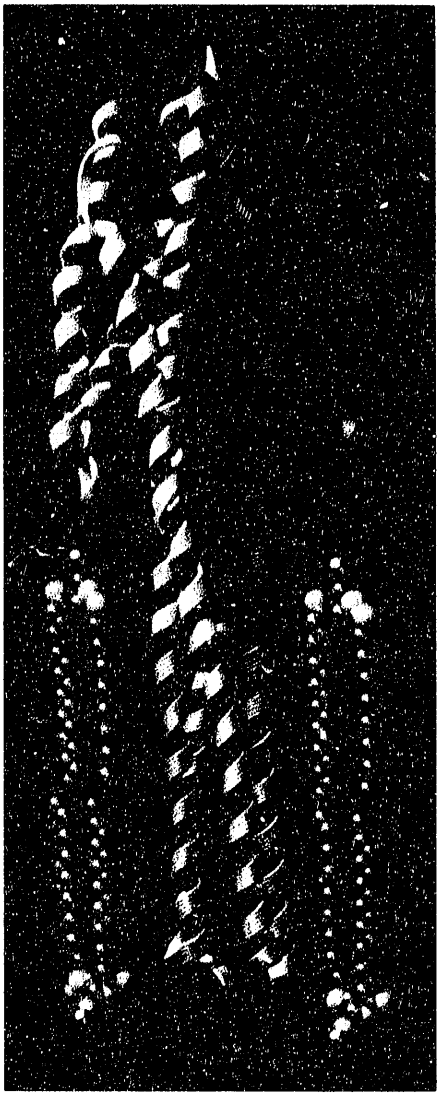
LAWRENCE BERKELEY LABORATORY

LIFE SCIENCES AND ENVIRONMENTAL SCIENCES



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A. Role

Research Programs

The DOE laboratories play a unique role in bringing multidisciplinary talents—in biology, physics, chemistry, computer sciences, and engineering—to bear on major problems in the life and environmental sciences. Specifically, the laboratories utilize these talents to fulfill OHER's mission of exploring and mitigating the health and environmental effects of energy use, and of developing health and medical applications of nuclear energy-related phenomena. At LBL support of this mission is evident across the spectrum of OHER-sponsored research, especially in the broad areas of genomics, structural biology, basic cell and molecular biology, carcinogenesis, energy and environment, applications to biotechnology, and molecular, nuclear and radiation medicine.

Programs in biomedical and environmental sciences at LBL are at the cutting edge of modern biology, with a commitment to excellence in both basic and applied research. LBL's special facilities and new programs such as the Advanced Light Source (ALS) and the Human Genome Center (HGC) build on strengths in structural biology and human genetics.

The Human Genome Center at LBL focuses expertise in cell and molecular biology, instrumentation, structural biology, and data management and analysis on the formidable task of physically mapping large portions of the human genome. In line with the DOE's strategy for developing advanced tools for the effort before undertaking large-scale mapping or sequencing projects, the Center is the focus of activities in several LBL divisions, including Engineering and Information and Computing Sciences, as well as the Life Sciences Divisions. The national and

international significance of the human genome project, together with new initiatives in other areas of modern biology, places new emphasis on the importance of life sciences research in relation to the total research effort at LBL.

The proposed Life Sciences Initiative at the ALS has broad, multidisciplinary implications. This initiative would provide synchrotron radiation beamlines and experimental facilities for protein crystallography, x-ray microimaging and microholography, and x-ray spectroscopy. It would also provide offices and laboratories for local and visiting scientists interested in biological structure and function, from the molecular to the cellular level.

Yet another portion of the OHER program is research and development related to new measurement methods and instruments for radiation detection, environmental analysis, and determination of molecular structure. LBL has responded to the country's need in the area of space-related research. New programs funded by the National Aeronautics and Space Administration (NASA) are underway, and new programs related to DOE's space exploration initiative have been formulated.

In addition, LBL will remain responsive to important environmental issues, such as waste management, environmental restoration, and the assessment of human risk. At LBL we recognize that concerns for the environment and safety must go hand in hand with pioneering research. LBL intends to put together competitive and more active programs in atmospheric research, global climate change, and human risk associated with waste remediation. These directions—combined with our strong emphasis on education, training and technology transfer—define the new spirit and excitement in life and environmental sciences at LBL. Finally, along with the goals outlined by the Secretary of Energy at his summit meeting with the National Laboratory Directors, LBL endorses the concept of partnerships with other U.S. government agencies—including NIH, NASA, and EPA—that are engaged in health and environmental research.

LBL Mission

The Lawrence Berkeley Laboratory, operated by the University of California for the Department of Energy, provides national scientific leadership and technological innovation through its mission to:

- Perform leading multidisciplinary research in the energy sciences, general sciences, and life sciences in a manner that ensures employee and public safety and the protection of the environment;
- Develop and operate unique national experimental facilities for use by qualified investigators;
- Educate and train future generations of scientists and engineers; and
- Transfer knowledge and technological innovations and foster productive relationships between LBL research programs and industry.

OHER-sponsored research programs in life and environmental sciences are in full support of this mission.

Technology Transfer

LBL has developed technology transfer plans to support the development and use of LBL technology by industry and to strengthen the value of the Laboratory's research programs for the nation. To fulfill the Laboratory's mission, LBL's Technology Transfer Plan establishes long-term objectives to:

- Develop technology research programs and Collaborative Research and Development Agreements (CRADAs) involving U.S. industry for long-term advancement of energy research and national competitiveness;
- Enhance technology transfer connections with industry through improved access and dissemination mechanisms, including training, personal exchanges, publications, and conferences.
- Optimize the use of intellectual property to serve the interests of U.S. industry and DOE, including reducing barriers and improving information use.

To meet these long-term objectives, specific goals have been formulated to enhance technology research opportunities, strengthen LBL/industry connections, and facilitate patent processing:

- Strengthen research centers and management organizations that promote fundamental innovative science and technology development germane to industrial research needs;
- Develop specific innovative technology research projects and advanced technology demonstrations to the point where industry commercial interest is attained;
- Develop research staff awareness and recognition of technology transfer opportunities;
- Target key industries and industrial groups with a focused dissemination program of research results, new processes and technologies, and licensing of intellectual property;
- Develop and implement proactive programs for mobilizing Laboratory scientific staff to establish working relationships with industrial scientists;
- Improve and diversify mechanisms for access and use of national user facilities;
- Maintain a program of successful patent processing and reduce the real and perceived barriers to patent application; and
- Reduce the time between prepublication review, invention disclosure, patent application, and utilization.

To achieve these goals, LBL's Five-Year Technology Transfer Plan is directed toward effective organizational structure and utilization of the Laboratory's principal support resources. LBL implements the plan and promotes interactions with industry through the Technology Transfer Office, the Patent Office, and the Office of Sponsored Research Administration, by specific collaborative research projects. Technology transfer is also facilitated through research centers and through industry involvement in advisory committees, panels, and review groups.

Cooperative Research LBL supports strategic national goals to rapidly transform the Laboratory's research into economically practical technologies for U.S. industry. These efforts include collaborative technology research participation, and active involvement in the Laboratory Technology Exchange Program. Through Energy Research's Technology Transfer Program, support for Collaborative Technology Research projects is initiated and financial assistance is provided for extended visits by senior American industry scientists to the national laboratories. These visits are highly productive, and the Laboratory has requested program expansion. LBL engaged in more than 300 industrially sponsored research agreements in FY 1990 and is currently involved in 18 industry cooperative research agreements.

Several technology research participation programs have been initiated to develop and improve the transfer of emerging technology for the energy industry, including forefront developments in advanced nanostructures fabrication and in novel biomedical instrumentation.

Technology Transfer Activities. LBL continues to emphasize technology transfer through the publication of research results, technical consulting and personnel exchanges, and conferences. An important Technology Transfer mechanism is training students who ultimately work for industry, universities, or government. More than 700 advanced students are supported at LBL. About 100 advanced degrees based on LBL research are granted annually, and approximately half of these students bring their technical talents to industry.

In the past year, LBL developed a 27-page "Technology and Invention Inventory." The inventory lists 162 technologies (including patentable inventions, public domain technologies, and copyrightable developments) in database form. The database yields information regarding subject area, patent and licensing status, scientists, and activity comments.

LBL has implemented a new multistep approach to inform industry about LBL technologies. First, the attributes of the invention are summarized using attractive layouts and highlighting potential product applications. This package is sent to corporate executives in charge of company development; they are targeted through a high-technology corporate database that lists companies by product subject area. In addition, notices describing the inventions are distributed through technology newsletters that specialize in announcing new ideas to corporate executives. Articles are also sent to trade journals and are announced in general press releases. Other examples of new technology transfer activities include the following:

- In FY 1992 LBL will join with the Haas School of Business on the UC Berkeley Campus to initiate several new projects in the MBA Engineering and Technology program. The students will work with the UC Business schools, to develop the economic data that attract industry interest to LBL technologies.
- LBL has recently established an Inquiry Database that allows the Laboratory to keep inquirers updated as new laboratory developments arise in a particular field of interest. The database now has over 400 entries expressing corporate interest in an LBL technology. There have been approximately 1000 additional inquiries resulting from trade journal articles on LBL technology.
- New CRADA opportunities at LBL are also being supported. LBL has made pilot projects to promote cooperative research opportunities within specific program areas. These projects were successful in attracting U.S. corporate interest.

More than twenty CRADAs are in preparation at LBL, and one has been approved. These are in various stages of completion, ranging from initial discussions between LBL and participant scientists and management, to drafting of a Joint Work Statement (JWS).

LBL has also focused attention on informing its scientists and potential inventors of technology transfer opportunities. A technology transfer newsletter describes the many technology transfer approaches and services available to the LBL investigator. The newsletter features an ongoing series that details patent, copyright, and licensing procedures. The LBL Technology Transfer Employee Recognition Program acknowledges the accomplishments the Laboratory staff has made toward technology development and transfer to industry or other parts of the private sector. Award ceremonies recognize investigators for their technology transfer endeavors. LBL's highest honor for accomplishments in technology transfer is the Technology Transfer Excellence Award, and certificates of merit are also awarded.

Patents and Licensing. LBL seeks to patent and license its intellectual property to strengthen the value of its inventions, both for use and application by industry and to promote the research and technology transfer interests of the Laboratory and its research staff. LBL made 18 patent applications in FY 1991, and 12 patents were issued.

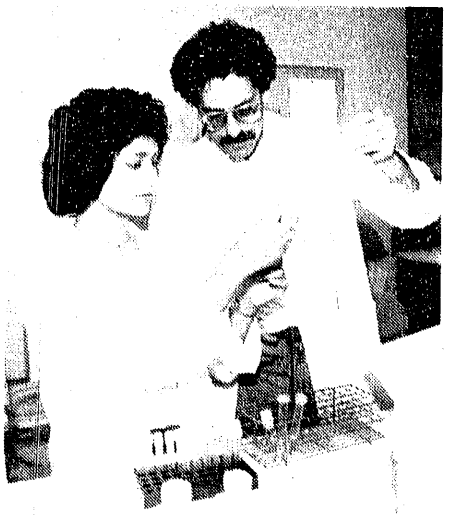
LBL licensing activity has increased significantly since the 1980's when relatively few agreements were made during the decade. During the part 2 fiscal years, eleven agreements licenses have been made.

The East Bay Emerging Technology Advisory Board (EBETAB) was established in 1989 to promote early-stage technologies for first-round, startup ventures. The board plans to hold annual briefings to showcase new technologies to venture capitalists. LBL works with EBETAB to present LBL's latest promising technologies that have strong potential for licensing or to form startup companies.

Science Education Programs

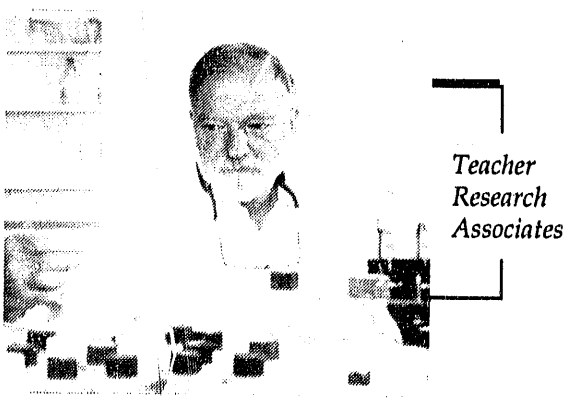
LBL's educational programs advance precollege, undergraduate, graduate, and minority educational opportunities. These programs support the objectives of the National Energy Strategy and the By the Year 2000 Report of the Federal Coordinating Council for Science, Engineering, and Technology. Through the Center for Science and Engineering Education, LBL is responding to the national education goals developed following the 1989 Education Summit attended by the nation's governors. The key strategies are to utilize the resources of LBL to:

- Provide access to modern science for K-12 science students and teachers,
- Develop education partnerships for outreach and impact, and
- Deliver programs specifically for women and minorities.



Minority Access to Energy Research Careers

Approximately 2000 visitors a year to LBL are exposed to LBL's frontier science and technology, and many more are exposed through the partnership with the UC Lawrence Hall of Science (LHS), an acclaimed education research center and science museum. To plan and conduct educational programs effectively, the Center for Science and Engineering Education (CSEE) was established in 1987. The mission of CSEE is to develop, implement, and evaluate programs that utilize LBL resources to improve the quality of mathematics, science, and technology education.



Teacher Research Associates

OHER investigators play an active role in all major areas of CSEE activity.

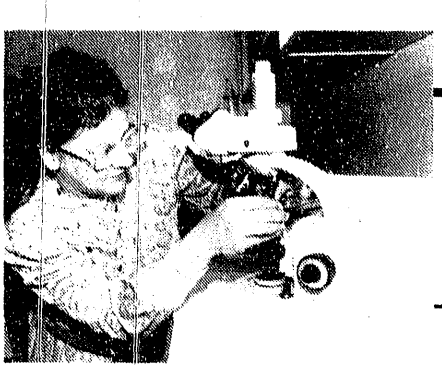
CSEE supports both formal and informal education program activities from public science and technology literacy, precollege (K-12), community college, and technical training through undergraduate and graduate education. The goals of the CSEE programs are to:

- Promote equal access to scientific and technical careers for all students, including women, minorities, the handicapped, and the economically disadvantaged;
- Improve the quality of science and engineering teaching by supporting increased classroom emphasis on the scientific process and exposure to frontier science and technology;
- Increase the number of U.S. students who become scientists and engineers by developing and implementing strategies to provide continuity of opportunity from elementary school through graduate school; and
- Promote scientific literacy, including an understanding of relationships among frontier science, technology, and society.

Community College Transfer

Precollege Programs. Lawrence Berkeley Laboratory is working together with three other national laboratories and 18 other colleges, universities, and organizations under the Bay Area Science and Technology Education Collaboration (BASTEC), to assist the Oakland Unified School District in restructuring and revitalizing mathematics and science education. The district serves

over 50,000 students and has 3000 teachers and administrators. LBL, LLNL, SLAC, and Sandia National Laboratory Livermore have signed a formal memorandum of understanding with the Oakland Unified School District. BASTEC has been adopted by the District and serves to coordinate teacher enhancement opportunities in science and mathematics. Mini grants have been awarded to 22 teachers within the District. In March of 1991, 472 Oakland school teachers participated in a one-day BASTEC workshop focusing on hands-on science and the new California State Science Framework. During the summer, BASTEC sponsored workshops for over 200 teachers. Department of Energy support for BASTEC has generated energy and enthusiasm for science, mathematics, and technology education within the district.



Science Consortium — Faculty Development

LBL provides community college, high school, and junior high school science and mathematics teachers with summer research positions. Teachers of chemistry, physics, biology, and mathematics spend eight weeks during the summer at LBL assigned to a research group to work along with scientists, graduate students, and technical support staff. Through this experience, teachers update their knowledge and revitalize their interest in science teaching. More than 70 teachers have been placed in life sciences and environmental science laboratories since 1983.

The High School Honors Program in the Life Sciences brings 64 outstanding high school science students---one from each of the 50 states, the District of Columbia, Puerto Rico, and several foreign countries—to LBL for two weeks of frontier science lectures and hands-on laboratory experience. LBL's focus on life sciences not only gives students an opportunity to develop skills in recombinant DNA technology, but also prepares

High School Honors Program in the Life Sciences

them for social and ethical issues in science and technology. Mina Bissell, Coordinator for Life Sciences and Director of LBL's Cell and Molecular Biology Division, has consistently been rated by the students as the best High School Honors Program speaker each year.

The New Perspectives in Mathematics and Sciences program has been developed to improve inner city minority students' math and science retention. The program develops school leadership, works with parents, and provides students with weekend academic activities in exciting scientific breakthrough areas. Over a thousand middle and high school students are being reached through Berkeley High School and the Berkeley and Richmond school districts. The

Science Consortium — Student Development

New Perspectives program supports science education materials development for the mathematics class entitled "LBL Mathematics in Action" and uses video to feature scientists and laboratory data for the classroom.

In addition, LBL cosponsors activities with LHS to promote public understanding of science and technology and to enrich teaching in local schools. A joint colloquium entitled "Updating Science Knowledge for Instruction" provides academic-year follow-up for teachers who have participated in LBL and LHS programs. Approximately 200 teachers attend each colloquium. Usually, two of the four colloquia each year are given by LBL life scientists. Another cosponsored program, the High School Science Symposium on Biotechnology and Genetic Engineering, involves hundreds of high school students and many OHER-sponsored researchers each year.

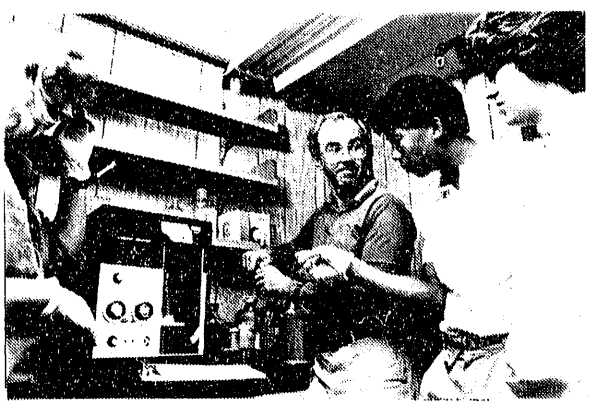
High School Science Symposium

Undergraduate Programs. Through CSEE and the scientific divisions, more than 400 undergraduate students were research assistants or guests in FY 1991. Of these, about 85 worked on OHER—or OHER-related—projects.

Two undergraduate programs, the Laboratory Co-op Program and the Science and Engineering Research Semester (SERS), are national programs for talented students, but with strong support for women and minorities. These research participation programs provide advanced research participation for the top undergraduate students from colleges and universities throughout the nation. The primary goal is to attract, educate, and train scientists and engineers to meet the nation's future manpower requirements. Through a combination of hands-on laboratory research and direct interaction with scientists, the LBL Co-op and SERS programs provide undergraduate students with practical insight into research, a positive influence on educational goals, and a model for career opportunities.

The Faculty/Student Team Research program started in FY 1988 is expanding and provides faculty from predominantly minority universities and colleges with an opportunity to develop collaborative research programs. LBL, in cooperation with Associated Universities, provides opportunities for underrepresented students through a number of programs. These include Minority Access to Energy Research Careers, (MAERC) for students from the California State Universities, Environmental Management Career Opportunities for Minorities (EMCOM), Environmental Management Career Opportunities Research Experience (EMCORE) for students and faculty, and a California community college transfer program for students entering UC Berkeley. These ongoing collaborations serve as a pipeline for minority students to work at LBL. This is the third year LBL has provided community college transfer students entering UC Berkeley with an opportunity for research and academic year mentorship at the Laboratory.

Graduate and Postgraduate Training and Research. LBL has a strong relationship with UC Berkeley, involving 218 faculty members who are LBL staff and about 500 graduate students (80 in life and environmental sciences). In addition, the



High School Honors Program in the Life Sciences

Laboratory provides more than 80 postdoctoral appointments for researchers (about 35 in life and environmental sciences). Each year, typically over 100 doctoral dissertations and masters theses are completed on the basis of research performed at LBL.

LBL also attracts about 350 faculty visitors from 100 other academic institutions to participate in its research programs. The biomedical programs provide research and clinical opportunities for the medical faculty at UC San Francisco and for other physicians in the region. The LBL CSEE provides

High School Honors Program in the Life Sciences

opportunities for post-baccalaureate-level minority students to continue research at LBL while preparing for graduate studies and acceptance into a graduate school in science or engineering.

Minority Education and Research Programs. LBL's primary program to further minority education in science is operated under a consortium of LBL, Jackson State University (JSU), and the Ana G. Mendez University System (AGMUS). Joint scientific research is conducted among the participating institutions, as well as a strengthening of academic and research capabilities of JSU and AGMUS. The original Memorandum of Understanding establishing the Science Consortium set forth the following goals: To improve

- Faculty research opportunities;
- The quality of research seminars;
- Academic support systems for minority students;
- Undergraduate and graduate programs in the natural sciences, mathematics, computer science, engineering, and other math-based disciplines;
- Pre-university programs to better prepare minority students for college programs;
- The number of graduates from math-based programs; and
- Institutional capabilities to engage in competitive research and academics.

Several JSU and AGMUS faculty members are currently collaborating with LBL scientists on life and environmental science research projects, including development of biomarkers for detection of environmental pollutants in marine waters and development of a hemoglobin database to be used by clinicians and researchers around the country.

In support of the student-development efforts of JSU and AGMUS, two programs are conducted at LBL: the Semester Cooperative Program and the Summer Internship Program. Semester Cooperative Program students from JSU come to LBL for a full academic semester to work with LBL staff scientists. The program is offered to a limited number of eligible students who are majoring in a biological or physical science, mathematics, computer science, or pre-engineering. The Semester Cooperative Program is designed to be as complete an academic research experience as possible.

Future Educational Program Plans. DOE has a growing commitment to science education, and LBL expects to continue to expand its activities. Integration of minority education programs with other activities has resulted in over 51% minority participation in undergraduate programs. Undergraduate programs are targeted for the largest relative expansion among the education activities in FY 1992. Support for the base undergraduate education activities has been relatively constant to provide resources for development of precollege programs. The faculty/student team research approach and community college transfer/technical programs provide the most promise for expanding

High School Honors Program in the Life Sciences

LBL's efforts to keep underrepresented students in the pipeline leading to graduate school and eventually to science and engineering careers.

Professional development of minority precollege teachers is being piloted in FY 1991 and will be expanded in the coming years.

CSEE's precollege activities are also expected to increase in FY 1992. Maintaining the momentum and successes of BASTEC in its first year will be a high priority. The addition of new partners from industry into BASTEC is planned. A number of LBL division-centered initiatives with strong precollege components are under development. Topics in life and environmental science range from brain imaging to bioremediation technologies. These initiatives represent internal partnerships between the Center for Science and Engineering Education and LBL's scientific divisions. They also represent full integration of the precollege education and research activities at the division level. The development and inter-agency funding of these activities will be a major thrust for the next few years.

The Science Consortium (LBL, JSU, and AGMUS) will shift resources to strengthen precollege programs at JSU and AGMUS. Faculty and student development through collaboration with LBL scientists will continue, with the goal of developing centers of research excellence.

B. Facilities and Resources

Laboratory Facilities

Bevalac. In addition to its programs in high energy and nuclear physics, the Bevalac has long supported research medicine and radiation biology and biophysics. This facility, a combination of the Bevatron positive-ion synchrotron and the SuperHILAC heavy-ion linac, can supply beams of any of the naturally occurring elements at energies from 20 MeV/nucleon to a few GeV/nucleon. With production targets, secondary radioactive beams can also be produced. Approximately one-third of the Bevalac's research beamtime is dedicated to the life sciences; it is apportioned by a program advisory committee to the various research proposals. The DOE nuclear-science program that currently operates the Bevalac is expected to end in the mid-1990s, probably giving way to a National Aeronautics and Space Administration program that will study the effects of cosmic rays upon living and nonliving materials. Financial and scheduling arrangements for continued operation of other programs during that time are being studied.

Imaging Facilities. The Donner 600-Crystal Positron Tomograph was designed and built at LBL to provide better than twice the spatial resolution of any previous tomograph. The very high resolution is achieved by six hundred 3-mm-wide bismuth germanate crystals, coupled individually to 14-mm phototubes. A commercial single-photon emission tomograph has been provided by the manufacturer. Magnetic resonance imaging facilities are also available for medical use; in particular, facilities for safety research into extending the use of NMR for noninvasive human studies are centered at LBL. The Laboratory is also home to a unique array of electron microscope facilities, whose purchase and operation are funded from several sources.

These facilities include the Atomic-Resolution Microscope and the High-Voltage Electron Microscope at the National Center for Electron Microscopy, as well as an Intermediate-Voltage Electron Microscope, funded by NIH, for high-resolution electron crystallography. In collaboration with the Lawrence Livermore National Laboratory, LBL has also developed the capability of imaging biological macromolecules by scanning tunneling microscopy. Several STMs are operational at LBL.

National Tritium Labeling Facility. This national facility, supported by the NIH, carries out research into the labeling of compounds to high specific activity with tritium and provides a tritium-labeling service for investigators throughout the country. A primary direction for this facility is now the development of tritiated reagents and techniques for NMR studies of biological macromolecules.

Radiopharmaceutical Facility. Nuclear and organic chemical synthesis instrumentation and laboratory facilities at LBL include the 88-Inch Cyclotron and radiation-containment devices for rapid synthesis of radiotracers. A mini-cyclotron facility is being acquired through support of OHER to provide positron-labeled isotopes for the PET nuclear medicine program.

Advanced Light Source. The Advanced Light Source (ALS) will offer dramatic new scientific opportunities in the areas of x-ray microscopy, x-ray crystallography, and x-ray spectroscopy. In these areas, the opportunities are unique and the research will break altogether new ground. Research at the facility will center initially around experimental stations at the ends of two beamlines from the ALS. The first beamline—from an undulator source of ultrabright, laserlike soft x-rays—will illuminate two x-ray microscopy stations, one for use in ongoing research programs and the other for use in developing new imaging techniques. The second beamline, from a wiggler source of both soft and hard x-rays, will branch into two experimental areas, one broadly designated for spectroscopy, the other for diffraction and crystallography. The ALS will be housed in an enlarged version of the domed hall that was the home of the historic 184-Inch Synchrocyclotron at LBL. A mezzanine will provide space for offices and laboratories for staff and users who may be on site at any time when all beamlines are in operation. In summary, the scope of the ALS Life Sciences facilities includes:

- Two insertion devices—one undulator and one wiggler,
- An undulator beamline equipped for x-ray microscopy and a wiggler beamline for x-ray diffraction and spectroscopy, and
- About 10,000 gross square feet of fully equipped support laboratory and office space.

Proposals have been submitted to OHER to provide beamlines at the Life Sciences facilities at the LBL Advanced Light Source for structural biology studies, including imaging intact cells with soft x-rays and x-ray crystallography of biological molecules.

Other Facilities. Complex biological phenomena require sensitive and specific analytical techniques for analysis. OHER programs at LBL have pioneered the use of such techniques as x-ray and electron crystallography, NMR spectroscopy, flow cytometry, and chemical probe analysis to study biological problems. Instrumental techniques such as analytical electron and x-ray microscopy, gas chromatography/mass spectrophotometry, confocal microscopy, fluorescent-detected circular dichroism, and differential polarization microscopy are also utilized for analytical purposes in the life sciences program. X-ray photoelectron and laser Raman spectroscopies are used to study atmospheric processes, and equipment and techniques have been developed to provide near real-time measurements of environmental concentrations of absorbing aerosols and of radon and its decay products.

Standard laboratory facilities and instrumentation include laminar flow biosafety cabinets, incubators, warm rooms, fermenters, cold rooms and ultracold storage units, fluorescence microscopes, all types of gel electrophoresis apparatus, cryostats, scanning densitometers, ultracentrifuges (analytical as well as preparative), high-pressure liquid chromatographs, dark rooms, automated DNA and peptide synthesizers and sequencers, amd polymerase chain reaction (PCR) apparatus. We also maintain an AALAC-accredited animal colony, which has facilities for housing rodents (including transgenic mice), dogs, cats, rabbits, guinea pigs, goats, and monkeys.

Engineering facilities include (i) a fully equipped semiconductor materials/detector fabrication facility with extensive diagnostics capabilities; (ii) a Van de Graaff accelerator (2-MeV protons) equipped for backscatter and x-ray fluorescence studies; (iii) extensive electronic design and development facilities, with particular emphasis on very low-noise measurements required for high-resolution spectroscopy; (iv) an ultralow-background radiation-counting facility equipped with high-resolution gamma-ray spectrometers; and (v) a clean-room facility devoted to the fabrication of microsystems such as detectors and electronic devices with micrometer-size structures. In addition, LBL's Information and Computing Sciences Division maintains state-of-the-art information and computing resources. These resources include SEEDIS, the LBL Socioeconomic Environmental Demographic Information System, which contains the country's most complete computerized archive of U.S. health, demographic, and socioeconomic data. This archive is now being integrated with the OHER Comprehensive Epidemiologic Data Resource (CEDR) for use in OHER epidemiologic research activities.

Laboratory facilities of the Indoor Environment Program include the Indoor Air Quality Research House, which contains a three-room test space instrumented for studies of radon decay product behavior and for investigations of other specific pollutants, such as environmental tobacco smoke. A controlled 20 m^3 chamber is also available for detailed studies of pollutant emissions and behavior. A new facility, consisting of two intensively instrumented, basement-like concrete structures in the Santa Cruz mountains, has been built for a detailed examination of radon transport and entry processes, including a more rigorous experimental validation of theoretical predictions based on complex numerical codes than has been possible previously. Modeling is conducted on a Sun 4-280 and a Hewlett Packard series 7000 computer operated by the Indoor Environment Program and on OER-sponsored CRAY supercomputers.

Additional facilities for environmental research include a field station for cloud studies and a cloud chamber for studying cloud chemistry and physics.

Laboratory Funding and Organization

On the following page are tables summarizing OHER funding and personnel levels, in the context of the Lawrence Berkeley Laboratory as a whole. More detailed information on personnel involved in OHER activities is tabulated in Section I. Also reproduced on the following pages are organization charts for the Laboratory and for the three Life Sciences Divisions, where the bulk of the OHER-sponsored research is conducted.

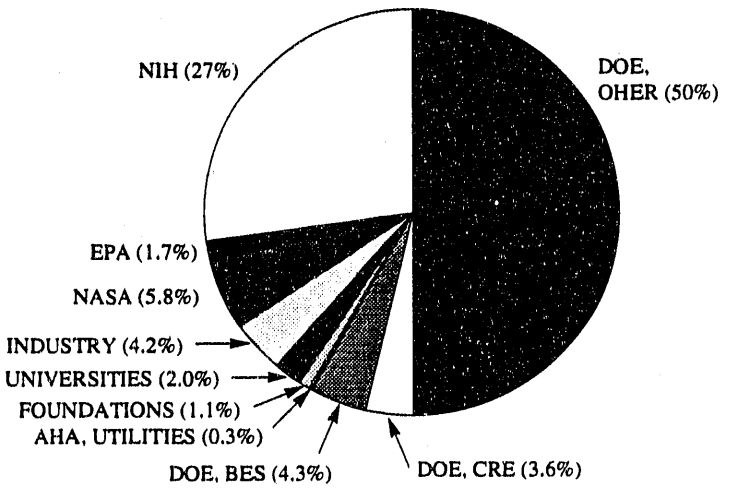
Laboratory Funding (millions of dollars)

Source	*1990*	*1991*	*1992**
OHER			
Operating	15.2	14.9	16.8
Capital equipment	1.2	1.0	1.3
Construction	0.0	0.0	0.0
Total	16.4	15.9	18.1
Other OER			
Operating	91.6	99.9	112.5
Capital equipment	14.4	12.1	12.7
Construction	30.5	22.5	22.5
Total	136.6	134.5	147.7
Other DOE			
Operating	36.0	43.3	44.1
Capital equipment	0.7	0.7	1.0
Construction	0.3	1.3	0.5
Total	37.0	45.3	45.6
WFO	37.0	36.0	34.5
Total lab funding	**226.9**	**231.7**	**245.8**

Laboratory Personnel (FTEs)

	1990	*1991*	*1992**
OHER direct	111	103	110
Other DOE direct	1402	1397	1410
WFO	321	334	330
Indirect	725	726	750
Total lab personnel	**2559**	**2560**	**2600**

*Figures for 1992 are estimates.



FY 1992 ($32M)

Sponsors of life and environmental sciences reseach programs at Lawrence Berkeley Laboratory. AHA–American Heart Association; BES–Basic Energy Sciences; CRE–Conservation and Renewable Energy; EPA–Environmental Protection Agency; NASA–National Aeronautics and Space Administration; NIH–National Institutes of Health; OHER–Office of Health and Environmental Research.

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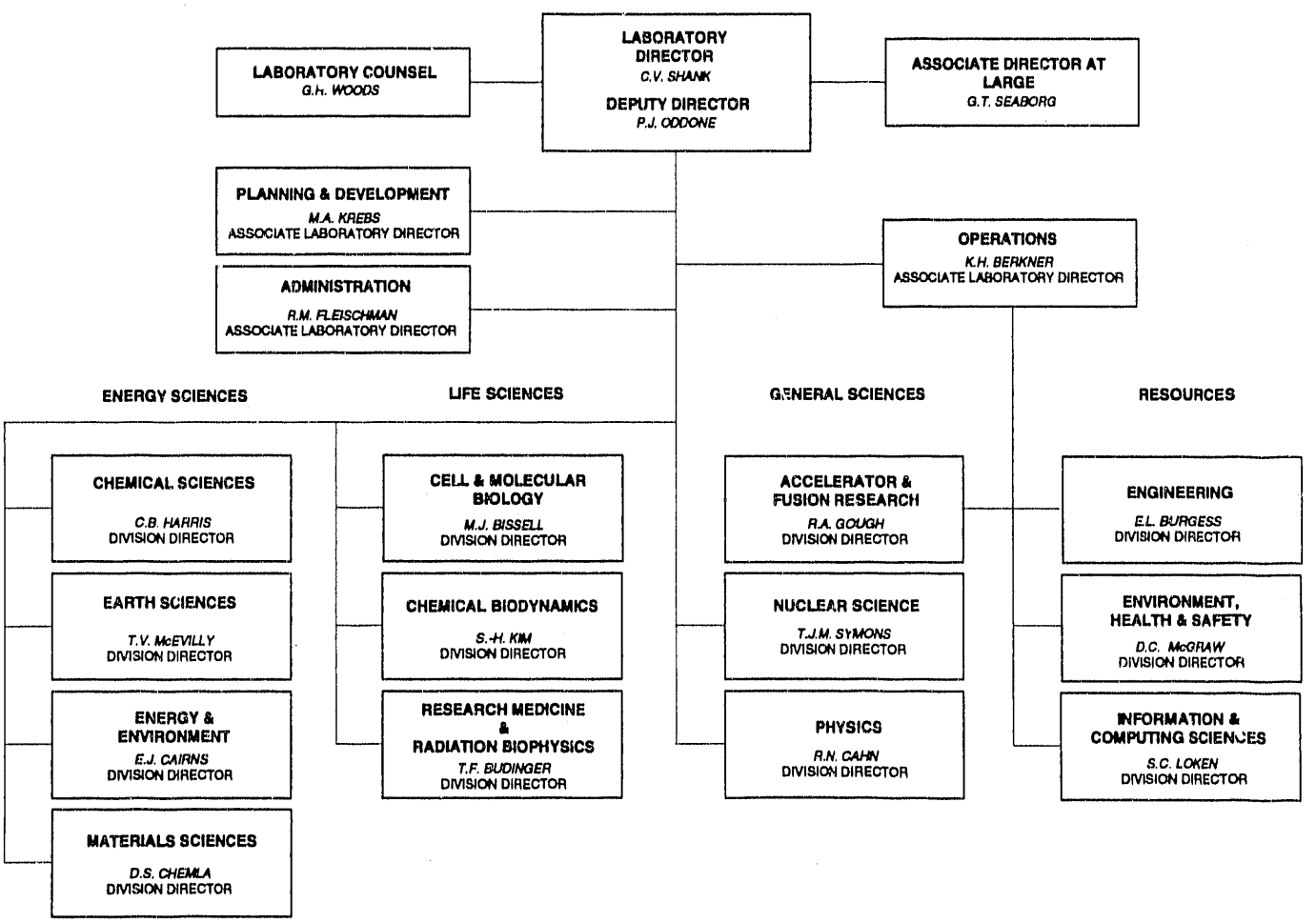
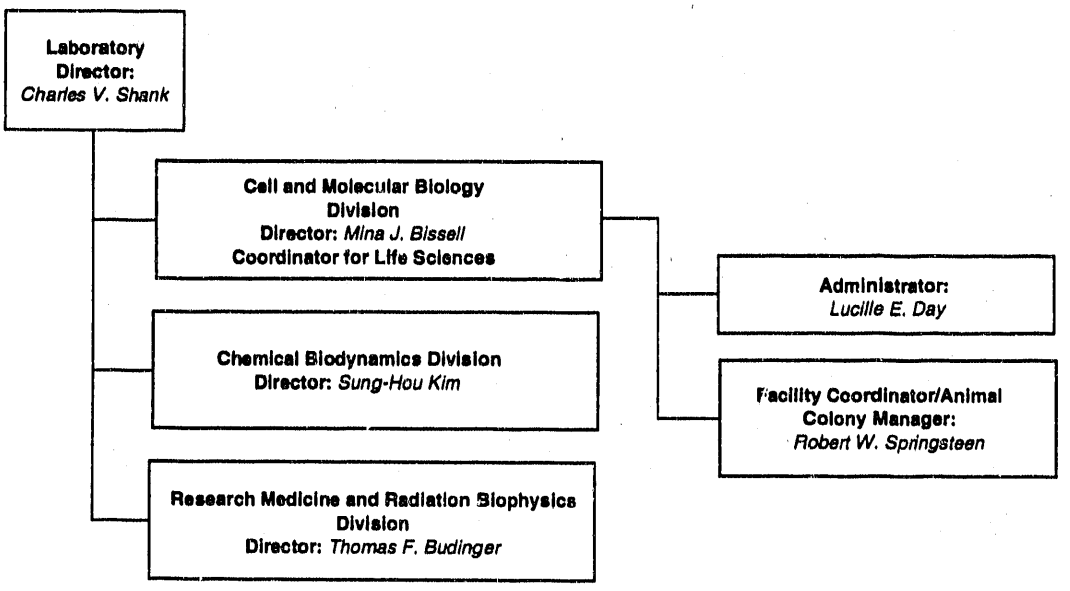
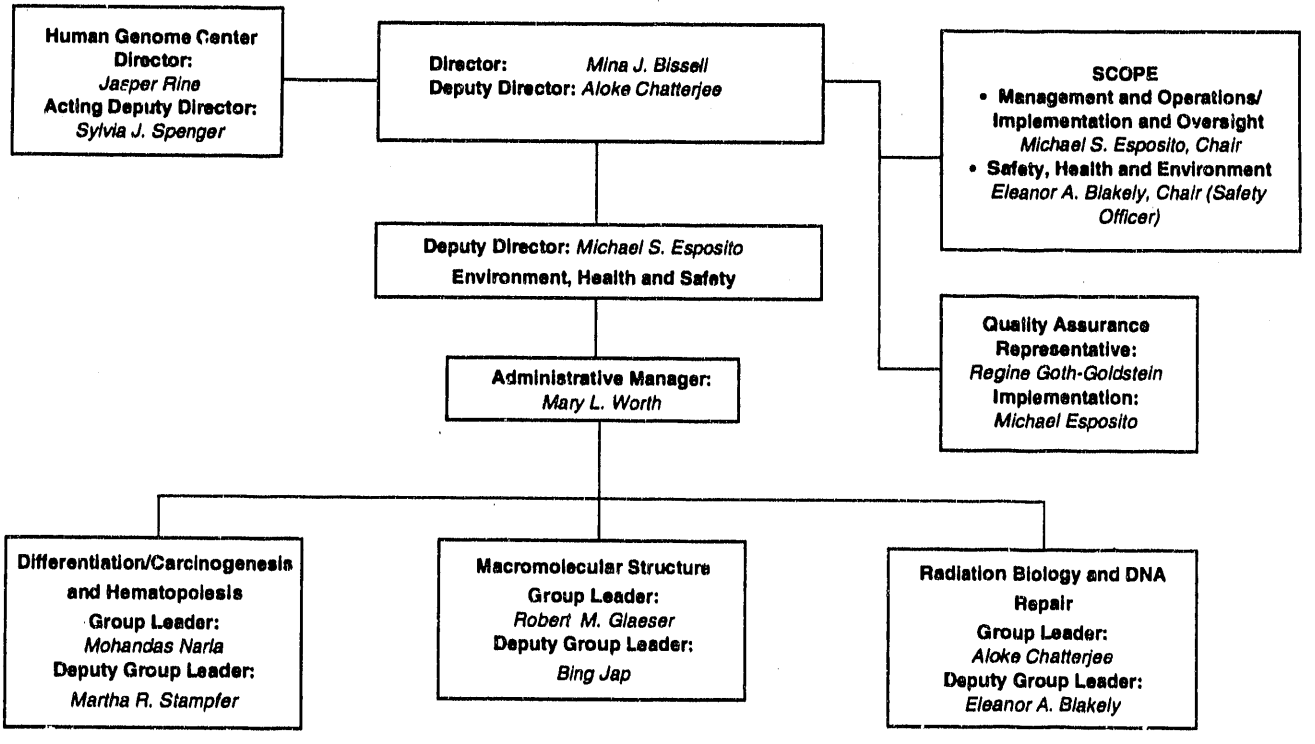


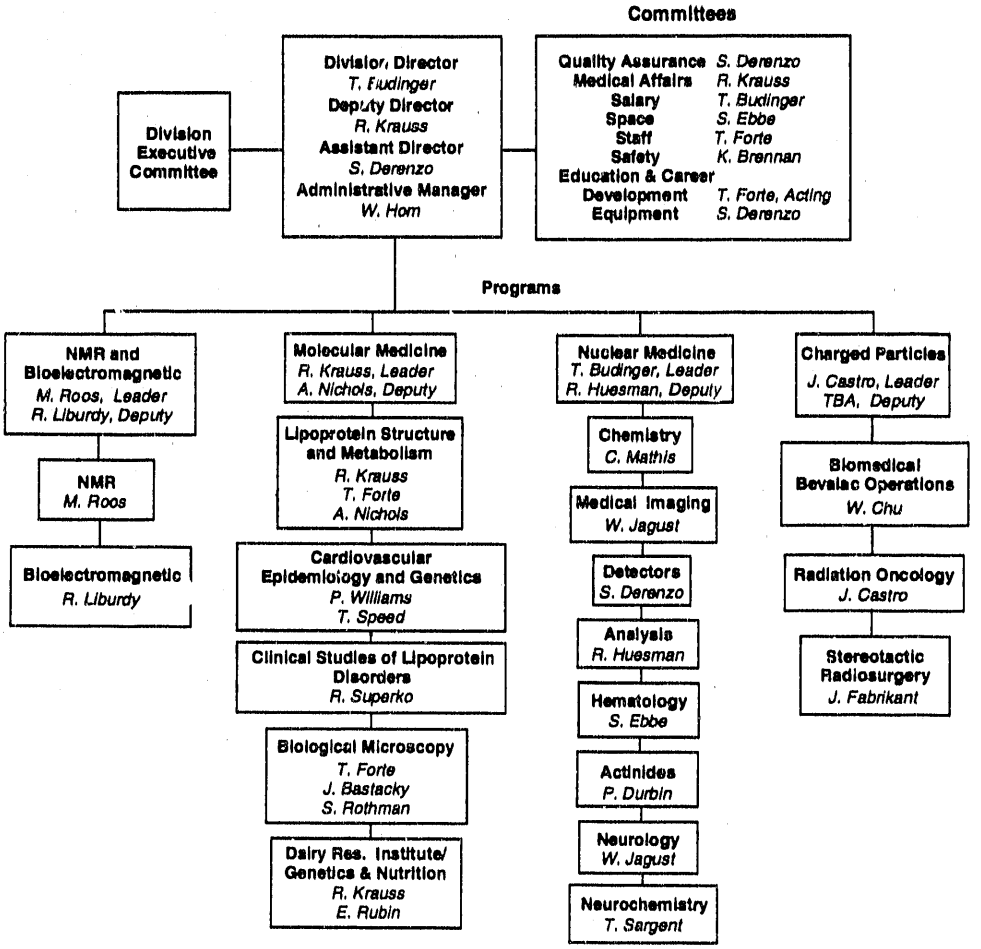
LIFE SCIENCES



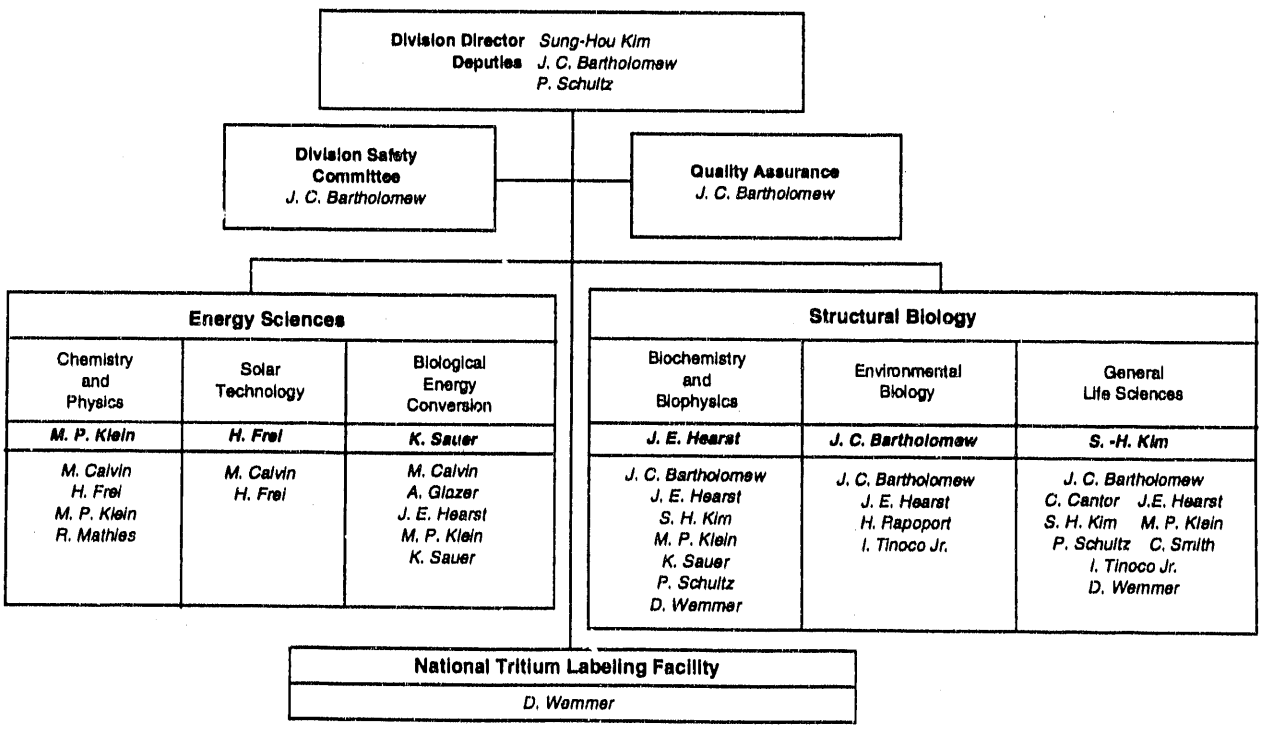
CELL AND MOLECULAR BIOLOGY DIVISION



RESEARCH MEDICINE AND RADIATION BIOPHYSICS DIVISION



CHEMICAL BIODYNAMICS DIVISION



C. Research Management Practices

Scientific Review

In addition to being evaluated in reviews in which OHER plays a direct role, the quality and direction of research in life and environmental sciences at LBL is evaluated within each of the four divisions conducting such research. In particular, an annual "Director's review" is mandated for each division as an opportunity for senior scientists from around the country to review the division's programs and to report their findings directly to the Laboratory Director. The current committee membership for the four divisions is as follows:

Cell and Molecular Biology Division

Harold F. Dvorak (Chair)
Professor and Chief, Department of Pathology
Beth Israel Hospital/Harvard Medical School

Charles Daniel,
Professor, Department of Biology
University of California at Santa Cruz

Errol C. Friedberg
Professor, Department of Pathology
University of Texas Southwestern School of Medicine

Yuet W. Kan
Professor, Department of Laboratory Medicine
University of California San Francisco

J. Richard McIntosh
Professor, Department of Molecular, Cell and Developmental Biology
University of Colorado

Robert L. Ullrich
Professor, Department of Radiation Therapy
University of Texas Medical Branch

In the Cell and Molecular Biology Division, a separate Human Genome Advisory Committee also reports to the Laboratory Director:

David Botstein
Professor and Chair, Department of Genetics,
Stanford University School of Medicine

David R. Cox
Professor, Department of Psychiatry
University of California at San Francisco

Leroy Hood
Professor, Division of Biology
Director, NSF Science and Technology
Center for Molecular Biology
California Institute of Technology

Jasper D. Rine
Professor, Department of Molecular
and Cell Biology
University of California at Berkeley

Gerald M. Rubin
Professor and Head of Genetics
Department of Molecular and Cell Biology
University of California at Berkeley

Chemical Biodynamics Division

Steven Boxer
Professor, Department of Chemistry
Stanford University

Winslow R. Briggs,
Professor, Department of Biological Sciences
Carnegie Institution
Stanford University

Donald Bryant,
Professor and President, Carteret Technical
Institute
Pennsylvania State University

Robert Fletterick
Professor, Department of Biochemistry
University of California at San Francisco

Christofer S. Foote
Professor, Department of Chemistry
University of California at Los Angeles

Irwin D. Kuntz
Professor, Department of Pharmaceutical
Chemistry
University of California at San Francisco

Olhe Uhlenbeck
Professor, Department of Chemistry
and Biochemistry
University of Colorado at Boulder

Research Medicine and Radiation Biophysics Division

Eleanor Adair
Fellow, Department of Physiology
John B. Pierce Laboratory

Robert Hamilton
Professor, Department of Anatomy
University of California at San Francisco

Kenneth A. Krohn
Professor, Department of Radiology
University of Washington

David Larson
Associate Professor, Department of Radiation Oncology
University of California at San Francisco

Robert Lees
Chief, Division of Peripheral Vascular
Disease
New England Deaconess Hospital, Boston

Gustav Schonfeld
Professor, Lipid Research Center
Washington University

Michel Ter-Pogossian
Professor, Division of Radiation Sciences
Washington University

Energy and Environment Division (1990-91)

Clark W. Bullard
Professor, Department of Mechanical
Industrial Engineering
University of Illinois-Urbana

Arnold P. Fickett
Vice President, Department of Customer
Systems
Electric Power Research Institute

William Fulkerson
Associate Director for Advanced Energy
Systems
Oak Ridge National Laboratory

Henry C. Kelly
Senior Associate, Office of Technology
Assessment
U.S. Congress

Howard B. Palmer
Professor, Department of Energy Science
Senior Associate Dean, Graduate School
Pennsylvania State University

James N. Pitts, Jr.
Professor Emeritus, Department of Chemistry
University of California at Riverside

At a higher level, the Laboratory is reviewed biannually by the Scientific and Educational Advisory Committee, which reports to the President of the University of California. The current membership of this committee is given below.

Scientific and Educational Advisory Committee—Current Membership

Edwin L. Goldwasser (Chair)
Professor, Computer-Based Education Research Laboratory
University of Illinois

Stanley Brodsky
Professor, Stanford Linear Accelerator Center
Stanford University

Douglas Fuerstenau
Professor, Department of Materials Science and Mineral Engineering
University of California at Berkeley

Ernest Henley
Professor, Department of Physics
University of Washington

C. Judson King
Professor, Provost, Professional Schools and College
University of California at Berkeley

Robert Langridge
Professor, Department of Pharmaceutical Chemistry
University of California at San Francisco

Dr. Eugene Meieran
Fellow, Intel Corporation

Dr. Mortimer L. Mendelsohn
Associate Director, Biomedical and Environmental Research Program
Lawrence Livermore National Laboratory

Warren Miller
Professor, Department of Nuclear Engineering
University of California at Berkeley

Dr. Martin Walt
Director of Research
Lockheed Missiles and Space Company

To advise the Division Directors on a more frequent basis, both with regard to scientific priorities and operational matters, each division collects and collates information from the research staff and from outside the division. Typically, a standing advisory committee comprising senior scientists from within the division meets periodically and discusses divisional issues. In several divisions, these committees (or councils) serve as the review panels for new Field Task Proposals and for proposals for Laboratory-Directed Research and Development funds. Group leaders' or project leaders' meetings also serve as forums for discussion, though in some cases the group leaders may constitute the advisory committee.

The Directors of the three life sciences divisions also meet regularly, and one of the Directors (currently the Director of the Cell and Molecular Biology Division) is designated as the coordinator for communication among the three divisions and between the Laboratory and OHER, as well as coordinator of other multidivisional administrative functions. The coordinator is a member of the Laboratory Director's Action Committee, which meets weekly.

Finally, mention should be made of the several specialized committees in each division, which support but do not influence directly, the conduct of scientific research. These include, for most divisions of the Laboratory, a professional staff committee, a safety committee, a salary committee, and others.

Laboratory-Directed Research and Development Program (LDRD)

LDRD funding provides initial support for innovative research projects and encourages pursuit of promising new institutional directions in ongoing research. The goal of support for new initiatives is to produce preliminary results that will provide a credible basis for seeking long-term funding from DOE or another agency. In the case of ongoing projects, the objective is to test the feasibility of a new research direction quickly and, if truly promising, to provide documentation for future proposals to support those new aspects of the program.

LDRD proposals originating in a given division are reviewed each year by the Division Director, who prepares a prioritized list, typically based on the recommendations of a divisional advisory committee. This list is submitted to a Laboratory-

wide review panel, which makes a final recommendation to the Laboratory Director.

A list of life sciences research projects that received LDRD funding during FY 1991 is given below.

LDRD—FY 1991 Awards Related to Life Sciences

T. Budinger, D.T. Attwood: $75,000
ALS Life Sciences Initiative

J. Campisi: $150,000
Protooncogenes and Tumor Suppressor Genes in Normal and Transformed Growth Control

J.M. Daisey: $85,000
Biologically Based Risk Assessment: a Novel Approach Based on First Principles

A.N. Glazer: $50,000
Novel Fluorescent Probes from Nucleic Acid-Dye complexes

T.L. Hayes: $32,000
Viability in Synchrotron Microscopy

W.W. Moses: $50,000
Scintillation Mechanisms of Heavy Atom Scintillators

P. Yaswen: $74,000
Calcium Signal Transduction During Human Mammary Carcinogenesis

Animal Welfare and Human Use

The LBL Animal Welfare and Research Committee (AWRC) oversees procedures that ensure compliance with policies of the U.S. Department of Agriculture and the NIH's Office for Protection from Research Risks (OPRR). The AWRC has the responsibility and the authority to deny animal use privileges to investigators found in noncompliance. Once approved, each research protocol is reviewed annually and prior to implementation of any changes in the protocol. The annual review verifies past and continued compliance with LBL and OPRR policies and evaluates research progress derived from animal use. Members of the AWRC are selected in strict compliance with NIH principles.

In October 1975, following the recommendations of the Director, a Memorandum of Understanding between the Chancellor of the University of California at Berkeley and the Director of LBL was issued regarding the use of human subjects in clinical research. The campus Committee for the Protection of Human Subjects (CPHS) assumed official responsibility for reviewing and approving all LBL activities involving human subjects, pursuant to Office of Science and Technology Policy (OSTP), UC Systemwide, and campus directives. An LBL advisory committee assists the CPHS in their review of LBL projects, and LBL research scientists serve as committee members. LBL protocols are submitted to the LBL Human Use Committee (HUC), which reviews all submissions and approves them before submission to the CPHS for review. The LBL HUC keeps LBL Administration advised of all actions taken with respect to human use approvals, maintains a permanent file of all documents pertaining to human subjects, and serves as an advisory group for investigators on matters concerning human use.

Safety Committees

Each of the LBL divisions has a safety committee that includes staff members from all levels within the division. Committee members receive specialized training in federal, state, and local safety, environmental, and operational laws and regulations. The committees are appointed by the Division Directors and charged with the responsibility of conducting annual inspections of all divisional laboratories, offices and shops to uncover any safety violations or lack of compliance with environmental requirements. They also assist in the implementation of lab-wide directives by the Environment, Health and Safety Division and the Office of Assessment and Assurance. The primary activity of the safety committees is to carry out the self-assessment of divisional compliance with safety and environmental regulations on a pro-active, continuous basis, including maintaining documentation of reports from walk-through and follow-up inspections and alerting Division Directors to problem areas.

In addition, LBL is using the safety committee network as a resource to assist in the installation of recommended operational procedures required of management by specific DOE orders and federal and state laws. For example, conduct of operations requirements include detailed documentation of compliance with specific procedures related to record-keeping of visitors to controlled

areas where radiation hazards exist. DOE orders also require detailed records of laboratory procedures and employee safety training. The safety committee network has been used to assist supervisors in complying with these responsibilities. Federal and state laws also require documentation of appropriate disposal of medical and biohazardous waste. New federal and state laws are now in effect that require individual laboratories to retain documentation of annual reporting of hazardous chemical inventories and of compliance with measures to ensure that the atmosphere and the water supply are not fouled by effluents from laboratories and shops. In some cases, permits are required to assure adequate monitoring of waste streams. LBL administration has chosen a "notebook" approach to consolidate documentation required by regulations related to environment, health, safety, and operations. Project, Facility and Function Notebooks have been formatted to assist LBL staff. Prototype testing of notebooks has begun, and in the near future requirements for full implementation will be underway. The safety committee network will provide assistance to responsible supervisors in meeting the requirements.

D. Research in Progress

Analytical Technology

Indoor Atmosphere

We are characterizing the sources of indoor radon and the concentrations of indoor radon and radon decay products, with particular attention to processes that affect the migration of radon through soils, entry into buildings, and the build-up and removal processes for radon progeny in indoor air. We are working to improve the assessment of indoor radon progeny exposures and the associated health risks under a wide variety of conditions, and to understand influencing factors so that they may be used as a basis for identifying where and under what conditions excessive levels may occur and for developing control strategies appropriate to such occurrences.

Typically, concentrations of radon, volatile organic compounds (VOCs), and nitrogen dioxide (NO_2) are two to ten times higher in indoor than outdoor air, with total VOC concentrations in the range of tens of milligrams per cubic meter. Existing information suggests that the radioactive decay of radon and its progeny in homes with high concentrations of VOCs and NO_2 may generate gaseous products and condensation nuclei. The chemical composition and particle size distribution of these nuclei are likely to be significant to radon lung dosimetry but have not been investigated. We are working to provide information on and to understand the nature of the interactions of radon and its progeny with gaseous indoor pollutants found in high concentrations in homes, and to elucidate the potential significance of this interaction to human health. The research approach is based on both theory and experiments.

Semiconductor Detector Technology

Recent work on semiconductor radiation detectors for biomedical and environmental applications has been aimed toward position-sensitive detectors, improved contacts, detectors with reduced capacitance using new shaped-field approaches, and background sources in semiconductor detectors. New signal-processing techniques have been developed to correct for ballistic-deficit effects arising from fluctuations in signal rise-time and to correct for trapping effects in detectors. The application of these techniques to large detector systems such as GAMMASPHERE results in major advantages in cost and performance.

Continued research and development is needed on the application of semiconductor detectors to synchrotron radiation experiments. Exploitation of flux capabilities possible with future synchrotrons requires detector performance parameters that are currently unavailable with existing semiconductor x-ray spectrometers. We are working to adapt our specialized skills in the area of semiconductor x-ray detector instrumentation to the design and fabrication of spectrometer systems especially adapted to the needs of synchrotron experiments.

Environmental Research

Atmospheric Aerosols and Global Climate Change

Experiments are underway to study aerosol-water interactions of several types that occur in clouds and fogs. The approach involves laboratory simulations in a cloud chamber, as well as in reactors with highly dispersed liquid water. This work is pertinent to heterogeneous aqueous chemical reactions, aerosol scavenging by clouds, and the interplay between the chemical properties of aerosols and cloud physical properties.

The radiative properties of clouds depend on cloud extent and morphology and on their microphysical characteristics such as drop number, size, and possibly chemical composition. These in turn depend on the chemical and physical properties of aerosols that serve as cloud condensation nuclei. Aerosol-cloud interactions are not currently treated in global circulation models (GCMs), which are the principal tools for forecasting the climatic influences of increasing CO_2 concentrations. Such interactions, however, must be considered, by GCMs or otherwise, because of the possibility that current and future anthropogenic and biogenic activities, through their influence on aerosol particles and consequently on cloud microphysics, could increase the albedo of clouds, thereby causing climate cooling sufficient to mitigate the predicted warming caused by increasing CO_2. At this time it is not known whether such compensatory effects actually exist. However, because of potential implications to national and international energy policy, the resolution of this question is urgently needed. At LBL we are experimentally quantitating the links between the optical properties of clouds and atmospheric aerosols such as sulfate and carbonaceous particles.

How do optical properties of clouds respond to changing concentrations of anthropogenic, biogenic, and natural aerosols? The approach to answering this question consists of a combination of field and laboratory experiments. To assess the importance of aerosol-cloud interactions, an important prerequisite is to obtain data to derive horizontal, vertical, and seasonal variations in global concentrations. This task relies on compilation, evaluation, and analysis of existing ambient and source emissions data.

We perform field experiments to measure the radiative properties of natural clouds, determine the relative impacts of energy-related crustal and biogenic aerosols on radiative properties of clouds, and determine the soot content of natural cloud drops. Results obtained from these field studies are used to design laboratory simulation experiments with the LBL cloud chamber to identify the physics and chemistry of dominant importance in modifying the optical properties of clouds, with special emphasis on enhanced absorption by soot-associated clouds. Finally, compilation and analysis of ambient and source emissions data, pertaining particularly to soot aerosols, provide insight into horizontal, vertical, and seasonal variations in global aerosol concentrations.

Radon Entry Into Houses

We are also using both experiments and theoretical studies to advance and confirm our understanding of radon transport through soil and entry into basements. Specific objectives include quantifying the effects of different transport mechanisms, driving forces, and controlling parameters on the radon entry process, including the following: soil characteristics (permeability, moisture, radium content, and heterogeneous features); building characteristics (size and location of penetrations to the soil, presence of subslab aggregate, presence of high-permeability backfill); steady-state and time-varying indoor-outdoor pressure differences caused by a variety of factors; and meteorological factors such as temperature, wind, precipitation, and barometric pressure changes. The experimental approach involves construction of precisely designed and fabricated room-sized basements at several geologically different sites, detailed site characterization, and installation of complex multi-parameter instrumentation to characterize the soil, pressure fields, and radon entry rates. Numerical models are used to evaluate transport mechanisms for parametric assessments and to guide experiments. The models are evaluated using the experimental data.

Subsurface Transport

Fundamental knowledge of the basic chemical processes that occur between radionuclides and organic chemicals present in mixed wastes at DOE sites will allow more accurate predictions of the processes that control contaminant mobilization and transport in the subsurface environment. Existing thermodynamic databases used as input for transport modeling are either incomplete or completely lack data for complexation, speciation, and solubility of most mixed-waste complexes and compounds. We experimentally determine these missing thermochemical constants, as well as the nature of the compounds that can form between the actinide elements neptunium, plutonium, and americium and selected hydrophilic and hydrophobic organic compounds. Whenever no data are available, the complexation behavior of Am^{3+}, NpO_2^+, Pu^{4+}, PuO_2^+, and PuO_2^{2+} is measured with the organic ligands. The results of this work will provide suggestions for possible pathways to manipulate the geochemistry to achieve site remediation by either stabilizing or mobilizing contaminants in the subsurface.

Organic complexation is one of the most important mechanisms that affects toxic metal subsurface transport. Cobalt, uranium, and chromium—all documented health hazards in the biosphere—have been shown to undergo a significant increase in ground transport kinetics when complexed with organic molecules as mixed co-contaminants. The experimental database for organic/metal ion co-contaminant systems, however, is relatively non-existent; virtually no experimental, spectroscopic data for these organic/metal ion mixtures exist with respect to the use of unique, state-of-the-science instrumental techniques to characterize them.

To provide this data, we are (i) synthesizing organic/metal ion complexes involving cobalt, uranium, and chromium with multidentate chelating carboxylic acids, and (ii) using Auger, x-ray photoelectron, Fourier transform infrared, and Raman spectroscopies both to study the chemistry and spectroscopy of the mixed contaminants and to devise new analytical methods for the detection of mixed contaminants in soil and groundwater. The information derived from this research will provide an extremely critical experimental chemical base for purposes of modeling hydrologic transport of co-contaminant organic/metal ion species in subsoils and groundwater.

In other studies of subsurface transport, we are using tomographic seismic imaging to quantify the interrelationships between soil types and transport properties in a spatially heterogeneous hydrophysical system, e.g., natural conditions of porous media in an uncontaminated or contaminated aquifer. The approach is to characterize the in situ properties controlling fluid flow vital to the prediction of contaminant migration in natural systems. This research involves a joint geophysical-hydrologic approach to characterizing and identifying the fundamental properties necessary to map contaminant transport in media in shallow toxic-waste sites. The approach iterates between the laboratory and the field, using the information from each setting to progress toward more complex cases to characterize the properties controlling contaminant flow.

Health Effects

Air Pollutant Exposures in Buildings

To advance scientific understanding of human exposures to and health risks from indoor air pollutants, we are assessing pollutant exposures and risks associated with reductions in building ventilation and technologies to reduce energy usage in buildings. Two basic approaches are taken in this work: (i) existing data on various indoor pollutants are assembled, integrated, and critically evaluated to assess indoor exposures to various pollutants (e.g., radon, combustion pollutants, and volatile organic pollutants) and the risks associated with these exposures; and (ii) physico-chemical models are developed for the estimation of population exposures and to develop and test models.

Population exposures to radon, based on mobility and measured indoor concentrations, are being evaluated; and association of exposure with geological factors is being investigated. Indoor exposures to volatile organic compounds (VOC) are being determined and evaluated. Efforts are underway to develop metrics of exposure to complex mixtures of VOC. These metrics are to be based on biological mechanisms of toxicity. Metrics which can be readily related to adverse health effects from indoor air exposures are being sought.

In a project initiated at the start of FY92, a method is being developed for using indoor radon monitoring data jointly with information on causative factors to identify geographic areas of the United States where most of the houses with indoor radon concentrations above 20 pCi/L are located. For this purpose, candidate indices of expected indoor radon concentrations are developed based on soil, structural, and meteorological factors. The correlations of these indices to indoor radon concentration data are evaluated. Through this process, suitable indices for estimating the concentration distributions of variously sized geographic regions will be developed.

Biological Effects of Ionizing Radiation

To obtain a quantitative understanding of the nature and kinetics of biological responses produced at the molecular and cellular level by accelerated atomic nuclei of varying energy density, we are identifying the yield of heavy-ion-induced DNA lesions that presumably originate as DNA strand breaks or DNA-DNA or DNA-protein crosslinks and then result in chromatin breaks. We are examining how the chromatin break, which may be a complex lesion representing multiple strand breaks, is modified by the cell, and how this type of damage affects the cell's ability to deal with additional insults. We have shown that there is an LET-dependent variation in the efficiency per unit dose for the production of initial chromosome breakage, that the distribution of breaks becomes progressively overdispersed with increasing LET, and that there is an LET-dependent increase in the proportion of nonrejoining breaks. Recent progress has been made in showing for the first time that there is a synergistic effect on normal hamster cell survival when moderate heat is applied immediately after heavy-ion irradiation, while in the absence of normal protein synthesis in a temperature-sensitive hamster mutant, the effect is merely additive. Increased new synthesis of proteins appears to interfere with cellular processing of radiation-induced damage, and there are also indications of differences in the handling of high- versus low-LET damage. We have begun an investigation to characterize protein synthesis profiles of these cells to understand the involvement of new protein synthesis in the processing of x-ray and heavy-ion -induced DNA damage. Future directions will emphasize a search for specific LET-dependent radiation-induced alterations in genetic expression.

We are examining the effectiveness of radiation at the high end of the LET spectrum for inducing radiogenic neoplasia in the mouse Harderian gland. Research to date has not shown the decrease in biological effectiveness that is expected to be seen at very high LET values. Cell killing and neoplastic transformation in vitro have maximum effectiveness associated with LET values around 100 keV/mm, while in vivo neoplasia shows no reduced effectiveness at LET values has high as 650 keV/mm. Animals are now being included in the study following irradiaton with ion beams at 1000 keV/mm. Several years will elapse before the observation period ends and the data become available. Data are also being collected on low-LET particle irradiation (200MeV protons) to provide a low-

LET reference for the construction of the LET-dependent risk coefficient for carcinogenesis.

Another approach is the development of theoretical models to correlate DNA double-strand breaks with mutation (specific types) and transformation frequencies as a function of dose for different types of ionizing radiation. The types of ionizing radiation being considered are x-rays, Co^{60}-g rays, energetic protons, helium and other heavy charged particles. In the last several years, we have developed a mechanistic model that is based on basic physical and chemical laws and can quantitatively estimate yields of strand breaks (single and double), base alterations by water radicals and base deletions for any type of ionizing radiation. We are now using the yields of strand breaks as fundamental quantities in modeling mutation and transformation frequencies. For mutation studies, we are limiting ourselves, for the next milestone, to those cases where a foreign gene transfected into a host genome gets deleted as a result of two double-strand breaks. To model transformation effects we are using available experimental data on partially transformed cell lines.

Biological Effects of Magnetic Fields

Mechanisms of interaction of ultrahigh intensity, ultrahigh frequencey, and ultrafast switched magnetic fields with biological systems are being investigated. Exposure frequencies ranging from DC to GHZ are employed. This research effort is unique in that it utilizes a wide range of frequencies and spans cellular, tissue, and animal systems. The work is providing essential input to the development of exposure guidelines for industrial, research, and medical facilities. We are now focusing on single-cell responses using high-resolution fluorescence microscopy and intracellular probes to define spatial and temporal field interactions. New biotechnologies based on magnetic field interactions with biological systems are being developed with industry. Development of these technologies is an important program goal.

Specific bioeffects research indicates that activated lymphocytes undergoing signal transduction respond to static and time-varying magnetic fields. We have observed that 9.0 Tesla magnetic fields inhibit calcium transport in mitogen-stimulated rat lymphocytes. In contrast, a 60-minute exposure of activated lymphocytes from humans to the three field components that occur during a typical NMR scan causes a 30% increase in calcium uptake. Exposure to individual field components does not effect cells.

Advanced biotechniques and technology transfer are evolving in three areas: microwave-triggered drug delivery from liposome vesicles, which has potential for cancer therapy; pulsed-field HPLC, which is effective in separating large biopolymers such as DNA faster than gel electrophoresis; and magnetic circular dichroism spectroscopy, which enables the study of DNA in living cells.

Carcinogenesis: Transformation And Risk Assessment

We are developing methods for detecting carcinogen-induced transformation of human mammary epithelial cells (HMEC) in vitro such that we can (i) define the characteristics that distinguish normal from transformed HMEC in culture, and (ii) determine what agents, alone or in combination, may be capable of inducing human carcinoma. The immediate objective is to understand the relationship between the differentiated state of mammary epithelial cells and their potential to undergo malignant transformation. In particular, a newly isolated gene, NB-1, which may play a key role in both mammary cell differentiation and transformation, is under investigation.

The NB-1 gene, recently identified at LBL, encodes a protein that is expressed in a tissue-specific manner and is often downregulated or absent in tumors of the corresponding tissues. Because of the close resemblance of the NB-1 product to the ubiquitous calcium regulatory protein, calmodulin, and because of the known effects of calcium on the growth, differentiation, and transformation of epithelial cells, we have begun to examine the biological characteristics of the NB-1 protein in order to learn more about changes in control of growth and differentiation that occur after transformation of human epithelial cells.

Expression of the NB-1 protein is restricted to certain histological cell types in normal breast, prostate, skin, and cervix. Lowered NB-1 expression in tumors may result from alterations in the

proportions of cell types of different differentiation states. These alterations could be either a direct result of malignant transformation or a necessary precondition for carcinogenesis to proceed. Experiments are currently in progress to determine whether expression of the NB-1 protein is responsible for maintaining specific differentiated traits in normal cells and whether NB-1 expression is incompatible with tumor cell growth.

Another aspect of our research on carcinogenesis is determination of the relative risk associated with various carcinogens. There is an enormous background of natural chemicals in the diet, such as plant pesticides and the products of cooking, that have not been a focus of carcinogenicity testing. In order to set priorities for laboratory or epidemiological research and for regulatory policy, a broadened perspective including these natural chemicals is necessary. Using results in LBL's Carcinogenic Potency Database, we ranked possible carcinogenic hazards for 79 daily human exposures to rodent carcinogens using an index (Human Exposure/Rodent Potency, or HERP) to relate rodent carcinogenic potency to human exposure; a similar ordering would be expected using standard risk assessment methodology for the same exposure values. Results indicate that when viewed against the large background of naturally occurring chemicals in common foods, such as plant pesticides and the products of cooking, the residues of synthetic pesticides or environmental pollutants rank low. The findings do not indicate that these natural dietary carcinogens are important in human cancer, but rather cast doubt on the relative importance of low-dose exposures to synthetic chemicals. Extrapolation to low-dose human exposures from results of animal cancer tests done at high dose should be based on knowledge about mechanisms of carcinogenesis for each chemical, particularly mitogenic effects that are present at high and not at low dose.

We are proceeding with work to prioritize chemicals according to how they might rank as possible hazards if they were to test positive in rodent bioassays. We have identified chemicals that appear in relatively high concentrations in the most commonly consumed foods and will search for toxicity data (LD_{50}) to rank them on the HERT index (Human Exposure/Rodent Toxicity). Since the rank order correlation between HERP and HERT is 0.9, the HERT index can provide a useful first approximation of possible carcinogenic hazard. We are also ranking possible carcinogenic hazards in the workplace based on the new Permitted Exposure Limits (PEL) of the U.S. OSHA. We use an index PERP, that compares permitted exposure to rodent potency. Work on interspecies extrapolation between rodents and nonhuman primates is in progress.

General Life Sciences

Structural Biology

Structural biology research at LBL takes a multidisciplinary approach. The objective of this branch of science is to understand the function of biological molecules and molecular complexes from the viewpoint of their respective three-dimensional structures. To achieve this objective we are using physical techniques such as x-ray crystallography, NMR, electron crystallography, and spectroscopy, as well as biological and biochemical techniques such as protein engineering and genetic engineering.

Ras oncogene products: In these genes, which are commonly found in human cancer cells, the difference between a protooncogene and an oncogene is often a point mutation. The current view of the function of *ras* proteins is that an extracellular signal for cell growth is received by a presumed transmembrane receptor protein (or proteins), which induces exchange of GDP for GTP in the *ras* protein inside the cell. The GTP complex is then recognized by one or more effector proteins as an indication for growth. Thus, conformational changes from the GDP- to the GTP-bound state of *ras* proteins represent the molecular switch from the "off" to the "on" state, signaling cell growth. Most of the in vivo transforming *ras* oncoproteins are thought to be stuck in the signal "on" state. This prolongs the transmission of the growth signal, resulting in unregulated cell growth. To understand the mechanism of the molecular switch, we have been comparing the three-dimensional structures of both GDP- and GTP- bound forms of the *ras* proteins, as well as comparing the structures of the proteins encoded by the protooncogene and the oncogene.

Structures of membrane proteins at atomic resolution using electron crystallographic methods: Specific membrane proteins that are under study are LamB porin, "band-3" protein, and cytochrome bc1 complex. The research involves (i) membrane protein purification, (ii) a continuing development of crystallization methods that will lead to obtaining crystalline membrane patches, and (iii) molecular structure determination by electron crystallographic methods. Knowledge of the molecular structures of these proteins would provide information about the detailed folding of peptides that form the pathways for solutes and/or ions, and about the molecular design of the pathway in terms of surface charge distribution, which plays an important role in the regulation of the transport of ions and solutes across the membrane. The overall goal of these structural studies is to give a rigorous conceptual framework for the rational understanding of the molecular mechanism of membrane transport systems and their specificity for the transport of solutes and ions across the membrane. The understanding of the transport across these distinct membrane systems will provide insight into the general principles that govern the behavior of membrane transport systems.

Three-dimensional structure of a catalytic RNA: The finding that RNA can have catalytic activity has had profound implications for our understanding of catalysis. Since this discovery, the biological role of RNA has been found to be quite diverse and the occurrence of RNA self-processing much more widespread than expected. Biochemical evidence so far strongly indicates that the three-dimensional structures of the RNAs are essential for their autocatalytic activities. NMR studies have been applied to self-cleaving "hammerhead" RNAs from plant virusoids. An analysis of imino proton spectra from both cleaved and uncleaved hammerhead RNAs were carried out. The assigned residues indicate that the proposed secondary structure is basically correct, but that there is significant destabilization of base pairs near the junction of duplexes in the uncleaved form. We have been able to show that there is segmental flexibility in one of the stems in the cleaved form of the molecule, again underscoring the minimal stability of the tertiary structure. There are a few resonances in the uncleaved molecules (probably arising from tertiary interactions) which appear at low temperature, especially in the presence of magnesium.

DNA, RNA and protein structures by NMR: We are developing new NMR methods for the analysis of biomolecular structure and are carrying out structural studies on biologically important molecules. The systems presently under study include DNA models with backbone nicks and gaps; DNA triple-helix structure models; and protein-DNA, protein-ligand, and protein-protein interactions, as well as highly stable RNA stem-loop structures.

During the past year, we have analyzed two protein systems. The first is the Bowman-Birk protease inhibitor, whose structure was determined to fairly high resolution using NMR and simulated annealing calculations. This structure showed that there are two similar domains, each with a β-hairpin containing the inhibitory site. Complexes of maltose binding protein with maltodextrans were analysed using tritium NMR. With this approach we could follow very broad resonances that demonsrated two binding modes (for β anomers) for the first time.

We also determined the structure of several protein cofactors, including a new redox active tryptophan dimer (from methylamine dehydrogenase), and antenna pigments in phycobiliproteins (from cryptomonad algae). These are novel structures with functional groups that were not previously known. The structures help to explain the function of these molecules.

Catalytic antibodies: We are altering the structure of proteins to change their function. Antibodies bind a wide variety of molecules with enzyme-like affinities and specificities. Because an antibody combining site can be generated to virtually any molecule of interest, the development of general strategies for introducing catalytic activity into antibodies should provide tailormade catalysts for use in biology, chemistry, and medicine. Antibodies are being generated that catalyze stereospecific epoxide ring opening reactions and stereospecific HCN addition to a ketone. Esterolytic antibodies are being generated capable of activating prodrugs for selective delivery of chemotherapeutic agents. In addition, mechanistic studies are being performed to determine the degree to which an esterolytic antibody functions by transition-state stabiliza-

tion. Efforts continue toward generating antibodies with amidase activity. A related immunochemical project involves the development of new drug strategies based on antibody targeting. Finally, stabilized α-helical peptides are being designed that bind site-specifically to DNA.

NMR has been used for determining which amino acids are involved in the binding and possibly in catalysis by catalytic antibodies. The antibodies were generated using transition-state mimics, with the expectation that there would be chemical complementarity in the hapten binding site. Studies of a carbonate hydrolysis antibody put a limit on the involvement of charged residues by determining the pK of a phosphate-bearing residue in the binding site. For an antibody which acts as a photolyase (photoreversing thymine dimer formation), it was shown that there is a tryptophan in the binding site.

The Advanced Light Source (ALS) will add an important new dimension to our structural biology program in the areas of x-ray microscopy, crystallography, and spectroscopy. We are seeking to study substantive biological problems with these techniques and to develop the necessary tools to do so effectively. Initial experiments have provided proof of principle for the method of imaging biological samples in the native state in physiological environments at high resolution and have made use of the elemental information provided by the method to obtain quantitative values for the protein content of cellular organelles. Our success in this regard has opened the door to many opportunities to study the relationship between native state structure and function at the subcellular level with spatial resolution almost an order of magnitude beyond that of the optical microscope. Thus far we have focussed our efforts on the central cellular processes of protein secretion and intracellular transport.

In anticipation of the ALS, we are developing applications of sulfur spectroscopy to problems in biology. Sulfur is an important element in biology and chemistry: In essentially all of its states, it is spectroscopically silent and hence inaccessible for study or evaluation without degradation or destruction of the sample. However, x-ray absorption spectroscopy (XAS) at the sulfur K-edge (E = 2.4 keV) can be performed readily with synchrotron radiation sources. Our objectives are to determine the intracellular quantities of sulfur-containing molecules in the several oxidation states, to measure the changes induced by drugs, and to explore the idea that radiation damage to cells may be determined by the state of sulfur.

We are developing a novel, multi-user configuration to serve several end stations in an energy-separated or time-separated mode for the ALS user facility. For this purpose two different x-ray optical elements for "splitting" x-ray beams will be used. First we will fabricate high quality, multi-layer mirrors on very thin substrates. Second, we are planning to evaluate the performance of thin silicone crystals or other crystals as a transmission x-ray monochrometer. These two x-ray optical elements will be used to multiplex the use of a single x-ray beam line, thus enlarging the number of facilities available for protein crystallography with synchrotron radiation.

Recombination And DNA Repair

The radiation-sensitive mutants of Saccharomyces cerevisiae are a valuable genetic resource for studying repair in a eukaryote. We are studying the roles played by the RAD50 to RAD57 genes in recombinational repair and in mitotic and meiotic recombination. Areas of emphasis include (i) transcriptional regulation, (ii) characterization of primary gene products, and (iii) visualization of recombination and recombinational repair by pulsed-field gel electrophoresis. In the first of these areas, deletion analysis has identified the sequences involved in regulation of these two genes. In our efforts to characterize the primary gene products, we have already sequenced *RAD51*, *RAD54*, *RAD55*, and *RAD57*. We have identified the product of *RAD54* on gels and hope to isolate the protein within a few months. Purified *RAD* proteins will be tested for various enzymatic activities such as ATPase, nuclease, and DNA-binding activities. The electrophoresis work focuses on the use of orthogonal-field-alternation gel electrophoresis (OFAGE), which has been used to study DNA double-strand breaks and repair of linear chromosomes, as well as interhomolog recombination and sister chromatid exchange.

We have identified three novel genes of *Saccharomyces cerevisiae* (*REC1*, *REC3*, and *REC4*) that are required for mitotic gene conversion, intragenic recombination, intergenic recombination, genomic stability and meiosis. Using temperature-conditional mutations of these three genes (*rec1-1*, *rec3-1*, and *rec4-1*), we have demonstrated that *REC1* is an essential gene and is also required for repair of potentially lethal x-ray damage as well as DNA double-strand breaks that arise at the *MAT* locus during homothallic mating type interconversion. By contrast, both *REC3* and *REC4* are non-essential genes and are not required for x-ray damage repair and mating type switching.

We have mapped and cloned *REC1* and *REC3*. *REC1* controls the expression of the *KEM1* gene that encodes a 170 kilodalton DNA strand-transfer protein required for mitotic recombination and normal meiosis. *rec1-1* mutants contain an apparently novel 43 kilodalton DNA strand-transfer protein that partially compensates for absence of the *KEM1* encoded 170 kilodalton DNA strand-transfer protein. Current studies are focused on identifying the structural gene that encodes the 43 kilodalton protein and the *in vitro* properties of the purified 43 kilodalton protein with respect to types of joint DNA molecules that are made and presence of associated exonuclease activity.

Mutagenesis And Carcinogenesis

To study mechanisms of mutagenesis, we site-specifically modify DNA with psoralen. The complete stereochemical characterization of the adduct between the polynuclear photoreagent and the DNA allows for the separation of the various addition products to a chemically synthesized oligonucleotide. These modified DNA molecules are then used for in vitro and in vivo assays of DNA repair and the mutagenesis associated with that process. This study continues as a highly effective collaboration with the laboratory of Professor Aziz Sancar at the University of North Carolina Medical School.

To study the mechanisms controlling cell growth in culture, we are analyzing the expression of *onc* sequences in different types of cells and at different points in the cell cycle. The basic hypothesis is that these genes, which have been shown to be related to malignant transformation, normally function to control the growth of the cells. Our aim is to determine what role these genes and gene products play in growth control.

Another project focuses on factors that control gene copy number in the human genome and how chemical carcinogens interfere with this control. Our hypothesis is that adducts on the DNA induces an SOS-type response that results in gene amplification and/or rearrangements. The system we have been studying is the maintenance of episomal DNA in human cell lines. We have established an in vitro DNA replication system to study how these episomal DNAs function with factors from the cells known to control replication and gene expression. This system will also be used to develop a method for assaying for carcinogen-induced factors that are involved in DNA replication and/or gene expression.

Differentiation And Carcinogenesis

It is now well established that viral carcinogenesis, analogous to chemical carcinogenesis, is a multistep process. We have argued in the past that to understand malignancy one needs not only to define the oncogene or the carcinogenic damage but also to define the additional steps which allow the oncogene to become dominant, i.e., the steps that lead to loss of microenvironmental control. Having clearly established that oncogenes such as the avian *src* gene can be expressed in their active form within a normal-tissue context (in the embryo), we have sought to define the nature of the constraints.

Two findings have focussed our attention on the possible role of factors that are involved in wound healing and vascular differentiation: (1) our discovery that TGF-beta induced by wounding is a cocarcinogen with Rous sarcoma virus in the chicken, and (2) the discovery made both at LBL and elsewhere that vascular endothelial cells in the limbs of chick embryos are a specific target for oncogene-induced tumors in vivo.

To build on these findings, we (1) have developed a culture model to simulate limb tissue to see whether we can recreate the suppression phenomenon in culture and thus define the regulatory elements, (2) are developing cultures of functional endothelial cells from chick vascular

tissues to define the parameters that allow these cells to become transformed in ovo when other tissues are resistant to transformation, and (3) are determining the function of 9E3, a gene that has homology to inflammatory mediators and, like TGF-beta, is expressed soon after wounding.

We are also involved in studying the molecular mechanisms underlying tissue specificity. We have concentrated on the role of the extracellular matrix (ECM) in the differentiation of mammary epithelial cells. We have succeeded in producing, in culture, complete functional mammary "alveoli" capable of vectorial secretion. The morphology and size, as well as the biochemical capability, of these alveoli resemble the lactating gland.

In the last two years, we have made a number of significant advances. We now also have clear evidence that embedding cells in basement membrane can induce milk protein expression in the absence of cell-cell interaction and polarity. We have shown that ECM transmits signals through receptors which appear to be integrins because antibodies against β subunits of integrins block these signals. The challenge now is to determine how the signal is transduced across the membrane, which ECM molecules are involved, and which integrin is the receptor. We have isolated a mammary epithelial cell strain (CID-9) that is ECM- and hormone-responsive and can be stably transfected. We have shown that 5' sequences of bovine and rat genes for beta casein, a milk protein, are regulated by both substratum and hormones. In collaboration with the Monsanto Company, experiments are now underway to identify the ECM-regulated sequences of the beta casein gene. A 60-nucleotide sequence has been identified that appears to be an enhancer and specifically confers hormone and ECM-responsiveness to mammary cells. The enhancer appears to be mammary specific. We are now searching for the factors that regulate these sequences.

Human Genome Project

In September 1987, the Secretary of Energy designated the Lawrence Berkeley Laboratory as a center for human genome research. The purpose of the LBL Human Genome Center is to bring a focused and comprehensive fusion of interdisciplinary talents to the goals of the human genome initiative. Specifically, we are working to: (i) rapidly provide very high-resolution genetic maps of human chromosomes; (ii) develop efficient methods of physical mapping and contig construction of specific regions of human chromosomes; (iii) develop novel methods of sequencing DNA, including the use of mass spectrometry; (iv) develop efficient methods for assigning cDNAs to chromosomes and to subchromosome regions; and (v) develop the automation of laboratory infrastructure needed to achieve the other goals in a reasonable time at a reasonable cost.

The activities of the LBL HGC fall broadly into three areas: biology, instrumentation, and informatics. The aim is to make the principle consumers of the information from the genome initiative the primary beneficiaries of our data and technology, with instrumentation and software developed to address the real problems in acquisition and analysis of data.

Our goal in genetic mapping is to catalyze the development of high-resolution genetic maps of human chromosomes based upon genetic markers with universal availability, ease of use, and maximum possible informativeness. We have developed a strategy for selecting highly polymorphic microsatellite clones from libraries and are using this technique to clone, sequence and develop PCR-based primers for measuring every locus on human chromosome 21 containing a (CA) repeat. This map will be further refined by including a sample of tri- and tetranucleotide repeats using the same strategy. The successful completion of this goal requires the active support of the engineering group in order to develop robotics that will permit us to perform PCR reactions efficiently on the scale of tens of thousands. This genetic mapping project will also be used to test the potential of mass spectrometry for obtaining specific allele information. This is relatively simpler than actually sequencing with mass spectrometry, since the difference between the mass of two alleles is approximately 600 daltons, rather than the much smaller difference between a single G, A, T, or C.

Our physical mapping goal for the next year includes developing a complete contig for the distal 10 megabases of the long arm of human chromosome 21. We have identified over 50

clones, YACs and cosmids within the 10 megabases using fluorescence in situ hybridization. These clones are used to walk between YACs without excessive overlap by using the ends of known probes, selecting an overlapping cosmid, and then doing a double selection for new cosmids. A major benefit of this strategy is the signalling of possible cocloning artifacts before they become a critical part of a contig.

Robotic manipulations of clone libraries has enabled the LBL HGC to play a major community role in the duplication and distribution of libraries from other facilities to other research institutions and private industry. Robotic procedures eliminate human errors that lead to losses of efficiency. In addition to duplicating libraries, the high speed colony picker developed by the HGC instrumentation group creates arrayed libraries.

Our large-scale sequencing goal again involves development of both instrumentation and techniques for rapidly providing templates of known order for sequencing. The strategy is to use double-ended clones to provide order, followed by transposon-mediated primer introduction for sequencing. The initial target of this proof-of-principle effort is a cluster of genes that are among the most conserved genes known with respect to map order and primary sequence. Thus, our sequence data will provide key data to molecular biologists far beyond the genome program. We also anticipate that the technologies developed for this project can be transferred to the sequencing of YAC contigs from chromosome 21. The double-ended strategy can also be used to generate a physical map of an extended region as large as 100 megabases. Sequence tagged sites (STSs) will be used as identifiers of the clone and as probes to detect overlaps.

The informatics support of each of these projects must provide a way to accept and track data from each step of the process (cloning, mapping, subcloning, sequencing, etc.), provide high level analysis of the experimental results, and provide retrieval and reports concerning results and project status. In some cases, the software will actually implement the strategy of the experiments. The LBL HGC is developing a Laboratory Information Management System (LIMS) that is adapted to meeting the demand of rapidly evolving mapping and sequencing protocols and strategies. This is a collaborative effort between LBL and Leroy Hood's sequencing project at Caltech. The LIMS will be useful to a wide variety of molecular biology laboratories, including genome centers and other DNA-sequencing labs.

The main goal of the LIMS is to permit users to interact with the system in terms of graphical descriptions of biological protocols. This LIMS will allow specifying the structure of protocols, as well as querying the system in terms of protocols and objects. By allowing users to interact with the LIMS in terms of their own frame of reference, we expect the system to be easy to use, manage, understand and adapt. Our approach envisions the use of a graphical protocol editor that will permit biologists to specify new protocols by graphically constructing a protocol process flow diagram.

To sequence individual DNA molecules directly, it will be necessary to develop methods for manipulation and visualization of single DNA molecules at single-base-pair resolution and for base identification. We are now exploring methods for manipulation and visualization that would be a feasible first step to a general sequencing approach. The proposed manipulation method involves the use of the avidin-biotin reaction to attach end-labeled fragments to suitable electrode materials, followed by alignment of the fragments in an external electric field. Preliminary experiments are being performed in which the attached fragments are labeled with intercalated ethidium bromide and imaged in an epifluorescence microscope. Methods for immobilizing the attached fragment, followed by selective cutting of the DNA strand, are being explored. A parallel effort involves the design and fabrication of an atomic force microscope (AFM) dedicated to imaging biological molecules. This work is being done in collaboration with a research group in materials sciences at LBL that is experienced in STM techniques and applications and that has previously demonstrated the direct imaging of DNA using STM.

Another project is designed to advance the rate of making physical and genetic maps by at least an order of magnitude. The principle strategy is to improve methods for purifying human chromosomes or large fragments of these chromosomes. One approach is to enhance pulse-field gel electrophoresis to handle larger DNA fragments.

We are exploring the use of secondary pulses in attempts to fractionate DNA molecules the size of intact human chromosomes. A second approach is to develop sequence-specific DNA purification methods that can be carried out in the agarose gels needed to stabilize large DNAs. It is necessary that these methods work without conventional DNA denaturation, because that would damage chromosomal DNAs.

In continuing work on a macrorestriction map for human chromosome 21, we use restriction enzymes to generate megabase DNA fragments from this chromosome. The fragments are separated by pulsed field gel electrophoresis and ordered by hybridization experiments using cloned chromosome 21 sequences. Some of the chromosome 21 sequences have been previously mapped, genetically, to a variable extent. Other specialized mapping clones called linking clones have been isolated in the course of this work. The linking clones will be regionally assigned and hence will not only link up fragments but also anchor fragments to particular chromosomal regions. Cytogenetics, partial digestion strategies, and megabase polymorphism footprinting of chromosomal regions are used to provide supplementary and confirmatory information.

Medical Applications

Vascular and Blood Diseases and Radiation Effects

This program evaluates vascular diseases, blood platelets, and megakaryocytes in laboratory animals.

One goal of the project is to identify early and advanced vascular lesions in animals by their interaction with radioisotopically labeled substances. Three types of vascular disease are under consideration: (i) radiation-induced injury to small vessels, (ii) atherosclerosis induced by dietary or hereditary hypercholesterolemia, and (iii) catheter-induced deendothelialization of large vessels. Recent work has tended to focus on the first of these as manifested in tissues of mice during the first few days after whole body irradiation.

A second goal is to characterize platelet abnormalities associated with abnormalities of lipid metabolism. Blood platelets are involved in progression of advanced atherosclerotic vascular diseases, and their production, survival, and morphology in vivo are disturbed in rabbits with dietary or hereditary hypercholesterolemia.

A third goal is to define factors that influence the regulation of blood platelet production by bone marrow megakaryocytes. Experiments are in progress to determine if a superabundance of megakaryocytes can be produced by implanting excess bone and marrow from donor mice. Evidence for abnormalities of platelets, megakaryocytes, and total marrow mass is being sought.

A fourth goal is to evaluate interactions between megakaryocytes and components of the bone marrow stroma. It is likely that megakaryocyte interactions with the environment of the bone marrow influence the development of the megakaryocytes, and these interactions may also affect the marrow stroma. It is possible that the long-term effects of ionizing radiation on hematopoiesis may be, in part, mediated by damage to the marrow stroma, possibly the vasculature as in other tissues.

Heavy-Ion Radiosurgery and Radiobiology

The objectives of the radiosurgery program are to: (i) develop heavy-charged-particle Bragg peak radiosurgery, using focal beams for treatment of selected intracranial disorders (ii) examine metabolic mechanisms of reaction of CNS tissue to radiation injury; (iii) apply NMR and PET scanning procedures to examine metabolic events in the human brain following heavy-ion irradiation; (iv) investigate physical properties and beam quality of heavy ions for developing beam-delivery systems for medical applications; (v) establish RBE/LET and dose-effect relationships for different sites in the human brain; and (vi) develop charged-particle treatment strategies for clinical application through technology transfer to hospital-based facilities.

The experimental approach includes development and application of stereotactic neuroradiologic procedures, charged-particle treatment planning and dosimetry, and verification of dosimetry and dose localization and distribution. Nuclear medicine imaging procedures (NMR, PET, X-CT)

are used to study reaction of the brain to radiation injury. More than 450 research patients with intracranial vascular disorders have been treated and followed-up; 80 to 85 percent were cured. NMR and PET studies have been correlated on 25 selected patients with differing neuroradiological responses, and different radiation types and irradiation geometries have been compared.

In a related study of the effects of heavy-ion irradiation, we are investigating (i) physical characteristics of heavy ions, as well as their physiological effects and their applications to human health and disease, and (ii) cellular and metabolic events in mammalian brain-cell populations following irradiation. Post-irradiation studies include regulatory control mechanisms, cell-proliferation kinetics, regional cerebral blood-flow dynamics, and reaction of the brain to heavy-ion radiation injury.

Experimental approaches include examination of beam quality characteristics (straggling, fragmentation and multiple scattering), RBE/LET relationships, and effects of heavy ions on DNA damage and repair, protein, and lipid membranes under a variety of physical and metabolic conditions. Cell and tissue kinetics research examines brain-cell proliferation kinetic parameters following heavy-ion irradiation. Nuclear medicine imaging studies use NMR, PET and other imaging procedures. Experimental progress has been made in the following areas: physics of beam delivery, dose localization and distribution at the Bevalac; analysis of brain-cell and tissue kinetics, proliferation and differentiation; kinetics of myelin renewal and myelin maintenance; pathobiology of brain response to focal irradiation with heavy-ions (He, C, Ne); and NMR and PET scanning of mammalian brain and in selected patients in defined research protocols. The research significance of the program is (i) use of heavy-ion probes to investigate neuropathophysiologic responses, regulatory control, and CNS tissue injury and repair in mammalian brain in vivo, and (ii) diagnostic evaluation of late delayed radiation injury and modification of treatment strategies for human brain disease.

The Clinical Research Trial in Charged Particle Radiotherapy, which also uses heavy-ion beams accelerated at the Bevalac, has had considerable success in treating a wide array of tumor types in different parts of the body. Prospective randomized trials are now underway to confirm improved local control and survival, compared with historical data from treatments with conventional radiation modalities. A key element in the successful implementation of charged particle therapy is the requirement of in vitro heavy-ion biological dosimetry. To conform the high-dose treatment volume to each patient's tumor, ion beams of different types, different penetration depths, and different field sizes are required. Particle atomic number and energy, as well as the techniques used to enlarge the beam field, may significantly alter the biological effects in patients due to beam fragmentation and scattering processes that can change the effective LET value of the composite beam. The relative change in cell-killing effects, determined by cellular techniques, provides the quantitative basis for patient filter design and input into the treatment planning model. The cell data are then modified by known tissue data available from studies in animals and humans. The biological dosimetry support is needed to fulfill the ongoing need for verification of biological effects of new beam configurations, including new treatment protocols under development to compare the clinical usefulness of helium, neon and silicon ions.

A new method of beam delivery called raster scanning is being developed to allow more accurate delivery of the dose on the tumor target. Implementation of this technique in clinical practice cannot be done safely prior to appropriate biological screening and evaluation of dose rate effects. A five-year plan has been developed to obtain the radiobiological information necessary to optimize the clinical applications of charged-particle radiotherapy in three dimensions. We have already begun a radiobiological analysis of the neon response of two human tumor lines derived from patients who failed previous low-LET radiotherapy. This work will include an analysis of micronuclei induction as an indicator of high-LET radioresponsiveness. In coordination with physicists on the clinical and support projects, four raster-scanning experiments were recently completed, and this work culminated in the first successful clinical treatment of a patient with a charged-particle field using the raster beam delivery system.

Our work provides promising indication of the successes that can be achieved in creating large, uniform particle-field delivery by raster scanning. We are confident that our data will be pivotal evidence supporting our ultimate future goal of implementing 3-D conformal particle therapy. Painting tumors with particle doses in this fashion will increase dose to the tumor and reduce dose to surrounding normal tissue.

In addition, we are conducting tracer studies with radioactive beams to provide a technique that can be used routinely as a diagnostic procedure for localizing the Bragg peak (giving maximum ionization and maximum cell killing) on the tumor volume during cancer therapy with heavy ions. The approach is based on the use of high-energy radioactive beams (which decay by emitting positrons) produced as secondary particles from the Bevalac. These particles have similar penetration properties to those of the nonradioactive therapy beams; hence, measurement of the stopping region of the secondary beams by positron imaging can provide the information necessary to properly adjust the incident energy of the treatment beam. A special positron camera, called PEBA, is available and is capable of locating the stopping region with an accuracy of ± 1 mm. The radioactive beams being considered for these studies are neon-19, carbon-10, and carbon-11, for the corresponding therapy beams neon-20 and carbon-12. Currently, we are investigating which of these radioactive beams is the most suitable from the point of view of minimum diagnostic dose and efficient positron emission. Also, we are trying to improve the algorithm associated with the processing of data for image reconstruction to provide greater sensitivity.

Medical Imaging

We are developing advanced emission tomography and NMR systems with capabilities beyond those currently envisioned for commercial implementation. The purpose is to apply new technologies to the study of atherosclerosis, heart disease, aging, mental disorders, and radiation effects. The joint approach of new technologies and experimental physiology is applied to medical science problems by a team of physicists and research physicians devoted to development of quantitative methods of experimental medical science. In addition to the noninvasive methods of nuclear medicine and NMR, we use autoradiography, tracer studies in vitro and, most recently, synchrotron light source studies of elemental changes. There is a major emphasis on mathematical modeling and statistical analyses. Technological transfer in collaboration with private industry is an integral part of these instrument development efforts.

Early results of this work included the first demonstration of the clinical usefulness of the Anger camera and the tomoscanner. More recently, we developed quantitative reconstruction algorithms, new compartment modeling methods, and the statistical basis of dynamic positron emission tomography (PET). We have also conducted clinical studies of a unique 2.6 mm resolution PET instrument, tritium NMR studies of carbohydrate metabolism, and studies of calcium precipitation utilizing soft x-ray microscopy.

An important aspect of our medical imaging program is the development of methods for the incorporation of short-lived radionuclides into biochemical substrates for PET and single-photon-emission computed tomography (SPECT). We are investigating the use of both radionuclide generators and short-lived cyclotron-produced radionuclides for incorporation into useful radiopharmaceuticals. Each class of radionuclide has its own chemical and practical advantages and disadvantages. Radioactive metal ions eluted from generators pose difficult chemical problems associated with their incorporation into useful radiopharmaceuticals, and lipophilic complexes containing ^{68}Ga, ^{82}Rb, and ^{118}Sb remain to be fully exploited for blood-flow measurements and other in vivo applications. Towards this goal, we are synthesizing and evaluating various chelating ligands that will form ^{68}Ga-complexes of overall zero or +1 net charge for use as brain and myocardial blood-flow agents for PET. We are also attempting to synthesize complexes that will chelate $^{82}Rb^{+1}$ and form a neutral, lipophilic agent for PET brain blood-flow studies. In contrast to metals ions eluted from generator systems, short-lived cyclotron-produced radionuclides such as ^{18}F, ^{11}C, and ^{15}O can be incorporated into a wide variety of radiopharmaceuticals, and their applications are virtually unlimited. Work in this area is aimed at the synthesis and evaluation of new ^{18}F-radiolabeled dopamine and acetylcholine receptor ligands, as well as hypoxic cell markers for PET studies of physiologic function in brain, heart, and tumor tissue. In addition, we are

investigating single-photon ^{123}I-labeled agents for application to SPECT studies of brain receptor distribution and tissue hypoxia.

A small cyclotron to be installed at LBL will be dedicated to the production of positron-emitting radionuclides. Facility operating funds will be provided through six existing DOE-sponsored projects, as well as collaborative research programs at the UCSF Medical School and two San Francisco Bay Area Veterans Administration facilities. The accelerator will produce a beam current of approximately 100mA of 11 MeV protons, which will give adequate yields of the major positron-emitters (^{11}C, ^{13}N, ^{15}O, and ^{18}F) required for DOE-sponsored research projects at LBL. This facility will enhance molecular medicine studies of the genetic basis of atherosclerosis by investigation of carbohydrate and fatty acid metabolism in patients with known genetic traits and in transgenic mice; studies of brain metabolism and neuroreceptor chemistry changes in Alzheimer's disease and aging; studies of muscle metabolism and fatigue; and development of predictive assays for tumor therapy and evaluation of the efficacy of charged-particle therapy. Of equal importance is the use of the facility as a national resource for nuclear radiopharmaceutical chemistry technology.

We are also developing advanced detector concepts for the imaging of positron-labeled tracers in humans and animals, with substantial improvements in spatial and temporal resolution. To overcome the limitations in event rate that conventional tomographs have when imaging short-lived tracers in the heart, we are developing a detector module consisting of a group of small scintillation crystals coupled on one end to a square phototube for timing information and coupled on the opposite end to an array of silicon photodiodes for position information. In addition, this design will permit an improvement in spatial resolution from 5.5 mm to 3 mm. We are collaborating with a commercial tomograph manufacturer who is providing both a custom silicon photodiode array and a custom VLSI charge amplifier array for this research. For ultrahigh resolution (≤2 mm) imaging of tracer compounds in the brain, we are developing a version of this design that uses smaller crystals and can measure the depth of interaction in the crystal to correct for parallax error.

To overcome the limitations of existing scintillators for PET, we are developing new scintillators by (i) systematically searching pure and doped heavy-atom compounds to find those exhibiting fast fluorescence, (ii) measuring the scintillation properties of optical crystals of promising compounds, and (iii) investigating scintillation mechanisms through the use of synchrotron radiation. In addition, we are working with industry on the development of (i) improved positron tomographs, (ii) silicon photodiodes, (iii) novel solid state photodetectors, and (iv) new, fast, high-efficiency scintillation crystals. Technology transfer of these techniques and devices to other research institutions and industry will permit the production of improved positron tomographs for the benefit of medical research throughout the world.

Mathematical reconstruction strategies have been a major area of contribution from this program. New methodologies for use with PET, SPECT, and radioactive beam injection include maximum likelihood estimation and a new technique that uses singular value decomposition. Data for this work are obtained from our PET and SPECT instrumentation, as well as through collaborations with the UCLA Laboratory of Nuclear Medicine and the Mallinckrodt Institute of Washington University.

Statistically based algorithms that have been developed yield images from real PET data with a substantially lower expected error in image regions with low counts than when the same data are reconstructed by filtered back-projection methods. Tests using patient data to determine diagnostic quality are now under way.

The use of prior knowledge of the imaging system and the object being imaged also has significant benefits and is being developed both for the maximum likelihood and the singular value decomposition methods. The latter uses natural pixel-based iterative reconstructions employing the high-performance computing capacities of DOE.

Advanced methods of kinetic analysis have shown the capability of quantitative dynamic SPECT. These methods are now being directed toward realization of nuclear medicine's potential to probe messenger RNA and to target receptor proteins with radiopharmaceutical agents designed by molecular biology methods.

E. Program Accomplishments and Research Highlights

Analytical Technology

- Used a steady-state model of radon transport to investigate the impact of structural factors on radon entry rates into Florida-style slab-on-grade housing. The results of this technology-transfer activity will help Florida officials develop suitable building codes. Another model of mitigation-system performance has provided information for building codes in the Pacific Northwest.
- Using a novel geometry, fabricated low-capacitance SI (LI) semiconductor radiation detectors for synchortron applications in biomedical and environmental sciences. Preliminary measurements show that the detector capacitance is five to ten times lower than in conventional devices containing comparable active areas. The decrease in detector capacitance translates directly into an improvement in detector energy resolution.

Environmental Research

- Conducted experiments that yielded the first-ever data of sufficient quality and detail for validation of numerical models of soil gas and radon entry into buildings. Measured entry rates of soil gas and radon were initially compared with entry rates that had been predicted using a steady-state numerical model. These comparisons indicate a substantial underprediction of entry rates. Hypotheses and the cause(s) of this underprediction are under investigation.
- Developed a global inventory for black carbon aerosol emissions based on empirically determined characteristic worldwide concentration ratios of black carbon to SO2.

This inventory has been used in the LLNL global chemistry/climate model to simulate the worldwide distribution of black carbon. An extension of this joint LBL/LLNL study has revealed that the absorption of solar radiation by this species may substantially counteract the estimated cooling of the atmosphere by sulfate aerosol.

Health Effects

- HERP (Human Exposure/Rodent Potency) ranking of 79 exposures to rodent carcinogens revealed that some occupational exposures and pharmaceutical drugs rank near the top, whereas exposures to current synthetic pesticide residues rank near the bottom. Some indoor air pollutants rank above the median.
- Identified 138 rodent carcinogens to which some U.S. workers are exposed but that do not have an OSHA Permitted Exposure Limit (PEL).
- Linked a simple cancer model to a model for the bodily absorption, distribution, metabolism, and excretion of benzene. The resultant integrated model, based on fundamental biology, is an important step toward improving assessment of human health risks associated with indoor air pollutants.
- Showed that promotion of pituitary hormone is not necessary for development of Harderian-gland tumors after these tumors are exposed to high-LET beams (i.e., 600-MeV iron particle beams), although such promotion is highly effective for low-LET beams.
- Using NB-1-specific antibodies, demonstrated the presence of the NB-1 protein in normal breast, prostate, skin, and cervial tissues, as well as its absence or reduction in the corresponding tumor tissues.
- Developed a theoretical model that can evaluate cellular transformation frequencies at very low doses of ionizing radiation. This model is based on partial understanding of transformation mechanisms and fundamental physical and chemical laws of radiation interaction with matter.

General Life Sciences

- Demonstrated attachment of foreign genes to the regulatory sequences of genes for milk proteins in human mammary cells, thereby causing the foreign genes to be expressed at a very high level. This technology can be used to produce appreciable amounts of useful substances for medical or research applications.
- Used x-ray crystallography to determine the structure of the aspartate chemotaxis receptor of the bacterium Salmonella typhimurium. This receptor perceives the presence of aspartate and signals the cell to move toward an increasing concentration of this nutrient. Such research is useful for developing target-seeking microorganisms.
- Demonstrated ligand-mediated immunogenicity, a new strategy for altering the ability of a pathogen to initiate an immune response. LBL researchers used this strategy to target antibodies to an AIDS-virus envelope protein. Theoretically, this method should make it possible to generate a neutralizing antibody response against any cellular or viral target for which a selective ligand is known.
- Used NMR to characterize the structure of hairpin loops in dumbbell-like DNA molecules and explained the thermostability of certain nucleotide sequences. What was initially believed to be a four-base loop was shown actually to be a two-base loop.
- Obtained three-dimensional crystals of cytochrome reductase from beef-heart mitochondria and found that these crystals diffract to about 4.6 Å resolution; reconstituted potato cytochrome reductase with lipids to form two-dimensional crystal patches that are suitable for electron crystallographic study. Determination of the structure to cytochrome reductase will provide important information about electron transport in cells.
- Using the x-ray microscope, obtained direct visual and quantitative confirmation that the membrane of the pancreatic zymogen granule is permeable to its contained proteins.

- Demonstrated the accuracy of "random-breakage mapping," an innovative method for determining the positions of genes on chromosomes.
- Used fluorescence in situ hybridization and inter-*alu* PCR to map more than 100 human chromosome-21 fragments that had been cloned in yeast artificial chromosomes (YACs).
- Developed ANGEL, a computer program to assist biologists in interpreting data from the electrophoresis gels used in DNA sequencing.

Medical Applications

- Using soft x-ray microscopy, demonstrated the accumulation of minute calcium particles, probably calcium phosphate, in cultured heart cells stressed by oxygen deprivation. Unstressed cells did not show this accumulation. The calcium particles may play a role in cell death during heart attacks, when oxygen flow to the heart is severely decreased. The electron-dense bodies usually associated with calcium deposits were shown to be silicon, aluminum, and phosphates other than calcium.
- Discovered ultrafast fluorescent emissions of substantial intensity from $BaCl_2$, $CeCl_3$, CuI, and CdI_2; and completed first measurements of the scintillation properties of lead sulfate as a function of temperature. These compounds are promising candidates for use in radiation detectors for positron emission tomography (PET) and high-energy physics.
- To study brain disease, synthesized and developed the first successful radioiodinated serotonin uptake inhibitor for non-invasive imaging studies of the brain's serotonergic receptor system, and continued synthesis and in vivo studies of potent and selective ^{18}F-labeled dopamine D2 neuroreceptor ligands.
- Achieved radiosynthesis and completed the first successful in vivo PET studies of a heart blood-flow agent labeled with ^{68}Ga produced by an inexpensive Ge-Ga generator, making widespread heart imaging possible without the need for a cyclotron.
- Completion of radiobiological investigations of raster-scanning delivery of helium particle beams culminated in the first successful clinical treatment of a cancer patient with a charged-particle field. These studies provide pivotal evidence supporting the goal of 3-D conformal particle therapy, a technique that will increase the radiation dose to the tumor and reduce the dose to surrounding normal tissue.
- Showed that a 60-minute exposure to the three field components that occur during a typical NMR scan caused a 30% increase in calcium transport in human and rat white blood cells that had been stimulated to divide. Exposure to individual field components had no effect.
- Of 450 subjects with intracranial arteriovenous malformations (AVMs) treated with stereotatic heavy-charged-particle Bragg-peak radiosurgery, 94% had a long-term health outcome that was "excellent" or "good."
- Used transgenic mice containing the human apolipoprotein AI gene to demonstrate for the first time that high-density lipoproteins have a direct protective effect on the development of atherosclerosis.
- Located a gene that predisposes individuals to atherosclerosis, the leading cause of heart disease in the U.S. The gene, which was found on human chromosome 19, may account for one-fourth of all coronary artery disease.

Selected 1991-92 Awards, Honors and Editorships

James C. Bartholomew

- Outside reviewer, Lawrence Livermore National Laboratory, Biomed Division "Institutional Research and Development Grant Program"

Mina J. Bissell

- Associate Editor, *In Vitro Cellular and Developmental Biology*
- Member, Editorial Board, *Journal of Cellular Biochemistry*

- Member, Council, American Society of Cell Biology
- Member, Board of Directors, International Society of Differentiation
- Member, Pathology B Study Section, National Institutes of Health
- Elected to Governing Board, Gordon Research Conferences
- Co-chair, Gordon Research Conference, Biological Structure and Gene Function

Eleanor Blakely

- Member, Editorial Board, *Space Power*

Thomas F. Budinger

- Chair, IEEE Committee on Electromagnetic Field Standards
- Member, Institute of Medicine, National Academy of Sciences
- Chair, IEEE Standards Board, SCC28
- Member, Board of Trustees, Society of Nuclear Medicine
- Co-chair, Executive Committee, Graduate Group in Bioengineering, University of California (Berkeley and San Francisco campuses)
- Distinguished Scientist Award, Society of Nuclear Medicine

Judith Campisi

- Member, Biological and Clinical Aging Review Committee, NIH
- Member, Editorial Board, *Experimental Cell Research*
- Member, Editorial Board, *Journal of Gerontology*
- Member, Scientific Advisory Committee, Tobacco-Related Disease Research Program

Charles R. Cantor

- Member, National Academy of Sciences
- Member, American Academy of Arts and Sciences

Aloke Chatterjee

- Councilor (Physics), Radiation Research Society
- Member, Program Committee, Radiation Research Society

Stanley Curtis

- Member, Executive Committee, COSPAR Subcommittee F-2 on Radiobiology
- Member, Task Group of Committee 1 of the International Commission on Radiation Protection
- Member, National Council on Radiation Protection

Joan M. Daisey

- Associate Editor, *Journal of Exposure Analyses and Environmental Epidemiology*
- Member, Editorial Advisory Board, *Environmental Science and Technology*
- Member, Editorial Advisory Board, *Aerosol Science and Technology*
- Member, Science Advisory Board Committee on Indoor Air Quality and Total Human Exposure, U.S. Environmental Protection Agency
- Member, Air Sampling Procedures Committee, American Conference of Government Industrial Hygienists
- Member, Air Toxics Task Force, American Chemical Society

Stephen Derenzo

- Chair, IEEE 1991 Medical Imaging Conference, Santa Fe, NM
- LBL Technology Transfer Certificate of Merit
- Patent application (with W. Moses) for lead sulfate scintillator

Patricia W. Durbin

- Member, National Council on Radiation Protection
- Advisor to the U.S. Transuranium and Uranium Registries

Michael Esposito

- Member, Editorial Board, *Current Genetics*
- Member, Governing Committee, French National Center for Scientific Research
- Member, Executive Committee, Biotechnology and Research Education Program, University of California Systemwide

Jacob I. Fabrikant

- Member, International Commission on Radiological Protection
- Member, National Council on Radiation Protection and Measurements
- Adviser, Radiological Society of North America, Research and Education Fund
- Member, Committee on Biological Effects of Ionizing Radiations, Board of Radiation Effects Research, National Academy of Sciences
- Member, Advisory Committee on Nuclear Facility Safety, U.S. Department of Energy
- Member, Committee on Radiologic Units, Standards and Protection, Commission on Physics and Radiation Protection, American College of Radiology
- Member, Technical Advisory Committee for Epidemiological Study of Nuclear Utility Workers, Electric Power Research Institute

William Fisk

- Member, Advisory Council of the Bay Area Air Quality Management District, Chair of the Technical Committee
- Member, Editorial Advisory Board, *Indoor Air*

Ashok Gadgil

- Recipient, Pew Scholar's Award in Conservation and the Environment

Robert M. Glaeser

- Editor, *Journal of Microscopy*
- Associate Editor, *Journal of Structural Biology*

Lois Gold

- Member, Panel of Expert Reviewers, National Toxicology Program
- Speaker, Conference on Chemical Risk Assessment in the Department of Defense, Dayton, Ohio

John E. Hearst

- Executive Editor, *Nucleic Acids Research*
- Member, Editorial Review Board, *Molecular Toxicology*
- Member of Advisory Committee and invited speaker, Center for Molecular Toxicology, Vanderbilt University
- President, American Society for Photobiology
- Chair, Grants and Awards Committee, American Society for Photobiology
- Program Chair, Annual Meeting, American Society for Photobiology

Ronald H. Huesman

- Federal Laboratory Consortium Award for Excellence in Technology Transfer
- LBL Technology Transfer Excellence Award
- Member, Program Committee, IEEE 1991 Medical Imaging Conference, Santa Fe, NM

Bing Jap

- Member, NIH Biophysical Study Section
- Speaker, Twenty-fifth Congress of German Electron Microscopy Society, Darmstadt, Germany
- Alexander von Humbodt Award

Sung-Hou Kim

- Co-chair, Gordon Research Conference, Diffraction Methods in Molecular Biology
- Member, NIH Public Advisory Group, Molecular and Cellular Biophysics Study Section
- Member, U.S. National Committee for Crystallography, National Research Council, National Academy of Sciences
- Council Member, Korean Scientists and Engineers Association in America
- Member, Editorial Board, Annual Review of Biophysics and Biophysical Chemistry
- Member, Editorial Board, Current Opinion *in Biotechnology*

Melvin P. Klein

- Chair, Advisory Committee to the Pittsburgh NMR Center for Biomedical Research, Carnegie-Mellon University and University of Pittsburgh
- Charter Council Member, International EPR Society
- Member, Advisory Committee, Biotechnology Research Resource, SSRL
- Member, Executive Committee, Users Organization, Advanced Light Source, LBL

- Member, Advisory Committee, BioCAT, Advanced Photon Source, Argonne National Laboratory

Ronald M. Krauss

- Chair, Nominating Committee, Council on Arteriosclerosis, American Heart Association
- Member, Executive Committee, Council on Arteriosclerosis, American Heart Association
- Member, Nutrition Committee, American Heart Association
- Member, Data and Safety Monitoring Committee, Postmenopausal Estrogen-Progestin Intervention Study, NHLBI, NIH
- Member, International Committee for the Evaluation of Hypertriglyceridemia as a Vascular Risk Factor, 1990
- Chair, Deuel Conference on Lipid Metabolism, 1992

Robert P. Liburdy

- Member, American College of Radiology Committee on MR Biological Effects, Commission on Magnetic Resonance
- Member, IEEE Committee on Electromagnetic Field Standards
- Member, IEEE-USA Committee on Man and Radiation (COMAR)
- Patent Application Filed for Electromagnetic-Field-Triggered Drug and Chemical Delivery Via Liposomes

Jorge Llacer

- 1990 Annual Merit Award of the Nuclear and Plasma Sciences Society, Institute of Electrical and Electronics Engineers
- Fellowship from NWO, the National Organization for Scientific Research of the Netherlands, for six-month stay at University of Utrecht to research statistically based methods of tomographic image reconstruction

Ernest Majer

- NRC Panel for Annual Review of Rock Mechanics

Narla Mohandas

- Member, Editorial Board, *Blood*
- Member, Editorial Board, *Blood Cells*
- Member, Hematology Study Section, Division of Research Grants, NIH
- Member, Subcommittee on Red Cell and Hemoglobin, American Society of Hematology
- Chair, The Red Cell Gordon Conference, 1991

William Moses

- Co-chair, IEEE 1991 Medical Imaging Conference, Santa Fe, NM
- LBL Technology Transfer Certificate of Merit, 1991
- Patent application (with S. Derenzo) for lead sulfate scintillator

Heino Nitsche

- Member, Committee on Nuclear and Radiochemistry, National Research Council
- Member, International Editorial Board, *Lanthanide and Actinide Research*
- Member, International Scientific and Organizing Committee, *Third International Conference on Chemistry and Migration Behavior of Actinides and Fission Products in the Geosphere*, Madrid, Spain
- Member, international review panel for Neptunium and Plutonium Data Base at the Organization for Economic Cooperation and Development (OECD), Nuclear Energy Agency (NEA) Data Bank, Paris, France

Tihomir Novakov

- Co-chair, Fourth International Conference on Carbonaceous Particles in the Atmosphere, Vienna, Austria

Dale Perry

- Member, Corporate Participation Committee, Materials Research Society.
- Member, Panel for the Restoration and Remediation of the Fernald, Ohio, DOE Uranium Processing Plant.

Henry Rapoport

- Member, NIDA, Biochemistry Review Section
- Member, The Protein Society
- Member, International Society for History, Philosophy, and Social Studies of Biology

Peter G. Schultz

- Member, American Academy of Arts and Sciences
- Member, Editorial Advisory Board, *Biocatalysis*
- Member, Editorial Advisory Board, *Catalysis Letters*
- Member, Editorial Advisory Board, *Bioconjugates*
- Member, Honorary Advisory Board, *Synlett*
- Eli Lilly Award in Biological Chemistry, 1991
- Stein Lectureship, Rockefeller University, 1991
- Merck Lecturer, Rutgers University, 1991
- Samuel McElvain Lectureship, University of Wisconsin, Madison, 1991
- Member, Editorial Advisory Board, *Accounts of Chemical Research*, American Chemical Society
- Founding Scientist, Affymax Research Institute, Palo Alto, California

Richard Sextro

- Member, Radiation Advisory Committee of the Science Advisory Board, U.S. Environmental Protection Agency

Martha Stampfer

- Associate Editor, *Cancer Research*
- LBL Technology Transfer Excellence Award

Ignacio Tinoco

- Member, California Council on Science and Technology
- Member, Health and Environmental Research Advisory Committee, U.S. Department of Energy
- Member, Editorial Board, *Nucleic Acids Research*
- Member, Editorial Board, Bipolymers
- Member, Editorial Board, *Biochemistry*
- Member, Editorial Board, *Biophysical Chemistry*
- Member, Editorial Board, *Biochimica et Biophysica Acta*
- Member, Editorial Board, *Cell Biophysics*
- Fellow, American Physical Society

David Wemmer

- Associate Editor, *Biopolymers*
- Member, Editorial Board, *Concepts in Magnetic Resonance*
- Member, Editorial Board, *Molecular Structures in Current Biology*
- Member, Editorial Board, *Journal of Biomolecular NMR*

F. Program Orientation

In the coming decade, LBL will continue to exploit the same strengths that characterize its research in the life sciences today.

One broad topic—gene expression—encompasses an area of great growth potential in the biological sciences at LBL, as well as the areas of liveliest research interest nationwide. Both an internal life sciences task force and a multidisciplinary panel chartered to identify new research directions for LBL have pointed to gene expression as a subject demanding special focus as the Laboratory's research program evolves. Accordingly, we expect areas of future concentration to include fundamental studies of genetic makeup (dominated by the human genome project); research on transmembrane signaling; studies on the structure, function, and stability of mRNA; investigations on protein structure and function; and wide-ranging investigations of the relationships between the human phenotype and the genome, using modern methods of metabolic and physiologic measurements. Continuing emphasis will be placed on the underlying basic science of cell and molecular biology and on improving the instrumentation and chemical methods of measuring function in human biology. (A broader discussion of planning issues can be found in Section H.)

Two specific topics are also worth special mention: the Laboratory's participation as a designated research center in the human genome project and the exploitation of the Advanced Light Source for biological research, especially as part of the DOE's multilaboratory Structural Biology Facilities Initiative. The first of these projects has been launched and requires only a continuing commitment by the DOE. The particular strength of the program at LBL is the availability of resources in many different areas,

including engineering, computer science, and molecular genetics. Our continuing activity in these and other areas is reflected in the narratives below.

To make the Advanced Light Source truly a resource for biologists in the 1990s, LBL has proposed ALS Life Sciences facilities that would include two magnetic insertion devices (one wiggler and one undulator), beamlines for x-ray microimaging, crystallography, and x-ray spectroscopy, and fully equipped ancillary laboratories. We see such facilities, especially oriented to exploring biological structure and function over a range of physical dimensions, as reflecting a major national, as well as institutional, commitment in the coming years—and a logical complement to the human genome project in the context of ultimately understanding human genetics.

A second broad topic is study of the effects and uses of radiation at the molecular, cellular, and organismal levels. Important questions relate to cellular repair mechanisms, the optimal design and use of instrumentation for heavy-ion radiotherapy and radiosurgery, and the hazards of heavy-ion radiation exposures involved in manned interplanetary space exploration.

A third topic is the use of radionuclide tracers for studying biological processes at the cellular and organismal levels. Myocardial metabolism and blood flow, brain metabolism, and brain receptor kinetics are a few important areas of research. An important part of this effort is the development of improved instrumentation and radionuclide tracers. There is a new emphasis on the use of molecular probes to evaluate receptor biology in humans and to relate findings to the genome.

Analytical Technology

Research on radon progeny behavior indoors will continue, with a focus on the rates of progeny deposition and the interactions of progeny with particles. One goal is to resolve the current discrepancy between measurements and model predictions. Increased effort will be devoted to the development of a method for estimating long-term average indoor radon concentrations based on short-term diagnostic data. Limited field testing of diagnostic techniques will be undertaken. Assessments of available data on radon concentrations will also continue. The implications of new data for estimates of the US radon concentration distribution and for the US response to the radon problem will be discussed.

* * *

The program in semiconductor detectors and signal processing will continue to emphasize the development of improved methods applicable to current and future experimental needs. Current activities in detector technology are focused on the use of novel contact structures and their application to complex detector geometries. Alternative detector materials such as high-purity GaAs are also being investigated. Continued improvements in preamplifier and pulse-processing systems are underway. The growing use of synchrotron radiation sources and the corresponding need for advanced detection systems are also being addressed. Our efforts to provide specialized detection systems for these applications include studies in very-low-energy detection mechanisms, development of array detectors for improved sensitivity in fluorescence experiments, and design of a special low-capacitance detector geometry capable of operation at a shaping-time constant shorter than for conventional commercial systems. Custom devices incorporating new materials and integrated pulse-shaping electronics are also being explored. As a key component of these activities, the group working on detector research and development interacts closely with the community of synchrotron radiation users in the design and testing of the detector systems.

Environmental Research

Experimental and theoretical studies of the radon problem will continue. Data on radon entry processes will be collected from our unique research structures and used to upgrade and validate numerical models. We expect to determine the cause(s) of the present large discrepancy between measured and predicted entry rates. New methods of measuring soil permeability will most likely be required. We will also undertake experiments to assess the significance of transient radon entry and revise models as needed. Experiments will be initiated at a second geologic site with more heterogeneous soil. Validated models will be used in parametric studies to provide input for building codes.

* * *

To contribute to a better understanding of the role of atmospheric aerosols in modifying the albedos of marine clouds, a fully functional cloud observatory has been established on El Yunque peak in Puerto Rico. The measurement capabilities encompass the full range of instrumentation for characterization of cloud microphysical and optical properties, as well as aerosol physical and chemical properties. This complete set of in situ measurements will be complemented by satellite observation through a collaboration with NASA's Goddard Research Center. The combined in situ and remote observational data will be integrated through theoretical studies and numerical modeling simulations in a joint effort with LLNL.

* * *

Field research in the subsurface transport program will emphasize the development and testing of characterization, interpretation, and prediction techniques for understanding the role of natural physical heterogeneities in transport of contaminants. Expanded work would include emphasis on defining how chemical and biological processes are reflected in the physical parameters that can be measured with advanced imaging techniques.

One of the current focuses of the laboratory component of the subsurface program is to improve the understanding of plutonium redox and co-contaminant behavior to better predict the ultimate fate of plutonium in the environment. Plutonium is a major contaminant at DOE sites, and four different oxidation states (III, IV, V, VI) can coexist in equilibrium in aqueous solution. Plutonium(V) is expected to be predominant under environmental conditions. It should be the most mobile species and it forms the weakest complexes with most organic co-contaminants. We are studying the disproportionation reaction of Pu(V) species, to yield Pu(IV) and PuO_2^{2+} (VI) species, as a function of total metal concentration, pH, Eh (redox potential), and ionic strength.

Health Effects

Research on the effects of population mobility on radon exposure distributions in Minnesota and California will be completed. Work on the development of a method to identify high-concentration radon houses in the United States—based on housing stock, climate, geology and soil permeabilities—will continue. Exposures to volatile organic compounds (VOC) in energy-efficient office buildings will be measured in collaboration with the California Department of Health Services. Efforts will continue to develop metrics of exposure to complex indoor mixtures of VOC. These metrics will be based on fundamental principles of biology and will be possible to relate more readily to specific adverse health effects. Using a physiologically based pharmacokinetic model for benzene, we will examine dose-rate effects of exposures to benzene at indoor air levels.

* * *

The complex multifactorial, multistep nature of induction and progression of malignancy requires a multidisciplinary, multi-investigator effort. We intend to coordinate our programs in carcinogenesis more tightly with a major new effort to form an affinity group in tumor biology and to encourage interactions among investigators researching carcinogenesis induced virally, chemically, or by radiation.

A general approach of many of our studies, namely, using in vitro models with demonstrated in vivo significance, will continue. Basic studies in cellular and molecular mechanisms of carcinogenesis are the foundation of our program in this area and will continue to be emphasized. In cellular and molecular radiobiology, we will focus more heavily on studies of radiation damage to single human chromosomes, and unique chromosomal rearrangements due to exposure to densely ionizing radiation. Future work will address major questions such as whether cells are able to process this damage and, if so, how the repair mechanisms function.

The role of stress proteins in lesion repair is also under investigation, and we have shown that increased new synthesis of proteins appears to interfere with cellular processing of radiation-induced damage. In addition, we have seen indications of differences in the handling of high-LET versus low-LET radiation damage. Studies are underway to characterize cellular profiles of protein synthesis in order to understand the involvement of new protein synthesis in the processing of DNA damage induced by x-rays

and by heavy ions. Future directions will emphasize a search for specific LET-dependent, radiation-induced alterations in genetic expression. We believe that these results may be of importance ultimately to our understanding of mechanisms of cell killing, mutation, and transformation.

We continue to develop methods for detecting carcinogen-induced transformation of human mammary epithelial cells (HMECs) in vitro such that we can (i) define what characteristics distinguish normal from transformed HMECs in culture and (ii) determine what agents alone or in combination may be capable of inducing human carcinoma. Future studies will address the question of whether reduction in cellular levels of the protein NB-1 may facilitate the potential of HMECs to undergo transformation. In cases where animal studies are unavoidable (and, indeed, advisable)—for example, in the area of long-term effects of high-LET radiation—we plan to use molecular markers, such as expression of proto-oncogenes, to better delineate the early stages.

Our database containing the results of 4,000 animal cancer bioassays is being used to investigate the mechanism of carcinogenesis, as well as for interspecies extrapolation and risk assessment. Whether natural or synthetic, about half of the chemicals tested in rodents are carcinogenic at the high doses tested, and a high percentage of these carcinogens are not mutagens. This result is expected because chronic administration of high doses can cause chronic mitogenesis, and any agent causing chronic mitogenesis can be indirectly mutagenic (and consequently carcinogenic) becuase it increases the probability of converting endogenous DNA damage into mutations. Our discussion of these ideas has generated great interest, and we plan to continue this theoretical work.

To put into perspective the human hazards that might arise from energy-related exposures, we will expand research on the background of human exposures to natural chemicals. We will investigate the question of whether target organs of carcinogenesis differ for mutagens as compared to non-mutagens. Interspecies extrapolations will compare results from bioassays in rodents to positivity, target organ, and carcinogenic potency in recently completed bioassays in monkeys.

The influence of magnetic and electric fields on the immune system, with technology transfer of biomedical applications, is a focus of the research planned. Cellular studies will investigate the effect of NMR imaging fields on critical signal transduction pathways in activated lymphocytes. We have observed enhancement of calcium influx during mitogen activation in human peripheral blood lymphocytes, and we now have the capability to perform the first single-cell studies using quantitative microphotometry and CCD-based digital imaging to visualize spatial and temporal alterations in intracelular calcium movement during field exposures. Technology transfer of biomedical techniques based on magnetic field interactions are developing in the area of microwave-triggered drug delivery using liposomes, and in pulsed-field HPLC.

* * *

Our radiological physics and chemistry program, centered on research with energetic heavy ions, will continue to complement programs aimed at understanding DNA damage and repair, as well as programs in radiation medicine. Our efforts will remain focused on analysis of fragmentation data and on the investigation of the process of multiple scattering during the passage of heavy ions through matter. We will also continue to look at the energy deposition process and the subsequent physicochemical and chemical processes leading to DNA strand breaks, as well as the enzymatic repair processes for these types of damage. We already have preliminary results on these studies. These preliminary results are now being used to evaluate mutation and cell transformation frequencies involving large deletions (segments containing suppressor genes), point mutations, and oncogene activation. All the studies are currently being done with partially transformed cell lines. The next milestone in this project will be to start evaluating cell transformation frequencies in normal cells by calculating the probabilities for activation of oncogenes.

General Life Sciences

In a coordinated effort, we intend to maintain our emphasis on structural biology, in keeping with LBL's commitment to develop advanced technologies for the study of important biological macromolecules by microscopic, crystallographic, and spectroscopic

techniques and to develop technology for dynamic imaging of cellular processes. Drawing upon existing strengths in biophysical spectroscopy and crystallography, and upon the Advanced Light Source, this multi-investigator effort will continue its research in broad areas of structural biology.

Transmembrane signaling and transport systems are critical for the regulation of cell function. Transmembrane receptors play a key role in oncogene-associated transformation, proper levels of gene expression, and cell differentiation. Transmembrane transport systems respond to both external and internal signals and may even be coupled to the transmembrance signaling itself. The research group in this area will continue to pursue x-ray and electron crystallographic studies of membrane receptors, membrane-bound enzymes, and membrane transport systems. We anticipate that this group will represent one of the major users of the life sciences facilities at the ALS. We hope, for example, to establish a unique video-enhanced light microscopy workstation that will combine UV-compatible light microscopy and computer-based video image processing with the high brightness of the ALS to allow the study of macromolecular complexes and dynamic cellular processes in real time, at unprecedented resolution.

Another part of our structural biology effort will include the use of soft x-rays from the ALS to study the higher-order structural organization of subcellular components. Soft x-ray and UV scattering from macromolecular assemblies such as chromosomes, microtubules, and other cytoskeletal assemblies can provide unique structural information about the spacing and orientation of periodic structures. Accordingly, we plan to construct a vacuum polarization scattering instrument, together with associated polarized optics and detectors, to produce circularly polarized soft x-rays. The higher-order coiling of DNA in the chromosome will thus be directly accessible to study, without the need for crystals or oriented samples. The high brightness of the ALS will also allow time-resolved studies of important steps in the aggregation and formation of subcellular components—for example, those involved in cell and organelle motility. Work on sulfur-containing molecules of biological interest will also continue to lay the groundwork for spectroscopic studies at the ALS.

The Group in Biological Microscopy will emphasize different microscopic modalities to understand structural-functional aspects of cell processes using the unique technologies being developed at LBL. Special effort will be placed on developing a state-of-the-art environmental chamber and sample insertion device for the x-ray microscope. Resolution of the x-ray microscope will be improved to permit visualization of subcelluar structures such as ribosomes. The x-ray microscope will ultimately provide dynamic imaging of processes such as protein secretion and ion transport. We will develop methods to quantify important intracellular processes such as accumulation of ions, protein, and DNA, and distribution as a function of physiologic manipulation.

We plan also to continue studying the structure of nucleic acids, the aim being an ability to introduce a highly defined nucleic acid into cells to test its effect on the physiology of the cell. Modifications will be made in vitro to the DNA, the structure will be determined, and the effect of these modifications on the DNA's functions will be measured. A major new objective will be to determine the conformations and to understand the functions of noncoding sequences in DNA. This work will interact strongly with the human genome project.

We intend to continue to refine our approaches to the structural analysis of catalytic RNA. A major push will continue to be to get enough material for crystal studies. This work will continue in parallel with the work on the *ras* oncogene. The catalytic antibody projects will also continue, with special emphasis on the development of synthetic antibodies to detect and cleave damaged DNA. Another aspect of the antibody work is use of ligand-mediated immunogenicity to test the ability of a CD4-DNP conjugate to destroy HIV infected cells in the presence of complement (in collaboration with W. Williams of the University of Pennsylvania Medical School).

The NMR facility will continue to provide state-of-the-art instrumentation for biomolecular structure analysis and will support development of new techniques and applications in NMR. Structural problems will be developed by many workers in the area of biological sciences at LBL. A related effort is the continuing development of

tritium NMR spectroscopy and its application to problems of biomolecular structure, interactions, and dynamics. Tritium NMR offers the prospect of probing the details of molecular interactions between proteins and nucleic acids at a level inaccessible with other nuclei. We believe that highly significant new information on the structure and dynamics of biological molecules will evolve from these endeavors.

* * *

LBL has pioneered important genetic studies in yeast, an area that is now beginning to pay dividends in the efforts to map the human genome. Accordingly, our studies on genetics, recombination, and repair will continue to be emphasized. We are curently working on the eleventh edition of our widely used compilation of yeast genetic mapping data. We will initiate a new mapping effort in yeast that will involve cloning *Not*1 restriction fragments from the total yeast genome into the yeast artificial chromosome vector YAC5. The sizes of these clones will be compared with the known *Not*1 physical map of the yeast genome. The approach will complement, as well as provide a model for, the scheme proposed to obtain a macrorestriction map of the human genome.

LBL's genetic studies in yeast are also beginning to pay dividends in efforts to understand the biological impact of the space environment. *REC* gene mutants defective in repair of DNA double-strand breaks, as well as recombination and DNA repair-proficient controls, were flown aboard the NASA space shuttle as part of the first international microgravity laboratory (IML-1). The shuttle flight experiments detect and distinguish between cellular and genomic damage caused by microgravity and heavy-ion cosmic radiation. Accordingly, our studies of yeast genetic recombination and repair will continue to be emphasized. This work will rely heavily on the Bevalac to simulate exposure of the shuttle hardware (containing yeast strains) to cosmic radiation, especially HZE particles. Genetic analysis of *rec* mutants, molecular cloning and sequencing *REC* genes, and purification of *REC* proteins will be used to extend our understanding of vital repair processes. Yeast *REC* genes encode proteins that perform repair functions known to occur in human cells.

Among ongoing projects, the gene amplification study will continue to investigate the nature of cellular control of gene copy number, how environmental factors influence the copy number of genes, and what role the amplification process plays in the transformation of cells. A molecular model for chemical mutagenesis associated with psoralen photoaddition will also be pursued. The site-specific and stereospecific placement of psoralens into M13 and SV40 will continue.

* * *

Development of normal and functional cell models for understanding basic mechanisms in differentiation and cancer will remain a strength of our programs at LBL. In our ongoing programs, we seek to understand precisely how cells regulate tissue-specific function in response to signals from their environment, with special emphasis on the extracellular matrix (ECM). We have begun to extend these studies to the human system. With the discovery that skin fibroblasts from breast cancer patients have aberrant migratory behavior in agar, we are now in a position to ask whether their ECM is aberrant. Since we have developed both the molecular probes and the technology for the rodent model, we expect to be able to extend these to the human cells and to determine the composition of the ECM and whether or not it is responsible for the abnormal behavior. An extension to the human model will not only yield an understanding of the basic mechanisms involved in cancer induction, but also may aid in developing a diagnostic test for the population at risk for breast and other forms of cancer. In the area of viral carcinogenesis, we will continue to explore the dramatic influence of the microenvironment on expression of the malignant phenotype. We will use molecularly engineered viral vectors transmitted in our packaging cells, as well as growth factors involved in wound healing.

In addition, we have begun a systematic analysis of the regulation of a milk protein called whey acidic protein (WAP), using rat WAP constructs transduced into transgenic animals and transfected into CID-9 cells. Regulation of WAP and β-casein, while both ECM-dependent, differ in many significant ways. We have established that the specific WAP inhibitor is a 5-6 k protein, and we are beginning to characterize this protein in detail.

To establish that our findings in culture have direct relevance to the physiologic regulations in vivo, we have started to analyze the process of involution wherein the mammary gland *loses* its ability to make milk; we would predict that ECM-degrading proteinases may be directly involved. In collaboration with Professor Zena Werb of the University of California at San Francisco, we have characterized the ECM-degrading enzymes. Using implants, transfection into CID-9 cells, and transgenic animals (with activated stromelysin), we have shown that ECM-degrading proteases, as well as their inhibitors, are indeed involved in the regulation of involution.

A major ongoing effort is to develop a competitive program in hematopoiesis, which is related to our existing programs in differentiation and carcinogenesis. Reestablishment of at least one major program in hematopoiesis at a national laboratory appears especially timely in light of the Chernobyl accident. We have thus embarked on an ambitious reorganization program at LBL. We have recruited three highly competent investigators in this area, and have produced a comprehensive proposal, working closely with Lawrence Livermore National Laboratory. The major thrust of the program would be to determine the consequences of an irradiated environment on stem cell differentiation and survival and to assess the role of the ECM on stem cell differentiation. We have shown that passage of bone marrow through an irradiated host reduces the self-renewal of the stem cells. This leads to a reduced survival of the marrow in a second irradiated host. That reduction can be almost completely prevented by giving large inocula to the initial host. The marrow passaged through an irradiated host does not proliferate at all in a second normal, nonirradiated host, even when as many marrow cells as are normally present in the entire hematopoietic system of the mouse are passaged and retransfused.

The significance of these findings is twofold. First, it is now evident that in many radiation experiments, nonirradiated controls should be run. Second, it suggests that the irradiated hosts themselves may be responsible for the exhaustion of marrow after serial transfers. The findings raise some intriguing questions. What accounts for the passage through an irradiated host being "remediable" by a large inoculum when the secondary host is also irradiated, but not when it is unirradiated? Is the adverse effect of the passage through the irradiated primary host a dilution effect of stem cells or a direct effect of the microenvironment? In view of the present interest in the hematopoietic matrix and the expertise already existing at LBL in the extracellular matrix field, these questions are of particular interest.

* * *

The three major components of the Human Genome Center—biology, instrumentation, and informatics—will continue their close collaboration to achieve the goals of the human genome program.

Mapping of the distal 10 Mb of the long arm of human chromosome 21 will be completed in FY93. We anticipate that, in addition to achieving closure of this region with a mixture of YACs and cosmids, we will also have identified 50 to 60 informative genetic markers for chromosome 21 and the cDNAs associated with the 10 Mb contig. Our collaboration with LLNL should produce a similar number of genetic markers for chromosome 19.

Biologists working in the Center are using a double-ended, clone-limited strategy for mapping and sequencing. The project is expected to complete a proof-of-principle in FY92 and to participate actively in a scale-up test in FY93. The instrumentation group is already developing prototypes for sample handling, and the applications component of the computing group is developing software and interfaces for data handling.

Development of robotics and other instrumentation to support megabase mapping and sequencing will be enhanced by a new effort in detectors for mass spectrometry. This integrated effort should enable the Human Genome Center to produce the rapid sizing of genetic markers based on nucleotide repeats, as well as to produce the thousands of polymerase chain-reaction assays that would otherwise create a bottleneck.

We expect the LBL chromosome information system (CIS) to be available in FY93 for use by other genome programs in DOE, NIH, and

USDA. Further development of database design tools and query tools will permit rapid design response to new biological protocols and data connections/queries in mapping and sequencing. Development of new algorithms for assembling sequences and contigs of clones will be strengthened by development of a computational biology program by the computing division. We have received Laboratory-Directed Research and Development funds to initiate this effort, which involves the University of California (Berkeley and Davis campuses), as well as LBL statisticians and computer scientists.

Instrumentation developed in the first years of the human genome project at LBL has permitted us to become a community resource for arraying and replicating libraries from a number of sources. This effort has been enhanced by implementation of a new, high-speed colony picker. We anticipate that in the next year we will extend the usefulness of this facility to new libraries produced from flow-sorted chromosomes at LLNL and LANL.

Medical Applications

Heavy-ion radiosurgery successfully treats selected intracranial, vascular, and neoplastic disorders, with improved protection of normal CNS structures and with decreased complication rates. A future direction of the research program will be to combine application of charged-particle beams with 3-D conformal treatment planning for improved treatment strategies and health outcomes and reduced morbidity. We will also investigate (i) metabolic alterations in human brain and reaction to radiation injury, including altered blood-flow dynamics and tissue metabolism following heavy-ion irradiation; and (ii) physical and biophysical characteristics of heavy-ion beams at the Bevalac, including beam quality and RBE/LET relationships. We will continue using NMR and PET scanning to study cellular and metabolic events of heavy-ion radiation injury and repair. The aim is to optimize application of heavy ions at the Bevalac for stereotactic radiosurgery of intracranial vascular and neoplastic disorders in humans. We are pursuing technology transfer of radiation protection strategies, as well as of clinical radiation oncology and radiosurgery treatment procedures.

Another emphasis of high-LET charged particle studies during the next five years will be to provide important answers regarding the need for carbon and neon ion therapy to treat cancer. These studies are of vital importance both in the United States and to several facilities abroad that are either planning or interested in heavy-ion therapy. Studies will be focused on determining whether the heavy-ion treatment modality is superior to protons and other therapeutic modalities for certain types of cancers. Several focused clinical research trials in prostate, brain, bone/soft tissue and skull base tumors will be completed within the next five years at LBL to provide answers to this critical question.

Operation of the Bevalac during the next five years will also provide an important locus for space biological studies needed by NASA for manned space travel. The Bevalac is a unique facility for reproducing the cosmic particle environment encountered in space, and therefore can be utilized to provide important data regarding the safety and risks associated with manned space flight for prolonged periods. Collaboration between investigators in the human cancer clinical research trial and the NASA space studies will begin with a joint study of the effects of helium ion therapy on human eyes. Important data will be determined regarding cataract formation by assessing patients who have received helium ion irradiation in the past ten years for uveal melanoma in the eye. Over 200 such patients are alive and available for this combined study to be accomplished by members of the Research Medicine and Radiation Biophysics Division, the NASA Specialized Center of Research and Training (NSCORT), and the UCSF Ocular Oncology Unit. A study of the long-term effects of galactic iron particles on larger animals is also being planned. This research will explore the possible effects of charged particles on accelerated aging, life shortening, bone metabolism, and oncogenesis.

A proposed proton treatment facility at the University of California at Davis Medical Center Cancer Center will be developed through a collaborative effort between LBL and UC Davis. LBL is the recipient of an NCI Planning Grant in order to provide design studies for this facility. UC Davis will be the site of the facility and will

oversee actual construction when this begins in approximately two years. It is expected that this facility will be commissioned within five years and will be available for low-LET (proton) clinical research and treatment. This facility will function as part of the Cancer Center of UC Davis and as a regional proton facility for Northern California. It will be one of a group of facilities undertaking cooperative clinical research under the guidance of the newly formed Proton Radiation Oncology Group. LBL has an important role in this group and in the development of the proton facility at UC Davis, based on LBL's clinical experience with protons during the past ten years and our expertise in accelerator design and operation.

Also related to the use of heavy ions for therapy, we will continue our tracer studies with radioactive beams. At present, the characteristics of the Bevalac are such that it will be difficult to increase the flux of radioactive beams (10^6 per pulse) significantly. From our measurements in human phantoms (in the trunk), we have concluded that such a flux is inadequate for an acceptable-quality image of the stopping region, given the present PEBA and associated algorithm. We have thus decided that the next phase of our study will involve improving the algorithm so that we achieve greater sensitivity in image reconstruction. The currently available algorithm is adequate for the head and neck region, but not for thicker regions of the body.

Positron and single-photon-emission tomography studies at LBL have taken a number of important new directions. These directions are in radiochemistry development, quantitative analysis techniques, and new instrumentation.

A major emphasis is on the development of specific probes of genetic expression. Targets of imaging include the neuroreceptor proteins in Alzheimer's disease and other mental disorders, as well as the lipoprotein receptor proteins in atherosclerosis and heart disease. This theme involves new radiochemistry of fluorine, new instrumentation, and new approaches to kinetic modeling. The program direction is to quantitate phenotypic descriptions that can relate to the human genome.

The specific receptor proteins for which we are developing new probes include dopamine D2, serotonin S1, and α_2-adrenergic receptors. The lipoprotein studies have focused on the low-density lipoprotein receptors in organs and arterial endothelial cells. The studies rely heavily on a well-characterized patient base that includes subjects ranging from Alzheimer patients to patients with a particular genotype leading to abnormal lipoprotein metabolism. The patient base is from other clinical studies supported by NIH; the new chemistry and image-analysis instrumentation technology to relate these phenotypes to specific protein abnormalities is supported by OHER.

We also plan to continue our blood-flow and metabolism studies in the human brain and heart by exploiting several medical imaging techniques. Expected medical science studies will use our unique high-resolution PET and high-field NMR to better understand dementias, heart disease, and changes in tumor metabolism in response to various therapies. The future emphasis for quantitative image reconstruction and data analysis in emission tomography (both PET and SPECT) will be to build on the concept of an orthogonal natural pixel basis developed at LBL in the last few years. This new strategy has the potential of reducing statistical uncertainty in the analysis of emission tomographic data. The method allows formal analysis of heretofore poorly understood physical effects such as scatter, attenuation, intrinsic detector resolution, positron range, crystal penetration, and imperfect collimation.

As part of our radionuclide and radiopharmaceutical development program, we plan to continue research directed at the efficient incorporation of short-lived radionuclides such as ^{18}F into compounds useful for PET and SPECT studies of physiologic processes in normal and diseased states. We will use the dedicated minicyclotron for the production of positron emitters for this work, and we will also continue to develop and apply radioisotope generators and suitable generator-produced radiotracer compounds to PET and SPECT research.

An important component of our nuclear medicine program is the development of new instrumenta-

tion for improved 3-D imaging of gamma- and positron-emitting tracers in the body. This research has led to a number of inventions and technical advances, including the development of individual photodiode readout for small scintillation crystals, and the discovery of new scintillators. The work is specifically directed to the removal of limitations in existing technology.

We expect to overcome the slow event rates that conventional tomographs have when imaging short-lived tracers in the heart by developing a detector module using small scintillation crystals, arrays of silicon photodiodes, and VLSI charge amplifiers. This design will also improve the spatial resolution from 5.5 mm to 3 mm. We plan to transfer this technology to industry to make available tomographs with 24 rings, each containing 1024 crystals. We are also developing a version of this design for ultrahigh resolution ($\leq$ 2 mm) imaging of tracer compounds in the brain.

To overcome the limitations of existing scintillators for PET, we will continue to develop new scintillators by (i) systematically searching pure and doped heavy-atom compounds to find those exhibiting fast fluorescence, (ii) measuring the scintillation properties of optical crystals of promising compounds, and (iii) investigating scintillation mechanisms through the use of synchrotron radiation. Two important new developments in this work are (i) the collaboration with a research group at Brigham Young University, Utah, to compute molecular orbitals, compare with existing measurements, and guide the selection of pure and doped candidate compounds, and (ii) the fabrication of a table-top pulsed x-ray facility at LBL with an overall fluorescent timing resolution of 100 ps.

We are planning new projects on the following topics:

Nuclear magnetic resonance: We are proposing construction of a 0.4 m bore 9 T NMR imaging spectrometer as an intermediate step towards a whole body instrument. Operation of large bore instruments at 9 T will enable in vivo studies currently prohibited by data acquisition time at the fields currently available. The feasibility of both instruments has been established through DOE-sponsored workshops, a magnet design study, and analysis of the radiofrequency electromagnetic fields in the body at the relevant frequencies. The scientific objectives obtainable at 9 T include spectroscopic imaging of metabolites and ions, and anatomical and functional imaging of structures such as the brain cortex. It will be a significant new resource for the study of disease, gene expression, and the structural biology of higher animals.

The 0.4 m instrument will serve as a test bed to demonstrate proof of concept for the whole body imaging spectrometer. Predictions of rf electromagnetic fields, signal-to-noise ratios, and heating will be verified before undertaking the full-scale project. Scalable designs for gradient sets and rf probes will be tested. In addition, the 0.4 m instrument will permit spectroscopic imaging and micro-imaging studies in higher animals preliminary to human studies. It will be operated as a resource for LBL and University of California investigators.

R*adiation effects in a canine model*: This program is designed as a ground-base experiment for the Space Exploration Initiative to ascertain the long-term risks of high Z particles. Previous studies in dog hemi-brain irradiation by high-LET neon ions relative to low-LET helium ion controls in 15 dogs included clinical and multiple PET and NMR evaluations for up to two years. These acute exposures demonstrated no large differences between low- and high-LET in the onset of radiation necrosis of the central nervous system. However, neither these data nor existing cell and molecular data are adequate to allow predictions of high-LET effects for interplanetary travel. Thus, an eight-year experiment has been designed for whole-body low dose rate exposure and follow-up of 80 dogs irradiated with 500 MeV/amu Fe or protons. Exposures will simulate two-year and four-year space missions. Endpoints will be evaluated by multiple studies of central nervous, hematopoetic and cardiovascular systems with PET, NMR and x-ray CT.

Environmental air pollutants and heart disease risk: The objective of this program is to clarify the relation of environmental air pollutants to the development of coronary heart disease, with emphasis on pathologic changes in lipids and lipoproteins. A series of investigations will quantitate the effects of environmental air pollutants on plasma lipoprotein structure and metabo-

lism in humans and in mouse models. The basic study design will be to expose mice and human volunteers, with and without coronary heart disease, to acute and chronic exposures of the selected pollutants. An environmental chamber will be used to simulate ambient exposure to the pollutant in a controlled atmosphere. Exposures will use physical activity to increase pulmonary ventilation and will simulate pollutant doses that are routinely experienced by individuals in large metropolitan areas. We hypothesize that air pollutants have adverse effects on the pathophysiology of coronary heart disease. The first generation of experiments will focus on serum lipoprotein alterations due to selected air pollutants, including ozone, SO_2, NO_x, and CO. Results of these studies will be used to design the second generation of studies, which will focus on cellular and therapeutic aspects.

Molecular nuclear medicine: Studies in three new areas are being planned: (i) use of modern instrumentation and dosimetry, along with human genetic studies and transgenic animal models to pursue the relationship among variations in human low-density lipoprotein receptors, the genome, and the occurrence of atherosclerosis; (ii) use of advanced non-invasive methods of nuclear medicine and NMR to study the relationships among ion-channel protein aberrations, brain physiology associated with mental disorders, and the genome; (iii) use of ^{13}C-NMR metabolic studies to evaluate the carbon cycle in plants relative to environmental changes in temperature, CO_2, and nutrients.

Major Foreign Meetings

HUGO Executive Committee (Tokyo, Japan, November 4-5, 1991)

EMBL Workshop on DNA Sequencing (Heidelberg, Germany, November 17, 1991)

DOE/HUGO Meeting on SBH (Moscow, U.S.S.R., November 18-20, 1991)

Workshop on Quantitative Electron Microscopy (Schloss Ringberg, Rottach-Egern am Tegernsee, Germany, December 2-7, 1991)

Breast Cancer Symposium "Think Tank" (Bonaire, Netherland Antilles, January 12-17, 1992)

STA Meeting on the Human Genome (Tokyo, Japan, March 6-7, 1992)

First Multidisciplinary International Symposium on the Structure, Biology and Pharmacology of Abasic and Related DNA Sites (Paris, France, April 1-3, 1992)

Fukui Workshop on Health Risks: Perspectives and Research (Katsuyama, Fukui, Japan, July 17-19, 1992)

Fifth Asia-Pacific Electron Microscopy Conference (Special Session, *Symposium on Biological Macromolecules* (Beijing, China, August 2-6, 1992)

16th International Conference on Yeast Genetics and Molecular Biology (Vienna, Austria, August, 1992)

G. Work for Non-OHER Organizations

The success of DOE life and environmental sciences programs at LBL has depended not only on DOE support but also on complementary work, sponsored by others, that is closely coupled to the DOE programs and benefits directly form LBL facilities and expertise. Examples include the National Cancer Institute's support of development of new methods for biomedical charged-particle therapy at the Bevalac accelerator, the National Heart, Lung and Blood Institute's support of nuclear imaging methodologies, and the National Institute of Health's support of programs at the National Center for Electron Microscopy and the National Tritium Labeling Facility. Some projects supported by outside agencies have not been strictly dependent on large facilities or unique instrumentation but have made contributions that could only have been made in a national-laboratory type environment. Examples—in fields ranging from cell and molecular biology to environmental research to structural biology—abound. Non-OHER support expands the base of investigative activity and makes possible a wide diversity of staff expertise, thus greatly enriching the accomplishments of OHER programs themselves.

DOE Office of Basic Energy Sciences (BES)

The DOE Office of Basic Energy Sciences (BES) sponsors a continuing effort directed toward using knowledge of green plant photosynthesis to design artificial systems for the utilization and storage of solar energy. In addition, we focus effort on chemical reactions that suggest new concepts for photo-associated synthesis of high-valued chemicals from abundant chemicals, photocatalysis, temporary chemical storage of near infrared photons, and conversion of photon energy into electricity.

Also under the sponsorship of BES, we are studying the synthesis of chlorophylls and carotenoid pigments in a purple, nonsulfur photosynthetic bacterium, *Rhodobacter capsulatus*. We have recently completed the sequence of all of the genes required for pigment synthesis in *R. capsulatus*. As many as twenty gene products may be involved in bacteriochlorophyll (Bchl) production, and many of the enzymatic steps require the combined activity of two or more gene products. Our efforts are now concentrated on understanding how these enzymes work and how their gene expression is regulated by environmental factors. We are also studying photosynthetic oxygen evolution in higher plants and cyanobacteria.

Another BES-funded project concerns the absorption of visible light photons, followed in less than a nanosecond by excitation transfer and trapping in reaction centers of photosynthetic membranes. We are investigating the detailed kinetics and energetics of this process using wavelength-resolved transient absorption change and fluorescence decay measurements applied to well-defined preparations of antenna pigment proteins or reaction center complexes. Recent x-ray crystallography studies in several laboratories have provided detailed structural information for several of these proteins. This has enabled us to carry out excitation transfer calculations using exciton theory and/or Förster inductive resonance transfer applied to pigment arrays of known geometry.

DOE Office of Conservation and Renewable Energy (CRE)

Approximately 13 Quads of energy are used annually to condition and move the outside air supplied to residential and commercial U.S. buildings. This energy is used to maintain acceptable indoor air quality and occupant health, comfort, and productivity. A major goal of DOE, specified in the National Energy Strategy, is to increase the energy efficiency and ventilation efficiency of buildings, while maintaining or improving indoor air quality. The DOE Office of Conservation and Renewable Energy (CRE) supports an LBL project that is developing and disseminating the information and technology needed to achieve this goal. Research covers the relationships among building energy usage, ventilation and infiltration, indoor air quality, and human factors.

We employ a combination of modeling, laboratory experiments, and field studies. In addition to developing methods for reducing energy use by heating, ventilating, and air conditioning systems, we are investigating indoor air pollutant concentrations and source strengths and their dependence on ventilation and building characteristics. Factors that cause the occupants of large buildings to have building-related health symptoms are also being investigated. This work is complementary to OHER-sponsored studies in analytical technology and health effects related to indoor exposures to radon and other air pollutants.

National Institutes of Health (NIH)

Activities sponsored by the National Institutes of Health (NIH) complement OHER-supported work in the following theme areas: hematopoiesis, carcinogenesis, atherosclerosis, aging, mental disorders, and physical health effects. In these areas NIH-supported work is strongly related to OHER missions through exploitation of unique instruments, methods and scientific personnel at LBL.

An example of NIH's interest in improved instrumentation is support for the development of positron emission tomography tomography (PET) technology. Topics range from scintillation mechanisms for PET to algorithms and processing architectures for tomography. NIH also sponsors several studies that use LBL's unique PET instrumentation to characterize diseases of the brain.

A new emphasis in PET and nuclear magnetic resonance (NMR) is the practical interpretation of the human genome project. As the OHER program in medical applications seeks to modernize nuclear medicine activities and couple them with research in molecular genetics and gene expression, LBL has emphasized those areas of clinical medical science that have potential for correlation to genome mapping activities.

Another area of NIH's interest is atherosclerosis research based on unique methodology for lipoprotein analysis developed at LBL over the past 45 years. These tools are being applied in

NIH-supported studies directed at understanding genetic, cellular, and metabolic mechanisms of heart disease. In addition, the NIH-supported research on PET and NMR enhances our understanding of the pathophysiology of atherosclerosis. Transgenic mouse studies and other atherosclerosis research programs supported by NIH call on unique LBL facilities such as PET instrumentation, as well as the preliminary work for a very high field NMR spectrometer that will allow precise metabolic studies.

The symbiosis of NIH projects and the OHER mission is also evident in the development of charged-particle beams from the Bevalac. The accelerator physicists and radiologists working on DOE programmatic research are called upon and supported by NIH programs to assist in the application of available charged-particle beams to development of new methods to treat human diseases. These programs are medical research programs to develop methods that can be transferred to the private sector, which is now being done by radiotherapists at three sites in the U.S. The charged-particle therapy methods for tumors and arteriovenous malformations developed by joint DOE and NIH activity provide the gold-standard for radiotherapy.

Research support from NIH also encompasses broadly all areas of current LBL research activities in cell and molecular biology. One program project provides support for determining the high-resolution structure of various membrane proteins, while another program project provides support for delineating the detailed molecular structure of the red blood-cell membrane. In addition, a large number of research grants to individual scientists support research in various aspects of cell and molecular biology. Topics include growth regulation in normal and transformed cells, the molecular mechanisms of cell senescence, molecular analysis of differentiation of human mammary cells, the physical structure of viruses, molecular mechanisms involved in DNA damage and repair, mechanisms of mutagenesis in human cells, and the molecular and cellular basis for sickle cell anemia. These projects enhance OHER-sponsored studies in cell differentiation, carcinogenesis, and DNA damage and repair.

The National Tritium Labeling Facility (NTLF), which receives funding from NIH as well as DOE, serves as one of the few facilities in the nation equipped to label compounds to very high specific activities of ^{3}H. It thus serves as a laboratory where researchers from across the U.S. can carry out labeling and radiopurification procedures that would be impossible at their home institutions. The mandated functions of the NTLF are to engage in research and development of advanced labeling techniques and to disseminate the results, to promote collaborative research using labeled molecules, to provide labeling services to the nation's scientists, and to train researchers in labeling methodologies. One of the NTLF's most important activities is to supply labeled biomolecules for tritium-NMR spectroscopy, a key technique in our OHER-funded structural biology research.

Research supported by NIH complements OHER-supported research to characterize air pollutant exposures in buildings and to assess the risks associated with human exposure by providing information on the gas-particle distributions and particle-size distributions of carcinogens in environmental tobacco smoke. This information is needed to understand the risks from exposures to this complex mixture.

The National Institute for Environmental Health Sciences supports research that directly benefits work we are doing for OHER by providing information on a source and mechanism of indoor exposures, i.e., soil-gases. This research will also be of value to DOE in its environmental restoration efforts since it will provide information to assess the potential for human exposures at contaminated DOE-sites.

National Aeronautics and Space Administration (NASA)

The National Aeronautics and Space Administration (NASA) utilizes the unique capabilities of accelerators, detectors, and scientists at LBL to assess the health risks of space exploration. The nation's need for LBL facilities for the Space Exploration Initiative is readily understood by the following example: The major radiation on

extended manned missions to the moon and planets is galactic cosmic particles consisting of atomic nuclei from hydrogen to iron and even uranium. These particles penetrate the space craft and tissues at high velocity and cause biologic damage varying from cell death to cancer cell induction. Though the total conventional radiation dose is only a few rads to the whole body, the true situation is that each cell could be hit by one high-energy projectile on a two-year mission. Thus, to learn the consequences of this form of radiation, NASA needs the DOE facilities and personnel at LBL to perform cell and animal studies. NASA sponsors a number of research projects aimed at assessing radiation-induced DNA damage and the mutagenic and tumorigenic potential of radiation. In addition, NASA has recently begun sponsorship of a Specialized Center of Research and Training in Radiobiology at LBL. This cooperation between LBL's scientists and equipment and NASA in the form of work for others is seen by program managers and NASA as essential for the nation's space missions.

OHER-sponsored detector studies in the Engineering Division are supplemented by more applied research supported by other offices in DOE and by NASA. These projects benefit from the basic knowledge gained in the OHER projects and at the same time provide an excellent background of knowledge of real-world problems, which helps focus our fundamental OHER work.

Environmental Protection Agency (EPA)

The EPA is sponsoring research to develop bioassay-directed fractionation methods for identifying mutagens in the polar organic fraction of airborne particles found in indoor and outdoor air and to chemically characterize the subfractions. This research complements OHER-supported work by providing information on particulate organic matter to which humans are exposed. In addition, the information provided on the properties of the organic component of airborne particles is useful for advancing our understanding of cloud-nucleation in the troposphere, which is of importance to global climate research supported by DOE.

The EPA also supports research on numerical modeling of radon entry into houses, as well as analysis of animal cancer tests and studies of chemically induced damage to human mammary epithelial cells.

University of California Tobacco-Related Disease Research Program

Environmental tobacco smoke is a major indoor air pollutant. LBL has support from the UC Tobacco-Related Disease Research Program to investigate factors affecting the size distribution and concentration of environmental tobacco smoke particles to provide a more accurate estimate of the lung dose of particles and radon progeny attached to these particles. This research, thus, extends our OHER-supported research efforts to characterize indoor air pollutant exposures and assess their risks. It also complements and extends our OHER research to characterize indoor radon and radon decay products, their attachment to airborne particles, and their removal through deposition to indoor surfaces.

LBL also has funding from the UC Tobacco-Related Disease Research Program to conduct a more basic study aimed at establishing, at the molecular level in human epithelial cells, the mechanisms of the inter-related phenomena of procarcinogen activation, cocarcinogenesis, and oxidative DNA damage involved in tobacco-related cancer. A detailed understanding of these inter-related processes could lead to effective preventive treatment for individuals previously exposed to cigarette smoke.

The budgets shown on the following pages do not include Laboratory overhead costs.

Analytical Technology

J. Daisey	EPA Genotoxic Polar Organics in Airborne Particles	$93,200
J. Daisey	NHLBI Environmental Tobacco Smoke: Physico-Chemical Properties	$233,800
J. Daisey	DOE (CRE) Infiltration, Ventilation, and Indoor Air Quality	$1,000,000
J. Daisey	UCB/NIEHS Soil Gas Transport: A Mechanism of Indoor Exposures to VOC	$170,600
J. Daisey, R. Sextro	UC Tobacco-Related Disease Research Program, Characterization of Particulate-Phase ETS in Differing Environments	$193,600
R.Sextro	EPA Radon Entry into Florida Homes	$203,500
W. Fisk, J. Daisey	CIEE Phase II Study of Sick Building Syndrome	$59,700
E. Haller	NASA, Far-Infrared Semiconductor Detectors and Materials	$170,000
E. Haller	NASA, Far-Infrared Advanced Photoconductors	$80,000
J. Jaklevic	EPA Analysis of Air Filters	$25,000
R. Pehl	NASA Various Germanium Detectors for Space Applications	$500,000
G. Traynor	DOE (Policy Analysis) Combustion Pollution Exposure Study	$159,800
J. Walton	NASA Various Special Silicon Detectors	$100,000

Health Effects

E. Alpen	NASA Tumorigenic Potential of HZE Radiations	$123,900
A. Chatterjee	NASA Specialized Center of Research and Training	$351,700
G. Clemons	NIH grant Radioassay of Erythropoietin	$96,000
S. Curtis	NASA Deep Space Flight Radiation Risk Assessment	$33,600
S. Dairkee	EPA grant Human Mammary Epithelial Cells	$92,600
P. Durbin	NIH grant Biological Evaluation of New Actinide-Chelating Agents	$86,980
M. Esposito	NASA Effects of Microgravity and Heavy-Ion Irradiation	$163,300
L. Gold	EPA Analysis of Animal Cancer Tests	$100,800
A. Kronenberg	NIH grant Heavy-Ion Mutagenesis: LET Effects and Locus Specificity	$64,800
A. Kronenberg	NASA Mutagenesis in Human Cells	$81,300
R. Liburdy	NIH grant High Field NMR Bioeffects: Lymphocyte CA2+ Metabolism	$194,684
R. Ramirez	NIH fellowship Reg and Physiological Effects of Blocking PDGF	$25,000
M. Stampfer	NIH grant Characterization of Human Mammary Cells	$214,300
A. Tischler	UC Tobacco-Related Disease Research Program, Tobacco-Related Carcinogens	$30,200
A. Tischler	EPRI DNA Adducts and Oxidative DNA Damage	$46,300

General Life Sciences

M.H. Barcellos-Hoff	NIH grant Stromal Influence on Expression of Preneoplasia	$66,500
J. Bastacky	NIH grant The Alveolar Lining Layer in the Lung	$68,218
J. Bastacky	UC Tobacco-Related Disease Research Program. Effects of Tobacco on Rat Lung Alveolar Lining Liquid	$124,106
J. Bastacky	Subcontract from Harvard	$17,564
E. Berry	NIH grant 3-D Crystals of Cytochrome Reductase	$65,500
M. Bissell	Monsanto research gift	$23,600
Z. Cande	UCB IVEM Equipment Cost Sharing	$26,800
Z. Cande	NIH A West Coast Facility for IVEM	$179,800
C. Cantor	NIH grant Gene Structure	$1,088,000
J. Campisi	NIH grant Cellular Senescence and Control of Gene Expression	$100,300
J. Campisi	NIH grant Growth Requlation in Normal and Transformed Cells	$121,800
J. Campisi	AHA grant Antiproliferative Mechanisms in Growth Control	$28,400
J. Campisi	Juvenile Diabetes Fdn grant Mechanisms of Insulin and Insulin-like Growth Factor Function and Regulation	$29,900
J. Conboy	NIH grant Red Cell Band 4.1: Dev. Changes in RNA Splicing	$116,300
R. Glaeser	NIH grant Membrane Proteins: High-Resolution EM	$398,000
T. Jukes	NIH grant Coding and Noncoding Regions in DNA Sequences	$36,600
M. Maestre	NIH grant Physical Structure of Viruses	$198,400

R. Mortimer	NIH grant Yeast *RAD* Genes in Repair, Recombination, Meiosis	$154,000
M. Narla	NIH grant Red Cell Deformability In Vitro and Survival In Vivo	$80,300
M. Narla	NIH grant Red Cell Membrane Studies	$393,700
M. Narla	UCSF/NIH subcontract Rheological and Adherence Properties of Sickle Cells	$108,300
E. Rubin	UCSF/NIH subcontract Construction of a Transgenic Mouse Model for Sickle Cell Anemia	$87,800
G. Shayamala	NIH grant Estrogenic Regulation of Mammary Progesterone Receptors	$148,800
B. Singer	NIH grant Alkylation of Polynucleotides In Vitro and In Vivo	$129,700
B. Singer	NIH grant Biochemical Mechanisms of Vinyl Chloride Carcinogenesis	$172,900
D. Wemmer	NIH grant National Tritium Labeling Facility	$702,000
T. Yang	NASA Carcinogenic and Mutagenic Effects of Protons and Heavy Charged Particles	$87,000
P. Yaswen	NIH grant Suppression of Tumorigenicity in Human Breast Cells	$96,600

Medical Applications

J. Alonso	NIH grant Optimizing Proton Therapy at the LBL Accelerator	$339,030
A. Beigon	NIH grant Radiographic Mapping Opiate Receptors	$56,736
T. Budinger	NIH grant Cardiovascular Flow and Metabolism	$588,647

T. Budinger	NIH grant Cerebral Blood Flow Patterns in Alzheimer's Disease	$186,586
T. Budinger	NIH training grant Quantitative Cardiovascular Research	$147,348
J. Castro	NIH grant Treatment of Cancer with Heavy Charged Particles	$1,465,261
W. Chu	NIH grant Raster-Scanner Development for 3-D Conformational Therapy	$219,554
S. Derenzo	NIH grant Search for Ultrafast Heavy Atom Scintillators	$77,647
T. Forte	NIH training grant Lipoprotein Methodology, Structure and Function	$125,540
T. Forte	UC Tobacco-Related Disease Research Program, Effect of Cigarette Smoke on High Risk Lipoprotein Profiles	$99,078
W. Jagust	NIH grant Longitudinal SPECT and PET Studies of Dementia	$168,730
W. Jagust	NIH grant Alcohol and Memory: A PET Study	$114,418
R. Krauss	NIH grant Plasma Lipoproteins in Coronary Artery Disease	$115,489
R. Krauss	NIH grant Lipoprotein Subclasses: Structure, Origin, and Metabolism	$199,728
R. Krauss	National Dairy Board contract Genetic Influences on Lipoprotein and Atherogenic Responses to Dietary Fat	$1,293,436
R. Krauss	Kaiser subcontract Genetic Epidemiology of CHD Risk in Women Twins	$13,724
R. Krauss	Gladstone Foundation subcontract Identification and Characterization of Patients with Familial Defective ApoB-100	$29,125
R. Krauss	Gladstone Foundation subcontract Training Center for Clinical Management of Lipid Disorders	$40,411
C. Mathis	NIH grant Serotonin Uptake Inhibitor Ligands for PET Studies	$195,386

C. Mathis	NIH grant 18F-Labeled Benzamides for Dopamine D2 Studies Using PET	$129,306
J. Miller	NASA contract Measure Production of Neutrons by High Energy Heavy Ions	$235,294
W. Moses	Whitaker Foundation Study of Scintillation Mechanisms for PET	$50,677
A. Nichols	NIH grant Apolipoprotein-Specific HDL and Cholesterol Tansport	$208,543
P. Petti	NIH grant Multiple Scattering in 3-D Charged Particle TMT Planning	$55,191
M. Phillips	NIH grant Dose Comparison of Stereotactic Radiosurgical Modalities	$30,296
M. Roos	Whitaker Foundation Spectroscopic Imaging with Stochastic Excitation	$33,398
T. Sargent	NIH grant PET Brain Blood Flow and Metabolism in Alzheimer's Disease	$177,677
P. Williams	NIH grant Lipoprotein Subfractions and CHD During 25-Year Follow-up	$107,958
P. Williams	NIH RCDA Effects of Exercise, Diet and Fat Lost on Lipoproteins	$60,700
S. Wong	Whitaker Foundation Dynamic NMR Imaging with Stochastic Excitation	$46,752
NIH Biomedical Research Support Grant		$59,992
T. Forte	Cell Studies on CHO Cells Transfected with Human Genes	$8,000
T. Musliner	In Vivo Metabolism of Lipoproteins	$12,677
G. Parry	Regulation of Epithelial Cell Polarity	$20,585
M. Roos	NMR Spectroscopic Imaging with Oscillating Gradients	$11,730

H. Issues

OHER plays a significant and increasingly prominent role in many aspects of LBL's scientific programs. The Laboratory recognizes the importance of OHER support to the health of our scientific endeavors and is placing appropriately stronger emphasis in OHER areas.

In programmatic planning, our continuing goal is to maintain a research program that is

- *cohesive*—while encompassing diverse research areas;
- *stable*—yet flexible enough to respond to OHER priorities as they arise;
- *innovative*—while addressing national needs and federal/local safety laws;
- *balanced*—in that, while emphasizing "big" science, we also recognize the importance of investigator-driven small science.

To achieve this goal, we encourage a culture that enables rapid mobilization of researchers to address major topics of strategic national importance. Our proximity to one of the nation's best universities allows for a healthy exchange as long as we succeed in maintaining a critical mass of our own talented researchers. We endeavor to gather diverse talents under general research themes:

I. **Genomics, gene expression, and carcinogenesis** (and structural biology) have been identified by OHER and by internal Laboratory panels as areas of singular importance. These research areas encompass much work currently being conducted at LBL, including that in the Human Genome Center. Much of this work has relevance to biotechnology.

LBL has a significant research effort in *molecular medicine*, has initiated an ambitious and competitive program in *hemato-*

poiesis with strong encouragement and directive from OHER, and is striving to understand the *molecular mechanisms of radiation damage.*

II. In **structural biology**, another critical area of endeavor, researchers at LBL are seeking to understand the relation between structure and function of cellular molecules that play important roles in signal transduction and *energy production.* Structural biology provides the foundation for biomolecular design, protein engineering, and biotechnology, and has a broad impact in the field of health and environment. A strong connection to the Advanced Light Source is being encouraged and fostered.

III. Another major theme—one in which LBL already plays a unique role—is **nuclear medicine and radiation biology**. Much of our uniqueness rests with the availability of the Bevalac as a source of heavy ions, both for basic research on the effects of high-LET radiation and for clinical research on heavy-ion radiotherapy.

IV. A broad research theme is that of **environmental exposure assessment**, wherein we detect, measure, and evaluate environmental exposures to various agents. An important subject of this inquiry is the indoor air within residential and commercial buildings. A related topic, that of remediation of toxic wastes, is receiving increasing emphasis at LBL.

V. The **biospheric response to global climate change** is a theme of growing importance. LBL has already started a modest program in this area and plans to expand this work in the near future.

VI. **Development of semiconductor devices** constitutes an increasing part of LBL's engineering program.

There are a number of ways in which OHER can enhance our research efforts in these important areas:

Genomics, gene expression, and carcinogenesis:

A. Research Support. We need to maintain a *critical mass of basic research* in all of these areas. We are putting increasing emphasis on carcinogenesis and are recruiting new talent; in doing so, we believe it is important to strike a balance between OHER and work-for-others funding. OHER funding has been eroding during the past decade, and we welcome new discussions.

Currently, OHER does not support either molecular medicine or hematopoiesis research at LBL. These are highly visible, exciting and competitive programs. Furthermore, they are strongly related to the current OHER mission, and future support would therefore be an important contribution not only to the health of LBL's life sciences research but also to the vitality of the OHER-supported national research effort.

B. Space. The *Human Genome Center* is establishing a strong team and a comprehensive program in physical mapping, sequencing, informatics, and engineering. *Both the size and the multidisciplinary nature of the project at LBL require that the Human Genome Laboratory building be funded as soon as possible.* This year we will require $430K of the $615K needed to complete the Title I Design of the proposed building.

The construction of such a facility would not only contribute greatly to the success of the human genome effort but would also help bring together many of the life scientists who are now scattered in various buildings throughout Berkeley, LBL, and the UC campus, because these researchers could occupy space now used by the Genome Center. According to outside reviewers, *every effort needs to be made to make additional and contiguous space available so that different groups attempting to work on similar problems can be brought closer together.* The present dispersion of personnel undoubtedly results in lost research opportunities and increased operating costs. In the short run, we need additional funds fo renovate our aging facilities and to provide closer interaction among scientists.

Structural biology: To advance the field of structural biology, *LBL has proposed construction of additional beamlines and Life Sciences facilities at the Advanced Light Source (ALS).* In addition to the capacity for highly efficient x-ray crystallography, the proposed facilities would provide unique capabilities in both x-ray spectroscopy and soft x-ray imaging of cells and subcellular components. These facilities would be both an important component of LBL's structural biology

program and a response to the DOE's mandate to construct and operate major national resource centers for research and education.

There is a strong, collaborative structural biology initiative jointly between LBL and the University of California at Berkeley to combine LBL's unique facilities and technical capabilities in computer science, instrumentation, and detector technology with top human resources of the University to solve important problems of health and enivronment relevant to the DOE mission. This initiative includes an extensive training program for new scientists in the field.

Nuclear medicine and radiation biology: A major issue for life sciences research is continued operation of the Bevalac. By the mid 1990s, the Bevalac will no longer be a major nuclear physics user facility and could be decommissioned. Accordingly, *we are exploring with OHER alternative means for assuring the continuance of clinical and radiobiological research with heavy ions in the United States, including joint ventures with NASA.*

A new direction we envision in the area of nuclear medicine is to advance the field of diagnostic medical imaging and to reveal underlying biochemical mechanisms of disease by developing a 10-T Imaging Spectrometer. Imaging of ^{1}H, ^{13}C, ^{31}P and other nuclei with the 10-T Imaging Spectrometer promises to yield otherwise unobtainable information on metabolic processes and anatomy in healthy and diseased humans.

Environmental exposure assessment: *We would like to see DOE lead a national effort to identify those U.S. homes—approximately 100,000 in number—in which gaseous radon exposure exceeds safe levels.* Although some initial funding was received in FY92, additional funding is required for an aggressive effort. *Substantial efforts are also needed to identify, measure, and evaluate other indoor pollutants.* These efforts should include (i) characterizing the sources and physicochemical behavior of indoor airborne chemicals, (ii) estimating public exposures to these chemicals, and (iii) analyzing the biological doses received by humans, as well as any resultant cellular damage.

Exposure assessment in conjunction with toxic-waste remediation is an area ripe for development at LBL. We need to work closely with OHER to bring LBL' considerable talent in Earth Sciences, Energy and Environment, and Life Sciences to bear on these related problems.

Global climate change: *Given the continued use of fossil fuels, we must develop techniques and capabilities for predicting how disturbances of atmospheric conditions will influence global temperatures and impact the agricultural and natural plant communities.* Current models predicting enhancement of plant productivity as a result of fossil-fuel-induced changes in global climate are inadequate; to model accurately the biosphere's response to elevations in temperature and atmospheric CO_2 levels, we must identify and quantify the factors influencing development and productivity of our ecosystems. LBL is proposing a project to identify the roles of selected nutrients, commonly limiting in the biosphere, in photosynthesis, ecosystem function, and productivity—all in response to global atmospheric changes.

Development of semiconductor devices: Of necessity, this work involves the handling and use of dangerous chemicals and gases. Our increasing emphasis on safety, health and environmental effects presents our staff with a serious challenge. *Extensive upgrading of our laboratories will be essential in order to facilitate conducting the research program in compliance with the requirements now in force.*

In addition to the above, there are several major issues that cut across research programs:

I. **Work for others** is a foremost critical issue if Life and Environmental Sciences are to survive and thrive in the National Laboratories.

II. **Technology transfer** is another major issue. Every effort should be made to move critical technologies as rapidly as possible to the private sector.

III. An issue of growing concern is the current **public attitude toward research in molecular genetics and biotechnology, as well as research involving use of animals.**

IV. The impact of **costs of waste management** continues to grow. OHEK should consider obtaining new funds in this area so that already tight programmatic budgets will not become cost ineffective.

Work for others: Projects sponsored by NIH and other outside agencies are critically important to OHER programs at LBL. Approximately 40 percent of the funding for life and environmental sciences at LBL comes from non-DOE sources. These projects complement and build on work carried out by the Department of Energy. We recognize that changes have been recommended in how the Laboratory applies for and brings in NIH funding. *We want to work with DOE to develop a Memorandum of Understanding between the two agencies to ensure continuation of the DOE/NIH relationship that has so effectively served the nation.* There is also concern at LBL regarding the rules discouraging investigators from applying to outside agencies, such as the American Cancer Society, that do not offer the full DOE indirect cost rate. Continued outside funding will be necessary to keep life and environmental sciences programs competitive. Thus, we urge DOE to consider exceptions to full cost recovery for projects that support the OHER mission but are funded by outside agencies.

Technology transfer: In order for LBL to successfully carry out DOE's Technology Transfer mission, it is necessary that LBL and DOE significantly shorten the amount of time it takes for an approved CRADA to be established. Otherwise, private industry may become discouraged in its attempts to work collaboratively with the Laboratory. Industry business plans cannot accommodate the uncertainty that delays in timely approval can create, and their confidence in working with the Laboratory and DOE will erode. The Laboratory is committed to making DOE's Technology Transfer mission a success, and we will continue to work with DOE to improve the existing systems for obtaining DOE approval of CRADAs.

Public attitude toward research in molecular genetics and biotechnology, as well as research involving use of animals: A vocal minority continues to be heard and threatens to create an adversarial climate. Naturally, we hope to avoid such a situation, and we encourage OHER to consider steps that might be taken toward ensuring an educated public response to all research in the life sciences. Especially as we move into an era of growing environmental awareness—which demands that we solve increasing problems of toxic waste—we recognize the critical need to guarantee a proper role for biotechnology and genetic engineering. Indeed, researchers developing in situ bioremediation—one proposed method of environmental restoration—will rely heavily on advances in microbiology and biotechnology. Ethical issues related to the human genome project will require a concerted public education effort as well.

I. Resource Quantitation

The following information is tabulated by division; a summary table is given at the end. The totals (T) given in the tabulations of personnel data reflect DOE support of the entire division, except for the Engineering, Information and Computing Sciences, and Earth Sciences Divisions, where the totals reflect only effort directly related to OHER-sponsored research.

Cell and Molecular Biology

Personnel (FTE)	FY 1990		FY 1991[a]		FY 1992	
	BER	(T)	BER	(T)	BER	(T)
Professional (scientific)[b]	26.6	52.4	26.6	52.2	30.1	59.0
Post-doctorates	7.0	12.5	2.2	2.9	3.4	5.5
Technicians	21.9	40.7	16.2	35.5	18.7	41.0
Animal care	0.9	2.1	0.7	2.2	0.7	2.2
Total direct personnel	**56.4**	**107.7**	**52.0**	**92.8**	**52.9**	**107.7**
Professional (adm.)	2.5	5.1	4.8	7.1	6.6	8.0
Clerical, adm. support	5.3	8.7	5.7	9.6	6.1	9.3
Maintenance	2.6	4.7	4.0	4.5	4.6	5.2
Total indirect personnel	**10.4**	**18.5**	**14.5**	**21.2**	**17.3**	**22.5**
Visiting scientists[c]	42.0	79.0	24.0	44.0	29.0	53.0
Graduate students[c]	30.0	38.0	20.0	29.0	23.0	34.0
Undergraduates[c]	43.0	85.0	46.0	96.0	48.0	100.0

Information Transfer (OHER Sponsored Research)

	FY 1989	FY 1990	FY 1991
Journal articles (peer reviewed)	89	38	60
Chapters, reviews	26	17	13
Books, proceedings (edited)	9	24	3
Reports/documents	11	2	0
Presentations at technical meetings	104	143	121
Meetings organized	3	1	0

[a] Figures include Engineering and Information and Computing Sciences personnel supported by the Human Genome Center.

[b] Number of OHER-sponsored scientific professionals by highest degree:

1 M.D.
29 Ph.D
21 MS/BS

[c] Data given as head count (number of participating individuals).

Chemical Biodynamics

Personnel (FTE)	FY 1990		FY 1991		FY 1992	
	BER	(T)	BER	(T)	BER	(T)
Professional (scientific)[a]	3.1	12.3	3.0	12.5	2.8	12.0
Post-doctorates	0.0	2.7	1.0	3.0	1.5	3.5
Technicians	0.8	2.8	0.8	2.0	0.5	2.0
Animal care	0.0	0.0	0.0	0.0	0.0	0.0
Total direct personnel	**3.9**	**17.8**	**4.8**	**17.5**	**4.8**	**17.5**
Professional (adm.)	0.5	1.6	0.5	1.6	0.5	1.6
Clerical, adm. support	1.1	3.3	1.0	3.0	0.5	2.5
Maintenance	0.2	1.4	0.2	1.4	0.2	1.4
Total indirect personnel	**1.8**	**6.3**	**1.7**	**6.0**	**1.2**	**5.5**
Visiting scientists	0.0	1.2	0.0	1.0	0.0	2.0
Graduate students	5.2	10.3	6.0	11.0	5.5	10.1
Undergraduates	0.2	0.6	0.2	0.6	0.2	0.6

Information Transfer (OHER Sponsored Research)

	FY 1989	FY 1990	FY 1991
Journal articles (peer reviewed)	53	48	73
Chapters, reviews	0	0	0
Books, proceedings (edited)	0	0	0
Reports/documents	8	12	10
Presentations at technical meetings	28	26	21
Meetings organized	1	1	0
No. of user facility visitors[b]	20	20	20
No. of user days	100	100	100

[a] Number of OHER-sponsored scientific professionals by highest degree:
2 Ph.D
0.8 MS/BS

[b] Facilities used by others:
Facilities at the Calvin Laboratory used by collaborators from the University of California at Berkeley and elsewhere include the flow cytometer, x-ray spectrometer, NMR spectrometer, and the computer complex.

Earth Sciences

Personnel (FTE)	FY 1990		FY 1991		FY 1992	
	BER	(T)	BER	(T)	BER	(T)
Professional (scientific)[a]	2.0	2.0	3.0	3.0	3.5	3.5
Post-doctorates	0.0	0.0	0.5	0.5	0.5	0.5
Technicians	0.2	0.2	0.3	0.3	0.5	0.5
Total direct personnel	**2.2**	**2.2**	**3.8**	**3.8**	**4.5**	**4.5**
Professional (adm.)	0.0	0.0	0.0	0.0	0.0	0.0
Clerical, adm. support	0.1	0.1	0.1	0.1	0.2	0.2
Maintenance	0.0	0.0	0.0	0.0	0.0	0.0
Total indirect personnel	**0.1**	**0.1**	**0.1**	**0.1**	**0.2**	**0.2**
Visiting scientists	0.1	0.1	0.1	0.1	0.1	0.1
Graduate students	0.0	0.0	0.0	0.0	0.5	0.5
Undergraduates	0.2	0.2	0.2	0.2	0.2	0.2

Information Transfer (OHER Sponsored Research)

	FY 1989	FY 1990	FY 1991
Journal articles (peer reviewed)	0	0	6
Chapters, reviews	0	0	0
Books, proceedings (edited)	0	0	0
Reports/documents	0	0	0
Presentations at technical meetings	0	6	2
Meetings organized	0	0	0

[a]Number of OHER-sponsored scientific professionals by highest degree:

8 Ph.D.
2 MS/BS

Energy and Environment

Personnel (FTE)	FY 1990		FY 1991		FY 1992	
	BER	(T)	BER	(T)[b]	BER	(T)
Professional (scientific)[a]	5.2	91.0	3.2	93.0	3.7	68.1
Post-doctorates	0.0	17.0	1.3	24.0	0.8	21.0
Technicians	0.9	82.0	1.6	61.0	1.3	66.9
Animal care	0.0	0.0	0.0	0.0	0.0	0.0
Total direct personnel	**6.1**	**190.0**	**6.1**	**178.0**	**5.8**	**156.0**
Professional (adm.)	0.1	12.0	0.2	13.0	0.2	14.1
Clerical, adm. support	1.1	32.0	1.1	24.0	1.2	28.9
Maintenance	0.0	0.0	0.1	0.0	0.1	0.0
Total indirect personnel	**1.2**	**44.0**	**1.4**	**37.0**	**1.5**	**43.0**
Visiting scientists	0.0	1.0	1.6	n/a	1.3	91.0[b]
Graduate students	0.0	57.0	1.1	47.0	1.8	28.4
Undergraduates	0.0	60.0	0.0	35.0	0.0	7.9
Other Students	0.0	0.0	0.2	0.0	0.3	0.0

Information Transfer (OHER Sponsored Research)

	FY 1989	FY 1990	FY 1991
Journal articles (peer reviewed)	15	7	4
Chapters, reviews	1	0	0
Books, proceedings (edited)	0	0	1
Reports/documents	13	7	11
Presentations at technical meetings	3	2	4
Meetings organized	0	0	0

[a]Number of OHER-sponsored scientific professionals by highest degree:
11 Ph.D
3 MS/BS

[b]Data given as head count rather than FTE.

Engineering

Personnel (FTE)	FY 1990		FY 1991		FY 1992	
	BER	(T)	BER	(T)	BER	(T)
Professional (scientific)[a]	5.0	10.0	5.0	9.0	5.0	9.0
Post-doctorates	0.0	0.0	0.0	0.0	0.0	0.0
Technicians	2.0	4.0	2.0	4.0	2.0	4.0
Animal care	0.0	0.0	0.0	0.0	0.0	0.0
Total direct personnel	**7.0**	**14.0**	**7.0**	**13.0**	**7.0**	**13.0**
Professional (adm.)	0.0	0.0	0.0	0.0	0.0	0.0
Clerical, adm. support	0.5	1.0	1.0	1.0	1.0	1.0
Maintenance	0.5	0.5	0.5	0.5	0.5	0.5
Total indirect personnel	**1.0**	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**
Visiting scientists	0.0	0.0	0.0	0.0	0.0	0.0
Graduate students	1.0	1.0	1.0	1.0	1.0	1.0
Undergraduates	1.0	1.0	1.0	1.0	1.0	1.0

Information Transfer (OHER Sponsored Research)

	FY 1989	FY 1990	FY 1991
Journal articles (peer reviewed)	5	7	11
Chapters, reviews	0	0	0
Books, proceedings (edited)	0	0	1
Reports/documents	9	7	14
Presentations at technical meetings	4	7	12
Meetings organized	0	0	0
No. of user facility days[b]	20	20	20

[a]Number of OHER-sponsored scientific professionals by highest degree:
1 D.Sc.
4 Ph.D.
2 MS/BS

[b]Facilities used by others:
Semiconductor Detector Laboratory
Charged-Particle Backscatter Facility
Low-Background Counting Facility
X-Ray Fluorescence Analysis System

Information and Computing Sciences

Personnel (FTE)	FY 1990		FY 1991		FY 1992	
	BER	(T)	BER	(T)	BER	(T)
Professional (scientific, Ph.D.)[a]	1.2	1.2	0.0	0.0	0.5	0.5
Post-doctorates	0.0	0.0	0.0	0.0	0.0	0.0
Technicians	0.0	0.0	0.0	0.0	1.5	1.5
Animal care	0.0	0.0	0.0	0.0	0.0	0.0
Total direct personnel	**1.2**	**1.2**	**0.0**	**0.0**	**2.0**	**2.0**
Professional (adm.)	0.0	0.0	0.0	0.0	0.0	0.0
Clerical, adm. support	0.0	0.0	0.0	0.0	0.0	0.0
Maintenance	0.0	0.0	0.0	0.0	0.0	0.0
Total indirect personnel	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Visiting scientists	0.0	3.0	0.0	0.0	0.0	0.0
Graduate students	2.0	5.0	0.0	0.0	0.0	0.0
Undergraduates	0.0	0.0	0.0	0.0	0.0	0.0

Information Transfer (OHER Sponsored Research)

	FY 1989	FY 1990	FY 1991
Journal articles (peer reviewed)	2		0
Chapters, reviews	0		0
Books, proceedings (edited)	0		0
Reports/documents	7[b]		0
Presentations at technical meetings	3		0
Meetings organized	0		0

[a]Number of OHER-sponsored scientific professionals by highest degree:
0.5 Ph.D.
1.5 MS/BS

[b]Includes 3 theses in FY1989.

Research Medicine and Radiation Biophysics

Personnel (FTE)	FY 1990		FY 1991		FY 1992	
	BER	(T)	BER	(T)	BER	(T)
Professional (scientific)[a]	15.3	42.4	13.3	40.5	13.3	42.5
Post-doctorates	0.8	2.4	1.5	5.3	1.5	5.5
Technicians	5.8	29.8	5.0	28.0	5.0	31.0
Animal care	0.0	0.0	0.0	0.0	0.0	0.0
Total direct personnel	**21.9**	**74.6**	**19.8**	**73.8**	**19.8**	**79.0**
Professional (adm.)	1.0	8.0	1.0	7.0	1.0	7.0
Clerical, adm. support	1.0	9.5	1.0	7.0	1.0	7.0
Maintenance	0.0	0.0	0.0	0.0	0.0	0.0
Total indirect personnel	**2.0**	**17.5**	**2.0**	**14.0**	**2.0**	**14.0**
Visiting scientists[b]	8.0	20.0	12.0	22.0	12.0	22.0
Graduate students[b]	3.0	12.0	3.0	8.0	3.0	8.0
Undergraduates[b]	2.0	15.0	4.0	17.0	4.0	17.0

Information Transfer (OHER Sponsored Research)

	FY 1989	FY 1990	FY 1991
Journal articles (peer reviewed)	59	62	52
Chapters, reviews	28	17	10
Books, proceedings (edited)	3	6	12
Reports/documents	26	21	15
Presentations at technical meetings	51	81	75
Meetings organized	1	0	0
No. of user facility visitors[c]	17	20	36
No. of user days	25	25	24

[a]Number of OHER-sponsored scientific professionals by highest degree:
4 M.D.
17 Ph.D
1 D.V.M.
1 MS/BS

[b]1992 figures are estimates.

[c]Facilities used by others:
Positron-Emission Tomograph
Nuclear Magnetic Resonance Spectrometer

Summary Total

Personnel (FTE)	FY 1990		FY 1991		FY 1992	
	BER	(T)	BER	(T)	BER	(T)
Professional (scientific)[a]	54.1	192.1	54.1	210.0	58.9	194.6
Post-doctorates	12.3	26.6	6.5	35.7	7.7	36.0
Technicians	34.3	110.6	25.9	130.8	29.5	146.9
Animal care	0.5	3.9	0.7	2.2	0.7	2.2
Total direct personnel	**101.2**	**333.2**	**87.2**	**378.7**	**96.8**	**379.7**
Professional (adm.)	4.5	26.1	6.5	28.7	8.3	30.7
Clerical, adm. support	10.3	46.5	9.9	44.7	10.0	48.9
Maintenance	4.9	9.0	4.8	6.4	5.4	7.1
Total indirect personnel	**19.7**	**81.6**	**21.2**	**79.8**	**23.7**	**86.7**
Visiting scientists	32.2	73.0	37.7	67.1	42.4	168.1
Graduate students	31.6	117.3	31.1	96.0	34.8	82.0
Undergraduates	39.7	91.1	51.4	149.8	53.4	126.7

Information Transfer (OHER Sponsored Research)

	FY 1989	FY 1990	FY 1991
Journal articles (peer reviewed)	228	167	206
Chapters, reviews	55	35	23
Books, proceedings (edited)	14	30	17
Reports/documents	75	58	50
Presentations at technical meetings	197	272	235
Meetings organized	5	2	0
No. of user facility days	145	125	144

[a]Number of OHER-sponsored scientific professionals by highest degree:

5.0 M.D.
72.5 Ph.D/D.Sc.
1.0 D.V.M.
31.3 MS/BS

Appendix 1. Publications

Afzal, S.M.J., Tenforde, T.S., Kavanau, K.S. and Curtis, S.B. (1991) Reoxygenation in rat *rhabdomyosarcoma* tumor following x-irradiation. *Intl. J. Radiat. Oncol. Biol. Phys.*, **20**:437-477.

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Appendix 2.

Selected Research Highlights

The following brief narratives describe significant research highlights of OHER-sponsored research at LBL during FY 1991, including research funded by the Laboratory-Directed Research and Development Funds. This selection also reflects the diversity of research interests at the Laboratory and represents efforts in four research divisions—Cell and Molecular Biology, Chemical Biodynamics, Research Medicine and Radiation Biophysics, and Energy and Environment. While diversified, the research described here points to four broad areas of research emphasis at LBL: elucidation of gene expression, methodology for human genome mapping, applications of technology to medicine, and understanding of biological structure. The titles of the narratives follow.

- Random *Breakage Mapping: A New Method for Locating Genes on Chromosomes*
- *Yeast Artificial Chromosomes Used in Mapping Human Chromosome 21*
- *ANGEL Assists in Analysis of Genome Data*
- *Promoter Region of a Milk Gene May Benefit Biotechnology*
- *Soft X-ray Microscopy Reveals Calcium Deposits in Heart and Brain*
- *Three-dimensional Structure of a Chemotaxis Receptor*
- *New Risk Assessment Strategy for Indoor Air Pollutants*

Random-Breakage Mapping: A New Method for Locating Genes on Chromosomes

(John Game, 510/486-5651)

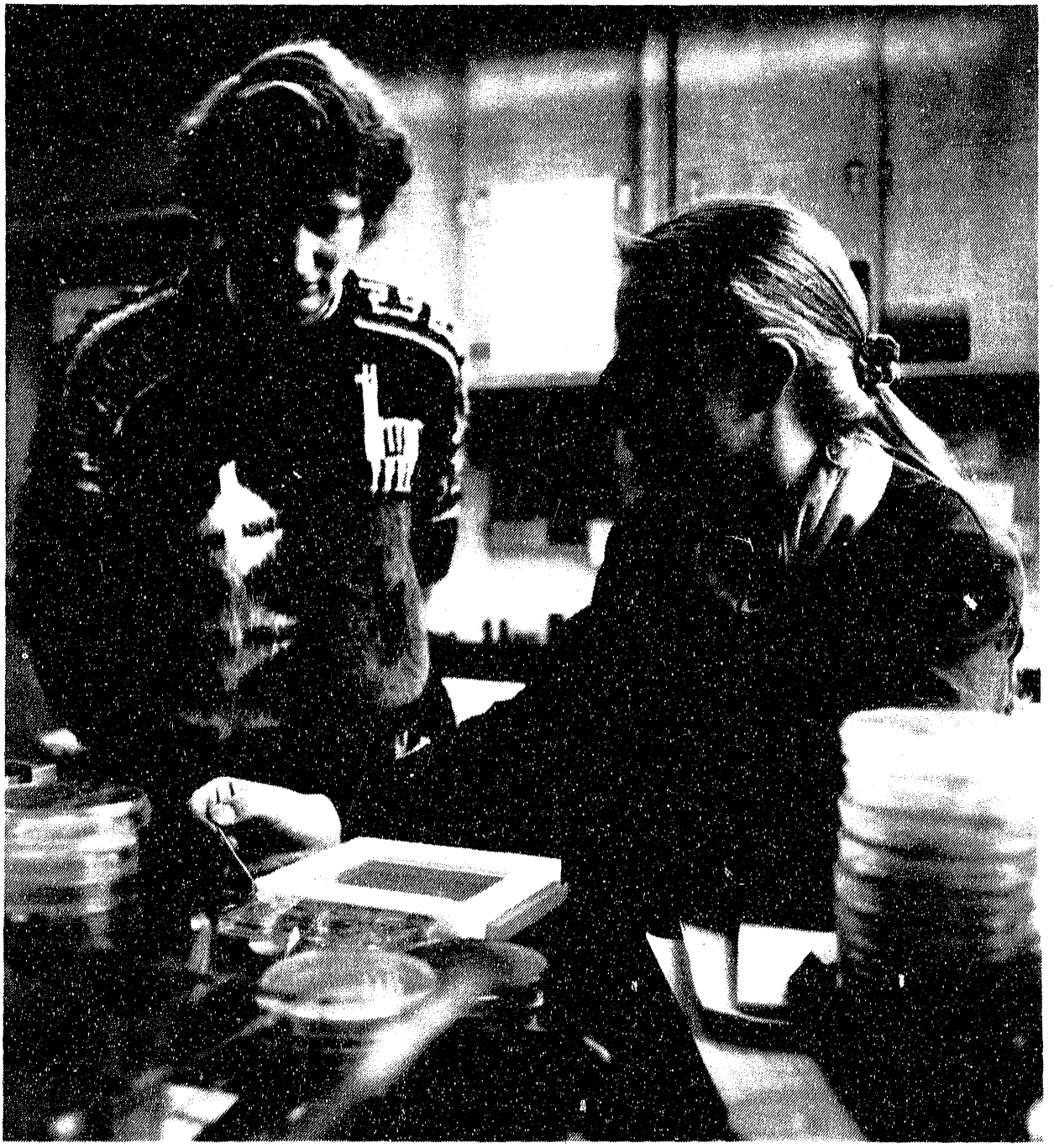
An innovative method for determining the positions of genes on chromosomes has been developed by researchers with Lawrence Berkeley Laboratory's Human Genome Center and the Department of Molecular and Cell Biology at the University of California at Berkeley. The researchers demonstrated the accuracy of the method, called "random-breakage mapping," by showing that it corroborates yeast gene positions previously determined by genetic techniques.

John Game, Maren Bell, Jeff King, and Robert Mortimer irradiated whole yeast chromosomes with x-rays to induce approximately one break per chromosome. To separate the fragments, they used gel electrophoresis, a method in which DNA moves through a two-dimensional gel in response to an electric field. After "Southern blotting" to transfer the separated DNA onto special paper, fragments were made visible by hybridization with radioactively labeled, cloned genes—which bind to their counterparts on the blot.

The distance of each gene from the ends of its chromosome was determined from the size distribution of the fragments in which the gene was found. The researchers verified the accuracy of the technique using four different yeast genes that had previously been mapped. They are now using it to determine the positions of yeast genes whose locations are unknown.

The technique cannot yet be used on whole human chromosomes, because human chromosomes (even once-broken ones) are too large to run in an electrophoresis gel with current technology. However, once a human gene known to be on a particular chromosome has been cloned, the technique could be used to help pinpoint its location. First, an enzyme such as Not I would be used to break the chromosome into fragments. After irradiation of the fragments, the technique would proceed as with the yeast chromosomes. Thus, the method will reveal a human gene's location within a particular fragment rather than within a whole chromosome.

Random-breakage mapping, which is much faster than older genetic mapping techniques, should prove especially valuable when genetic markers are not available, mating experiments are not feasible, and little information is at hand.



John Game (left) and Maren Bell propel chromosome fragments through a gel to separate them according to size—one of the steps in Lawrence Berkeley Laboratory's newly developed "random-breakage mapping" method for determining the positions of genes on chromosomes.

Yeast Artificial Chromosomes Used in Mapping Human Chromosome 21

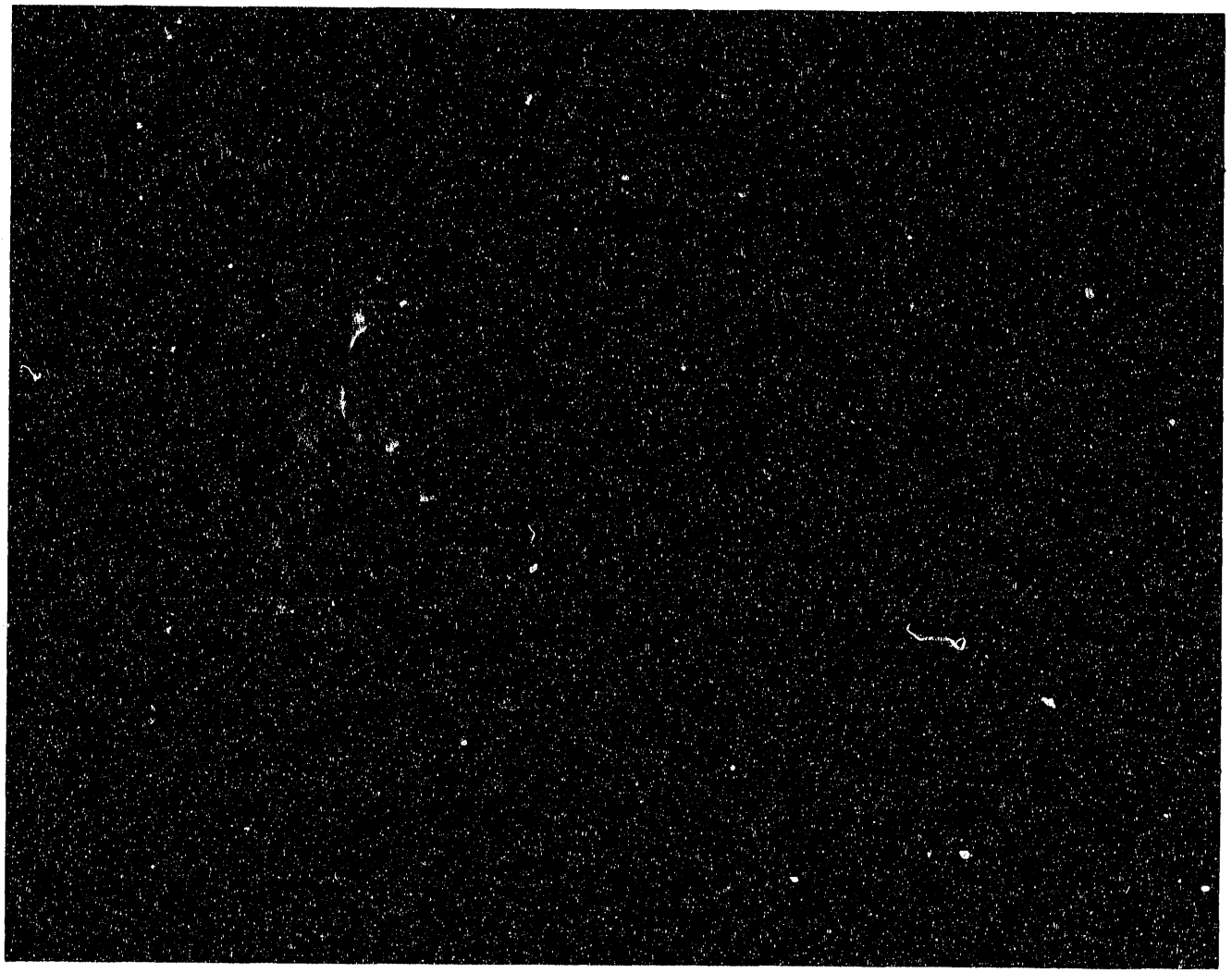
(Jeffrey Gingrich, 510/486-6549)

At Lawrence Berkeley Laboratory's Human Genome Center, researchers are using yeast artificial chromosomes (YACs) to clone fragments of human chromosome 21. Biologist Jeffrey Gingrich has mapped more than 40 such fragments onto specific regions of the chromosome. Mapping is a prerequisite step to achieving the goal of the human genome project: sequencing the three billion DNA nucleotides that determine all of the genetic characteristics of human beings.

Gingrich uses two different approaches to find out where the YACs map onto chromosome 21. One method entails using the polymerase chain reaction (PCR) to amplify the human DNA in the YAC. Because amplification takes place between the highly repeated *alu* sequences found in human DNA, Gingrich's procedure is called "inter-*alu* PCR." The amplified DNA, which is radioactively labeled, is then hybridized to DNA from hybrid cell lines that contain parts of chromosome 21 that have also been amplified by inter-*alu* PCR.

The second approach that Gingrich uses is fluorescence in situ hybridization (FISH). In this technique, biotin, a small molecule in the vitamin B family, is attached to the YAC DNA. This DNA is then hybridized to human DNA, and a fluorescein-labeled antibody to biotin is used to locate the YAC DNA on chromosome 21.

The inter-al*u* PCR and FISH techniques give hybridization signals in hours rather than the days or weeks required by older methods. As well as using these techniques with additional YACs, Gingrich and his colleagues are now sequencing the YACs that have been assigned to chromosome 21. These chromosome sites will be used as signposts for finer level mapping and gene locating.



Fluorescence in situ hybridization is being used at Lawrence Berkeley Laboratory to localize fragments of human chromosome 21 contained in YACs (yeast artificial chromosomes). The 48 condensed human chromosomes are stained with a red dye, and the YAC DNA is stained with a yellow dye. During the hybridization reactions, the YAC DNA finds its complementary DNA on the two copies of chromosome 21. In this figure, the YAC DNA attaches to the tip of chromosome 21; it therefore contains DNA derived from this region.

ANGEL Assists in Analysis of Genome Data

(Edward Theil, 510/486-6411; Suzanna Lewis, 510/486-7370)

The human genome project holds the promise of better understanding of DNA damage and repair, carcinogenesis, genetic diseases, and normal cell differentiation. Probably the single most important technique currently used for DNA mapping and sequencing in genome studies is gel electrophoresis, a method in which an electric field is used to separate DNA fragments on a two-dimensional gel.

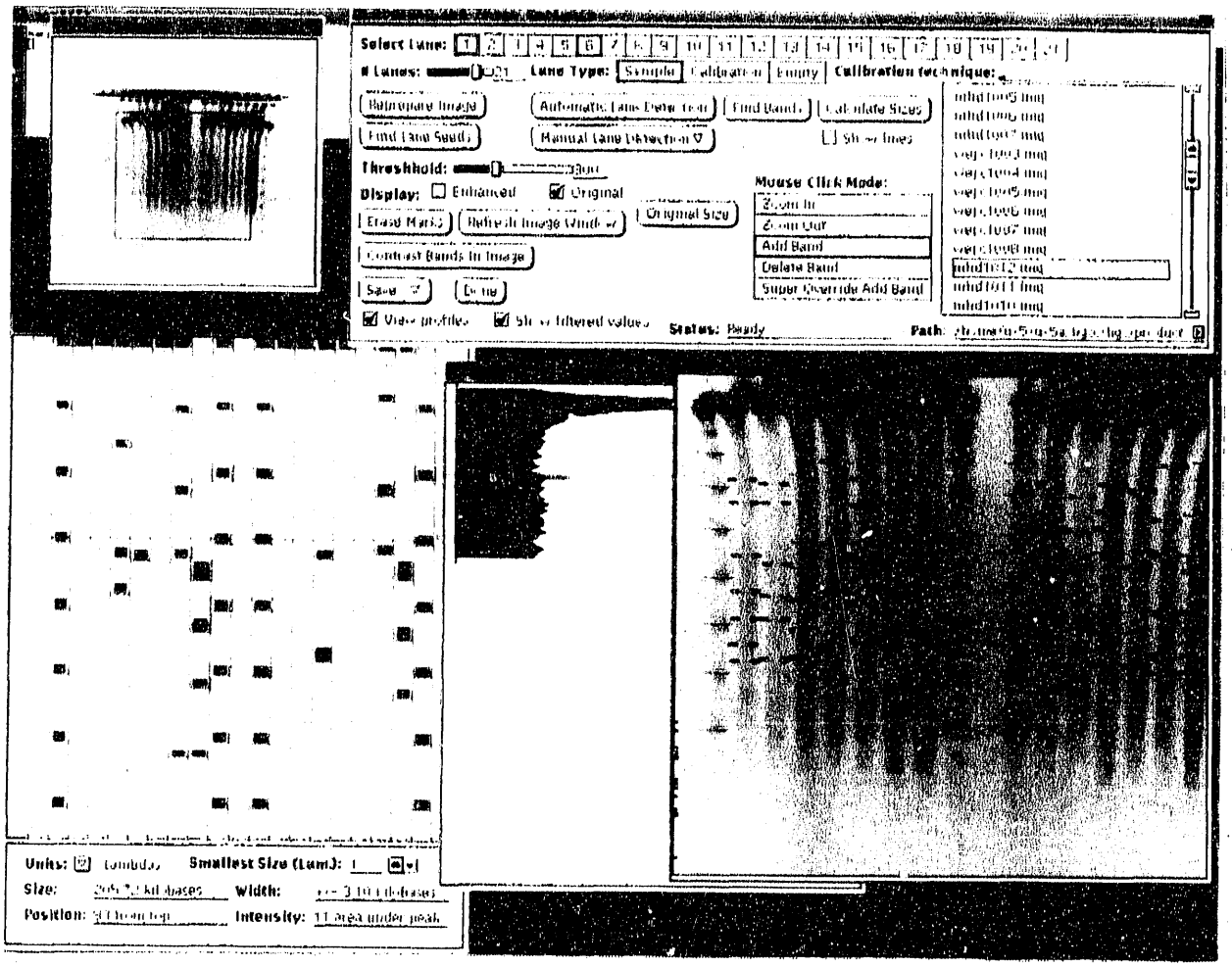
DNA fragments move along an electrophoresis gel in lanes; bands consisting of fragments of specific sizes form within the lanes. Traditionally, identification of the bands has been a manual activity. As such, it is a tedious, time-consuming process—and subject to error.

To assist biologists in gel analysis, a team of computer scientists and engineers with Lawrence Berkeley Laboratory's Human Genome Center—including Edward Theil, Suzanna Lewis, William Johnston, and Kevin Gong—has developed a gel image-analysis program called ANGEL. The program automatically finds gel lanes, with or without a simple initial indication of location from the experimenter. Lanes can vary significantly in curvature and still be located.

Within each lane, ANGEL automatically identifies bands as highly probable or merely possible candidates, based on gray-scale intensities and other criteria. Signal processing eliminates background. Once all bands have been identified, ANGEL calculates the size of the fragments each one contains.

An idealized image of the gel is formed and stored in the image database. This image can be used for fast comparisons to all other previously analyzed gels contained in the database.

ANGEL is currently undergoing user acceptance tests at LBL. The program was demonstrated at the 2nd Workshop for DOE Human Genome Contractors in Santa Fe, New Mexico, in February 1991.



ANGEL is a program that was developed at Lawrence Berkeley Laboratory to analyze data from electrophoresis separation of DNA fragments. The program automatically identifies DNA lanes (vertical lines in lower right window) and centers of bands for particular fragments (yellow). The lower middle window shows the bands in a single lane after digital filtering to remove noise. Electrophoresis is an essential step in DNA sequencing.

Promoter Region of a Milk Gene May Benefit Biotechnology

(Mina Bissell, 510/486-4365)

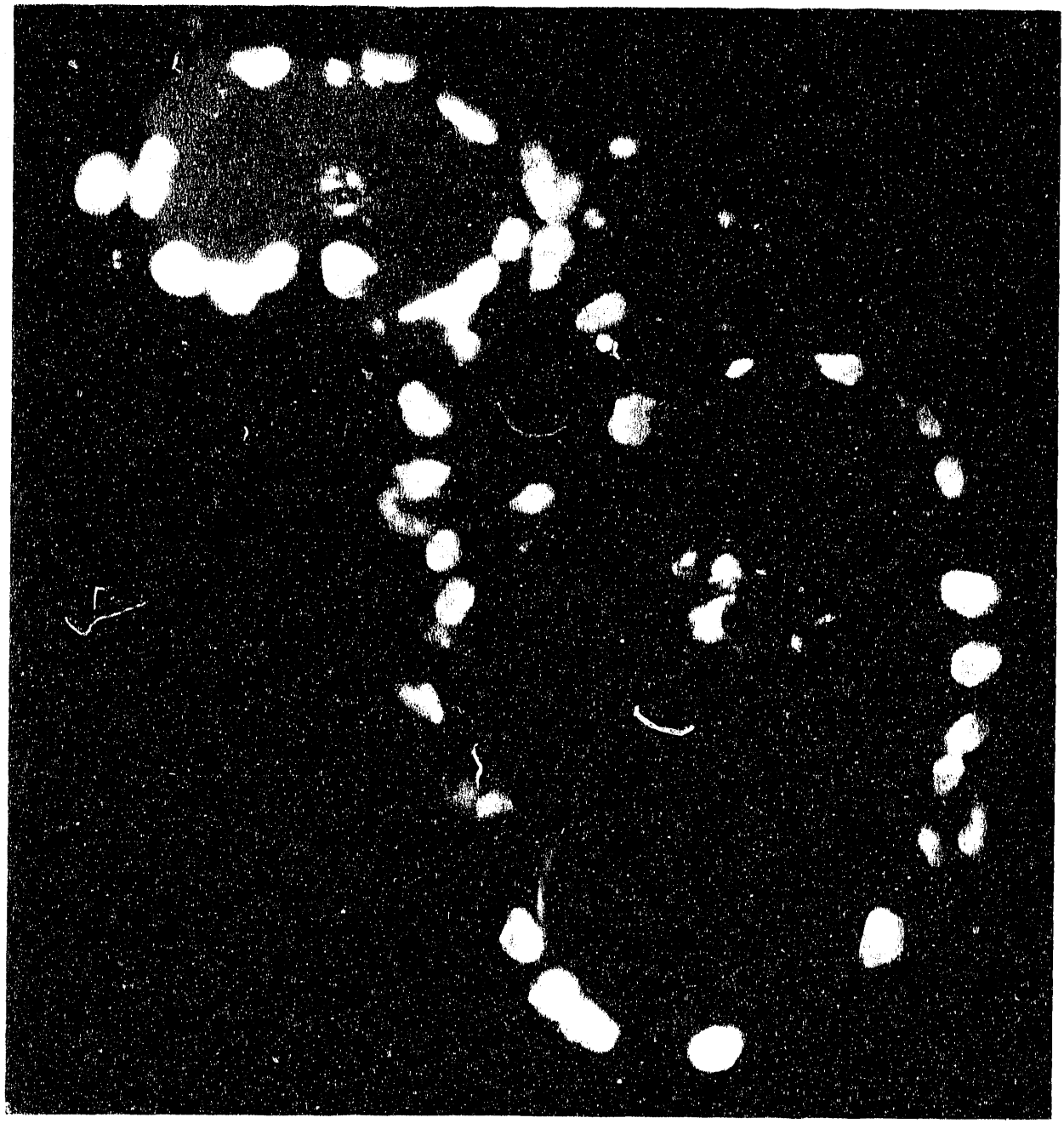
In collaboration with researchers from Monsanto's Life Sciences Research Center in Saint Louis, Missouri, Mina Bissell and Christian Schmidhauser of Lawrence Berkeley Laboratory's Cell and Molecular Biology Division have shown that the promoter region flanking the gene for a milk protein contains elements that respond to signals from the extracellular matrix (ECM). Promoters are the regions where transcription of the genetic code into mRNA (an event prerequisite to protein synthesis) begins.

The ECM, which consists of material secreted by living cells, shares with hormones the responsibility for regulating tissue formation and gene expression. The ECM also affects cell architecture: on reconstituted basement membranes (a type of ECM), separated mammary epithelial cells form structures remarkably similar to those of mammary glands during pregnancy and lactation.

Bissell and Schmidhauser attached the flanking regions of bovine genes for β-casein, a milk protein, to chloramphenical acetyltransferase (CAT) reporter genes. The resultant fusion genes were introduced into mouse mammary epithelial cells in culture. Expression of the CAT genes was up to 150-fold greater in cells grown on reconstituted basement membranes than in cells grown on plastic.

Regulation of the β-casein promoter region was cell-type specific: very little CAT activity could be observed in non-mammary cells. When the CAT gene was attached to a promoter region for a viral protein and inserted in mammary cells, high expression of CAT was observed, but this expression was regulated neither by the ECM nor by hormones.

The LBL researchers now hope to pinpoint the ECM signals to which the milk-protein promoter responds. Their findings, which were reported in the Proceedings *of the National Academy of Sciences* in December 1990, not only represent a significant breakthrough in the study of gene regulation by the ECM but also demonstrate a cell system for expression of foreign genes and correct secretion of gene products—a very exciting development for biotechnology.



Scientists at Lawrence Berkeley Laboratory have discovered how to grow mammary cells (nuclei stained blue) that produce a tremendous amount of milk protein (red stain) in tissue culture. In collaboration with the Monsanto Company, the researchers have shown how to attach foreign genes to the regulatory sequences of the milk genes, thereby causing the foreign genes to be expressed at a very high level. This technology can be used to produce appreciable amounts of useful substances for medical or research applications.

Soft X-ray Microscopy Reveals Calcium Deposits in Heart and Brain

(Thomas Budinger, 510/486-5453)

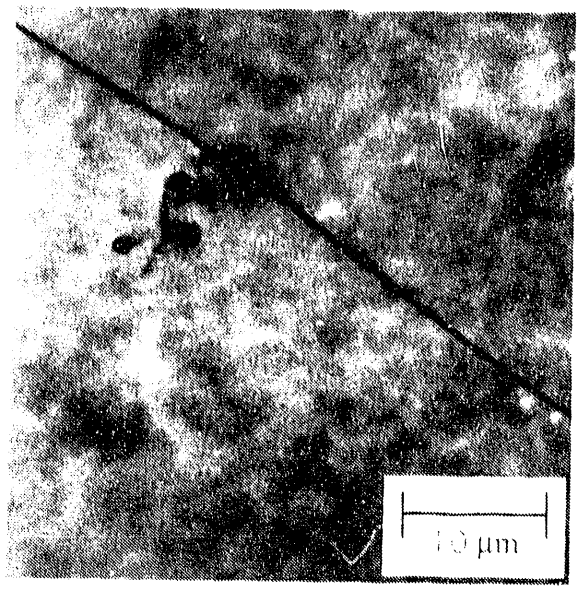
Using soft x-ray microscopy, investigators in the Research Medicine and Radiation Biophysics Division (RMRB) at Lawrence Berkeley Laboratory have demonstrated the accumulation of minute calcium particles, probably calcium phosphate, in cultured heart cells stressed by oxygen deprivation. Unstressed cells do not show this accumulation. The calcium particles may play a role in cell death during heart attacks, when oxygen flow to the heart is severely decreased.

The work was led by RMRB director Thomas Budinger at the National Synchrotron Light Source at Brookhaven National Laboratory in Upton, New York. It exemplifies one type of research that will be possible at the Life Sciences facilities proposed for LBL's Advanced Light Source.

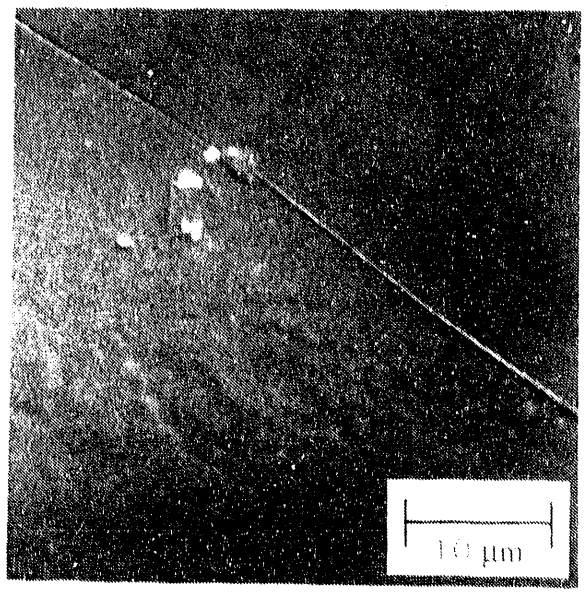
Soft x-ray microscopy enables study not only of oxidative stress in heart disease but also of pathological changes associated with aging and disease of the brain and other tissues. Budinger and his colleagues used this technique to examine a thin section of brain taken from a patient who had died of Alzheimer's disease. The resultant images revealed subcellular calcium deposits of about .2 microns diameter (1 micron equals 4 one-hundred thousandths of an inch).

Soft x-ray microscopy combines microimaging with x-ray spectroscopy, which is based on absorption of x-rays of specific wavelengths by elements of biological interest (in this case, calcium). The technique is unique in its ability to distinguish elements at 5 microns resolution in biological specimens as thick as 3 microns. The sensitivity for detection is less than 10^{-14} grams (about a millionth of a billionth of an ounce).

ALZHEIMER'S BRAIN UNSTAINED SECTION (0.5 μm)



36.3 Å λ Scan



Calcium L-Edge Image

Results of soft x-ray microscopy on a thin section of brain taken from a patient who died of Alzheimer's disease. The white spots in the image on the right are calcium particles ranging from .2 to 1 micron in diameter. The study, which was done by Lawrence Berkeley Laboratory scientists at the National Synchrotron Light Source at Brookhaven National Laboratory, illustrates the potential of soft x-ray microsopy to lead to a better understanding of pathological changes associated with aging and disease.

Three-Dimensional Structure of a Chemotaxis Receptor

(Sung-Hou Kim, 510/486-4333)

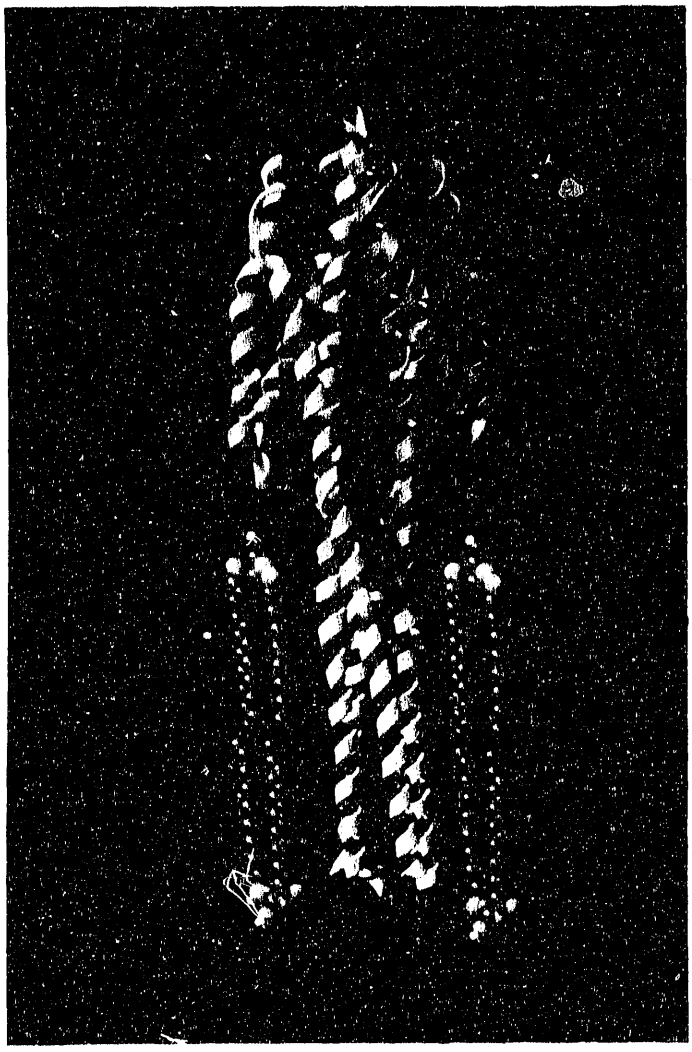
Transmembrane receptors are the proteins through which cells and organisms receive information from the environment and transmit it into the cell for processing. The aspartate chemotaxis receptor of the bacterium *Salmonella typhimurium* perceives the presence of aspartate and signals the cell to move toward an increasing concentration of this nutrient. LBL and UC Berkeley researchers recently determined the structure of the aspartate-binding region of the receptor both with and without aspartate attached.

Knowledge of the structures of the two forms of this protein provides a step towards understanding the mechanisms of transmembrane signalling. It also gives helpful information for the development of target-seeking microorganisms.

The aspartate chemotaxis receptor is a dimeric (two-subunit) molecule with an external aspartate binding site connected through the molecule's transmembrane region, or domain, to the effector domain inside the cell. The binding of aspartate to the extracellular domain causes a conformational change that is transmitted through the transmembrane domain to the effector domain, which changes its conformation to signal the bacterium's flagella to rotate in such a way that the organism swims toward the attractant.

Sung-Hou Kim of the LBL's Chemical Biodynamics Division, Daniel Koshland, Jr., of the UC Berkeley Department of Molecular and Cell Biology, and their colleagues used synchrotron x-ray crystallography to determine the three-dimensional structure of the receptor's aspartate-binding domain at a resolution of 2.4 Å (1 Å equals about 4 billionths of an inch), and that of the aspartate/receptor complex at 2.0 Å. Each subunit consists of a bundle of four structures called alpha helices.

The aspartate binding site is located more than 60 Å from the presumed membrane surface and is at the interface of the two subunits. Aspartate binds between two alpha helices of one subunit and one alpha helix of the other in a highly charged pocket. Comparison of the structure of the aspartate-binding domain to that of the aspartate complex reveals that the subunits appear to change orientation relative to each other when binding occurs, suggesting that such simple motion may be the way cells transmit information about the environment to their interior.



The aspartate chemotaxis receptor of the bacterium Salmonella Typhimurium *perceives the presence of aspartate and signals the cell to move toward an increasing concentration of this nutrient. The photograph above shows the three-dimensional backbone structure of this receptor, including the modeled transmembrane region (gold) as it may be in the cell. Recearchers at Lawrence Berkeley Laboratory determined the structure by x-ray crystallographic methods. Such research is useful for developing target-seeking microorganisms.*

New Risk-Assessment Strategy for Indoor Air Pollutants

(Joan Daisey, 510/486-7491)

Researchers with LBL's Energy and Environment Division and the School of Public Health at the University of California, Berkeley, have linked a simple cancer model to a model for the bodily absorption, distribution, metabolism and excretion of benzene. The resultant integrated model, based on fundamental biology, represents an important step toward improving assessment of human health risks associated with indoor air pollutants.

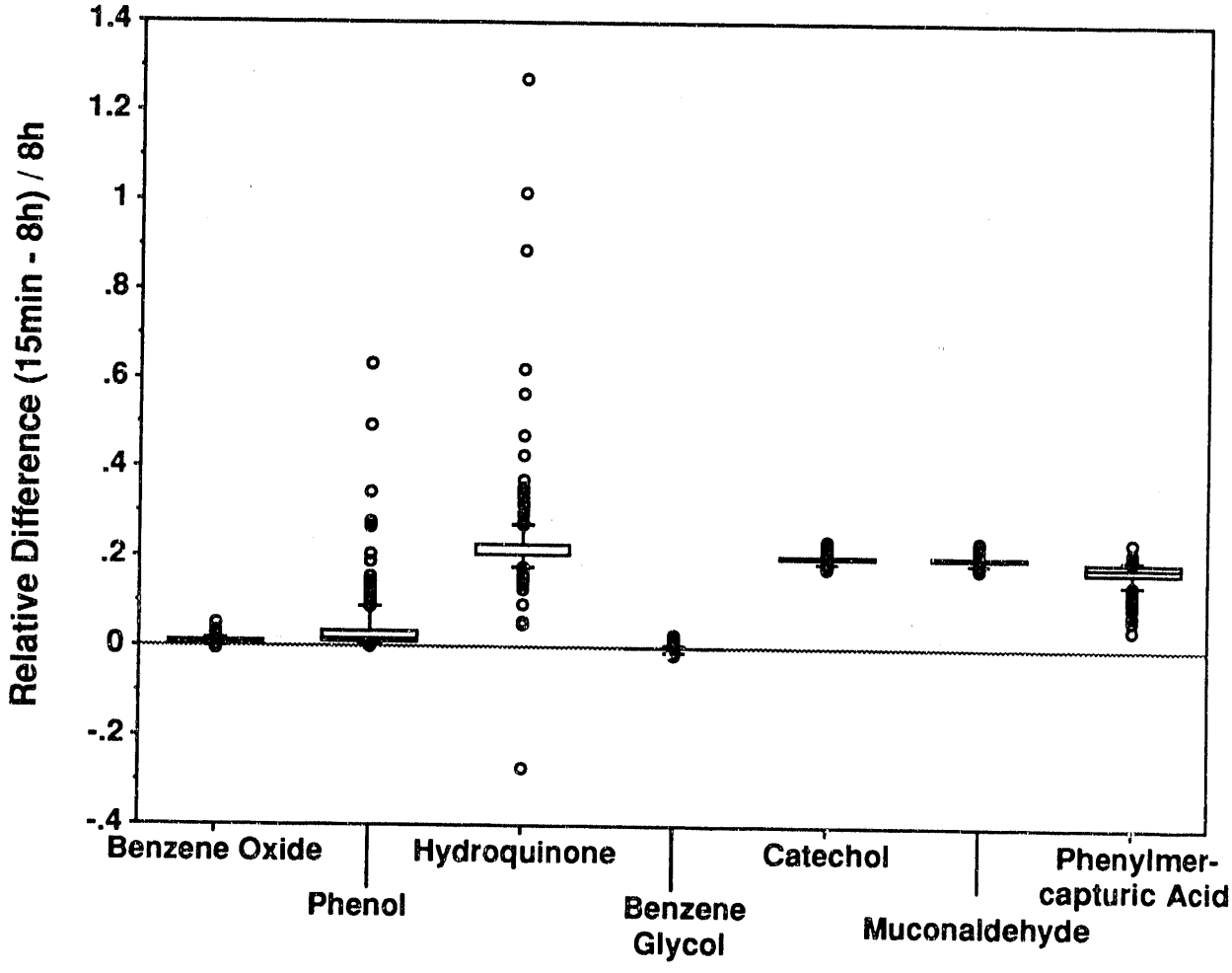
The work was carried out by an interdisciplinary, inter–institutional research project established in 1990 and led by Energy and Environment researcher Joan Daisey in collaboration with Robert Spear and Martyn Smith of UCB. The long-term goal of the project is to advance environmental health-risk assessment by placing it on a fundamental scientific basis.

Current methods for determining risks from exposure to toxic chemicals at levels found in indoor air are scientifically flawed and may overestimate risk by orders of magnitude. The new models under development will make it possible to use data from laboratory experiments and industrial settings, in which exposures to toxic chemicals are very high, to predict adverse health risks from exposures to such chemicals at the low concentrations typically encountered by humans in indoor environments. In addition, models based on human physiology will allow input of biological measurements made in people with known exposures to benzene. This further refinement of the models will increase the ability to predict the fate of benzene in the body and to assess the potential for damage at given exposure levels.

Benzene was selected as the first compound for study because much is known about it and because it emerged as a high-risk indoor pollutant from previous work at LBL. The initial model, developed using data from experiments with rats, is now being expanded to include data from human exposures. Work is also in progress to improve the integrated model by taking into account benzene metabolites and by incorporating a more complex, biologically based cancer (leukemia) model.

For the cancer part of the expanded model, the researchers will be using data from a new human somatic mutation assay, the HLA-A assay, which detects a number of important mechanisms of carcinogenesis in human white blood cells. The assay can be used both for monitoring human populations exposed to toxic pollutants and for studying mutation of cells in culture.

Dose-Rate Effects for Benzene Exposure



Differences in total amount of benzene metabolites formed in the body per day, after exposures at 1 ppm for 8 hr compared to peak exposure at 32 ppm for 15 min, based on PBPK model simulations. Concentrations of hydroquinone, catechol, muconaldehyde and phenylmercapturic acid were increased by 20% on average for the peak exposure. The first three of these compounds are suspected to be directly involved in the carcinogenicity of benzene.

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