospitals and research institutes could "milk" technetium-99m as needed from its longer-lived parent isotope. And in the years following, the next necessary step was also taken—the incorporation of the radioisotope into biologically active molecules, much of the work being done at the Argonne Cancer Research Hospital and at Brookhaven.



In medical diagnostics, radioisotopes serve as tiny sources of invisible but detectable light, revealing their presence as they accumulate in organs or tumors, or course through veins and arteries. Moreover, as long as a tracer's activity persists, its movements can be traced even as it

MILKING MOLYBDENUM Technetium-99m, a short-lived decay product of molybdenum-99 and the most widely used tracer in modern nuclear medicine, is a practical tool only because of a Brookhaven discovery in the late fifties. A chemical means, embodied in the early "generator" shown here, was found for separating the technetium from the molybdenum, thus providing hospitals a way to obtain the tracer on demand.

shuttles along metabolic pathways—even as it is incorporated into different biochemical compounds. Naturally enough, then, many of the earliest uses of radiotracers were in explorations of life's intricate biochemistry. During the AEC era, both carbon-14 and tritium (hydrogen-3) were used in notable experiments to trace metabolic pathways in animals and plants, and the utility of these isotopes as research tools continues today. Carbon and hydrogen are ubiquitous constituents of biomolecules, and the radioactive versions of these atoms do not alter the chemistry of life. Among the most celebrated of such metabolic studies was the unraveling of the complex cycles of photosynthesis, the process by which green plants convert atmospheric carbon dioxide and water into sugar. For this AEC-sponsored work, Berkeley chemist Melvin Calvin received the 1961 Nobel Prize for Chemistry.

More recently, studies with metabolic tracers have turned especially to the human heart and brain. But to make such studies possible, better ways were needed to "see" just where the tracers were.

Slices of Life: Medical Imaging

All that has been said about radioisotopes as tools for medical diagnosis and as keys to the mysteries of plant metabolism and

1938 Also in Berkeley, Glenn Seaborg (a future chairman of the AEC) and Emilio Segrè discovered technetium-99m. Berkeley's cyclotrons would also produce the first iodine-131, carbon-14, thallium-201, and gallium-67. Seaborg and Segrè would both win Nobel prizes for later achievements.

1946 Nuclear medicine's modern era began with the announcement in the June 14, 1946, issue of *Science* that radioactive isotopes from the Oak Ridge nuclear reactor, a secret wartime facility, were available to qualified researchers.

1947 Benedict Cassen at UCLA used radioiodine to determine whether a thyroid nodule accumulated iodine, a key to differentiating benign from malignant nodules.

1948 John Gofman and his colleagues at the University of California's Radiation Laboratory began ultracentrifuge studies that would allow them to identify the macromolecules involved in the development of atherosclerosis. This work would be largely responsible for focusing the world's attention on the role of cholesterol and lipoprotein patterns in coronary artery disease.

MEDICAL SERENDIPITY

■ It is a truism of scientific research that some of the greatest discoveries emerge as surprising revelations of research with its sights set elsewhere. Examples abound in the biological research supported by the DOE and its predecessors. Sodium's role in contributing to high blood pressure, for example, was revealed at Brookhaven in the early sixties during studies that were focused on another metabolic issue altogether—the retention of radioactively labeled salt in rats. Also at Brookhaven in the late sixties, the successful application of L-dopa as a medication for the treatment of Parkinson's disease was a tangential product of brain function studies using radioactive manganese. Following early clinical trials, a *New England Journal of Medicine* editorial in 1969 described this discovery by George Cotzias (pictured) as "the most important contribution to medical therapy of a neurological disease in the past fifty years." Today, second-generation drugs based on this research are the treatment of choice for tens of thousands of Parkinson's sufferers in the U.S. alone. ■ Another example of unexpected, though not entirely serendipitous, ramifications is the emergence of organ transplantation as a mainstream medical procedure from early research on irradiated mice. In the fifties, it was known that mice exposed to usually lethal doses of radiation survived if the damaged blood-forming cells of their bone marrow were replaced with healthy marrow. In 1954, however, Oak Ridge researchers showed that rat marrow could be used to save the mice as well. Contrary to conventional wisdom, the alien donor cells were not rejected by the host. This demonstration of immunosuppression, in this case induced by radiation, triggered a renaissance of thinking about tissue and organ transplantation. Further development of immunosuppressive techniques led to successful bone marrow transplantation for the treatment of leukemia and other diseases—and eventually to the practicality of kidney, heart, liver, and other organ transplants in humans. The ground-breaking work at Oak Ridge was one of the starting points for these striking developments, which would culminate in 1990 with the Nobel Prize for Physiology or Medicine, awarded jointly to Joseph Murray and Donnall Thomas. ■

1951 Benedict Cassen and his colleagues developed an automated "rectilinear scanner" to image the distribution of radioiodine in the thyroid gland. This followed on Cassen's construction of the first medical scintillation detector in 1949. The rectilinear scanner would become the workhorse of nuclear medicine for more than two decades.

1951 Iodine-131 became the first radiopharmaceutical approved by the Food and Drug Administration for routine human use.

1951 Frank R. Wrenn, Jr., an AEC Fellow at Duke University, published the results of a positron-counting study that used copper-64 placed within a brain preserved inside its skull—the first study suggesting the medical possibilities of positron emitters.

1952 John H. Lawrence and Cornelius Tobias used a helium-ion beam from Berkeley's 184-inch cyclotron to treat human patients suffering from pituitary tumors. Using particle beams for medical therapy had first been proposed by Robert Wilson in 1946.

GETTING THE INSIDE STORY Benedict Cassen (left) at UCLA and Hal Anger at Berkeley's Radiation Laboratory took major strides in diagnostic imaging by providing practical means for visualizing the distribution of radioactive tracers in the body. Descendants of Anger's camera remain the standard imaging tool of nuclear medicine around the world.

human physiology presupposes a way of observing the invisible emanations of the radioactive tracers. In the experiments of the thirties and forties, primitive by today's standards, the flow of a radionuclide through the body could only be monitored by Geiger counters or similar devices. A true image of the tracer's distribution was only a dream.

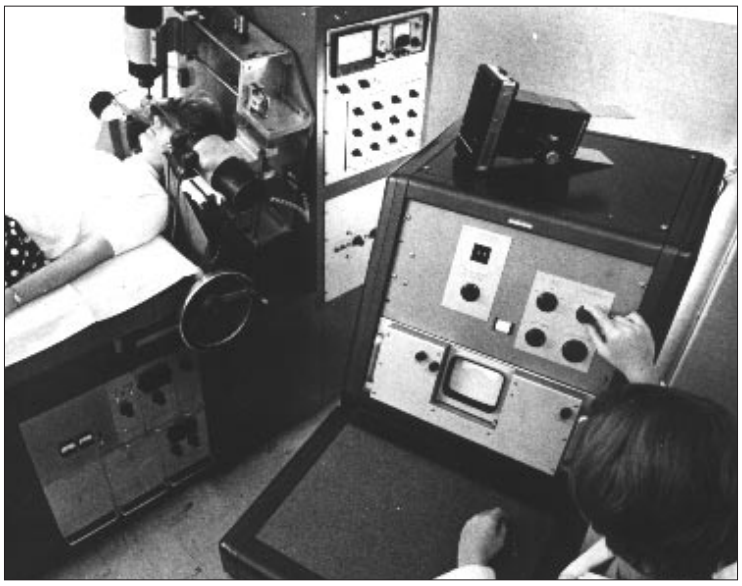
In the fifties, however, a new era was ushered in, first by the development of the rectilinear scanner by Benedict Cassen at UCLA, and then by Hal Anger's invention of the stationary scintillation camera at the Radiation Laboratory in Berkeley. Both of these instruments not only detected the gamma-rays (high-energy x-rays) emitted by radioactive tracers, but also precisely identified their origins in the body. Cassen's innovation was the mechanization of the earliest, point-by-point manual scanning techniques. Using his motorized raster-style scanner, Cassen and his UCLA colleagues performed diagnostic imaging studies of the thyroid using iodine-131, as well as some of the earliest scans to look for brain tumors. Anger's more revolutionary step was to build a stationary, cameralike system to do the same job much more quickly. Many of the most commonly used radiotracers, including thallium-201 and technetium-99m, owe their current utility to today's generation of Anger cameras; roughly a quarter of all patients in U.S. hospitals undergo tests using these devices.

The next step was an extension to three dimensions—a step that demanded a practical way of visually reconstructing "slices," or transverse sections, of the body, which might then be "stacked" together to produce a 3-D picture of internal structures. In the end, several contributions, in both instrumentation and computation, converged in what we now know as computed tomography, or CT. One of the earliest contributors was David Kuhl, working in part with AEC and ERDA support at the University of Pennsylvania. In 1959 Kuhl constructed a device that embodied many of the principles of today's single-photon emission computed tomography, or SPECT, instruments. With it,

despite the lack of sophisticated mathematical algorithms for doing tomographic reconstructions, he produced the first transverse section images ever obtained by single-photon imaging. As did Kuhl's prototype, today's SPECT scanners—mainstays of present-day nuclear medicine—detect a radiotracer's gamma-ray emissions by rotating detectors around the body. In today's machines, a computational algorithm then reconstructs the distribution of the tracer that gave rise to the detected signals. This reconstructed slice is then combined with others to produce a 3-D image. Six years later, Kuhl performed the first transmission transverse section scan of a patient's chest, this time producing images by detecting gamma-rays transmitted through the body from source to detector. This concept is similar to that now embodied in commercial x-ray CT scanners.

Yet another stride in medical imaging exploited a peculiar property of some radioactive isotopes: As they decay, they emit a positron, an elementary particle of antimatter that promptly undergoes mutual annihilation with a nearby electron. The product of this annihilation is two gamma-rays traveling in exactly opposite directions. Detecting this pair of gamma-rays thus fixes their origin along a straight line between the two opposing detectors. Detecting many such pairs can pin down the point of origin to within a few millimeters—a process called positron emission tomography. PET emerged as an important medical tool only in the seventies, its practical development supported by both the NIH and the AEC. The breakthrough was a series of machines constructed by Michael Phelps, Edward Hoffman, and Michel Ter-Pogossian at Washington University in St. Louis. But much of the groundwork had been laid earlier. In 1953, at MIT, Gordon Brownell fabricated the first detectors designed to take advantage of the positron-annihilation process, and in 1961 James Robertson at Brookhaven built a ring-shaped detector system that foreshadowed later instruments. One element missing from Robertson's prophetic device, however, was again an efficient mathematical algorithm for computing the three-dimensional tomographic images.

Today, more than 260 centers around the world make use of PET scanners, among them one at Berkeley with the world's highest resolution. PET scanning technology has been the key to a whole generation of metabolic studies, as well as clinical diagnostic tests. An organ of especially keen interest is the brain. Mapping its activity usually means following the uptake and metabolism of glucose, the brain's dominant source of energy. In the early seventies, a collaboration among Brookhaven researchers,



IN-DEPTH ANALYSIS Beginning in the late fifties, supported by the AEC and other agencies, David Kuhl at the University of Pennsylvania constructed some of the earliest forerunners of today's SPECT and CT scanners. The Mark III scanner shown here detected photons from an injected tracer and applied interactive reconstruction techniques using a built-in computer. The first quantitative three-dimensional measures of brain function were performed with this machine

1953 Gordon Brownell at MIT constructed the first device to exploit positron-electron annihilations as an imaging tool, another precursor of today's PET scanners.

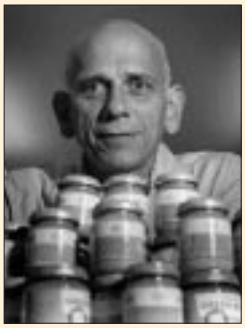
1954 Oak Ridge researchers successfully transplanted functional bone marrow from a rat to an irradiated recipient mouse, thus demonstrating the immunosuppressive effects of radiation, a key to future organ transplantation.

1955 At UCLA George Taplin used rose bengal labeled with iodine-131 to image the liver and similarly labeled hippuran to image kidney function.

1958 Walter Tucker and his coworkers at Brookhaven invented a means of making the short-lived nuclide technetium-99m available to sites far removed from research reactors. This isotope is now the most widely used radionuclide in medicine.

1958 Hal Anger at Berkeley developed the "scintillation camera," which would make dynamic studies with radionuclides practical for the first time. This updated instrument superseded Anger's first "gamma camera," which he developed in 1952. Anger cameras are now in use around the world.

1959 David Kuhl at the University of Pennsylvania made the first transverse section scan of the body with a device that was the forerunner of today's single-photon emission computed tomography (SPECT) scanners.



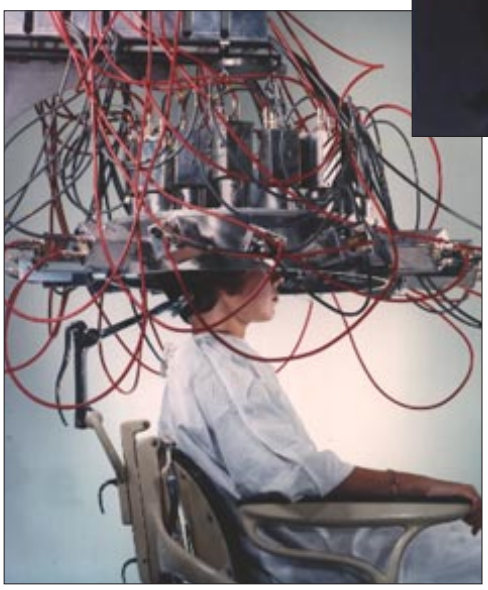
1960 While studying salt retention in different strains of rats, Lewis Dahl at Brookhaven discovered the link between salt consumption and high blood pressure.

1961 James Robertson and his colleagues at Brookhaven built a 32-crystal positron camera, the "head-shrinker," the first single-plane PET instrument.

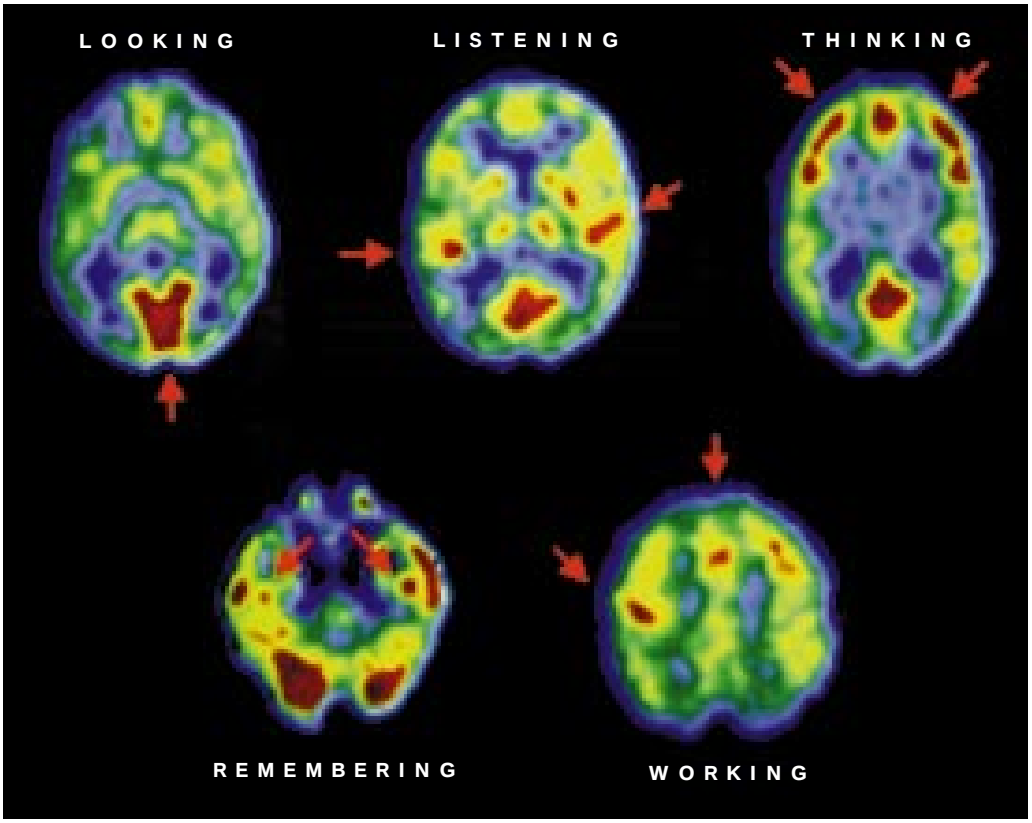
workers at the University of Pennsylvania, and scientists at the NIH produced the positron-emitting compound that made this practical—a compound known by its shorthand name ^{18}FDG. In 1976, at Pennsylvania, the same team used PET and ^{18}FDG to obtain the first images of glucose metabolism in the human body. Among subsequent studies, work at UCLA provided the first "brain mapping" of normal function and illuminated how the brain develops from childhood to adolescence. And at Brookhaven studies have revealed metabolic changes in the brain associated with smoking and drug use. Over the past two decades, BER-supported research has also used ^{18}FDG and other tracers labeled with positron emitters to study epilepsy, Alzheimer's disease, Parkinson's disease, schizophrenia, depression, and a host of other ailments. Some of these same compounds are equally useful as PET tracers in the diagnosis of heart disease and in searching for the sites of primary and metastatic cancers.

High-Tech Treatments: Isotopes and Particle Beams

Beyond diagnosis lies treatment, and here, too, radioisotopes have had enormous impact. One isotope, iodine-131, is still the most widely used radioactive substance for the treatment of diseases such as toxic goiter and thyroid cancer. As a result of its use, no other metastatic cancer is more effectively treated than thyroid cancer. Cancer treatment with radioactive iodine-130 was first tried at MIT and at Berkeley's Radiation Laboratory in 1941, and in 1946 iodine-131 was first used in an "atomic cocktail" for thyroid cancer therapy. After iodine-131 became available from the Oak Ridge reactor, it was widely



The birth of PET The "head-shrinker" (at left), developed by James Robertson at Brookhaven in 1961, was a direct forerunner of today's positron emission tomographs. The first practical PET camera built for human studies is shown above, with one of its developers, Michael Phelps. Called PETT III (the extra T was for "transaxial"), it was developed at Washington University in 1974. Unlike the Brookhaven prototype, the Washington University instruments embodied advanced mathematical algorithms for computing three-dimensional images.



THE BRAIN AT WORK These classic PET images, obtained at UCLA's Laboratory of Structural Biology and Molecular Medicine, depict brain activity during five typical tasks. The highest level of activity, meaning the highest rate of glucose metabolism, is indicated by the red areas. The five tasks were "looking" at a visual scene, "listening" to a mystery story that included both language and music, counting backwards from 100 by 7's ("thinking"), "remembering" previously memorized objects, and touching the thumb consecutively to the four fingers ("working").

used in both treatment and diagnosis; indeed, until the advent of technetium-99m, it was the most commonly used radioisotope for medical diagnosis. In 1951 it became the first radiopharmaceutical approved by the FDA for human use.

Many of the early radiopharmaceuticals were first produced at Berkeley's cyclotrons, which propelled atomic particles—protons and the nuclei of light elements, for example—into awaiting targets, thereby producing trace amounts of materials never before seen, many with medical applications. But as the cyclotrons grew in size, another enticing possibility emerged. In 1946 Robert Wilson, then in Berkeley and later director of the Fermi National Accelerator Laboratory, suggested that the racing beams themselves might be directed at deep-seated tumors. X-rays were already used for such purposes, but they are indiscriminate beams, depositing their potentially destructive energy all along their paths. Charged particles, on the other hand, behave more like explosive depth charges, doing most of their damage just before they stop. The trick would be to tailor a beam of such particles to stop exactly where a tumor was known to be.

With this vision in mind, researchers led by John Lawrence and Cornelius Tobias began to lay the groundwork for medical treatments with charged particles. Then, between 1954 and 1993, with the DOE (and its predecessors) and the NIH providing support, beams from two Berkeley accelerators were used to treat more than 2000 patients whose conditions were judged inoperable or surgically risky. In these clinical trials, striking successes were

1961 Melvin Calvin, a Berkeley chemist, received the Nobel prize for his elucidation of photosynthesis, the process by which plants convert carbon dioxide, water, and sunlight into chemical energy. His work was a landmark application of radiotracers to the study of metabolic pathways.

1966 The scanning transmission electron microscope (STEM) arose out of AEC-funded basic research under the direction of Albert Crewe, at Argonne and at the University of Chicago. In the eighties, Brookhaven scientists would develop heavy-atom-conjugated labels (yellow in the image above) for pinpointing specific molecules or sites in biological structures.

1968 George Cotzias at Brookhaven published the first report of long-term L-dopa treatment for Parkinson's disease. L-dopa analogs remain the medications of choice today.

1968 Brookhaven scientists developed the technique of neutron diffraction for the structural analysis of protein molecules. In the image above, neutron-scattering data were used to produce a picture of a bacterial ribosome subunit comprising twenty-one proteins.

1968 Researchers at the Oak Ridge Institute for Nuclear Studies (now the Oak Ridge Institute for Science and Education) discovered the affinity of gallium-67 for soft-tissue tumors, leading to its widespread medical use in imaging lymphomas, lung cancer, and brain tumors.

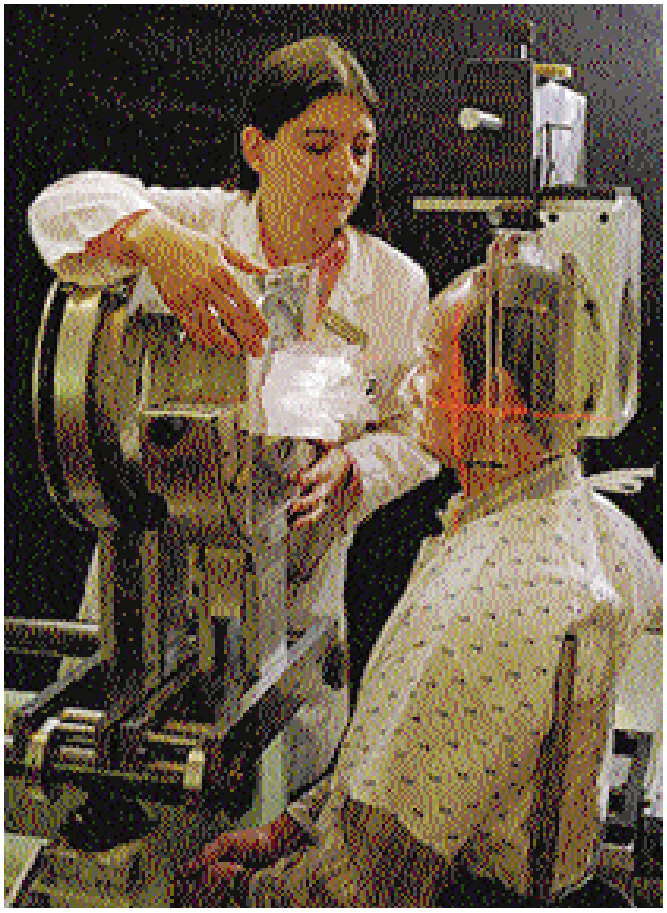
1974 Following work with several prototypes, a Washington University team partially funded by the AEC developed the first practical PET scanner (PETT III) designed for human use. The first studies of human brain and liver tumors and cardiovascular disease were carried out with this system

achieved in treating pituitary tumors, cancer of the eye, and a life-threatening malformation of cerebral blood vessels. Today, the legacy of these early experiments and clinical trials includes several proton accelerators around the world—including one at the Loma Linda University Medical School, designed and built by Berkeley and Fermilab physicists—and a heavy-ion accelerator in Japan dedicated to patient treatment.

An approach that is potentially even more effective in treating brain tumors that resist conventional therapies is being explored at several DOE and university laboratories. In boron neutron capture

BIG MACHINE BIOLOGY

■ Biomedical scientists continue to do some of their most notable research at the bench, using the tools and techniques of the small laboratory. But an increasing fraction of their research demands the involvement of physicists, chemists, and engineers. Indeed, throughout this account of biological and medical progress, the instrumental contrivances of science and medicine have shared the spotlight with biological insight. Not surprisingly, then, the resources of biology extend even to some of the nation's largest scientific facilities, national user facilities built and supported for the use of all qualified individuals and research groups. The DOE plays the preeminent role in constructing and operating these facilities. ■ Studying biological function, for instance, increasingly relies on uncovering the detailed structure of biological macromolecules. This is now commonly done by using the intense x-ray beams produced at synchrotron radiation facilities—machines often costing hundreds of millions of dollars to construct. X-rays are focused on a tiny protein crystal, producing a diffraction pattern that can reveal the protein's intricate structure. Today, almost half of the new structures of biological macromolecules reported in the leading journals have been refined using synchrotron data. The busy floor of Brookhaven's National Synchrotron Light Source, shown above, reflects this intense current interest in synchrotron radiation. Users of these and other major DOE facilities include scientists from many universities, medical schools, government laboratories, and pharmaceutical companies. ■



RAYS OF HOPE A patient is prepared for treatment with a beam of charged particles tailored to deposit most of its destructive energy within a malignant tumor. The tumor's proximity to critical neurological structures makes this form of therapy especially suitable.

therapy, or BNCT, a nonradioactive boron-labeled compound is administered that accumulates predominantly in the tumor, which is then irradiated with neutrons. The neutrons cause the boron atoms to fission, releasing energy that destroys the tumor cells. This kind of highly localized cell surgery was conceived in the thirties and tried clinically in the fifties, with inconsistent results. Following further refinements, however, clinical trials resumed in 1994 at Brookhaven and at MIT, in association with nearby medical schools and hospitals.

Human health has always been at the heart of biological research within the energy agencies, and it has thus been the central subject of the last two chapters. But from the earliest days of the AEC, at a time dominated by anxiety about radioactive fallout, environmental and ecological studies, too, have been a natural part of the picture. Next, then, a short history of environmental research—research born of worries about the fate of wind-blown products of nuclear blasts and sustained today by a much wider concern about the global effects, and lasting impact, of energy production and use.

1976 Scientists from Brookhaven, led by Alfred Wolf, synthesized 2-deoxy-2-fluoro-D-glucose (FDG) labeled with the positron emitter fluorine-18. This tracer was then used by a team from the University of Pennsylvania and the NIH to obtain the first images of energy metabolism in the human brain, an early step in a revolution in brain imaging using PET.

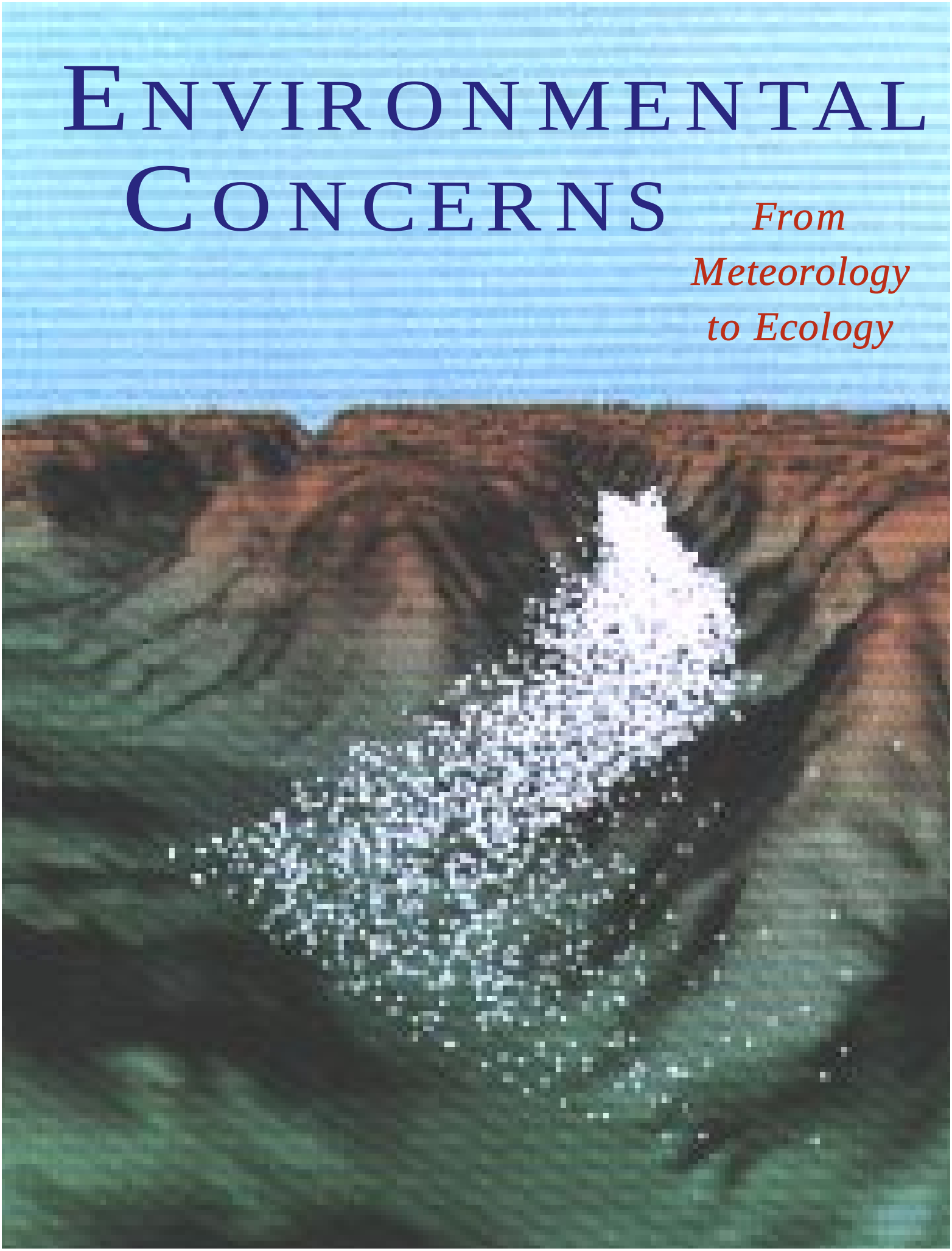
1987 At UCLA patients carrying the Huntington's disease gene were identified with PET about five years before damage from this abnormal gene could be identified by symptoms, behavior tests, CT, or MRI.

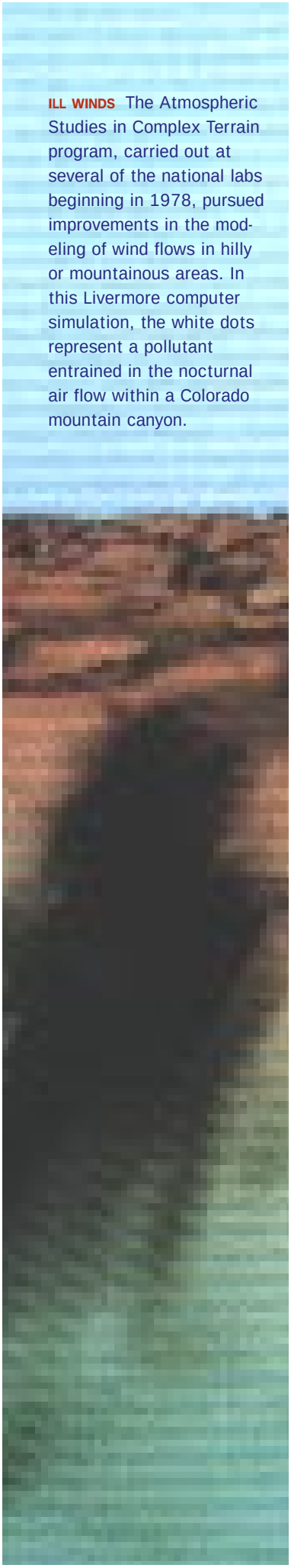
1994 Phase I clinical trials using boron neutron capture therapy to treat glioblastoma multiforme began at Brookhaven, in collaboration with the Beth-Israel Medical Center, New York.

1997 The Regional Neuroimaging Center was launched at Brookhaven, jointly funded by OBER and the National Institute on Drug Abuse. It will use state-of-the-art medical imaging technologies such as PET, SPECT, and MRI to study the biochemical roots of drug abuse and addiction in an effort to develop more effective treatments.

Environmental Concerns

From Meteorology to Ecology





ILL WINDS The Atmospheric Studies in Complex Terrain program, carried out at several of the national labs beginning in 1978, pursued improvements in the modeling of wind flows in hilly or mountainous areas. In this Livermore computer simulation, the white dots represent a pollutant entrained in the nocturnal air flow within a Colorado mountain canyon.

In matters of the environment, public awareness lagged far behind the activities of the energy agencies. As early as the forties and fifties, in an era when most people had never even heard the word "ecology," the AEC was forging an enviable record of environmental and ecological research. The initial catalyst was again the development of nuclear weapons and the two decades of atmospheric testing that followed. Estimating the health effects of released radioactivity depended not only on epidemiology and radiation biology, but also on knowing the fates of the airborne radioisotopes in the first place. Meteorology and oceanography were no less important than biology—as was research into the ecological processes that cycled materials through plants and animals to human beings. Atmospheric and environmental studies thus fell naturally within the purview of biomedical research.

An Eye on the Weather

In the postwar years, responsibility for fallout monitoring was spread among several laboratories. Chief among them was the Health and Safety Laboratory (now the Environmental Measurements Laboratory) in New York City, which established the earliest and most authoritative monitoring network in the world—and ultimately produced an integrated history of the distribution of nuclear weapons debris in the air, on land, and in water, as well as in plants and animals, especially the human food chain. As part of the High-Altitude Sampling Program, for example, instrumented balloons and aircraft were sent aloft to sample the stratosphere and to assess the exchanges of material between the stratosphere and the lower atmosphere. The resulting data contributed in a concrete way to the international moratorium on above-ground testing in 1963.

Beyond measurement, however, lay the more daunting challenge of prediction—a challenge that would naturally breed three distinct research thrusts: inquiries into the transport of radioactive materials released near the ground (a situation that might arise following, say, an accident at a weapons production facility), research into how clouds scavenge radionuclides and then deposit them in rain, and efforts to understand the global transport of materials released during atmospheric weapons tests.

In pursuit of answers to the near-surface question, several of the national laboratories installed meteorological facilities, including several Air Resources Laboratory (ARL) facilities operated by the U.S. Weather Bureau for the AEC. There investigators sought scientific methods to predict how airborne materials are transported in the lower atmosphere and how their eventual deposition depends on the nature of the material and on atmospheric and topographic variables, including the presence of complex mountainous terrain. Using the collective results of these efforts, Frank Gifford and his colleagues at the ARL Atmospheric Turbulence and Diffusion Laboratory in Oak Ridge then developed a set of curves for calculating the spread of pollution from a "point source." In a time when the slide rule was the dominant computational tool, these dispersion models won international acceptance as tools for predicting the fate of nuclear reactor emis-

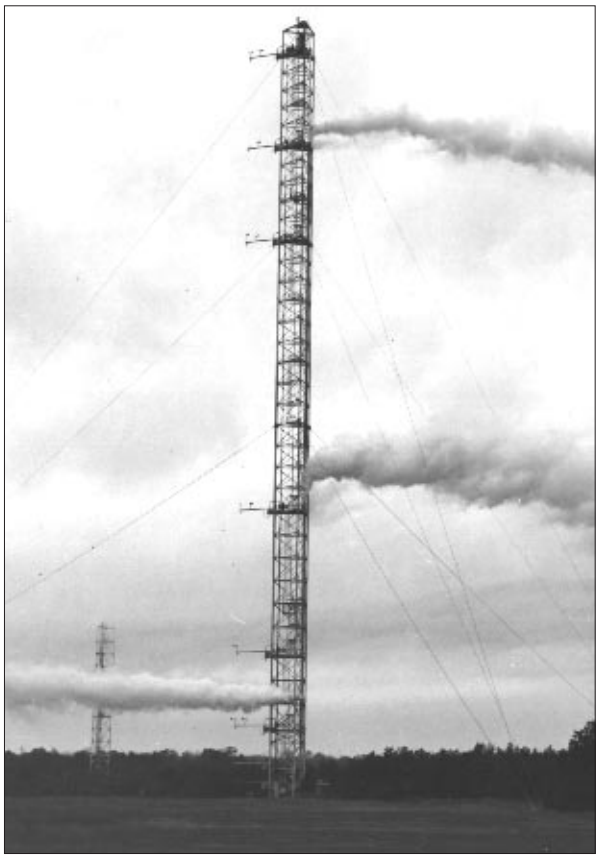
1949 Brookhaven scientists began a thirty-year program aimed at assessing the effect of radiation on living plants. Much of the work would take place at the cultivated Gamma Field, established in 1951. Results here and at Oak Ridge would confirm Brookhaven predictions that relative radiosensitivity among plant species varies with nuclear volume and chromosome size.

1950 Using phosphorus-32 in a Connecticut lake, Evelyn Hutchinson at Yale documented the quantitative cycling of the element—an essential and often limiting nutrient—within a lake ecosystem.

1951 The AEC supported the establishment of the Laboratory of Radiation Ecology at Savannah River, directed by Eugene Odum of the University of Georgia.

sions and industrial pollutants.

A natural part of the effort to understand atmospheric dynamics was the use of tracers to track the movement of materials, both locally and around the globe—not unlike the use of radionuclides to follow dynamic processes in the human body. Early "tracers of opportunity" included such natural constituents of the atmosphere as spores and ozone, as well as power plant emissions and debris from weapons tests. In at least one case, a nuclear weapon was even "salted" with tungsten, which could be conveniently traced around the world. Today's experiments in the outdoor laboratory are more benign. In the seventies, inert chemical tracers were developed at the ARL facility in Idaho Falls, at the Environmental Measurements Laboratory, at Brookhaven, and at Los Alamos. Together with ultrasensitive detectors, these tracers are now used in dispersion experiments extending up to 2500 kilometers.

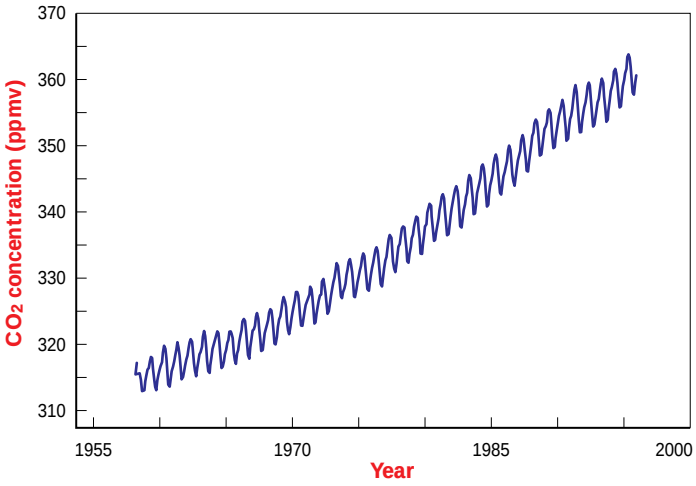


THE WAY THE WIND BLOWS Early research aimed at improving models to predict the near-surface dispersion of pollutants relied in part on special meteorological facilities such as this one at Brookhaven. On this particular day, as shown by the three plumes, the wind was blowing in different directions at three heights above the ground—a worst-case scenario for the spread of airborne materials.

Early AEC studies of cloud chemistry evolved no less dramatically. The initial studies focused on the scavenging and deposition of airborne radionuclides, but by the seventies, concerns had shifted to industrial pollutants. In this new era of environmental awareness, acid deposition—more popularly, acid rain—promptly blossomed into an international issue, blamed for the decline of forests, damage to aquatic ecosystems, and human respiratory illness. In the mid-seventies, building on the earlier AEC studies, ERDA scientists were among the first in the U.S. to tackle this problem. In 1976 ERDA established the Multistate Atmospheric Pollution Power Production Study, a program of atmospheric experimentation and modeling that focused on the regional transport and chemical transformation of emissions from oil- and coal-fired power plants. Working with the Environmental Protection Agency and the Electric Power Research Institute, this program provided part of the justification for subsequent controls on sulfur emissions from power plants. Then, in 1980, as part of the ten-year, multiagency National Acid Precipitation Assessment Program, OHER established the Processing of Emissions by Clouds and Precipitation program, which focused three decades of research experience on the acid rain issue.

A Changing Climate

In the area of atmospheric studies, the legacy of the fifties and sixties has thus been especially fertile. But perhaps the richest payoff has been a heightened awareness of our atmosphere's complexity and, in

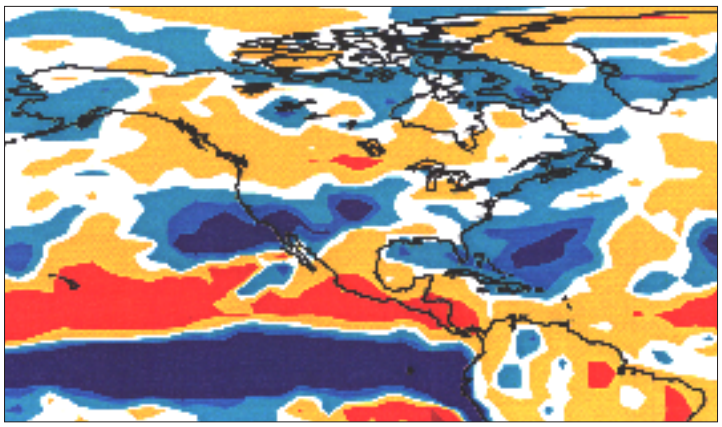


A DANGEROUS TREND? The forty-year record of atmospheric CO_2 concentrations on Mauna Loa in Hawaii depicts an undeviating upward trend, as well as predictable seasonal variations. Since atmospheric CO_2 concentrations have long been correlated with global temperature, these measurements by C. David Keeling of the Scripps Institution of Oceanography, supported in part by the energy agencies, were an important catalyst in stimulating today's research on global climate change.

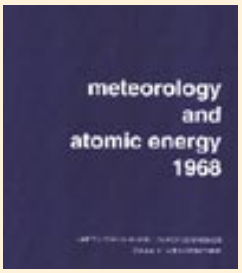
turn, a keener appreciation of its sensitivity to human activity. The third of the AEC's major research thrusts—atmospheric dynamics on a global scale—contributed in an especially important way to this growing environmental awareness.

In the early sixties, the AEC's interest was the global transport of weapons test debris. Accordingly, at Livermore, mathematical physicist Cecil Leith was one of only a handful of researchers in the world using the emerging power of scientific computing to simulate global atmospheric dynamics. Later, he would move on to the new National Center for Atmospheric Research (NCAR) in Boulder, where he established its reputation as one of the world's leaders in developing atmospheric general circulation models (GCMs)—advanced climate models that provide not short-term meteorological forecasts, but rather long-range prognoses of global climate. In the early seventies, with AEC support, NCAR's Warren Washington was the first to use their GCM to study the possible climatic effects of the heat generated by energy production.

Looming even larger, however, was growing evidence that human activities were tilting the worldwide balance of atmospheric gases: By the late seventies, the burning of fossil fuels was recognized as a principal culprit in a steadily rising level of atmospheric carbon dioxide (CO_2), a trend dramatically illustrated by the measurements of C. David Keeling at the Mauna Loa Observatory in Hawaii. A direct relationship between atmospheric CO_2 concentrations and air temperatures had been known since the turn of the century, so it was natural to be alarmed about the possibility of global warming if the trend continued unchecked. In 1977 ERDA was the first federal agency to outline a comprehensive research program on the CO_2-climate connection.



A CHANCE OF RAIN Global climate models aim at predicting the worldwide consequences of certain input assumptions—a rising concentration of atmospheric CO_2, for example. Here, a Livermore simulation predicts the changes in rainfall patterns during an El Niño event, a period of surface water warming in the tropical Pacific. Precipitation increases (compared with normal) are foreseen in areas shown in blue, whereas decreases are predicted for areas shown in red.



1955 Early efforts to understand atmospheric transport and dispersion led to the publication of *Meteorology and Atomic Energy,* which quickly became a basic meteorological reference. A second edition, published in 1968, would for years remain the definitive reference for small-scale meteorology. By 1984 it had evolved into the thousand-page volume, *Atmospheric Science and Power Production.*

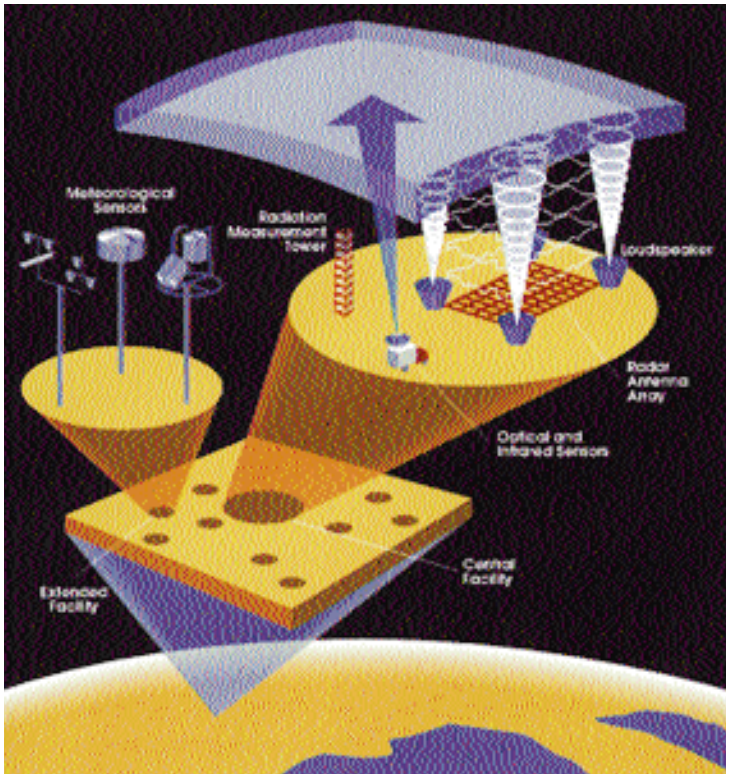
1956 The Environmental Research Branch was created within the AEC's Division of Biology and Medicine, for "research pertaining to man and his environment, including disciplines such as ecology, oceanography, marine biology, geophysics, and meteorology."

1959 Wallace Broecker at Columbia University used natural radiocarbon in the ocean to quantify ocean circulation processes.

1960 In advance of the proposed use of nuclear explosions to excavate a harbor near Cape Thompson, Alaska, AEC-sponsored scientists began an exhaustive ecological survey of the area. This "environmental assessment" predated by almost a decade the requirements of the National Environmental Policy Act of 1969.

1960 University of Wisconsin scientists used radiosodium and radioiodine to document the physical and biological mechanisms of material mixing and transport in a chemically stratified lake.

1961 Researchers at Oak Ridge developed a specific-activity methodology to estimate the bioaccumulation of radionuclides in terrestrial and aquatic organisms. The following year they would introduce the first analog models to simulate the distribution, cycling, and fate of radionuclides in ecosystems.



ARM'S REACH OBER's Atmospheric Radiation Measurement program will provide a firmer foundation for computer models used for atmospheric research and climate predictions. Data are being acquired from three Cloud and Radiation Testbed (CART) sites, located in the southern Great Plains, on the North Slope of Alaska, and in the western Pacific. Each CART site consists of a central facility and smaller clusters of instruments deployed over an area of 22,500 square kilometers.

Over the past two decades, the DOE has tackled some of the central tasks in global climate research. One has been to examine the global carbon cycle, quantifying by way of modeling and measurement all significant natural sources and sinks of CO_2, as well as those attributable to human activity. One of the key figures in this area was Oak Ridge's Jerry Olson, who was among the first researchers to identify the importance of carbon exchange between terrestrial ecosystems and the atmosphere. A second task has been the continuous refinement of GCMs as tools for simulating climate dynamics and for predicting climate change. Using one such model, Warren Washington estimated in 1984 that a doubling of atmospheric CO_2 levels would produce a global temperature rise of 4 degrees Celsius. This remarkable early prediction has been revised only slightly, to 1.5–3.0 degrees Celsius, despite the availability today of far more elaborate models.

Yet another task was the continuing challenge of measurement. In 1989 the government launched the U.S. Global Change Research Program, an ambitious multiagency effort to focus on global environmental change and its impacts. The DOE responded by establishing the largest surface-based research program among the U.S. climate research efforts, the Atmospheric Radiation Measurement (ARM) program. This multiinstitutional effort strives to quantify the fate of solar radiation interacting with clouds and falling on the earth and to capture that knowledge in improved atmospheric models. Some fundamental questions drive the effort: How much solar energy is reflected or absorbed by clouds and atmospheric aerosols? How much is reflected or absorbed at the earth's surface? And how much is returned to space as heat? Only by understanding these processes can we hope to further refine models of the earth's climate and thus reconstruct the past and more confidently predict the future. Accordingly, the ARM sites represent the most intensively measured volumes of the atmosphere ever maintained for an extended period.

Today, global climate change research continues as a vigorous multiagency priority, propelled by the issue's overarching importance and challenged by the profound complexity of atmospheric and biological processes. The DOE is now one of several federal agencies, notably NASA, the National Science Foundation, and the National Oceanic and Atmospheric Administration, working as partners to predict future concentrations of greenhouse gases, to assess

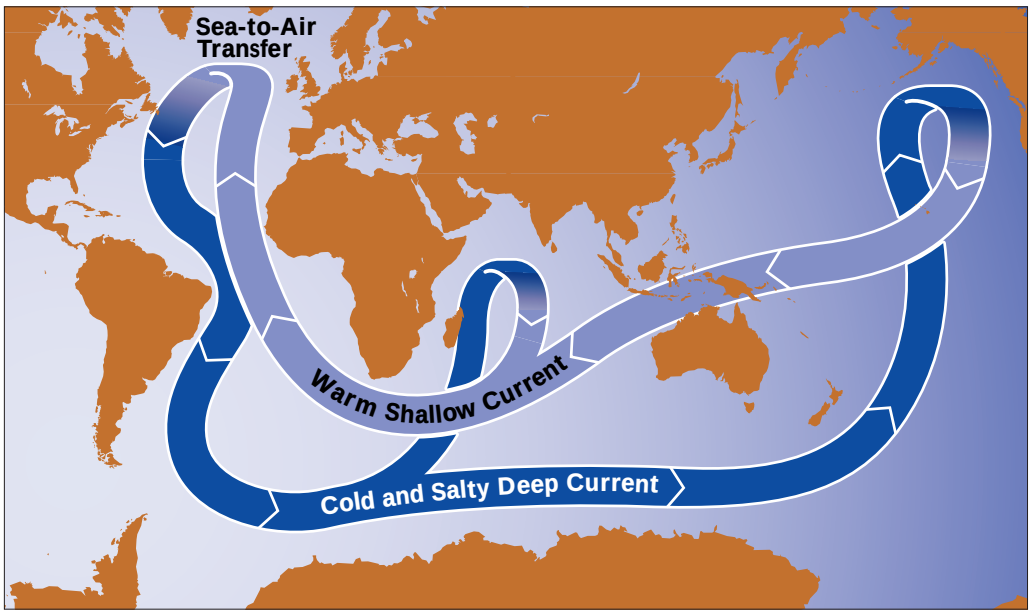
their likely effects on the climate, and to evaluate the resulting biological and economic impacts.

THE DYNAMIC OCEAN

Perhaps even more deeply mysterious than atmospheric dynamics are the workings of the oceans. From the earliest days of atmospheric testing, the AEC sought to understand the fate of radioactive fallout over Pacific waters. But the agency's interest was greatly heightened in 1954, when a Japanese fishing boat and its cargo of fish were contaminated following a Pacific Ocean nuclear test. Suddenly, the sea and its denizens were subjects of intense inquiry. Ensuing AEC support for oceanic research reaped unexpected rewards.

One of the pioneers was Wallace Broecker, of Columbia University's Lamont-Doherty Geological Observatory (now the Lamont-Doherty Earth Observatory). Soon after the 1954 incident, he began using natural and bomb-generated radionuclides as "clocks" to study ocean dynamics. By measuring the ratios of carbon isotopes, for example, he found that, whereas the average CO_2 molecule remains in the atmosphere for seven years, bottom water in the Pacific Ocean turns over only once every thousand years. His analyses of CO_2 absorption by the oceans also provided new data on the fate of atmospheric CO_2 more than a decade before it would become an important climate change issue. Broecker's methods were seminal: Distributions of stable and radioactive isotopes were subsequently used to measure the accumulation rates of deep-sea sediments and to develop the first records of climate change in the past. Broecker also turned to radionuclides as tracers. Using strontium-90 from fallout, for example, he was able to define the Atlantic Ocean "conveyor belt" that operates between Greenland and the equatorial tropics. In 1996, in part for work supported by the AEC, he was awarded the Presidential Medal of Science.

In the seventies, increasing attention turned to the ocean margins. Fallout from past decades was washing into lakes and rivers, then moving downstream into coastal waters. Toxic chemicals followed a similar path. At the same time, nuclear



A GLOBAL CONVEYOR BELT The connectedness of the world's oceans is suggested by this schematic depiction of the "great ocean conveyor." Evaporation in the North Atlantic and transfer of the vapor to the Pacific leaves behind saltier water, which then sinks and drives the cold deep current. The warm surface current has a direct impact on world weather, accounting, for example, for Northern Europe's relatively mild winters. Many of the details of this global conveyor were revealed by early AEC-sponsored research.

1962 Radiotracers were used by Oregon State scientists to show that fecal pellets produced by marine organisms are the major vector for transporting substances from the ocean surface to deep water.

1963 Cecil Leith at Livermore developed one of the first atmospheric general circulation models, providing the foundation for future global change calculations and global weather predictions.

1967 Oak Ridge began a major effort to understand the thermal effects of nuclear power plants. Aquatic ecology programs at Oak Ridge, Hanford, and Savannah River would expand dramatically in the seventies, in response to the National Environmental Policy Act. The research would reveal few adverse effects of thermal discharges into aquatic ecosystems.

1968 Two permanent sites were set aside for long-term ecological research: 120 square miles of sagebrush desert near Richland, Washington, and 100 acres of prairie forest border at Argonne. Field work was inaugurated at both sites.

1971 The first terrestrial carbon cycle models were developed from data obtained by the International Biosphere Program, jointly supported by the AEC, the National Science Foundation, the U.S. Forest Service, and other agencies.

1972 Oak Ridge and Columbia University scientists used carbon-14 and the inorganic chemical properties of seawater to quantify the ocean carbon cycle and to determine the fate of CO_2 produced by fossil fuel combustion.

1972 The AEC designated Savannah River as the first National Environmental Research Park.

1973 The Atmospheric Release Advisory Capability was established at Livermore to track and predict the transport of potentially dangerous atmospheric releases, both natural and anthropogenic.

facilities were being developed on major river systems throughout the U.S., and oil exploration and waste disposal were being proposed for offshore waters. The resulting interdisciplinary studies led to fresh insights into continental shelf dynamics—and ultimately to confident predictions of the consequences of oil spills, to standards for the release of hazardous substances at sea, and even to scientific fishing forecasts.

Impelling the earliest of this oceanographic work was concern about ocean-borne transport of radioisotopes away from the sites of atmospheric weapons tests in the South Pacific. But an equally vital human health issue was the accumulation of radioactivity in seafood. Accordingly, AEC-supported researchers founded the field of marine radioecology by studying the bioaccumulation of radionuclides in marine organisms and assessing the consequent ecological risks. One of the researchers, Roger Revelle, of the Scripps Institution of Oceanography, received the Presidential Medal of Science in 1990, in part for his pioneering work in this area. As part of this effort, the first application of carbon-14 as an ecological tracer was to measure photosynthetic rates in the world's oceans. For twenty years, AEC research provided fundamental insights into marine food chains and produced most of the world's information on the rate of CO_2 fixation and on its fate in the oceans—information that would feed naturally into later work on global climate change.

The Outdoor Laboratory

This prescient work on ocean ecosystems points, in fact, to yet another strand of environmental research, one intricately entwined with studies of atmospheric and oceanic dynamics and the dispersion of air- and waterborne contaminants. Its early theme was the fate and effects of radioactivity released into terrestrial and freshwater ecosystems. In concert with research on human health effects, these strands of environmental exploration thus sought a complete picture of the impacts of nuclear technology: What is the fate of the radioactive materials we release? What are their direct effects on humans? And what are their effects on the biosphere of which we are a part? The seventies would again broaden the charge to encompass all energy-related emissions, but the larger question would remain the same: What are the consequences of the energy choices we make?

In approaching such questions, the AEC's most pervasive contribution followed the theme of its efforts in nuclear medicine and atmospheric studies, namely, the use of radioactive tracers. Beginning with modest efforts at several universities and national laboratories, *radioecology* grew to encompass studies of material pathways and flow rates through terrestrial and aquatic ecosystems of every description. The research involved nearly all of the AEC national laboratories, in part because of their locations in different environments of the country.

At first, radiotracer studies dealt mainly with iodine-131, a short-lived fission product deposited on the landscape from

MEASUREMENTS AT SEA

■ In light of their research activities, it is not surprising that the energy agencies have also played a significant role in developing instrumentation for oceanography. Examples include acoustic sounders to measure the mass and movement of plankton, modified flow cytometers that have isolated new species of organisms, and expendable microcomputer-controlled sensors that can be dropped from airplanes or ships. Another was a fast-repetition-rate fluorimeter, developed by Paul Falkowski at Brookhaven, that measures real-time photosynthesis in seawater. Notably, this instrument played a central role in recent, highly publicized experiments that produced a short-lived phytoplankton bloom in the South Pacific by "fertilizing" the ocean with iron. ■

EXPLORING NEW FIELDS Eugene Odum, a young University of Georgia professor, pioneered the use of radionuclides as ecological tracers in the fifties at the Savannah River reservation. In recognition of his contributions to ecological research, Odum shared the 1987 Crafoord Prize, awarded by the Royal Swedish Academy of Sciences in areas not covered by the Nobel prizes.

weapons-material production plants, and with radioactive products released into the Columbia River from the reactors at Hanford. Later, nuclear testing led to the spread of radioactive cesium and strontium isotopes, which prompted research projects on soil migration, root uptake, uptake by grazing and browsing animals, and transfer to food products. A major part of the aquatic research was conducted at Oak Ridge, Hanford, and Savannah River, whereas much of the work on soils, plant uptake, and the dairy pathway was done at agricultural schools within major universities. Together, these research efforts pioneered the quantitative study of environmental processes and provided not only the mechanistic understanding, but also the historical databases that supported the DOE's early environmental restoration program, and that underlie today's ongoing cleanup of contaminated defense sites.

But the first ecological research linked to the nuclear era focused on radioactivity's direct effects—work that predated even the AEC. Already mentioned on page 12 were studies by fisheries scientists from the University of Washington, aimed at assessing the possible effects of effluents from Hanford's wartime reactors. And by 1946 the region's sheep and cattle were being monitored for radioactive iodine uptake. Nor was the plant kingdom ignored. For thirty years, starting in 1949, Brookhaven scientists studied the effects of radioactivity on plants, first on introduced species and plants of economic importance and later on native species. An important result of this work was the discovery that the volume of the cell nucleus in different plant species was an important factor in determining the species' relative sensitivity to radiation.

Then, in 1951, the AEC took a major step toward the systematic study of ecology: The agency granted $10,000 each to the University of South Carolina and the University of Georgia to conduct a biological inventory of the Savannah River site, in preparation for constructing a facility there to produce materials for nuclear weapons. Eugene Odum led the Georgia effort, in time putting together a research center of international repute, first called the Laboratory of Radiation Ecology, then the Savannah River Ecology Laboratory. Early studies of plant succession and pioneering applications of radiotracers to the study of food chains and food webs led to studies of wetlands ecology, endangered species of the Southeast, regional biodiversity, and the environmental chemistry of trace metals.

Also in the fifties, the AEC created its Environmental Sciences Branch to support studies of terrestrial, freshwater, and marine systems, with the emphasis on the long-term fate and effects of radionuclides. In this encouraging environment, Stanley Auerbach at Oak Ridge shifted his emphasis from laboratory experiments to field work focused on how radionuclides might migrate through the food chain, from water and soil to plants, animals, and humans. A

1975 ERDA established the first integrated program dedicated to understanding the movement of contaminants and other materials in coastal waters.

1975 Research at Oak Ridge documented the importance of dry deposition as a contributor to total acid precipitation in a forested watershed.

1976 Global carbon cycle models predicted the future doubling of atmospheric CO_2 from the combustion of fossil fuels. The following year, ERDA would launch the first systematic federally funded program to study global climate change as a possible consequence of this rising atmospheric CO_2 level.

1976 Edward Goldberg at the Scripps Institution of Oceanography used radionuclide profiles in marine and lake sediment cores to quantify the historical effects of human activities on aquatic environmental quality.

1977 An ERDA conference on CO_2 and climate change defined a multidisciplinary research agenda that would later be pursued by the multiagency U.S. Global Change Research Program.

1980 The DOE designated six additional National Environmental Research Parks at Fermilab, Hanford, the Idaho National Engineering Laboratory, Los Alamos, the Nevada Test Site, and Oak Ridge.

1980 A decade of research at the University of Texas on screwworm genetics, ecology, and radiation sensitivity, jointly sponsored by the DOE and the U.S. Department of Agriculture, concluded with the development of successful measures to control screwworm infestation in the U.S.

A TOWERING SUCCESS Oak Ridge's Walker Branch Watershed project is one of the two longest-running forest ecosystem studies in the U.S. The aerial photo on this *Science* cover shows a meteorological tower above the forest canopy. Information on weather and atmospheric deposition is among the baseline data being used in an effort to understand the dynamics of forest ecosystems.

particular public worry, for example, was strontium-90, which can reach humans via cattle fodder and cow's milk and then accumulate at dangerous levels in bones. As a result of his pioneering field work, Auerbach would establish a reputation as one of the country's leading ecologists.

Auerbach and his colleagues pursued some of their first studies in the dry bed of White Oak Lake, where Oak Ridge once flushed low-level radioactive wastes. In the process of their studies, Oak Ridge ecologists introduced computer simulations to ecological science, a striking innovation in 1958. Products of this and other AEC research on radionuclide transport and bioaccumulation still provide the basis for models used to assess the impact of radioactive emissions on living organisms, including humans.

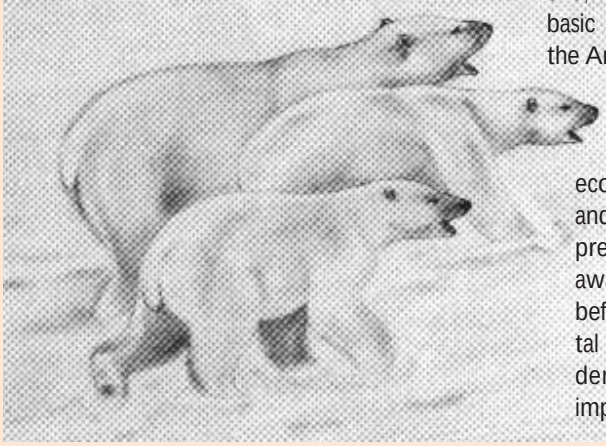
In the early sixties, attention at Oak Ridge shifted to the "cesium forest," a stand of radiolabeled tulip poplars, which produced some of the first research to document the extent to which an element is recycled within a forested ecosystem. Efforts then expanded in 1966 to include

EL VERDE: ECOLOGY OF A TROPICAL RAIN FOREST

■ Based on experimental evidence that plant resistance to radiation is a function of cell nuclear volume (see page 37), it appeared likely that some tree species would be highly sensitive to gamma and neutron radiation. To assess the potential effects of nuclear warfare or a major reactor accident on forest ecosystems, the AEC thus began a broad program of forest radioecology. Beginning in 1963 and continuing into the seventies, the AEC funded a comprehensive study of the effects of gamma-rays (high-energy x-rays) on a tropical forest at El Verde in the Luquillo Mountains of Puerto Rico. Howard Odum, who would share the Crafoord Prize with his brother Eugene, headed the study. A 10-kilocurie cesium-137 gamma source was placed by helicopter at the center of a selected site. At the end of three months, it was removed and a large team of scientists began detailed comparative studies of the irradiated site and two nearly identical control sites. The study represented one of the most comprehensive and detailed experimental investigations of a terrestrial ecosystem ever conducted. The disordering stress of the radiation served as an especially illuminating experimental tool for studying the mechanisms that maintain order in ecosystems. ■

CAPE THOMPSON: BALANCING TECHNOLOGY AND THE ENVIRONMENT

■ By the late fifties, thoughtful scientists had become deeply aware of the intricacy and sensitivity of the ecological web. At the same time, proponents of the Plowshare program were proposing to use nuclear detonations to excavate harbors and construct canals. To pave the way for such projects, an experimental harbor excavation, dubbed Project Chariot, was proposed for Cape Thompson in northwest Alaska. In a landmark effort, the AEC sent a team of scientists to survey the area beforehand—the first major ecological survey ever done in advance of proposed development. Among the goals were to gather enough information to allow credible estimates of the biological cost of the harbor project and to establish a baseline for assessing future change, natural and otherwise. In the end, the study contributed more basic ecological information about the Arctic than all previous investigations combined. Further, it suggested that Project Chariot would entail unacceptable ecological and public health risks, and, perhaps most important, it presaged a new era of ecological awareness, almost a decade before the National Environmental Policy Act of 1969 would demand such environmental impact assessments. ■



ecosystem metabolism, thus forming the basis for the DOE's later terrestrial carbon cycling research and becoming the centerpiece for the International Biological Program's global woodlands research effort in 1968. Still later, ecologists launched the Walker Branch Watershed project, which continues today, one of the two longest-running studies of a forest ecosystem in the U.S. Over the years, it has afforded deep insights into the flow of nutrients, water, and contaminants through a forested watershed and on the physical, chemical, and biological processes that control this flow. More broadly, it has provided new tools for evaluating the effects of human activities on natural environments.

The AEC was no less committed to supporting ecological research in universities, where ecologists and limnologists used tracers to study the transport of materials in lakes and rivers, sometimes using entire small lakes as experimental ecosystems. In 1951, for example, Arthur Hasler at the University of Wisconsin took a whole-ecosystem approach in testing a way to manipulate algal and fish production. He separated the two halves of an hourglass-shaped lake in northern Wisconsin with an earthen barrier, thus creating two separate lakes. One was then treated with lime to reduce the acidity and thus the concentration of dark organic matter in the water, while the other remained untreated as a control. Early efforts such as this paved the way for much of modern limnology by offering key insights into how lake ecosystems work and how they might be managed to enhance their intrinsic and utilitarian values.

On another ecological front, the late sixties saw growing environmental concern over the nonradioactive thermal discharges from nuclear power plants (which typically used river water as a coolant, heating it in the process). The lack of information on the sensitivity of aquatic organisms to heated discharges was highlighted in envi-

1980 The Congress established the ten-year National Acid Precipitation Assessment Program, involving several DOE national laboratories as major participants. Four years earlier, ERDA had responded to acid rain concerns by launching the Multistate Atmospheric Pollution Power Production Study.

1981 Tomas Hirschfeld at Livermore developed the remote fiber fluorimeter, an early application of fiber optic technology. Such instruments are now widely used for remote monitoring of environmental contamination.

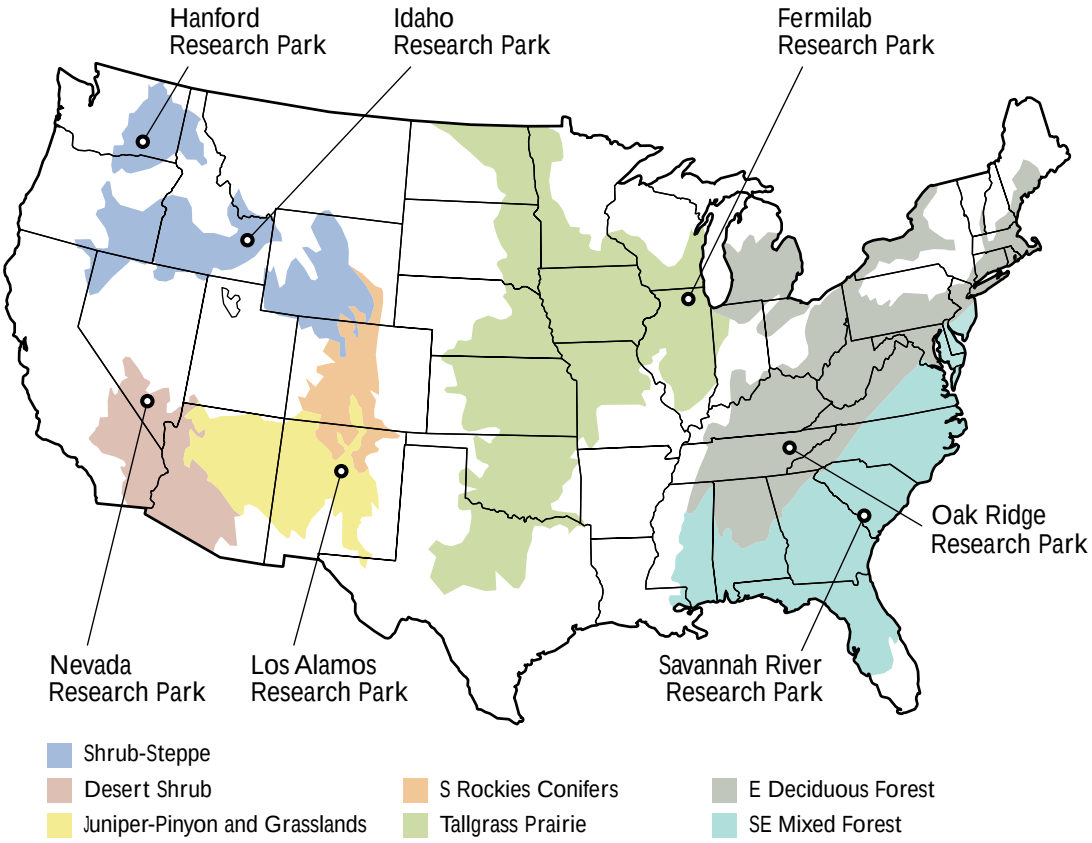
1984 With OHER support, Warren Washington at the National Center for Atmospheric Research used a coupled atmosphere-ocean general circulation model to predict that a 4 degree Celsius global temperature increase would accompany a doubling of the atmospheric CO_2 concentration.

1985 Pacific Northwest published in book form the first energy-use model of CO_2 emissions; it would subsequently be adopted internationally to predict global emissions as a function of future energy and economic development.

1988 OHER initiated the first theoretical ecology research program devoted entirely to developing a theoretical basis for understanding and predicting the behavior of complex ecological systems.

1990 Oak Ridge's Carbon Dioxide Information Analysis Center produced a report entitled "Trends: A Compendium of Data on Global Change." It would become the global change data most often requested by government, academic, and private customers.

1991 Successful remediation of contaminated sediments began at Savannah River, based on stimulating the activity of native subsurface microorganisms capable of degrading the contaminants.



NATIONAL PARKS Seven DOE National Environmental Research Parks represent major ecoregions covering more than half of the lower 48 states. The parks are open to researchers for ecological studies and to the general public for environmental education.

ronmental impact statements prepared by AEC scientists in response to the requirements of the National Environmental Policy Act. As a result, in the early seventies, the AEC expanded its aquatic ecology efforts to include programs at Oak Ridge, Hanford, Argonne, and Savannah River. The products would include data that underlie today's national water quality standards for the protection of fisheries and aquatic ecosystems from heated discharges.

But perhaps the most visible symbol of an early commitment to ecological research is a system of seven National Environmental Research Parks, each representative of an important ecoregion in the U.S. The AEC established the concept of these parks in 1972, underscoring its leadership among federal agencies in environmental research. This farsighted step led eventually to more extensive ecological research and assessment programs in other agencies, especially the National Science Foundation and the Environmental Protection Agency. Today the parks continue to serve as outdoor laboratories, where resident scientists and visiting researchers study ecosystem responses to a whole gamut of environmental changes.

Taken together, ecology programs within the energy agencies have had a profound effect. AEC biologists pioneered and, for years, dominated ecosystem studies, touching every facet of ecological research, from the cellular to the global. Collectively, they created the new field of radioecology and in so doing were largely responsible for changing ecology from a mainly descriptive discipline to a fully analytical and quantitative science. AEC biologists were among the first using tracers to track the pathways of chemicals through animals and food chains, to follow the movements of animals, and to study the natural cycling of materials. They also pioneered the use of a systems analysis approach to model the fate and effects of

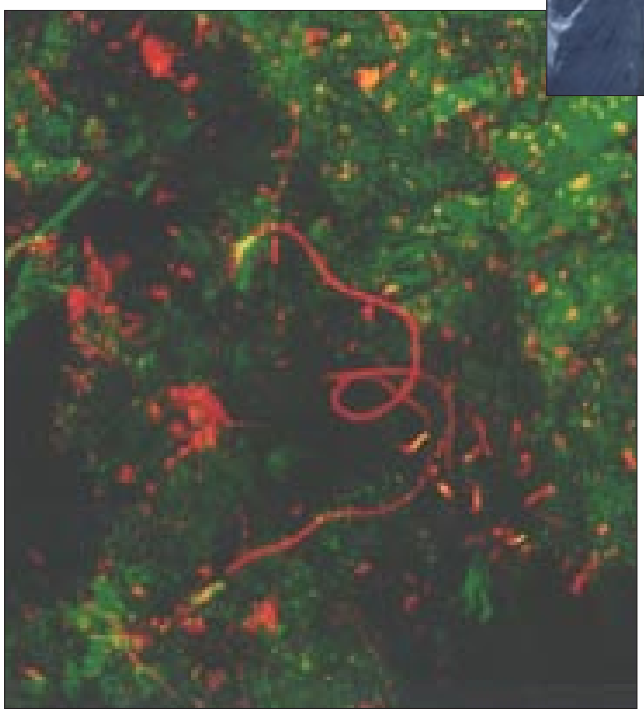
environmental contaminants, and they were early leaders in the study of large ecosystems. The spirit of these efforts continues today in studying global climate change and its environmental effects.

RECLAIMING THE PAST

A half-century ago, environmental research emerged in response to concerns about fallout and the effects of atmospheric weapons tests. Following the 1963 ban on aboveground tests, and in concert with a growing environmental movement, attention shifted to a much broader set of issues—ecosystem modification, acid rain, even the possibility of global climate change. Over the past decade, OHER and OBER have widened the scope of their environmental research still further, impelled by a commitment to clean up the contamination left by past generations.

From the dawn of the Atomic Age, workers were well aware of the potential for harm harbored by the radioactive waste they produced; much of the research described in the preceding pages testifies to their concern. But treatment and storage technologies were relatively primitive, and the needs for weapons research and nuclear power production were compelling. The result was a legacy of contamination. In the same era, nonnuclear wastes were also handled carelessly: Organic solvents were discarded with little thought to the consequences, and toxic materials were often simply buried and forgotten. Today, we are less tolerant of environmental insults and more confident of our ability to avoid them—even to remedy those of the past. Among the means available to us are the tools of modern molecular biology.

The first forays into bioremediation, the use of biological processes to address the problems of waste management, came in the late sixties, when Oak Ridge sought to harness microbes to clean up wastes from coal conversion reactions and nuclear materials processing. More recently, Brookhaven patented a process that relies on naturally occurring citric acid to treat



NOTES FROM UNDERGROUND Once considered a lifeless place, the earth's deep subsurface has now been shown to be home for a host of microorganisms. Using innovative aseptic techniques, scientists supported by OHER's subsurface science program isolated microbes such as the red bacterial cells shown in this confocal microscope image. Associated with basaltic rock several kilometers beneath the surface in the state of Washington, these organisms obtain their energy and nutrition exclusively from the rock. Such microbial systems as this may be models for early life on earth and perhaps on other planets.

1992 Pacific Northwest developed techniques for aseptic drilling and microbiological sample-handling to collect and preserve microbial populations from the subsurface for potential application to bioremediation and pharmaceuticals.

1993 OHER Global Change Research (conducted by scientists at the National Oceanic and Atmospheric Administration, Columbia University, and East Anglia University) produced a historical climate database revealing a global trend of increasing nighttime temperatures over the past fifty years, a finding consistent with the greenhouse gas warming theory.

1994 OHER launched the Microbial Genome Initiative to understand the workings of the simplest life forms. Within three years, Craig Venter at The Institute for Genomic Research would sequence the complete genomes of four microorganisms.

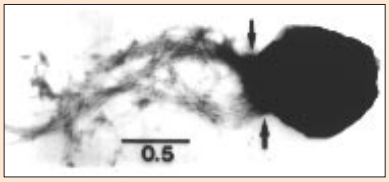
1995 Research at Pacific Northwest led to the development of an in situ redox manipulation technique to immobilize or destroy selected contaminants in ground water. The technique would be promptly applied at DOE sites to clean up ground water contaminated with chromium.

1995 OHER conceived the Natural and Accelerated Bioremediation Research program, a multidisciplinary program designed to enhance the potential of bioremediation as a useful, reliable, and cost-effective technique for cleaning up contaminated environments.

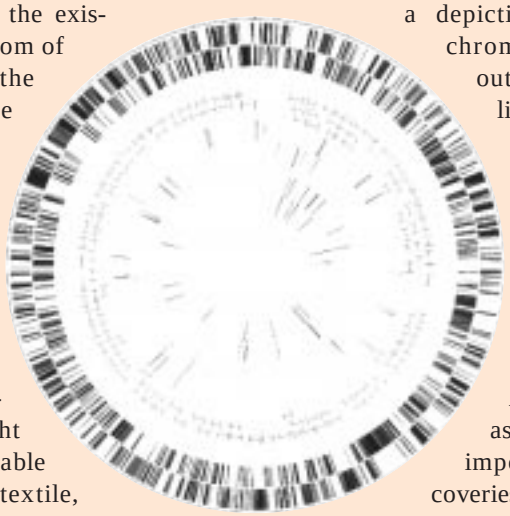
1995 Livermore researchers contributed a news-making analysis to the second Intergovernmental Panel on Climate Change Scientific Assessment: The "balance of evidence suggests a discernible human influence on climate."

1995 Field experiments at Oak Ridge, Kansas State University, and the Smithsonian Institution on plant responses to elevated CO_2 demonstrated enhanced plant growth and productivity and increased carbon sequestration by ecosystems.

DEEP SECRETS



■ In 1996 scientists supported by the DOE's Microbial Genome Program reported the complete genome sequence of *Methanococcus jannaschii,* a methane-producing microorganism that dwells around "white smokers" on the seafloor. The details of the genome confirm the existence of a third kingdom of living organisms, the Archaea (from the Greek word for "ancient"), distinct from other microbes lacking a cell nucleus, as well as higher plants and animals. Details of the genome and the proteins it codes for might well lead to heat-stable enzymes for the textile, paper, and chemical industries; to systems that produce methane for chemical feedstock and renewable power; and even to tailor-made proteins that rid living cells of toxic contaminants. Shown above is a photomicrograph of the microbe itself; at left a depiction of its circular chromosome. The two outer rings of colored lines show the predicted protein-coding regions. The sequencing of *M. jannaschii* was prominently described in the *New York Times* and was chosen by *Discover* magazine as one of the two most important scientific discoveries of the year. ■



waste contaminated by toxic metals. The metals, even uranium, form water-soluble complexes with the citric acid, allowing them to be precipitated by bacteria or, in the case of uranium, by light. The usual products are a relatively small volume of recoverable metal and clean, reusable soil. Apart from its use at contaminated DOE sites, this process has been used successfully to remove cadmium and lead from municipal incinerator ash.

Two other recent thrusts likewise underscore the likely value of microorganisms. First was a careful look underground. In the mid-eighties, a program was inaugurated to explore the deep subsurface environment for microorganisms that might be useful in new bioremediation strategies. Microbiologists, geohydrologists, and geochemists from about thirty universities and national laboratories took part, probing deep beneath the surface at Savannah River, Hanford, and the Idaho National Engineering Laboratory, as well as non-DOE sites. As a result, previously unknown microbes and microbial ecosystems have come to light, including ecosystems that have been isolated for hundreds of millions of years, microbes that thrive at 60 degrees Celsius (140 degrees Fahrenheit) in brine twice as salty as the sea, and nonphotosynthetic bacteria whose only energy source appears to be the hydrogen produced in reactions between water and rock. The resulting Subsurface Microbial Culture Collection, housed at Florida State University, has attracted wide scientific attention—including the interest of pharmaceutical companies, for whom the collection has significant potential market value as an aid to drug screening and discovery.

Direct descendants of this program have included highly successful bioremediation schemes. During demonstrations in the early nineties, underground organic contaminants at Savannah River were effectively eliminated

by injecting air and methane to enhance the activity of bacteria already present in the subsurface. This remediation technology is now in use around the world. Meanwhile, at Hanford, researchers developed a process that exploits natural chemistry in the subsurface to form a barrier permeable to ground water that efficiently removes contaminants as the water passes through.

A second BER research thrust, focusing the technologies of the Human Genome Project on remediation needs, is even more fundamental. If the genetic details of key microbes could be obtained, they would afford profound insights into the workings of these "minimal" forms of life, some of which inhabit environments notable for extremes of temperature, pressure, acidity, and salinity, as well as high concentrations of toxic chemicals and even high fluxes of radiation. In addition to enhancing our understanding of evolution and the origin of life, the benefits would extend to medicine, agriculture, industrial processes, and, not least, environmental bioremediation. Such were the incentives for the Microbial Genome Program, launched by OHER in 1994. Among the program's early successes were the complete genomic sequences of *Mycoplasma genitalium*, the smallest-known free-living organism—and a key to understanding the minimum requirements for life—and *Methanococcus jannaschii*, an evolutionary throwback that survives entirely on inorganic nutrients near hot vents on the ocean floor. Of particular current interest is the microorganism *Deinococcus radiodurans*, which prospers even when exposed to doses of radiation that would kill the typical microbe many times over. The secret is not avoidance of damage, but rather a remarkably efficient DNA repair mechanism—one that might be engineered to allow bioremediation of dangerously radioactive wastes.

Environmental remediation thus completes a research picture that encompasses a lasting emphasis on public health and safety, a noble record of medical breakthroughs, and a deep concern for the environment. But in fact, this canvas of achievement is no more complete than any other description of scientific advance. It is more like a mural in progress than a completed portrait. The only proper conclusion must be a glimpse of the future, a look to the promise of the genome project, to the latest advances in medical imaging, and toward an era of swift environmental cleanup. In closing, then, a brief forecast for the coming years.

1996 Pacific Northwest scientists provided the first scientific evidence of active, anaerobic microbial ecosystems in the deep subsurface that derive metabolic energy from geochemically produced hydrogen. Their discovery would offer opportunities for low-cost bioremediation of ground water and for improved methods of microbially enhanced oil recovery.

1996 After receiving EPA approval, Oak Ridge conducted the first field trial of a genetically engineered microorganism in the U.S., a first step toward developing a process to degrade polycyclic aromatic hydrocarbons in contaminated soils.

1997 The William R. Wiley Environmental Molecular Sciences Laboratory at Pacific Northwest began full operation as a state-of-the-art research facility. Using advanced analytic and computational capabilities, scientists there focus on forefront research in environmental chemistry and on environmental cleanup.

AN ENDURING MANDATE

Looking to the Future

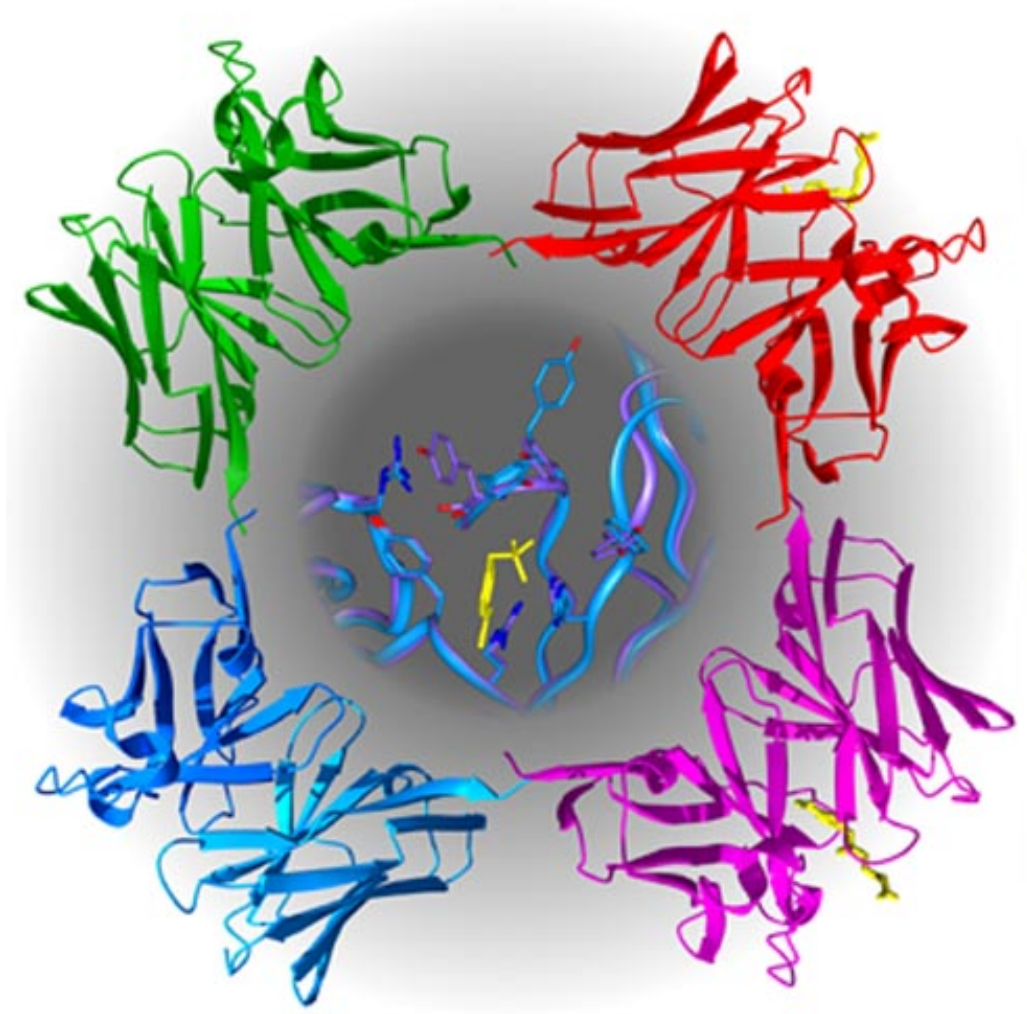
The DOE's Office of Biological and Environmental Research (OBER) currently supports research at more than 200 institutions around the country—a research portfolio that, for all its diversity, reflects a direct lineage from the earliest charge to the AEC: to exploit the promise of a new age and to safeguard the public health in the face of its uncertainties. And yet, this constancy of purpose has demanded inevitable change, as new ideas have emerged, as tools have evolved, and as the foundation of knowledge has grown. Underscoring this truth is the example of the Human Genome Project, unthinkable little more than a decade ago and yet a direct descendant of the AEC's earliest concerns about radiation's unseen effects. Seen in this light, the birth of the genome project within the Biological and Environmental Research (BER) program is no surprise.

Often characterized as the Holy Grail or the Rosetta Stone of biology, the genome project is more aptly compared to the chemists' periodic table. Just as the periodic table transformed chemistry into a rigorous and quantitative science, so will sequencing the human genome pave the way for a systematic study of biological function and dysfunction—at the same time answering some of the AEC's oldest questions about radiation and genetic damage.

The genome project links past and future in another way, as well. It points to an enduring strength of today's OBER that is again a legacy of the AEC and the national laboratories that were born of the war years: a tradition of multidisciplinary teamwork, historically grounded in daunting scientific challenges. Taking advantage of this unique asset, the BER program is contributing significantly to the nation's genome sequencing effort.

The BER program also pioneered the Microbial Genome Initiative, which, in a few short years, has already delivered news-making discoveries holding great promise for the Department's missions. Deciphering, then perhaps reengineering, the genetic organization of microorganisms opens exciting new prospects for environmental bioremediation and sustainable energy production. The future promises even more exciting developments as the fruits of this Initiative mature.

Two other forward-looking disciplines are structural and computational biology, where advances rely in large part on long-standing BER commitments to synchrotron light sources and neutron sources at our national laboratories—and on the labs' advanced computational resources. Indeed, structural biology is the linchpin in one of modern biology's central research paradigms: *sequence to structure to function*. Using a variety of techniques, most prominently x-ray crystallography, structural biology seeks to determine the structures of key biological macromolecules as clues to biological function. If we can now only learn to deduce the three-dimensional structure of proteins from genomic sequence—a challenge for computational biology—the product of the Human Genome Project will be not just sequence, but insights into countless biological processes pertinent to the future environmental and energy needs of the DOE and the nation.



UNLOCKING AN ANTIBODY'S SECRET One of the body's mysteries is how the immune system responds to the virtually unlimited variety of foreign molecules it must combat. However, insights are emerging from images such as these, produced from data obtained at the DOE-supported Stanford Synchrotron Radiation Laboratory. X-ray crystallography reveals the detailed molecular structures of a "naive" antibody in both its free form (blue) and with an antigen bound to it (purple), as well as a "mature" antibody (green and red). The binding of the antigen (yellow) to the naive antibody leads to structural changes in the antibody that establish a more secure lock-and-key interaction with the antigen. This effort by Berkeley scientists working at SSRL was supported by the DOE, the NIH, and the Howard Hughes Medical Institute.

To take but one example, understanding the genome-structure-function connection will reveal the genetic and functional reasons behind individual susceptibilities to various environmental insults—and may lead ultimately to reliable screening tests for susceptible populations. Such breakthroughs will protect DOE workers involved in environmental cleanup, as well as the population at large.

In reaching to the genome for an understanding of biological function, the new research paradigm extends to nuclear medicine as well—thus the nascent field of molecular nuclear medicine. The BER program has been the principal steward of nuclear medicine for fifty years, touching millions of lives with epochal developments. No more than enticing novelties in the forties, radiotracers, radiopharmaceuticals, and advanced medical imaging systems are now staples of medical practice and biological research. Today, molecular nuclear medicine offers prospects no less bright. The promise of directly imaging gene function in living tissue, already realized in recent research, dramatically enhances the prognosis for treating diseases such as cancer, since it would allow genetic dysfunction to be detected long before the resulting ail-

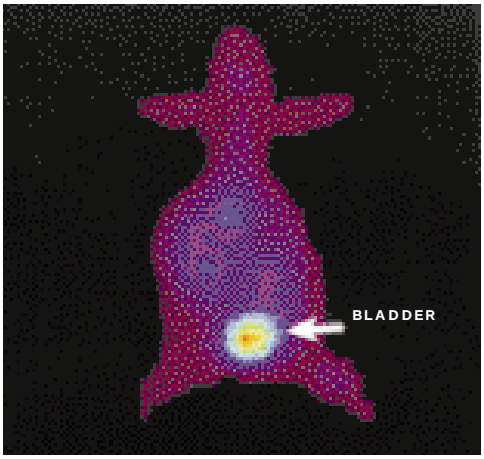
ments become clinically manifest.

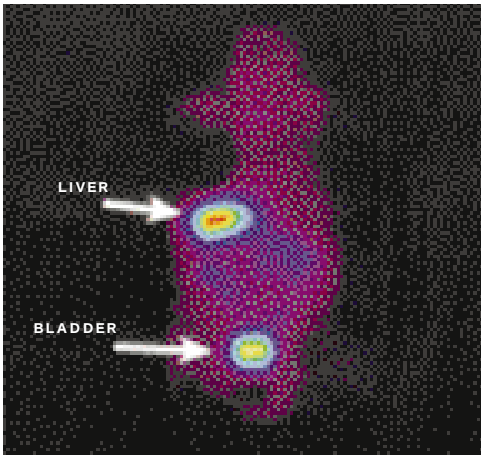
The BER program will also press ahead with the basic environmental research that must undergird the Department's cleanup commitments, particularly the stubborn, long-term restoration problems that are beyond the reach of today's remediation technologies. The Microbial Genome Initiative is one part of this continuing research. Another is a coordinated effort at the William R. Wiley Environmental Molecular Sciences Laboratory (EMSL), whose operational start-up corresponds with the 50th anniversary of the AEC's Division of Biology and Medicine. EMSL is the first major facility for which the BER program assumed principal stewardship and represents an important transition to "big science." This facility will open new vistas on the chemistry of our environment, including insights into how chemical waste streams and contaminated environments can be cleaned up, as well as clues to the long-term fate of chemicals released into the ground, air, and surface waters. In the years ahead, 200 staff scientists will work here at the forefront of such fields as waste processing, bioremediation, and atmospheric chemistry. OBER is also committed to seeing EMSL become an internationally recognized user facility, where visiting scientists can study environmental processes at the molecular level, with applications to environmental cleanup and sustainable development.

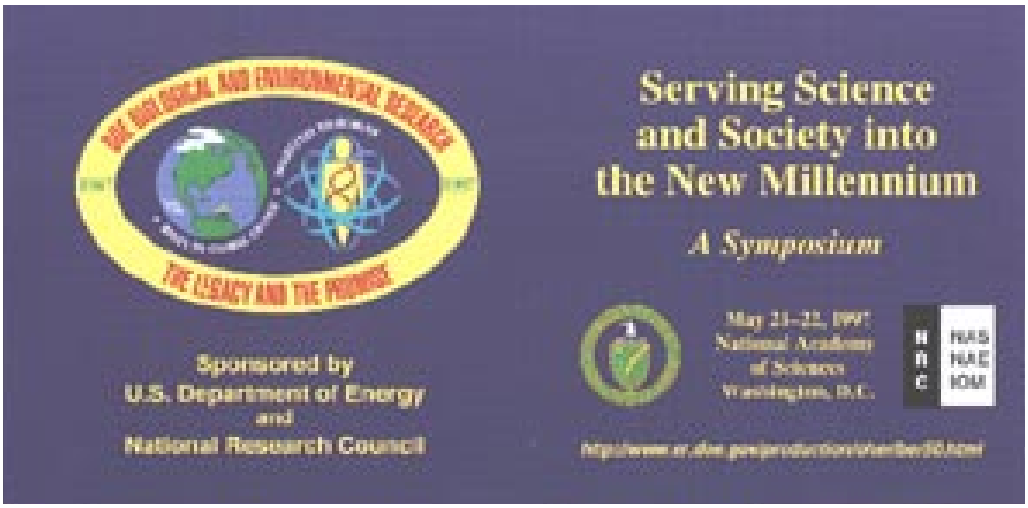
Yet a third facet of the BER program's environmental commitment is the Natural and Accelerated Bioremediation Research (NABIR) program, conceived in 1995. NABIR is building on the foundation laid by the subsurface science program, bringing together geologists, chemists, biochemists, molecular and cellular biologists, microbiologists, and ecologists to focus on important bioremediation questions. The goal is to combine laboratory studies, field studies at contaminated sites, and theoretical research to enhance the scientific basis for using bioremediation to restore and protect the environment.

Also part of the environmental picture is global environmental change, an understanding of which must be a critical ingredient in our technological choices. The sub-

REPORTING FROM THE SCENE Positron emission tomography has now been used to detect the details of genetic activity. In these two images, a living mouse has been injected with a reporter probe that discloses itself to PET imaging, as well as an adenovirus (which accumulates in the liver) carrying both a gene-therapy gene and a PET "reporter gene." In the left-hand image, neither gene is active, so the probe has diffused through the bloodstream and passed through the kidneys to the bladder. In the right-hand image, both genes have been activated by a genetic promoter carried by the adenovirus. The reporter gene produces a protein that binds the reporter probe, which thus reveals the simultaneous activity of the therapeutic gene in the liver. Experiments such as this, performed at UCLA, are hopeful harbingers of an age of molecular nuclear medicine.







THE LEGACY AND THE PROMISE To look at both the past and the future of the BER program, the DOE and the National Research Council (NRC) of the National Academy of Sciences cosponsored a symposium in May 1997, entitled "Serving Science and Society into the New Millennium: The Legacy and the Promise of DOE's Biological and Environmental Research Program." The symposium celebrated five decades of achievement by the DOE and its predecessor agencies, often in partnership with the NRC, and explored the promise of its current programs at the threshold of the next century. Speakers reflected on the implications of changing paradigms, enabling research, and science policy on biotechnology, medicine, and the environment, and discussed the BER program directions that could best serve the needs of the Department and society. The symposium was held at the National Academy of Sciences, Washington, D.C.

tlety of global systems continues to challenge DOE scientists today, just as it did their AEC forebears. Global environmental change is sure to remain a major issue for years to come, and efforts to understand the causes and ramifications of this change will continue to receive the highest priority. One of the central global issues is the impact of greenhouse gas emissions. International agreements on such emissions, aimed at preventing dangerous climatic change, will demand increasing attention to the ecological impacts of environmental change, and the concept of sustainable development will dominate many research and development agendas in the coming years. The BER program will thus expand its research on environmental impact to address the Department's objective of sustainable energy development.

The pioneers of biological and environmental research within the AEC could hardly have predicted the course BER research would take. Efforts focused on the fate of radioactive fallout would evolve into today's global climate research. Exploratory studies of human metabolism using radiotracers would lead to high-resolution PET and molecular nuclear medicine. And questions raised by early epidemiological studies would ultimately give rise to the Human Genome Project. The next fifty years are equally unpredictable. The future, as usual, promises unknown challenges—and unexpected opportunities. It is certain only that as technology evolves, so will our responsibilities for understanding the impact of our decisions on human health and the health of our environment. And as long as our well-being depends on the wisdom of our choices, the enduring mandate of the AEC will continue to inform the research of the DOE scientists charged with its legacy.

ACKNOWLEDGMENTS

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Though this account was edited and produced at the Ernest Orlando Lawrence Berkeley National Laboratory, it aims to provide the general reader with a broad but brief overview of the entire BER program: its role, its contributions to science and society during five decades of research, and its exciting prospects for the future. For their help in this effort, many deserve our thanks for elucidating historical highlights, tracking down illustrations, and offering their advice and criticism: At DOE, David Bader, James Beall, Michelle Broido, Pat Crowley, Roger Dahlman, Jerry Elwood, Ludwig Feinendegen, Marvin Frazier, Roland Hirsch, Peter Lunn, Curtis Olsen, Rick Petty, Michael Riches, Susan Rose, Prem Srivastava, Marvin Stodolsky, David Thomassen, Matesh Varma, and Frank Wobber, and former staffers Gerald Goldstein, Joshua Holland, Helen McCammon, William Osburn, Charles Osterberg, David Slade, Joop Thiessen, Robert Thomas, and Robert Wood; at Argonne National Laboratory, Jeff Gaffney, Douglas Grahn (retired), Karen Haugen, Eliezer Huberman, David Nadziejka, Chris Reilly, and Marv Wesley; at Brookhaven National Laboratory, Paul Falkowski, Kathy Folkers, Joanna Fowler, A. J. Francis, Dawn Mosoff, Richard Setlow, Suresh Srivastava, Jack Van't Hof, Nora Volkow, and Alfred Wolf; at Columbia University, Eric Hall; at the Environmental Measurements Laboratory, Phillip Krey (retired); at the Hanford Site, Michele Gerber; at the Harvard Medical School, James Adelstein; at Johns Hopkins University, Henry Wagner, Jr.; at Lawrence Berkeley National Laboratory, David Gilbert and Sylvia Spengler; at Lawrence Livermore National Laboratory, Linda Ashworth, Anthony Carrano, Kenneth Sperber, and Gordon Yano; at Los Alamos National Laboratory, Scott Cram and James Jett; at the Lovelace Respiratory Research Institute, Charles Hobbs and Joe Mauderly; at Oak Ridge National Laboratory, Murray Browne, Donald Hunsaker, Jr., Sheryl Martin, David Reichle, and Barbara Walton; at Pacific Northwest National Laboratory, Nancy Burleigh, Ted Cress, Jake Hales (retired), Ray Stults, and Ray Wildung; at Savannah River Ecology Laboratory, Marie Fulmer; at Savannah River Technology Center, Robert Addis; at Stanford Synchrotron Radiation Laboratory, Peter Kuhn; at the University of California, Berkeley, Bruce Ames; at the University of California, Los Angeles, School of Medicine, Michael Phelps; at the University of California, San Francisco, Sheldon Wolff; at the University of Florida, Howard Odum; and at the University of Michigan Hospital, David Kuhl.

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