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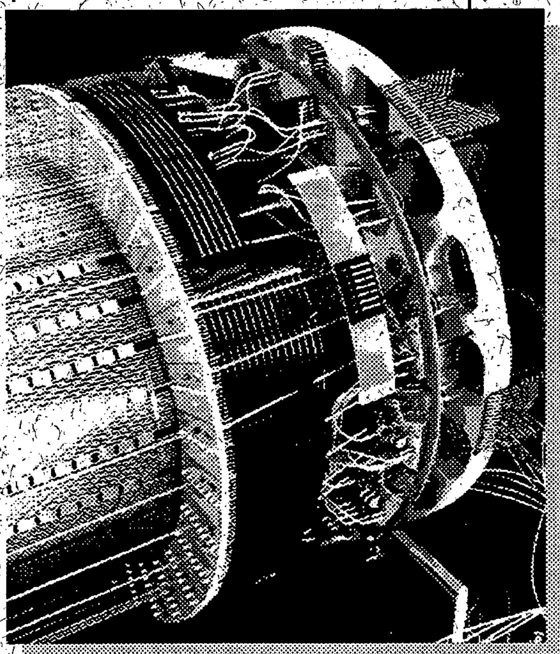

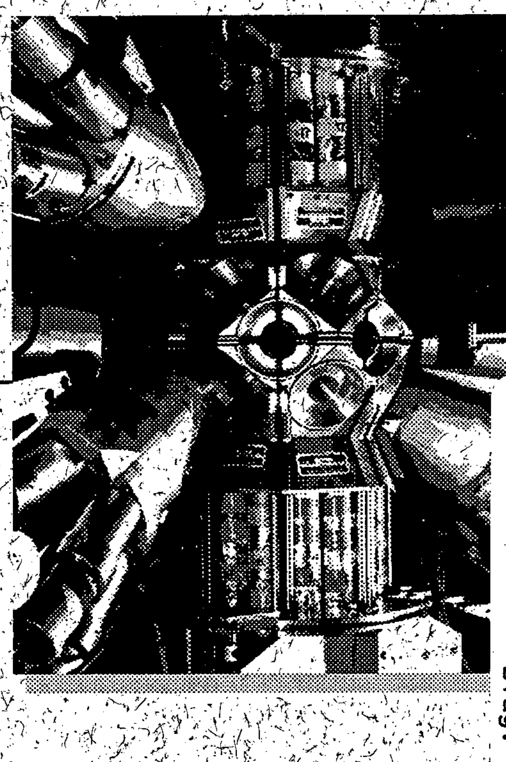

LBL

Partnership Opportunities at Lawrence Berkeley Laboratory

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CATALOG OF RESEARCH ABSTRACTS

Partnership Opportunities at Lawrence Berkeley Laboratory

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Lawrence Berkeley Laboratory
University of California
Berkeley, CA 94720

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INTRODUCTION

The 1993 edition of Lawrence Berkeley Laboratory's *Catalog of Research Abstracts* is a comprehensive listing of ongoing research projects in LBL's ten research divisions. Lawrence Berkeley Laboratory (LBL) is a major multi-program national laboratory managed by the University of California for the US Department of Energy (DOE). LBL has more than 3000 employees, including over 1000 scientists and engineers. With an annual budget of approximately $250 million, LBL conducts a wide range of research activities, many that address the long-term needs of American industry and have the potential for a positive impact on U.S. competitiveness.

LBL actively seeks to share its expertise with the private sector to increase U.S. competitiveness in world markets. LBL has transferable expertise in conservation and renewable energy, environmental remediation, materials sciences, computing sciences, and biotechnology, which includes fundamental genetic research and nuclear medicine.

This catalog gives an excellent overview of LBL's expertise, and is a good resource for those seeking partnerships with national laboratories. Such partnerships allow private enterprise access to the exceptional scientific and engineering capabilities of the federal laboratory systems. Such arrangements also leverage the research and development resources of the private partner. Most importantly, they are a means of accessing the cutting-edge technologies and innovations being discovered every day in our federal laboratories.

For more information, please contact:

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How To Work with Lawrence Berkeley Laboratory

Technology transfer at LBL is administered by the Technology Transfer Department.

The role of the Technology Transfer Department is to make technology and expertise developed at LBL available to industry.

Technology transfer depends on communication between those generating knowledge and those able to put it to use. The Technology Transfer Department acts as a focal point to foster productive relationships between LBL research programs and the private sector. If you have questions regarding research areas of interest or wish to have an answer regarding working relationships with LBL, start with the Technology Transfer Department. Call or visit the Technology Transfer Department to

- **Pinpoint research areas of common interest**
- **Negotiate rights to LBL's intellectual property**
- **Discuss current patent and copyright licensing opportunities**
- **Set up meetings with specific investigators; arrange LBL tours**
- **Learn the names of people in charge of sponsorships, collaborative projects, and staff-exchange programs**

As part of the Technology Transfer Department, the Office of Sponsored Research Administration (OSRA) is the administrative liaison for sponsored research and research collaborations between LBL scientists and the private sector.

If your company would like to use LBL facilities or have work performed by or jointly with LBL investigators, contact OSRA. OSRA's experienced staff coordinates proposal submissions and contract negotiations. Call or visit OSRA to inquire about

- **Research performed by LBL scientists under sponsorship by industry**
- **Use of LBL User Facilities by industry personnel**

- **Collaborative research—sharing of LBL and industry costs, facilities, equipment, or research capabilities**
- **Industry support of LBL researchers through gifts, grants, or fellowships**
- **Proposal submissions**
- **Contract negotiations**

Choosing Your Technology Transfer Vehicle

LBL's research produces innovative technologies and inventions, many with commercial value. LBL's resources, expertise, and project-oriented teams can help make your company's R&D effort more effective. From acquiring written information on a special project to establishing research collaborations or licensing available technology, there are many ways to work with Lawrence Berkeley Laboratory—many ways to leverage your research activities.

Licensing New Technology

LBL's work produces a large number of innovative and inventive discoveries, many of which have commercial value and are available for licensing. To discuss licensing possibilities, ideas for new technology applications, markets, or products—*contact the Technology Transfer Department.*

Sponsored Research

A company may sponsor LBL scientists to perform specific research compatible with LBL's research in the company's field of interest. The unique equipment and specialized staff expertise at LBL provide research opportunities that would not otherwise be available. *Discuss research concepts with scientific staff. To coordinate efforts—contact OSRA.*

Visitor/Staff Exchanges

University and industrial scientists may visit LBL to conduct research. Each year DOE sponsors a Laboratory-Industry Exchange Program, offering opportunities for researchers from industry and DOE laboratories to work in areas of mutual interest and benefit at one another's sites. *For more information about this program—contact the Technology Transfer Department or Research Division. For visits or staff exchanges that require a contractual relationship—contact OSRA.*

Collaborative Research and Development Agreements (CRADA)

Some of the most innovative technology transfer at LBL today involves collaborative projects with industry. In collaborative research arrangements, DOE and industry jointly sponsor a research project. Costs, personnel, facilities, equipment, or research capabilities may be shared for mutual benefit. This provides industry with an excellent way to leverage their research activities. *Discuss technical points with scientific staff. Contact OSRA for proposal, contractual, and administrative matters. Discuss intellectual property arrangements with the Technology Transfer Department.*

Gifts and Graduate Support

Gifts to LBL are received in the form of equipment, research materials, and funds. Gifts are undesignated or are designated for a particular research area or research group. A fellowship may be given to support a graduate student's research. If a company is interested in acquiring expertise in a particular area, a specific student may be supported with the intention of bringing the student into the company after graduation. This is an efficient way to transfer technological expertise from LBL. *To coordinate gifts and fellowship support—contact OSRA*

User Facilities

Certain facilities at LBL and other DOE laboratories are considered "National User Facilities" offering unique opportunities. LBL has a range of such facilities available to qualified investigators from universities, industry, and government. They have national Program Advisory Committees to review research proposals by qualified investigators. DOE allows proprietary work by industry under some circumstances. Many sponsored projects take advantage of these facilities. *User Facility arrangements are administered through OSRA.*

Getting Started

If you have not worked with LBL, these four basic steps will help you choose the technology transfer vehicle that will work best for your company.

Identify a need

- A company identifies a problem it needs solved or identifies a general subject area in which it wants to broaden its expertise.

Make contact

- The Technology Transfer Department offers help in determining access to LBL technology.
- A direct relationship is developed with the scientist or division.
- OSRA offers the company guidance or contractual approaches.

Initiate discussion

- A dialogue between the company and LBL technical managers is initiated.
- Contractual and administrative issues are discussed with OSRA.
- Intellectual property matters are discussed with the Technology Transfer Department.

Choose a vehicle

- A choice is made regarding a technology transfer method that will produce the desired results.
- Administration of industrially sponsored research and research collaboration projects are finalized with OSRA..

BIOSCIENCES

LIFE SCIENCES DIVISION

Department of Cell and Molecular Biology

The Department of Cell and Molecular Biology pursues multidisciplinary basic research in the broad areas of gene expression and molecular genetics. Its activities encompass a wide range of research topics. Macromolecular structure is studied by using electron crystallography; mechanisms of carcinogenesis are investigated; and basic radiation biology is also studied. All of the efforts, however, are united by their ultimate focus on understanding how an organism's genomic program is expressed and regulated, how it maintains itself, how it is affected by radiation and toxic substances, and how it goes wrong in tumorigenesis.

Long-Term Biological Effects

EDWARD ALPEN

The goal of this project is to evaluate the relationship between the linear energy transfer (LET) of radiation and its carcinogenic potential. The RBE at low doses of high-LET radiation is needed to estimate risk coefficients for induction of radiogenic cancer in human beings. We are evaluating low dose carcinogenesis from high-LET radiation, using the murine Harderian gland as a test system. This system is useful because tumor prevalence can be estimated at low doses in the presence of relatively low background tumor rates. We are using non-stopping charged particles (particles in the plateau region of the Bragg peak) at any given LET from < 1 to > 1000 keV/µm, assuring a very well-defined LET for the irradiations.

The Harderian gland tumorigenesis dose-response curves for heavy ions have been defined for a wide range of LETs, and we have determined the initial slope of the dose-response curve for ^{60}Co gamma rays and for a number of ions. The RBE does not decrease at very high LET as expected. Preliminary data show that fractionated doses of ^{56}Fe ion irradiation have little or no effect. RBE values for high-LET radiation are at least an order of magnitude higher than for other late or acute effects or for *in vitro* transformation. There is no reduction of this effect at very high LET.

We plan to increase the data at very high LET to estimate at what value of LET there is evidence of a decreased effectiveness. We will measure the clonogenic survival of Harderian gland cells with high-LET radiations to permit an estimation of transformation frequency. We will also develop data on fractionation effects at high LET and examine the role of prolactin in the promotion of tumors as a function of LET.

Tumorigenic Potential of HZE Radiation
EDWARD ALPEN

Exposure to radiation of human beings traveling outside of the Earth's magnetosphere is of significant importance on missions to the Moon and beyond. HZE particles are able to penetrate the space craft and still have residual ranges adequate for penetration of the human body.

For this study, we will use the mouse Harderian gland, which is an ideal organ to study radiogenic cancer produced by both high-LET (linear energy transfer) and low-LET radiations. The gland is a secretory epithelium arranged in a tubulo-alveolar structure. Naturally occurring neoplasms in this gland are rare benign adenocarcinomata (2.7% lifetime incidence). Hormonal promotion of neoplasia by implanted pituitary glands enhances the expression of radiation-induced tumors and increases malignancy of the neoplasms. The Harderian gland system has been widely used in the study of chemical carcinogenesis and has found wide support and application as a test system for estimation of risk coefficients for human beings.

We irradiate mice and implant two pituitaries within 24-27 hours of irradiation. Sixteen months later, the prevalence of Harderian gland tumors is measured histologically.

Stromal Influence on Expression of Preneoplasia
MARY H. BARCELLOS-HOFF

Carcinoma of the breast, which is a major neoplastic disease of women, often has a strong stromal component. Some data indicate that an abnormal stroma may precede the development of malignancy in familial breast cancer. The documented sensitivity of the human mammary gland to radiation-induced cancer is noteworthy in this context as well. Radiogenic cancer is distinguished from other breast cancers by its stromal response. The involvement of the stroma is indicated by changes in the quality of both interstitial and basement membrane ECMs following radiation exposure, which can lead to clinically relevant fibrosis. The widespread use of x-rays in diagnostic applications make it relevant to study the basis of this sensitivity. We hope to identify the stromal factors that influence an initiated epithelial cell to express its altered phenotype.

We will investigate stromal influences on the expression of preneoplasia *in vivo* using the unique model of the mammary gland stromal fat pad. The distinctive architecture of the mammary gland makes it possible to easily separate the epithelium from stroma, leaving the fat pad intact for subsequent transplantation of initiated epithelial cells. We will irradiate the recipient stroma or subject them to chemical inhibition of ECM deposition to establish a model of abnormal stroma in the neoplastic process. We will evaluate epithelial outgrowths in damaged and normal stromal fat pads for the frequency of preneoplastic lesions as characterized by clonal expansion (hyperplasia) or focal lesions that exhibit abnormal cytological characteristics (dysplasia) and their progression to neoplasia. We will analyze the character of the ECM produced by irradiated cells *in vivo* and in culture and by tissue treated with ECM inhibitors using histological, immunochemical, and molecular assays. Given the significance of the extracellular milieu in maintaining normal tissue-specific function, it is reasonable to consider that an abnormal stroma, mediated via alterations in the ECM, may promote the expression and progression of preneoplasia.

Three-Dimensional Crystals of Cytochrome Reductase, a Membrane Protein
EDWARD BERRY

X-ray diffraction data provide the main source of three-dimensional (3D) structure information at atomic resolution for proteins. While a great deal of information is potentially available from this technique, its application requires the ability to prepare crystals of size and order suitable for x-ray analysis. This has proved especially difficult for membrane proteins.

Cytochrome reductase (the cytochrome bc_1 complex) is a membrane protein complex which makes up the middle segment of the mitochondrial respiratory chain. The respiratory chain is responsible for biological oxidation and for conservation of the energy released in the form of a proton electrochemical potential gradient across the mitochondrial inner membrane. Energy from this gradient is then used to synthesize ATP or to do work by transporting substances across the membrane. In recent years a number of mitochondrial myopathies have been shown to be due to defects in the mitochondrial electron transport chain and in some cases in cytochrome reductase.

We have recently developed a procedure for preparing crystals of bovine heart mitochondrial cytochrome reductase. In addition to needle-shaped crystals, which have been reported by others, we have obtained crystals in the shape of hexagonal bipyramids. One can produce these with a good rate of success by using a seeding technique. It seems likely that these crystal forms, when conditions for growth are optimized and crystals are larger, will prove suitable for x-ray diffraction analysis and eventually lead to a 3D structure of the complex at atomic resolution.

The purpose of this research is to find conditions for growth of such suitable crystals. Our efforts will focus on improving the homogeneity of the purified enzyme, choosing additives such as specific inhibitors or substrates that may stabilize one particular conformation of the enzyme, and optimizing conditions of crystallization (temperature, ionic strength, protein concentration, precipitant species and concentration, detergent, and specific ions). We will monitor results by the size of the crystals obtained and by x-ray diffraction intensity and resolution. Once suitable crystals are available the effort will shift to collection of diffraction data and obtaining suitable heavy atom derivatives for subsequent structure determination.

Mechanism of Tumor Promotion
MINA BISSELL

It is now well accepted that viral carcinogenesis, analogous to chemical carcinogenesis, is a multistep process where at least two or more events are required to induce transformation. The larger questions of how carcinogenic insults converge to free a cell from its normal constraints and what are the underlying common steps now need to be answered. We have argued in the past that to understand malignancy one needs not only to define the oncogene or the initial carcinogenic damage but also to define the steps that lead to the loss of microenvironmental control. Having clearly established that potent oncogenes such as *src* can be expressed in their active form (phosphotyrosine positive) but be contained within a normal tissue context, we have sought to define the nature of these constraints. Two findings have focused our attention on the possible role of factors that are involved in wound healing and angiogenesis: a discovery in our laboratory that TGF-ß induced by wounding is a cocarcinogen in RSV-tumorigenicity in the chicken; and the discovery made both in our lab in chick embryos and by others in mice that endothelial cells are a specific target for oncogene-induced tumors *in vivo.*

We are testing the hypothesis that endothelial cells contain factors that are analogous to wound-healing factors. These include TGF-ß, bFGF, and *ets*. We are making replication-defective retroviruses which express both active v-svc and either bFGF, TGF-ß, or *ets*. The correct combination should cause tumors in non-endothelial tissues of the limb if our hypothesis is correct. Furthermore, antisense constructs to these genes should delay endothelial transformation. Additionally, we have succeeded in developing a culture model for embryonic chick limb cartilage where the behavior of RSV infection *in vivo* is simulated in culture. The use of this culture system should aid our ability to define the mechanism by which sarcoma transformation is suppressed.

We also have defined the differential expression pattern of 9E3 (*gro*) gene *in ovo*, at the wound site and tumors, have succeeded in making peptide antibodies to the protein, and have shown the gene to be involved in cell cycle regulation.

Molecular Carcinogenesis
MINA BISSELL

The major aim of this task is to understand the molecular mechanisms underlying tissue-specificity, which is one of the most fundamental problems in modern biology. How these mechanisms are subverted in cancer initiation and progression are intimately linked to our understanding of how tissues remain normal. The mammary gland provides a versatile model for such studies because we now know how to induce these cells to differentiate with precision in tissue culture. We also have specific molecular markers to ask a number of fundamental questions. In addition, breast cancer afflicts one woman in eleven in the United States, and breast is a radiosensitive tissue. The model system, therefore, is important for basic fundamental studies as well as for clinical application. We have succeeded in producing complete functional "alveoli" with capacity for vectorial secretion in tissue culture. The morphology, size, and biological capability of these alveoli bear an uncanny resemblance to the alveoli of the lactating gland. We showed last year that in the cases where functional differentiation is induced in the absence of exogenous basement membrane (BM), there is endogenous elaboration of BM, the appearance of which correlates precisely with increase in milk production. We have made a number of significant advances very recently. 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) ß-casein gene (attached to choramphenicol acetyl transferase; CAT) contain sequences that are dramatically regulated by substratum and hormones: we have further shown that there is indeed an ECM response element which is tissue-specific and functions also with heterologous promoters. In addition, we now have clear evidence that embedding cells in BM can induce milk protein expression in the absence of cell-cell interaction polarity. We have shown that ECM transmits signals through ECM-receptors (integrins) because blocking antibody against integrins blocks function. Thus ECM, in conjunction with hormones, is necessary to direct transcription of tissue-specific genes, a finding of fundamental importance also for expression of foreign genes. We have made cDNA libraries of cells on plastic and ECM. Using subtractive hybridization, we are isolating genes that are differentially expressed.

Having established the normal regulatory mechanisms, we have begun a systematic study of growth regulation in mammary cells to define how growth and differentiation are linked and how they are altered when cells are transformed with oncogene-bearing virus. In addition, we have begun to apply our extensive knowledge of mammary differentiation in the rodent to normal and malignant human breast cells in primary culture.

Molecular Mechanisms of Cell Effect
ELEANOR BLAKELY

The goal of this project is 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. To elucidate relevant mechanisms of action, we are measuring the dose-dependent 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. We are examining how the chromatin break, which may be a complex lesion representing multiple strands from DNA-base or DNA-sugar damage, how the cell modifies chromatin, and how this type of damage affects the cell's ability to deal with additional insults. We characterize chromatin damage and restitution using the premature chromosome condensation (PCC) technique to rapidly evaluate early yields of DNA damage. We follow the chromatin rejoining kinetics and quantitate the resulting aberration yields that are inherited by daughter clones. We have shown that there is an LET-dependent variation in the efficiency for the production of initial chromosome breakage per unit dose. We have also shown that the distribution of breaks becomes progressively overdispersed with an increase in the proportion of non-rejoining events as the LET increases. An *in situ* hybridization technique coupled to fluorescent staining of PCC spreads has confirmed the linearity of the dose response for initial chromatin breakage in a single human chromosome #2 in a human-hamster hybrid cell and has allowed an assessment of a class of misjoining events. Recent progress has been made in quantitating particle-induced DNA-protein crosslinks as a function of LET; investigating the nature of insistent chromatid and chromosomal aberrations appearing in first and second generations arising from particle-irradiated populations; and observing a novel LET-dependent change in the rate of new protein synthesis in cells post-irradiation. The fact that there are differences in the synthesis of selected groups of heat-induced proteins post-neon- or x-irradiation may be significant to our understanding of genetic control in response to DNA damage from ionizing radiations of different quality. Additional experiments with a cell-cycle dependent, DNA double-strand break repair-deficient mutant XR-1 cell have been initiated. These studies will allow us to investigate genetic control of particle-induced double-strand break repair at different phases of the cell cycle in the same cell system and to propose genetic mechanisms of action that are triggered by specific classes of DNA damage from ionizing radiation.

Anti-Proliferative Mechanisms in Growth Control
JUDITH CAMPISI

Cell proliferation *in vivo* is precisely related by both positive and negative signals. Soluble growth factors provide important positive signals and exert acute control over the expression of several cell-cycle-dependent genes, including the c-fos and c-myc proto-oncogenes. Less is known about the nature and mechanism of negative growth signals. This project explores the mechanism(s) by which cell contacts and interferons suppress the proliferation of fibroblasts. Using primary and established cells in culture, and integrated techniques of cell biology, biochemistry, and molecular biology, we will determine how these negative signals affect growth factor signal transduction and proto-oncogene transcription, mRNA metabolism and translation. These studies will provide important information regarding the homeostatic mechanisms that may operate to ensure the balanced growth that is necessary for the maintenance of complex tissues.

Cellular Senescence and Control of Gene Expression
JUDITH CAMPISI

Although 30 years of gerontologic investigation utilizing various cell culture model systems has provided many tantalizing clues regarding the general loss of cellular response to physiologic signals, the mechanism of cellular aging remains quite obscure. We propose to extend studies undertaken 2 years ago, employing a powerful combination of molecular biology and cell culture to advance our understanding of age-associated changes in cellular proliferative capacity and differentiated function. The project draws upon the different perspectives and expertise of four principal investigators and upon extensive data generated during the first phase of this work. Dr. Gilchrest's project will use early passage human keratinocytes and fibroblasts derived from skin biopsies of healthy newborn, young adult, and old adult donors to determine whether age-associated loss of growth factor responsiveness is attributable to reduced expression of genes whose products are required for cell division and/or to a more advanced state of cellular differentiation. Dr. Campisi's project will use human fetal lung fibroblasts to define the mechanisms by which changes in the expression of pHE-7, histone, c-fos, and ornithine decarboxylase occur in late passage WI-38 cells. Dr. Hiller's project will seek to define further the biochemical defects that underlie changes in calcium-mediated signal transduction and gene expression that occur following mitogenic stimulation of old vs. young murine lymphocytes. Dr. Dobson, a new member of the program project team, proposes to study differentiation-associated gene expression in the 3T3F442A murine pre-adipocyte cell line aged *in vitro* and in short-term adipocyte cultures obtained from young, old, and old diet-restricted mice. These separate projects will share molecular biology and administrative core facilities and will interact extensively with regard to both technical and conceptual issues. It is anticipated that the proposed studies will provide major new insights into cellular senescence generally, as well as age-associated changes in the skin, immune system, and adipose tissue of intact organisms. Furthermore, the proposed studies will permit corroboration of findings among widely differing model systems.

Growth Regulation in Normal and Transformed Cells
JUDITH CAMPISI

In multicellular organisms, cell proliferation is regulated by the cellular environment and the differentiated state of the cell. The cellular environment and state of differentiation determine which genes are expressed by a given cell and frequently how particular genes function and are regulated. Common features of tumor cells are their insensitivity to environmental signals and their abnormal differentiated characteristics.

Much of our understanding about cell proliferation derives from studies of cultured fibroblasts. These studies have established that growth factors are important positive, external regulators of cell growth and that they act ultimately by regulating gene expression. Genes that are induced by growth factors include several proto-oncogenes which act as positive intracellular growth regulators. Fibroblasts have provided valuable paradigms for understanding growth control in other cell types, but the growth control mechanisms for a number of cell types are still largely unknown. In particular, little is known about how proliferation of differentiated epithelial cells is regulated, despite the fact that most human cancers are epithelial in origin.

This proposal examines proto-oncogene expression, immortalization, and transformation in lung epithelial cells derived from adult and neonatal rats. We will define the pattern regulation and function of growth-regulated and differentiation-specific gene expression in primary rat epithelial cells and in cell lines that we have derived by immortalization with wild-type and mutant SV-40 T antigens. We will focus on two types of cellular genes, the c-fos proto-oncogene and the vimentin and keratin cytoskeletal genes. Our preliminary data suggest that the primary cells do not express c-fos; we will define the basis for this repression and explore the role of T antigen in alleviating the repression and explore the role of c-fos expression in regulating the proliferation of primary and immortal epithelial cells. Our data also suggest that immortalization alters cytoskeletal gene expression, and we will examine the role of T antigen in these alterations and explore the consequences of these changes for cell proliferation.

These studies will provide a deeper understanding of relationships between growth control and differentiation in a well-differentiated epithelial cell type.

Mechanisms of Insulin and Insulin-Like Growth Factor Function and Regulation

JUDITH CAMPISI

Diabetic children with a primary deficit in insulin (IN) production commonly show a parallel deficit in circulation insulin-like growth factor (IGF) levels and a general retardation of growth. IN and IGF are related polypeptide hormones that bind to distinct, albeit related, cell surface receptors. A large number of studies suggest that most, if not all, mammalian cells—both *in vivo* and in culture—require one or both of these hormones for optimal growth and proliferation. Despite a reasonably good understanding of the biochemistry of IN and IGF and their interactions at the cell surface, the molecular mechanism(s) by which these hormones regulate cell proliferation remains poorly understood. This proposal focuses on two aspects of the role of IN and insulin-like growth factor-I (IGF-I) in the control of normal and abnormal cell proliferation.

First, we have found that IN or IGF-I stimulates the expression of a necessary, positive-acting proto-oncogene (c-ras-Ha) in cultured murine fibroblasts that have been made proliferatively quiescent by depriving them of serum growth factors. The c-ras-Ha proto-oncogene is unique in this regard. The expression of many genes needed for the proliferation of these cells—including two additional, necessary proto-oncogenes (c-fos and c-myc)—are not stimulated by IN or IGF-I, but rather are regulated by other polypeptide growth factors such as the epidermal or platelet-derived growth factors. Because much is known about the structure of the c-ras-Ha gene, it provides an excellent opportunity to study how an important cellular gene is regulated by IN and IGF. We will analyze the primary and processed transcription products of the c-ras-Ha gene in murine and human fibroblasts and identify the nuclear site(s) at which IN and IGF-I exert their effects.

Second, we have identified a chemically transformed derivative of our murine fibroblasts that appears to produce an autocrine IGF-I, or IGF-I-like, growth factor. This autocrine factor is at least partially responsible for the unregulated growth control shown by these cells. We will more completely characterize the autocrine factor. We will also begin studies to determine whether the basis for its effects are the result of transcriptional or post-transcriptional mechanisms.

Both aims of this proposal will use the techniques of cell and molecular biology and will provide a molecular framework for understanding the mechanisms of IN and IGF-I function and regulation.

A West Coast Facility for IVEM
W. ZACHEUS CANDE

We wish to establish a West Coast Regional Facility for Intermediate Voltage Electron Microscopy (IVEM) at the University of California, Berkeley. The IVEM facility will be integrated into an interdepartmental electron microscopy service laboratory (EML) already existing on the Berkeley campus. The EML already serves the large Northern California biological community as a *de facto* regional facility for training and research in electron microscopy. Research activities of the IVEM facility include core research and development, collaborative research, and service to biomedical research investigators outside the resource. Core research deals with several aspects of IVEM methodology: construction and testing of a high-resolution cold stage, to be used in several research projects; development of high-resolution imaging techniques and their application to the analysis of two-dimensional macromolecular assemblies; integrated use of video-enhanced light microscopy and IVEM on the same specimen; exploration of improved cryo-electron microscopic procedures as applied to IVEM; and development of computer-assisted procedures for the retrieval and storage of structural information obtained with the IVEM. Collaborative research will involve the application of image analysis to a three-dimensional measurement and reconstruction problem. Further collaborations are expected to evolve as IVEM technology becomes known to and used by others in the service area. Service will be provided to all interested biomedical researchers on the West Coast. A representative sample of research projects has been selected for initial review. It is anticipated that the IVEM facility will provide a catalytic environment for the development of this emerging technology and a framework for fruitful collaborations.

Radiological Physics and Chemistry
ALOKE CHATTERJEE

Several types of damage can be inflicted on DNA by ionizing radiation. DNA contains the important genetic codes, and hence its damage, if unrepaired, can have serious consequences. In this project the long-term goal is to correlate the physical and chemical changes that precede any specific type of damage to DNA with observable biological consequences to a cell. Ionizing radiation can cause strand breaks (single and double), base alterations, released bases, DNA-protein crosslinks, DNA-DNA crosslinks, etc. The short-term goal of this project is to correlate double-strand breaks with mutation (specific types) and transformation frequencies as a function of dose for different qualities 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. Each of these radiation qualities has a characteristic physical pattern of energy deposition (track structure) which is primarily responsible for chemical changes which can be sometimes qualitatively and quantitatively different. In addition the proximity of various types of damages (which is a function of radiation quality) on DNA may have a strong influence on the observable biological effects. In the last several years, we have developed a mechanistic theoretical model based on basic physical and chemical laws which can quantitatively estimate yields of strand breaks (single and double), base alterations by water radicals, and base deletions for any quality of ionizing radiation. Now our approach is to use 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. Modeling of transformation effects is being initiated using available experimental data on partially transformed cell lines such as C3H10T1/2 and NIH3T3. We seek to determine if is it true that a minimum of two mutational events are needed for radiation-induced neoplastic cell transformation. We hypothesize that for partially transformed cell lines, only one specific mutation is required for cells to undergo activation. Since it is becoming clear from experimental measurements that it is highly improbable to activate proto-oncogenes directly, we are focusing on events which lead to deletion of large DNA segments containing suppressor genes.

Training and Basic Research Related to Health Effects of Exposure to HZE Particles in Extended Missions
ALOKE CHATTERJEE

Several distinct but highly interactive research programs which will provide training in Radiation Health are presented by a Consortium of the Lawrence Berkeley Laboratory and Colorado State University. The focus of these programs is directed toward assessment of the risk of carcinogenesis and cataractogenesis associated with protons and HZE exposure to humans during extended space missions. Theoretical studies will allow assessment of initial DNA damage for all HZE particles of interest. Experimental studies will address DNA repair, mutagenesis, and cellular transformation. Enzymatic repair processes will be characterized in normal and mutant human cells and then compared with the repair responses of rodent cells. Mutagenesis research will be conducted with two different cell systems, one human and one rodent, to evaluate mutational risks under different genetic constraints and to determine the effect of genetic linkage and of DNA repair capacity on types of mutations recovered. Transformation of mouse mammary epithelial cells will be quantitated *in vitro*, and the ability of the transformed cells to undergo neoplastic progression in the mouse will be investigated, including a determination of the effect of tissue environment on progression. Applied research will involve an assessment of cataractogenesis risk through a retrospective analysis of available human data from uveal melanoma patients treated with helium ions at Lawrence Berkeley Laboratory. The human data will be compared with an extensive database available from animal cataractogenesis studies. Integration of the results obtained through basic research for the purposes of human risk assessment will be done as a part of the overall extrapolation procedures across species for carcinogenesis and cataractogenesis. This research effort will be directly coupled with the training of students and postdoctoral candidates.

Radioassay of Erythropoietin
GISELA CLEMONS

The objectives of this project are to investigate the interaction of the hormone erythropoietin (Ep) with its respective receptor(s) at the cellular and molecular levels and study the Ep gene expression. We intend to characterize the Ep receptor with respect to affinity, capacity, and determination of the molecular size of the receptor. We will carry out dissociation and rebinding studies in isolated membrane preparations in order to avoid intracellular metabolic events and secondary reactions. We will study phenomena such as internalization of the receptor moiety, possible up- and down-regulation, and degradation in intact mouse leukemic cells and compare them with normal erythroid spleen and bone marrow cells. We will also investigate the dependence and/or influence of other differentiating and metabolic hormones on Ep receptor gene expression. For example, certain hematological disorders in humans, such as aplastic anemias, are manifested by high endogenous Ep levels to which the bone marrow is unresponsive unless androgens or corticosteroids are administered. This steroid-hormone-dependent erythropoiesis appears to be due to hormone-dependent Ep receptor gene expression. We will investigate the ontogeny of the Ep receptor as a function of other hormones in the newborn rat, in which erythropoiesis switches from the liver to the bone marrow neonatally, a time when other developing tissues are also critically dependent on the presence of a variety of hormones. We intend to identify the cells of origin of Ep in renal tissue with *in situ* hybridization using the cDNA probe for mouse Ep. We will study the Ep gene expression at the renal level as a function of oxygen availability in relation to the sexual genotype of the animal. We will also apply the *in situ* hybridization technique to the mouse submaxillary gland (SMG) in an attempt to clarify whether the high Ep concentrations observed in this tissue are the result of synthesis (Ep gene expression) or the result of accumulation (Ep receptor gene expression). We will investigate whether Ep in SMG is a source of extrarenal Ep during steady state. We also plan to test secretory ability *in vitro* with respect to basal release, to determine whether and how it can be altered by adrenergic or cholinergic agonists and antagonists.

Red Cell Band 4.1: Developmental Changes in RNA Splicing

JOHN CONBOY

As part of a long-term commitment to understand the structure and function of the mammalian erythrocyte, we are studying the genetic mechanisms that regulate synthesis of the unique constellation of membrane skeletal proteins expressed in red cells. One of these skeletal components, protein 4.1, is a multifunctional structural protein that interacts with several other skeletal elements and exhibits a broad spectrum of molecular weights in erythroid and non-erythroid cells. Multiple isoforms of this structural protein are translated from a family of differentially spliced mRNAs that are derived from a single large 4.1 gene but have distinct tissue-specific expression patterns. This project seeks to investigate the role and mechanism of alternative RNA splicing events responsible for tissue-specific expression of protein 4.1 "spliceforms." We will investigate erythroid-specific splicing events in two regions of the gene: one regulates utilization of alternative translation initiation sites located in two different 5' exons of the gene, while a second controls expression of several structurally different spectrin-actin binding domains.

We intend to develop cellular models that reproduce developmental splicing switches in protein 4.1, such as mouse erythroleukemia (MEL) cells; we will prepare *in vitro* nuclear splicing extracts by standard techniques; and we will synthesize splicing substrates in the form of pre-mRNAs transcribed from protein 4.1 genomic "minigenes." Experimental manipulation of these critical components will allow us to characterize regulatory nucleotide sequences within the premRNA, as well as putative trans-acting nuclear splicing factors that interact with these sequences. Ultimately, we will clone putative splicing factor cDNAs using either specific probes (antibodies or oligonucleotides) or eukaryotic expression cloning techniques. We will adapt specific methodologies employed previously in characterization and cloning of DNA binding proteins, such as gel shift mobility assays, DNA-affinity chromatography, prokaryotic expression cloning with oligonucleotide probes, and eukaryotic expression cloning using biological activity assays, for use in studying putative RNA binding proteins that mediate alternative splicing.

Erythropoiesis constitutes a remarkable differentiation process in which nucleated erythroid precursor cells are extensively remodeled until they achieve the unique morphology characteristic of mature erythrocytes. The research proposed here should elucidate the mechanism(s) whereby alternative splicing effects important structural changes in red cell membrane proteins during erythropoiesis. In a broader sense, however, this proposal represents an exploration of a major question in hematology research, namely, what genetic strategies are utilized to effect the substantial changes in gene expression that underlie the dramatic phenotypic differentiation in erythropoiesis? These studies will ultimately reveal whether alternative RNA splicing is a major effector of erythropoiesis, as in the *Drosophila* somatic sexual differentiation pathway, or simply an economical genetic mechanism for changing the structure of selected membrane proteins.

Deep Space Flight Radiation Risk Assessment
STANLEY CURTIS

We are addressing two aspects of the problem of assessing the radiation risk to travelers in deep space in this project: the risk of radiation-induced cancer from the heavy galactic cosmic rays (HZE particles); and the risk of acute effects from large solar particle events. Because the galactic cosmic rays and their secondaries are highly penetrating and will traverse virtually all the cells of the body as single particles, the idea of the risk per unit fluence or *risk cross section* has been introduced. This study will develop this concept to include human cancer induction for those cancers considered to be radiogenic. We will determine what is known about the shape of the cross sections for appropriate biological end points as a function of linear energy transfer. Using heavy ion beams, we will develop a ground-based plan of studies to obtain the shape of the LET-dependence of risk cross sections for various end points passing as "surrogates" for the human situation. This approach eliminates the need to use absorbed dose, quality factors, and dose-equivalence in the risk assessment process, thus alleviating the effort and expense of obtaining data with x-rays or gamma rays at low dose. For the acute deterministic effects of erythema and the prodromal syndrome (fatigue, nausea, vomiting, and diarrhea) in large solar particle events, dose rates are such that repair of tissues during the event itself will play an important role. We will study models of cell killing which include repair as appropriate and incorporate them into calculations of the effect of shielding provided by solar "storm shelters" and regolith, thus taking into account the fact that the doses received from such large events are not truly acute doses. These studies will provide information necessary to better assess the risk and make design decisions on shielding from radiations found on space missions beyond the confines of the earth's magnetosphere.

Human Mammary Epithelial Cells, As Defined by Monoclonal Antibodies

SHANAZ DAIRKEE

The overall goals of our research are:

- To identify and characterize cellular phenotypes underlying carcinogen-induced alterations in human mammary epithelial cultures;

- To determine the relevance and relationship of these phenotypes to normal development and differentiation, and to transformation and malignant progression of the human mammary gland; and

- To apply these phenotypes toward the development of rapid, quantitative *in vitro* predictive assays for carcinogenicity in humans.

In order to make a meaningful beginning toward achieving our long-term goal, we have successfully developed a panel of novel monoclonal antibodies (moabs) which can differentiate between benzo(a)pyrene [B(a)P]-transformed human mammary epithelial cells (HMEC) and non-transformed counterparts on the basis of qualitative and/or quantitative differences in cellular antigens. Furthermore, we have determined that these phenotypes are also associated with the normal resting mammary gland and/or with malignant human mammary tissue. Thus we have essentially completed developmental aspects of an antigenic phenotype-based epithelial transformation assay.

We propose to further develop and expand this aspect of our research program toward the overall goal of understanding the biological significance of these phenotypes in the transformation of HMEC. Consequently, the following major areas will be investigated: biochemical characterization of antigens targeted by a panel of novel transformation-associated moabs; regulation of antigen expression; and determination of the earliest stage of expression of the transformation-associated phenotype during *in vitro* carcinogenesis

Structure of Cytoskeletal Elements
KENNETH DOWNING

Microtubules are an essential component of the cytoskeleton, with critical roles in the life cycle of the cell and responsibility for moving various organelles through the cell. At the molecular level, little is known about the structure of tubulin, the principle component of microtubules. We are currently engaged in determination of the structure of tubulin by electron crystallography, and the goal of this proposal is to take advantage of our new structural information to understand the mechanisms of interactions between tubulin and the many proteins and drugs with which it interacts.

We can investigate these interactions with the use of mutant tubulins which are modified at putative sites of interaction. We will study the assembly kinetics and stability of modified tubulin by time-resolved solution x-ray scattering at the Advanced Light Source. We can crystallize complexes of some important drugs with tubulin in a form that could be studied by x-ray diffraction, using the Microcrystal Diffraction Camera proposed for the ALS. These studies will provide an understanding of the functional mechanisms that give tubulin its wide range of functions and, eventually, a way to control these functions through rational drug design.

Effects of Microgravity and Heavy-Ion Radiation on Chromosome Recombination and Segregation
MICHAEL ESPOSITO

Exposure of eukaryotic organisms to the space environment has the potential for being genetically hazardous, due to the individual and combined effects of microgravity and cosmic radiation. These effects have been reported to go beyond the simple generation of mutations and involve more severe and extensive DNA damage at the level of chromosome structure and segregation during cell division. Therefore, a deeper basic knowledge of the molecular process involved in chromosome behavior during mitotic and meiotic cell division provides the background information to better analyze and understand how microgravity and cosmic radiation can generate genomic alterations in model microorganisms during space flight experiments. In previous work, we have used the common yeast *Saccharomyces cerevisiae* as a cellular and molecular model system for the study of chromosome aberrations and the preparation of the experimental space flight package. Our experiment, coded LS-001/US-2 YEAST, is part of the First International Microgravity Laboratory (IML-1) mission.

The ultimate goal of this project is the assessment of the potential genetic risk of the space environment to man. To achieve this goal, we have the following specific objectives:

- To improve the genetic sensitivity of the yeast strain system to be used for the space flight experiments;
- To continue the background basic research on the molecular mechanism of chromosome repair, recombination, and segregation during mitosis and meiosis;
- To fly our experimental system inside the Spacelab module aboard the space shuttle; and
- To conduct genetic and ultrastructural post-flight analysis of the samples.

Our method of approach to achieve these objectives employs classical genetics, recombinant DNA technology, and aspects of modern molecular biology techniques. First, our experimental strains incorporate genetic markers that permit the detection of mutation, recombination, chromosome loss, and malassortment in the space flight environment in mitosis and meiosis, and a genetic system which enables detection of the copy number of several chromosomes by the color of the colonies. Second, we will characterize the gene product of the recently cloned *CDC6* gene required for correct chromosome replication and transmission and will attempt to determine its intracellular localization and specific function during the process of nuclear division. Third, we will further characterize the strand exchange protein encoded by the *REC1* gene, which initiates recombinational repair of chromosomal DNA double-strand breaks induced by ionizing radiation. Fourth, we will perform post-flight analysis of the genetic alterations of the yeast sample using our newly developed analytical system for high-speed screening of single cell color via fluorescence-activated cell sorting.

Mitotic Recombination and DNA Repair
MICHAEL ESPOSITO

Recombinational repair of chromosomal DNA double-strand breaks during both mitosis and meiosis is an important eukaryotic DNA transaction related to human health. Recombination occurring in somatic cells is a major route for repair of DNA damage implicated in cancer etiology and is involved in development of the immune system. Recombination in meiotic cells is a prerequisite for normal meiotic chromosome segregation.

The long-term goal of our proposed research is to understand the molecular mechanisms of recombinational DNA double-strand break repair in mitosis and meiosis of eukaryotic organisms. Our experimental program involves molecular genetic analyses of hyper-recombination (*rec1-1, rec3-1,* and *rec4-1*) and hyper-recombination (*rec46-1*) mutants of *REC* genes of *Saccharomyces* identified in our laboratory, whose mutations confer drastic mitotic and meiotic phenotypes. Employing the temperature conditional *rec1-1* mutant, we have shown that *REC1* is required for expression of the Mr~170,000 major ATP independent joint DNA molecule forming protein (encoded by the structural *KEM1* gene) of mitotic cells, DNA double-strand initiated mating type switching, survival following x-irradiation, general mitotic recombination, meiosis, and sporulation. We mapped and cloned *REC1 and REC3* and demonstrated that *REC1* is an essential gene and *REC3* is a non-essential gene. We are sequencing the *REC1 and REC3* genes in order to further understand the functions of the proteins they encode. REC-fusion proteins will be purified to homogeneity by immunoaffinity chromatography and assayed for biochemical reactions implicated in genetic recombination and DNA repair.

rec1-1 KEM1 cells, grown at their permissive temperature for general mitotic recombination, mating-type switching, survival following x-irradiation, meiotic development, and sporulation, contain an apparently novel Mr~43,000 ATP independent joint DNA molecule forming protein which does not react with monoclonal antibodies to the Mr~170,000 protein of control *REC1 KEM1* cells. We have purified the Mr~43,000 and the Mr~170,000 proteins to greater than 95% homogeneity. We will compare them with respect to their amino acid sequence, tryptic peptide fingerprints, cross reaction of polyclonal antibodies, associated nuclease activities, and types of joint DNA molecules formed *in vitro,* in order to evaluate their relatedness and biological roles.

ALS Protein Microcrystal Diffraction Camera
ROBERT GLAESER

There are many cases where protein crystallography has succeeded in modeling microcrystals, i.e., crystals in the size range of 10 μm to 50 μm on edge, but where large crystals needed for diffraction experiments (300 μm or larger) have not been obtained. There are two factors that limit how small a protein crystal can be and still provide high-quality diffraction data: background scattering overwhelms diffraction from the protein crystal if the x-ray beam area is significantly larger than the protein crystal; and source intensity may be limiting, so that *single* x-ray photographs take days or weeks to complete. Radiation damage is not a limitation until the crystal size gets well below 1 μm, if very short exposures are possible or, alternatively, if the crystals are frozen in liquid nitrogen. We will exploit the high brightness of the hard x-ray beam produced by the wiggler insertion device at the ALS to produce an x-ray beam focused to ~10 μm diameter at the specimen, thereby reducing unnecessary background scattering. At the same time, the high intensity in this small beam will reduce the exposure times at least 1000-fold compared with the best rotating anode source. We will base the camera optics upon the x-ray microprobe developed by J. Underwood, A. Thompson, and others, and used at Brookhaven National Laboratory. The microprobe has been used with a focused spot approaching 1 μm in size.

Our research program will pursue x-ray crystallographic structure analysis on already existing microcrystals of tubulin and of two different membrane proteins.

Membrane Proteins: High-Resolution Electron Microscopy
ROBERT GLAESER

We propose to solve the structure of a few specific cell membrane proteins by high-resolution electron crystallography. Our research will focus on bacteriorhodopsin and the various intermediates in its photocycle, PhoE porin, LamB porin, the adenine nucleotide exchange protein from mitochondria, and a plasma membrane protein ATPase. Our approach will include isolation and purification of the desired proteins, biophysical and biochemical characterization (and modification, as desired), reconstitution as two-dimensional crystalline sheets, and crystallographic structure analysis.

Analysis of Animal Cancer Tests
LOIS GOLD

We wish to assess the validity of interspecies extrapolation in carcinogenesis and to rank the possible carcinogenic hazards to humans from a variety of chemical exposures. We use animal cancer test results that have been standardized in our Carcinogenic Potency Database in the analysis. Currently, the database includes 4000 experiments on 1050 compounds, including results from the National Cancer Institute/National Toxicology Program and from the general literature. We will investigate interspecies extrapolation by comparisons between non-human primates and rodents; between different routes of administration; and between strains of rats or mice. We plan to compare the carcinogenic response in terms of positivity, target organ, and carcinogenic potency (tumorigenic dose-rate for 50% of the animals, TD_{50}). We will rank possible carcinogenic hazards to humans from various chemical exposures on an index, HERP (Human Exposure/Rodent Potency), that expresses each human exposure (daily lifetime dose in mg/kg) as a percentage of the rodent TD_{50} (in mg/kg/day). We will gather exposure data to calculate HERP values for exposures to synthetic pesticide residues, to carcinogens that occur naturally as food constituents in edible plants, and to synthetic chemicals in indoor air. Ranking by HERP may help to put possible human hazards in perspective and to suggest priorities for epidemiological testing and regulatory policy. We propose to investigate mechanisms of carcinogenesis in animal cancer tests by examining the associations among mutagenicity, maximum tolerated dose, and positivity of the carcinogenic response.

Interspecies Extrapolation and Risk Assessment in Carcinogenesis
LOIS GOLD

A major focus of this project is to develop strategies for setting research and regulatory priorities that can improve current methods of risk assessment. Our results challenge many assumptions of current regulatory policy and necessitate a rethinking of policies designed to reduce human cancer rates. We will broaden the perspective on human chemical exposures to include the enormous background of naturally occurring chemicals in the diet, which are the control for evaluating risks from synthetic chemicals. In order to evaluate energy-related risks, it is important to know more about the background of natural carcinogens. Half the chemicals tested for carcinogenicity, both natural and synthetic, are positive. We will use our Carcinogenic Potency Database, which includes results of more than 4500 animal cancer tests on 1100 chemicals, in the proposed analyses. We are ranking possible carcinogenic hazards to humans from various chemical exposures on an index, HERP (Human Exposure/Rodent Potency), that expresses each human exposure (daily lifetime dose in mg/kg) as a percentage of the rodent TD_{50} (in mg/kg/day). We are comparing HERP values for synthetic pollutants; chemicals that occur naturally as food constituents or from the cooking of food; drugs; and permitted chemical exposures for U.S. workers. Our ranking work indicates that carcinogenic hazards from current levels of water pollution or pesticide residues are likely to be of minimal concern relative to the background levels of natural substances.

Few of the many chemicals that humans are exposed to will ever be tested for carcinogenicity in rodents. To select chemicals for testing, we will use an analogous index, HERT (Human Exposure/Rodent Toxicity), to prioritize chemical exposures according to how they would rank in possible hazard if the chemicals were rodent carcinogens. HERT uses readily available LD_{50} values instead of the TD_{50} values of HERP; we have found that the rankings by HERT and HERP are similar.

Extrapolation from the high doses of rodent tests to the low doses of most human exposures should be based on knowledge of mechanisms of carcinogenesis. Our series of theoretical papers (Bruce Ames and Lois Gold) on the importance of cell division (mitogenesis) in mutagenesis, and therefore carcinogenesis, has generated great scientific and regulatory interest. Mitogenesis at the high doses of rodent bioassays is mutagenic (and consequently carcinogenic) because it increases the probability of converting endogenous DNA damage into mutations. Our analyses of rodent bioassays are consistent with this hypothesis. We will continue this theoretical work and conduct relevant analyses on mutagenicity, toxicity, target organ, and shape of the dose response.

We plan to examine the validity of qualitative extrapolation between species by comparing results on positivity, target organ, and carcinogenic potency between rats and mice; between non-human primates and rodents; and between different routes of administration.

Molecular Cytogenetic Technology
JOE GRAY

The goal of this project is to develop molecular cytogenetics for assessment of genetic damage in humans. Specific work planned in this project includes development of computer-assisted microscopy to facilitate interphase and metaphase analysis, isolation of informative nucleic acid probes and application of these technologies to genetic disease diagnosis and analysis. We will develop computer-assisted microscopy to allow: multicolor display of hybridization signals, high-speed multiplex probe mapping, automated analysis of metaphase spreads stained using fluorescence *in situ* hybridization (FISH) with probes distributed along each chromosome, enumeration of hybridization signals, identification of rare genetically distinct cells, and simultaneous analysis of cellular genotype and phenotype. We will develop large insert nucleic acid probe sets (i.e., mapped or acquired collaboratively), initially for chromosomes 3, 9, 16, 17 and 21. We will distribute probes on these chromosomes at ~5 Mb intervals and select them so that they hybridize with high efficiency in interphase and metaphase. We will apply FISH with these probes in collaboration with colleagues at the University of California, San Francisco, in studies of the genetic events associated with genesis and progression of cancers of the breast, bladder, and prostate and in studies of the molecular biology of Down syndrome.

Molecular Structure of Membrane Transport Systems
BING JAP

The objective of our research project is to determine the molecular structure of selected membrane proteins at atomic resolution with the use of electron and/or x-ray crystallographic methods. Our major focus is on membrane transport systems such as cytochrome reductase and Band 3 protein. Our research involves membrane protein purification; a continuing development of crystallization methods for obtaining two-dimensional and three-dimensional crystals; and molecular structure determination using electron and/or x-ray crystallographic methods. The molecular structures of membrane transport systems obtained will provide us with the detailed folding of the polypeptide, the structural design of the transport pathway in terms of charge distribution, and the active sites for the selectivity of the charmers. The structural information gained from structural determination of a variety of membrane transport systems will provide an understanding about the general principles that govern the functional mechanism of membrane transport systems. This may, in turn, give a rational understanding of the molecular basis for diseases such as cystic fibrosis, which has been linked to a defect in chloride channels, and Kearns-Sayre syndrome, which has been associated with defects in the respiratory chain of mitochondria.

Compositional Variations in Coding Regions of DNA
THOMAS JUKES

Our long-term objective is to improve our ability to analyze DNA sequences, with the eventual goal of applying this knowledge to the analysis of the human genome. The human genome consists essentially of four variables, the nucleotides A, C, G, and T. The information that eventually will emerge from the human genome project will be sequences of about 3 billion of these variables. This information is the product of 3 to 4 billion years of evolution. It therefore seems that studies of molecular evolution must be included in analyzing the human genome.

This proposal focuses on variations in the composition of DNA sequences in terms of G+C content. Vertebrate genomes appear to be composed of a "mosaic" of regions of differing base compositions. This heterogeneity may be related to mutational biases favoring the creation of either GC or AT base pairs (GC pressure or AC pressure, respectively). The project aims to investigate this phenomenon from an evolutionary point of view; specifically it affects coding regions of DNA and the amino acid composition of encoded proteins. The work will be done using sequences obtained from the GenBank database.

The project will also develop and evaluate new methods of classifying genes and searching databases. These methods involve describing genes with a nomenclature based on DNA sequence rather than one based on gene function. The goal is to enhance current methods for searching and structuring databases of genetic information and locating related genes.

Mutagenesis in Human Cells

AMY KRONENBERG

One of the many hazards which must be considered for long-duration manned exploratory missions in space is the exposure of astronauts to ionizing radiations. The risks to be evaluated include the effects of acute exposures to protons and the effects of low-fluence exposure to near-relativistic heavy charged particles. In the latter case, the endpoint of concern is not likely to be cell death but rather the risk of induction of heritable genetic alterations. Stable genetic alterations such as point mutations, partial gene deletions, and allele loss have been shown to be an important component in the process of carcinogenesis. The overall objective of this proposal is to provide quantitative information on the risk of mutation induction in a sensitive human cell line following exposure to a series of accelerated protons and iron ion particles, which are representative of the major sources of astronaut exposure to ionizing radiation. We will make a qualitative assessment of the spectra of DNA structural alterations associated with these specific locus mutations arising after exposure to protons and iron particles. We will perform these studies using two distinct loci representative of the majority of human genes: one autosomal (tk) and one X-linked (hypoxanthine phosphoribosyltransferase). The types of DNA structural alterations which may be detected at these two loci include point mutations, intragenic rearrangements, and allele loss. Analysis of the spectrum of DNA structural alterations produced by these unique radiations will contribute to our understanding of the influence of gene dosage and linkage on the nature of non-lethal mutations. Multilocus analysis will permit a more complete description of the magnitude of DNA alterations encompassing the target locus and extensive regions of the chromosome containing the target locus. The studies described herein will provide preliminary data which would be directly relevant to development of an *in vivo* monitoring system for mutation induction in astronauts using mutations in the hgprt gene of circulating lymphocytes as an endpoint.

Heavy-Ion Mutagenesis: LET Effects and Locus Specificity
AMY KRONENBERG

Previous work has shown selected heavy ions to be potent inducers of mutations in human TK6 lymphoblasts at two distinct genetic loci: thymidine kinase (tk) and hypoxanthine phosphoribosyltransferase (hgprt). The kinetics for mutation induction appear to depend on the genetic context of the particular locus in addition to LET. We propose a systematic investigation of the dependence of mutation induction on particle charge, velocity, and fluence for both the hemizygous hgprt locus and the heterozygous tk locus. Specifically, we will test the hypothesis that considerations such as gene dosage and linkage to essential genes influence not only the kinetics of induction but also the LET vs. RBE response for a given genetic locus. Secondly, we will determine whether the mutation rate may saturate more readily for a hemizygous locus with respect to particle fluence than for a heterozygous locus. This may be a result of the propensity with which accelerated heavy ions induce large-scale genetic changes, including extensive deletions, such that the magnitude of those alterations resulting in viable mutants is limited by genetic linkage. We will test this assumption by examining the spectrum of DNA structural alterations in clonally derived populations of $tk^{-/-}$ or $hgprt^{-}$ mutants arising in cultures exposed to a single particle beam. We will examine intragenic and multilocus change to determine the magnitude and polarity of structural alterations. We will also examine the effect of particle fluence on the spectrum of DNA structural changes for each locus. We intend to explore the dependence of the mutation spectrum for a given locus on the absorbed dose to the nucleus. Finally, we will examine the possibility that cryptic lethal alleles linked to the active tk or hgprt alleles of TK6 cells influence the spectrum of recoverable mutants by introducing an additional copy of chromosome 17 containing the gene for neomycin resistance into mutant TK6 subclones harboring large deletions of active tk or hgprt sequences. We will remutagenize Neo^+ revertants to tk^+, or revertants to $hgprt^+$ with a heavy-ion beam. We will compare the spectrum of DNA structural alterations in neo^+/tk^- or newly made $hgprt^-$ lines with those obtained for tk^- or $hgprt^-$ mutants of wild-type TK6 cells after exposure to the same heavy-ion beam. These studies will contribute to our understanding of the influence of genetic constraints on possible mechanisms of mutagenesis in human cells by densely ionizing radiations.

Physical Structure of Viruses, Chromosomes, and Cell Nuclei

MARCOS MAESTRE

Our main objective is to study *in vivo* and *in vitro* the structure of nucleic acids, viruses, nucleoproteins and chromosomes, and other significant biological structures such as red blood cells. We are putting particular emphasis on the internal organization of nucleic acids and, in the case of red blood cells (RBC), the internal organization of polymerized sickle cell hemoglobin (Hb S). To accomplish this, we will use the remarkable optical properties of nucleic acids and proteins in their various chemical and physical states.

The most important methods will be:

- Circular dichroism (CD) and flow oriented CD;
- Circular dichroic microspectrophotometer;
- Differential imaging polarization microscopy;
- Fluorescence-detected circular dichroism (FDCD);
- Scattered corrected CD by fluorscat and FDCD methods; and
- Intensified images of fluorescent labeled nucleic acids.

The above techniques will give information concerning the following properties: the interactions between the bases of the nucleic acids, the nucleic acids and protein complexes, and the protein components with themselves in such biological structures as viruses, chromosomes, and intact nuclei; the electric and hydrodynamic properties of the protein coats and the average orientation of nucleic acids in viruses, nucleoprotein-DNA and RNA aggregates and/or complexes; and the degree of coiling of nucleic acids in intact nuclei and intact cells.

Genetic Study on Yeast
ROBERT MORTIMER

For the past several years, our activities have been centered on gaining an understanding of a set of eight recombinational repair genes in the yeast *Saccharomyces cerevisiae.* The principal mutant phenotypes of these genes are sensitivity to ionizing radiations, recombination deficiencies, and meiotic abnormalities. We have mapped all of these genes and have cloned and sequenced several of them. We have shown that at least two of these genes are inducible by DNA damage and have identified a 29-base-pair sequence needed for induction of one of them. Some of the mutants in this set of genes are blocked in the repair of DNA double-strand breaks and we are using pulsed-field gels to study this phenomenon. In addition to these activities, we have for several years assumed the responsibility of collating all the genetic mapping data for yeast. Related to these studies is our recent work on genetic interference. We have developed a reasonable model of this phenomenon and have tested this model against data from yeast and Drosophila with very encouraging results. We also maintain and operate the Yeast Genetic Stock Center, which is used by hundreds of investigators worldwide.

Yeast RAD Genes in DNA Repair and Reconstruction
ROBERT MORTIMER

The x-ray sensitive mutants of the yeast *Saccharomyces cerevisiae* are a valuable genetic resource for understanding repair of ionizing radiation damage in eucaryotes. In yeast, double-strand DNA breaks caused by x-rays and some chemical mutagens appear to be repaired by a recombinational mechanism, which probably involves both recombination between homologues and sister-chromatid exchange (SCE). Many genes, including *RAD50* to *RAD57*, are thought to be involved in recombinational repair, and we have cloned several of these genes. We plan to continue existing projects aimed at characterizing repair of x-ray induced DNA damage in yeast and the relationship between repair and recombination, using both Rad^+ and Rad^- strains. The various approaches proposed are different mechanistically, yet all address questions aimed at a better understanding of repair and recombination, particularly the role of *RAD* genes in these processes.

We will use our existing clones to continue a molecular and genetic analysis of the *RAD24, RAD51, RAD54, RAD55,* and *RAD57* loci. We will also more thoroughly characterize mutations of *RAD17* and *RAD53* and clone these genes. *RAD51* and *RAD54* have been shown to be transcriptionally induced by

DNA damage and *RAD52* and *RAD54* to be induced by meiosis; northern hybridizations and *lacZ* fusion techniques will be used to continue studying the regulation of *RAD51, RAD52,* and *RAD54.*

We will also isolate from yeast the proteins encoded by *RAD51, RAD54, RAD55,* and *RAD57* after first placing these genes under the control of a strong yeast promoter. We also plan to overexpress derivatives of our cloned genes in *E. coli* to produce fusion proteins which can then be used to raise antibodies. The antibodies will be used both in the identification and purification of these proteins from yeast and in studies of the subcellular localization of the *RAD* gene proteins. Isolated proteins will be tested for enzymatic activities such as ATPase, nuclease, and DNA binding activities.

We will use pulsed-field gel electrophoresis in molecular studies of repair and recombination. We have developed a method that uses a circular derivative of a yeast chromosome to detect double-strand DNA breaks (dsb) and recombinant DNA molecules on pulsed-field gels. During meiosis, we can detect both sister-chromatid exchanges and two types of molecules resulting from recombination between the circular chromosome and its linear homologue. We hope to detect similar molecules arising from repair in mitotic cells, to characterize wild-type strains and study the molecular relationship between dsb and SCE after x-rays in Rad^+ strains, and to determine whether *rad* mutants that abolish dsb repair also abolish SCE. Further meiotic experiments are also planned using this system, with the aim of examining at the molecular level both wild-type meiotic recombination and the severe meiotic defects of many of the *rad* mutations.

Bone Marrow Stem Cells and Stromal Microenvironment

MOHANDAS NARLA

The objective of this new research, consisting of two distinct projects, is to further our understanding of the biology of the hematopoietic stem cells. Long-term repopulating stem cells (LTRC) cannot be replaced after birth except by self-renewal or transplantation, yet they are the source of all blood cells throughout an animal's lifetime. Hence LTRC must balance self-renewal (maintenance of the LTRC compartment) vs. differentiation (supply of blood cells to periphery) to fulfill both functions. The regulation of this balance is thought to be mediated by stromal cells. We plan in Project I to study functional characterization of embryonal sources of LTRC and, in Project II, the role of stromal cells in the regulation of these primitive stem cells. The rationale for focusing on these two lines of investigation is our belief that improved understanding of these two key areas in stem cell biology is likely to make a significant impact on the rational design of future bone marrow transplantation protocols that are the keystone of therapy for radiation exposure and many cancers.

In the first project, we delineate approaches using embryonal sources to obtain enriched populations of LTRC and the use of genetic constructs in transgenic animals to study their biology and function. The second project examines the role of stromal cells in regulating stem cell self-renewal vs. stem cell differentiation. We believe that delineation of the critical factors regulating LTRC maintenance in culture requires modification of the adherent cell layer by providing an ECM to the stromal cells, which will allow them to express their physiological functions appropriately.

Red Cell Deformability *In Vitro* and Survival *In Vivo*
MOHANDAS NARLA

The overall objective of this project is to determine the contributions of reduced cellular deformability and cell surface changes to increased red cell destruction in various human hemolytic disorders and to define the biochemical and structural basis of the deformability and cell surface changes. In order to accomplish these objectives, we have designed a series of studies with the following specific aims:

- Establish that maintenance of redundant surface area is essential for normal red cell life span;
- Determine if increases in cytoplasmic viscosity or in membrane rigidity, in and of themselves, decrease red cell life span;
- Establish that interaction of hemoglobin and excess unmatched globin chains with red cell membrane results in marked alterations of cellular properties;
- Define the contribution of increased pathologic red cell interaction with monocytes and macrophages to decreased red cell life span in various hemolytic anemias;
- Define the functional role of membrane skeletal proteins, glycoproteins, and other antigenic determinants in regulating cellular properties; and

- Establish the importance of glycolytic enzymes in maintaining the structural integrity of the membrane and the cell.

We will use ektacytometry of cell suspensions and micromechanical experiments on individual red cells to quantitate the deformability of red cells. We will use a newly developed micromechanical method to study the interaction of individual red cells with monocytes to document cell surface changes. We will perform measurements on density-fractionated cell populations in order to document the heterogeneity of various cellular changes. Detailed characterization of cell deformability and cell surface changes in various hemolytic anemias, and relating the measured changes to severity of the anemia, may enable us to define the important cellular determinants of red cell life span. Our emphasis on obtaining basic biological and biophysical information using novel techniques may also provide new insights into the structural organization of the red cell membrane, which should contribute to a better understanding of the pathophysiology of various human hemolytic anemias.

Red Cell Membrane Studies
MOHANDAS NARLA

The overall aim of this project continues to be to define the genesis, evolution, and premature senescence of the red cell membrane. A long-term objective for these studies is the development of a new understanding of the pathophysiologic mechanisms involved in hemolysis. Model information gathered on red cell membrane development and maturation should also contribute toward the understanding of these processes in other somatic cells.

Six complementary approaches toward our overall aim will be employed:

- Study the role of protein 4.1 polypeptides, a family of multifunctional binding proteins co-expressed in the red cell membrane skeleton, in regulating membrane function;

- Explore changes in protein 4.1 isoform expression during erythroid maturation and define their role in membrane reorganization during the genesis of the normal red cell membrane;

- Study the functional consequences of oxidatively induced damage to phospholipid species composition of the red cell membrane and explore the repair process involved in restoring normal phospholipid species composition and structural organization following damage;

- Characterize the mechanisms of senescence of thalassemic red cells in the bone marrow and in peripheral blood and define the potential contribution of oxidative damage to the membrane in the cell destruction process;

- Define the nucleotide and amino acid sequence of protein 7.2b to explore its postulated function as a component of an ion channel and establish the molecular basis for a red cell cation transport system; and

- Examine the functional consequences of interaction between the red cell membrane skeleton and proteins elaborated by intra-erythocytic stages of the malarial parasite *Plasmodium falciparum* so as to gain insights into normal functioning of the red cell membrane skeleton and into the biology of an important human pathogen.

We will utilize a broad range of methods from the disciplines of molecular biology, biochemistry, immunology, cell biology, and biophysics in these studies. We anticipate that this effort to gain improved understanding of the red cell membrane structural organization will eventually provide insights which will be useful for the management of hemolytic anemias and other clinical conditions where membrane structure, function, and development are deranged.

Rheological and Adherence Properties of Sickle Cells
MOHANDAS NARLA

The overall objective of this research program is to determine the rheological and adherence properties of sickle blood cells and to establish the relative contributions of these two factors to flow disruption and stasis in the microcirculation. In order to accomplish this objective, we have designed a series of experiments with the following specific aims:

- To determine the effects of reduced oxygen tension of the rheological properties of sickle red cells;

- To determine if the membrane is a structural site for damage in the disease;

- To examine the potential for micro-occlusion as caused by increased adherence of sickle red cells to vascular endothelium;

- To examine the possible contributions of altered rheological and adherence properties of granulocytes to flow disruption and stasis; and

- To define the role of sickle red cell-monocyte interactions in premature and red cell destruction.

We will use direct micromechanical experiments to measure the viscoelastic and plastic properties of sickle red cells as a function of oxygen tension, the rheological properties of granulocytes, the adherence of sickle red cells and granulocytes to vascular endothelial cells, and the interaction between sickle red cells and monocytes. As these red cell properties appear to depend on cell age and/or cell hemoglobin concentration, we will perform the experimental studies on density-fractionated red cells with narrowly defined ranges of hemoglobin concentration. We will monitor temporal changes in sickle cell adherence properties and in the proportion of red cells with various red cell densities in a large group of patients using newly developed methods. Detailed understanding of the biophysical and biochemical basis for the rheological and adherence properties of sickle blood cells and a study of variations in these properties in a large group of patients with varying degrees of clinical severity may enable us to define clinically important rheological and adherence properties.

Molecular Cloning and Characterization of REC1
ROBERT RAMIREZ

The capacity to repair DNA damage and undergo proper chromosome segregation are fundamentally important processes in living cells. Mitotic and meiotic recombination are two mechanisms used by cells to repair DNA damage and ensure proper chromosome disjunction during reduction division. However, the regulation of and the molecular mechanisms of recombination in eukaryotes remain largely unknown. Recently, several investigators have purified proteins from the eukaryote *Saccharomyces cerevisiae* that display DNA strand transfer activities. Such activities are thought to be implicated in mediating recombinational events. Investigators have cloned the genes encoding these strand transfer proteins; sequencing analysis has revealed that two independent clones (SEP1 and DST2) are equivalent to a previously cloned gene denoted KEM1. Mutations generated within these cloned genes result in anomalous recombinational capacities.

Recent work by others has led to the genetic identification of a novel gene in *Saccharomyces cerevisiae*: REC1. A mutation in this gene (rec1-1) displays a reduced ability to carry out mitotic recombination, is temperature-sensitive for meiotic sporulation, and is defective in the repair of x-ray damage. We believe REC1 to encode a novel 43-kDa strand transfer protein. Furthermore, REC1 has been shown to genetically map to chromosome VII, but is unrelated to KEM1, and the 43-kDa protein does not cross-react with antibodies to the Kem1 protein.

We propose to clone and characterize the REC1 gene and its protein product. We will transform a yeast YCp50-genomic library into a rec1-1/rec1-1 diploid yeast strain and plate it at the permissive temperature of 24°C. We will screen REC1 transformants by their ability to sporulate at the non-permissive temperature of 36°C. We will indentify haploid cells that survive the sporulation screen by plating on single nutrilite omission media.

Unidirectional exonuclease III digestion of the REC1 DNA will yield a set of deletion-bearing plasmids that will be used to determine the borders of the REC1 gene. We will transform these deletions into rec1-1 cells to test their ability to complement the rec mutation. We plan to accomplish verification of the REC1 clone by labeling the putative REC1 DNA and seeing whether it hybridizes to the DNA of chromosome VII on a Southern blot of a chromosome gel.

We will sequence the minimum REC1 clone identified in the set of deletions generated above to determine a) the nucleotide and primary amino acid sequence of the REC1 gene and its encoded protein, and b) the relatedness of the Rec1 protein to other known proteins by scanning a computer database.

We will mutate the cloned REC1 gene; we will reintroduce the mutated gene and recombine it into the native REC1 locus and determine the phenotype of the resulting null mutant.

Construction of Transgenic Mouse Models for Sickle Cell Anemia
EDWARD RUBIN

The long-term objective of this proposal is to continue the development of transgenic mouse models for sickle cell anemia and to use these models to study *in vivo* the pathogenesis of this disorder. Previously, we introduced human sickling globin transgenes in two mutant murine backgrounds (ß-thalassemic and a newly developed strain of mice with a high oxygen affinity murine hemoglobin) in order to favor the *in vivo* deoxygenation and polymerization of the human sickling hemoglobins in murine red cells. The resulting animals exhibited a phenotype similar to that of individuals with sickle trait but not with sickle cell disease. Thus our principal objective is the construction of murine models for sickle cell anemia that mimic severe sickle cell disease. The methods we will use to genetically engineer mice so that their red cells contain exclusively or almost exclusively human sickling hemoglobin will include:

- Homologous recombination in embryonic stem cells to inactivate the murine globin genes,
- Introduction of genes that code for murine globin antisense RNA, to decrease the expression of the murine globin genes, and
- Introduction of high-expression human sickle globin constructs to direct the high-level expression of the human globin chains in murine red cells.

With these animals and with the previously developed murine models for sickle cell anemia, we plan to investigate *in vivo*:

- The effect that small amounts of HbF and HbA have on murine sickle red cells;
- The origins of different density populations of sickle red cells and the survival and adhesive/occlusive properties of these cells; and
- The pathophysiological effects that red cells containing primarily human sickling hemoglobins have on transgenic mice.

Estrogenic Regulation of Mammary Gene Expression

SHYAMALA HARRIS

The female steroid hormone, estradiol (E_2), is required for the proliferation of mammary epithelial cells occurring during puberty and pregnancy. However, once the epithelial cells achieve full functional differentiation accompanying lactation, mammary glands become refractory to the action of E_2, despite the presence of estrogen receptors (ER). The overall objective of this project, therefore, is to examine the molecular mechanisms responsible for E_2-dependent gene expression in undifferentiated mammary epithelial cells and those which impede this expression during lactation using progesterone receptor (PgR), a well-defined end product E_2 action, as the target gene. The specific aims are to:

- Identify the DNA elements on murine PgR gene which mediate its E_2-dependent expression by cloning and sequencing its promoter and the 5'-flanking regions and testing the various DNA sequences in standard transfection assays;

- Delineate the molecular basis for E_2-dependent activation of KB-specific proteins and assess its importance in mediating E_2-dependent gene expression. The KB enhancer is present in the regulatory regions of a wide variety of genes and serves as a recognition site for the transcription factor, NF-KB and other KB-specific proteins. Thus, KB proteins have the potential to regulate pleotropic responses characteristic of the wide spectrum of biological responses elicited by E_2 in its target tissues. Recently we have obtained evidence, for the first time, that E_2 can activate KB-specific proteins. To identify the KB-specific protein activated by E_2, we plan to clone its cDNA and examine its potential along with ER to mediate E_2-dependent gene expression; and

- Identify and characterize the cellular factors in the E_2-insensitive lactating mammary gland that have the potential to compete with ER for binding to regulatory elements on target genes. Recently we have found that lactating mammary glands contain nuclear proteins, other than ER, which can also bind to estrogen responsive element (ERE) *in vitro*, and these proteins are in huge abundance in this tissue. These as-yet unidentified proteins have the potential to compete with ER for its binding to regulatory sequences on target genes and impede E_2 action. We propose to clone the cDNA encoding this ERE-binding protein and examine its potential to impede E_2-dependent gene expression.

The studies outlined here have a direct and major relevance to our understanding of mammary carcinogenesis, for two important reasons: the involvement of E_2 in the growth of human mammary carcinoma is well known, and our studies will provide important information regarding the mechanism of F-2 action in mammary tissues; our studies will also offer critical insights regarding the cellular mechanisms which govern the proliferative vs. differentiated state of the cell, and often it is the uncoupling of this otherwise well-coordinated process of proliferation and differentiation which results in neoplasia.

Alkylation of Polynucleotides *In Vitro* and *In Vivo*

BEA SINGER

O^2-Alkyl (methyl, ethyl) thymidine, O^4-alkyl thymidine, and O^2-alkyl cytidine are formed *in vivo* by a variety of N-nitroso carcinogens. In all organs and eukaryotic cells examined, these derivatives persist for long periods. The promutagenic nature of each of these pyrimidines has been demonstrated *in vitro* and *in vivo* for O^4-alkyl T. O^4-Methyl and -ethyl thymidines are also directly implicated in initiation of hepatocarcinogenesis. This project is directed toward understanding how the presence of O-alkyl pyrimidines in DNA or model oligomers affects secondary structure and polymerase recognition in replication.

We will site-specifically incorporate O^2- and O^4-alkyl thymine in template-primer complexes by DNA polymerases of varying fidelity. We will place them opposite A or G, the known partners, or T, a mismatch. We will determine the kinetics of insertion and elongation (K_m, V_{max}) by gel electrophoresis or radiolabeled nucleotide incorporation. We intend to examine structures of complete duplexes, e.g., a 22-mer, containing 0 to 3 alkyl thymines, by thermal denaturation, enzyme sensitivity, and antibody recognition. We plan to synthesize a hexamer capable of the B to Z transition with a single alkyl thymine and study the result of the substitution by circular dichroism. We will use duplex oligomers with 2-aminopurine opposite O^4-alkyl thymine to measure fidelity and structure in the absence of steric hindrance. Fluorescence changes are a sensitive indicator of the degree of stacking and bonding. We will determine sequence effects on kinetics and structure by varying the template oligomers. Sequences with greater stability may be less likely to be repaired, so mutation can occur.

In the preparation of O^2-alkyl CDP and CTP we will use mild chemical or enzymatic methods to attempt prevention of dealkylation depyrimidination. If we obtain the desired products, we can make polymers for mispairing studies. Finally, we will use a pair of cell lines isolated from human brain tumors to study the time course and extent of O-alkyl pyrimidine repair. These cells differ greatly in their ability to repair the initial O^6-alkyl G adduct formed by chemotherapeutic halonitrosoureas. Either cell line may be suitable for further study of pyrimidine repair mechanisms.

Biochemical Mechanisms of Vinyl Chloride Carcinogenesis

BEA SINGER

Over 3 billion kg/yr of vinyl chloride (VC) are produced in the U.S. VC has been amply documented as a human carcinogen associated with liver haemoangiosarcoma and tumors of the brain and lungs. No mechanism for its tumorigenicity has emerged, even though tumors are easily induced in rodents, and VC and its mutagenic metabolites, chloroethylene oxide (CEO) and chloroacetaldehyde (CAA), have been intensively studied. The known *in vivo* products of VC are three cyclic etheno bases, apparently derived from CAA, while 7-(2-oxoethyl)G is apparently derived from CEO. Our long-term objective is to understand the molecular mechanism of initiation of related carcinogens and their common metabolites by VC.

This approach has three specific aims:

- To use physical, chemical, and biochemical methods to study three known etheno products (1, N^6-etheno A; 3, N^4-etheno C; and N^2, 3-etheno G) of VC-nucleic acid reaction in terms of effect on polymer structure, replication, and fidelity. Special emphasis will be placed on N^2, 3-etheno G, which can form two hydrogen bonds with C or T;

- To investigate the formation of additional derivatives by epoxides and aldehydes, including several biologically important simple mono- and bifunctional agents (e.g., ethylene oxide, cyanoethylene oxide, chloroacetaldehyde); and

- To study the initial chemical steps in formation of cyclic derivatives and crosslinks by the aldehyde and halide functions of the VC metabolites.

Our purpose is to search for biologically significant chemical events that could be mutagenic or lethal.

The methods and approaches will utilize chemical synthesis of modified dNTPs, rNTPs, with and without radiolabel; kinetics and sequence of aldehyde/epoxide reactions; helix-coil transitions of polymers and oligomers containing modified etheno derivatives; optical methods (UV, IR, fluorescence); High Pressure Liquid Chromatography (HPLC), gel electrophoresis, nucleotide sequencing; *in vitro* replication of defined oligomers; and utilization of etheno NTPs in site-directed mutagenesis.

Characterization of Human Mammary Cells
MARTHA STAMPFER

The long-term objective of this research is to develop, characterize, and utilize a human mammary epithelial cell (HMEC) system for studies of human cellular differentiation and carcinogenesis. The goal is to examine well-defined human epithelial cell cultures as a means of understanding the normal mechanisms which control proliferation and differentiation in these cells and to determine how these normal processes are altered as a result of immortal and malignant transformation. We have already developed the necessary HMEC cultures for such studies in this laboratory; we can achieve active, long-term, serum-free growth of HMEC from normal tissues; we have two independent immortally transformed HMEC cell lines derived from one normal specimen; we have malignantly transformed HMEC derived from the immortal cell lines exposed to specific oncogenes. The necessary characterization of these HMEC is ongoing in our laboratory and those of several collaborators. The aim of this characterization is to provide an overall picture of the behavior of the normal and transformed HMEC and to use this information for further, more detailed analyses of particular mechanisms. Our specific aims are largely concerned with the question of the relationship between proliferation and differentiation in the normal and transformed cells. One hypothesis being considered is that transformation of HMEC involves a dissociation in the control mechanisms governing proliferation vs. differentiation in response to differentiating agents, such that the cells maintain the capacity to divide but still respond to the differentiation signals with expression of a "terminal" differentiation phenotype. Breast cancer cells and cell lines almost uniformly express properties associated with terminal differentiation in normal HMEC, particularly keratin 19 and the human milk fat globule antigen. To address this question we will:

- Examine the normal and transformed HMEC for expression of markers of functional and terminal differentiation under culture conditions that may enhance normal differentiated development, e.g., growth on extracellular matrix substratum or within collagen gels and in the presence of specific growth factors;

- Introduce specific genes (e.g., c-erbB-2, keratin 19) into the HMEC and look for possible effects on growth and differentiation;

- Use subtractive hybridization methods to isolate and identify genes differentially expressed in finite life span vs. transformed HMEC;

- Examine expression of cellular oncogenes in the normal and transformed HMEC, with emphasis on possible effects of TGFß;

- Look at the effects of TGFß on protein secretion in the HMEC, and identify proteins shown to be induced; and

- Collaborate with other laboratories in providing HMEC for studies on growth factor synthesis and responses, aging, and the consequences of cell fusions involving normal, immortal, and tumor HMEC.

Rapid Transformation Assay
MARTHA STAMPFER

Our long-term objective is to develop methods to induce reproducibly transformation *in vitro* of human mammary epithelial cells (HMEC) by physical carcinogens such that we can define what characteristics distinguish normal from transformed HMEC in culture and determine what agents alone, or in combination, may be capable of inducing human carcinoma. Our immediate objective is to understand the relationship between the differentiated state of the mammary epithelial cell and its potential to undergo malignant transformation.

To achieve our objectives, we are utilizing the well-characterized HMEC culture system developed in our laboratory. Normal HMEC, which proliferate rapidly both in mass culture and as colonies, are available from donors of all ages and pathologies. These HMEC rapidly metabolize benzo(a)pyrene (BaP), forming products and DNA adducts in a pattern similar to that found in cells transformable *in vitro*. BaP exposure of HMEC from one normal individual has led to the development of two immortally transformed cell lines. These lines have been malignantly transformed by exposure to viruses and oncogenes.

The main problems in developing assays for transformation of HMEC lie in the general difficulty of obtaining any induced transformation of normal human cells by physical carcinogens and in defining quantifiable markers of mammary epithelial cell transformation. As a result, we have focused our effort on understanding the factors which might influence the capacity of HMEC to transform in culture. In particular, we are investigating how the differentiated state changes as a result of immortal or malignant transformation and if it might affect the ability of the cell to undergo transformation. Specifically, we are extensively studying a newly isolated gene, NB-1, whose protein product bears 85% homology with calmodulin. This protein is expressed in normal cells from stratified and pseudo-stratified epithelium, but is greatly reduced or absent in transformed cells from these tissues. We are exploring the possibility that the loss of expression of this protein may be correlated with the capacity of the cells to become transformed, as well as with the differentiated state of the cell.

DNA Adducts and Oxidative DNA Damage As Biological Dosimeters

ALLAN TISCHLER

The purpose of this project is to develop an assay that will determine the extent to which various coal tar extracts mechanistically affect the activation of benzo(a)pyrene in cultured human mammary epithelial cells; to develop the technology for the preparation of biologically relevant extracts from various coal tars, particularly for use in *in vitro* carcinogenicity and toxicity studies; and to develop the analytical methods for determining the benzo(a)pyrene content of coal tar extracts already in use.

Tobacco-Related Carcinogens in Human Epithelial Cells

ALLAN TISCHLER

The objective of the proposed research is to establish, at the molecular level, and in relevant human epithelial cells, the mechanisms of the interrelated phenomena of procarcinogen activation, cocarcinogenesis, and oxidative DNA damage involved in tobacco-related cancer. There are many indications in the literature that some components of cigarette smoke, including polyaromatic hydrocarbons, phenols, and formaldehyde, can act as cocarcinogens that enhance the activation and carcinogenesis of key cigarette smoke procarcinogens, such as benzo(a)pyrene and tobacco-specific nitrosamines. We wish to investigate the likelihood that cocarcinogens act by inducing oxidative processes, such as the arachidonic acid cascade and lipid peroxidation, which can in turn enhance procarcinogen activation and oxidative DNA damage by known mechanisms. We have already demonstrated that both the oxidative DNA damage and DNA adducts induced by benzo(a)pyrene in human mammary epithelial cells are inhibited by cyclooxygenase and 5-lipoxygenase inhibitors, suggesting a significant role for arachidonic acid cascade. It is likely that cocarcinogens exert their procarcinogen-sparing effects by inducing these same oxidative processes. A detailed understanding of these interrelated processes could lead to effective preventive treatment for individuals previously exposed to cigarette smoke.

Recent indications in the literature, including a reevaluation of relevant epidemiological data by A. W. Horton, suggest that not only are cigarette smoke and breast cancer related, but that there is reason to believe that only relatively small exposures to cigarette smoke may be required to induce breast cancer. Consistent with this notion, previous work in this laboratory has demonstrated that human mammary epithelial cells readily activate, and are in turn immortally transformed by, benzo(a)pyrene. We hope to better establish a connection between cigarette smoke and breast cancer by conducting the studies described above in both a human airway epithelial cell (bronchial), where the relationship between cancer and cigarette smoke is not in doubt, and in human mammary epithelial cells. Considering that the great majority of human cancers originate in epithelial cells, human mammary cells will remain an excellent model for other epithelial cancers even if the relationship between cigarette smoke and breast cancer remains equivocal. They are a good model because of their proficiency in activating procarcinogens and the high degree to which they and their transformants have been characterized.

Carcinogenic and Mutagenic Effects of Protons and Heavy Charged Particles
TRACY C. YANG

Space radiations, which consist of energetic electrons, protons, and heavy ions, are hazardous to human health. Heavy ions with high linear energy transfer (LET) are particularly effective in causing various biological effects, including cell inactivation, mutation, and cancer. Among these biological effects, the induction of neoplasm is the most important late effect to be considered in radiation risk assessment because astronauts usually receive chronic exposure of low doses. During a long-term space flight, such as a mission to Mars, astronauts will be exposed to considerable amounts of cosmic rays. To ensure the proper protection of astronauts and the success of a long-term mission, a better understanding of carcinogenic effects of heavy ions is most essential. The major objectives of this project are to quantitatively determine the RBEs for heavy ions with various LETs and to gain significant insights into the mechanisms of radiogenic carcinogenesis, using human epithelial cells as a model system. We will test three key hypotheses:

- Neoplastic transformation of human cells by ionizing radiation is a multistep process, i.e. multiple exposures are required for transforming normal cells to fully tumorigenic ones;

- The RBEs for heavy ions do not differ significantly between human epithelial cells and mouse embryonic fibroblasts; and

- Radiation-induced transformation is irreversible due to genetic changes involving partial or total deletion of cancer genes.

To accomplish these objectives, we will use various cell and molecular biology techniques and methods, including foci assay, agar test, karyotyping, cell fusion, and genomic DNA analysis. Experimental results so obtained with human epithelial cells should significantly reduce the large uncertainty presently existing in our radiation risk assessment.

Calmodulin-Related Gene and Epithelial Transformation

PAUL YASWEN

The primary objectives of this research are to characterize the protein corresponding to a newly discovered calmodulin-like gene transcript and to learn why expression of the gene is down-regulated during transformation of human mammary epithelial cells (HMEC). This gene, designated NB-1, was recently cloned using a probe enriched by subtractive hybridization for sequences preferentially expressed in a normal HMEC strain in comparison with a closely matched tumorigenic HMEC derivative. Evidence that NB-1 expression is often depressed in primary breast tumor tissues and that NB-1 transcripts are undetectable in tumor-derived cell lines supports the possibility that loss of NB-1 expression is an important step in tumorigenic transformation of breast epithelial cells.

The 85% amino acid sequence similarity between the putative NB-1 protein and calmodulin suggests that the NB-1 product is a Ca^{+2} binding protein with similar signal transduction properties. However, calmodulin is expressed at relatively constant levels in most cells, whereas NB-1 exhibits tissue specificity, regulation by TGF-ß and extracellular matrix, and absence in transformed cells. Our working hypothesis is that the protein encoded by NB-1 functions as a regulatory molecule analogous to calmodulin, but that the range of proteins to which it binds and regulates differs from that of calmodulin.

In order to gain a better understanding of the function and regulation of NB-1 in normal and abnormal epithelial cells, we will initiate a number of biochemical and molecular biological studies, including:

- Raising specific polyclonal antibodies against a synthetic peptide and using them to localize the product of the NB-1 gene in individual cells and in tissues;
- Expressing recombinant NB-1 protein in *E. coli* and using it to identify the proteins to which NB-1 protein binds;

- Transfecting and expressing NB-1 cDNA under the control of a heterologous promoter in transformed human breast cells in order to assay its effects on tumor-associated properties;

- Performing *in situ* transcription assays and promoter strength assays in order to identify regulatory elements which function differently in normal and transformed HMEC; and

- Assaying biological activities of NB-1 in normal cells by testing its ability to perform essential yeast calmodulin functions and by blocking its translation in normal HMEC with throated antisense oligonucleotides.

The experiments proposed will begin to address the role of NB-1 in the coordination of growth and differentiation in normal breast epithelium. Calcium mobilization is known to be a critical determinant of both of these processes in epithelial cells. Disruption of Ca^{+2} mediated events is also one of the earliest detectable alterations in carcinogen-exposed epithelial cells. Down-regulation of NB-1 expression *in vitro* or *in vivo* transformation of HMEC may contribute to the pathology observed in breast carcinomas.

LIFE SCIENCES DIVISION

Department Of Molecular and Nuclear Medicine

The focus of the Department of Molecular and Nuclear Medicine is the study of human diseases using the tools of nuclear chemistry and instrumentation. Departmental researchers use radiopharmaceuticals as tracers in conjunction with advanced diagnostic imaging systems and perform cancer therapy trials with heavy ions. In addition, a major effort is under way to understand the genetic risk factors at work in atherosclerosis. Some other areas in which we anticipate continuing evolution and growth are: NMR electromagnetic effects on biological systems; biochemical mechanisms of mental disorders and aging; charged-particle radiotherapy; charged particle hazard evaluation for deep space exploration; development of improved instrumentation and chemistry for diagnostic medical imaging; new chemical detection methods for metabolic products; design of accelerators for therapy and radionuclide production; and development of instrumentation for life sciences experimentation at the Advanced Light Source.

Design Study for the UC Davis Proton Facility

JOSE ALONSO

The University of California at Davis is developing plans to build a proton therapy facility as a part of its Cancer Center in Sacramento. The UC Davis Proton Facility will be installed in a new building to be erected adjacent to the present Cancer Center building. UC Davis and LBL are developing an agreement to advance this project; LBL will design the accelerator, beam transport, and beam delivery systems, will oversee their construction, and will be responsible for commissioning and initial operation of the Proton Facility at the Cancer Center. As construction of the accelerator systems will probably be finished at least one year prior to the new building's completion, the accelerator will be installed within the experimental area of the Bevalac and connected to the currently operating treatment facilities. This will allow for full commissioning of the accelerator, from initial operation to full readiness for clinical use of the proton beam, prior to its transport to a permanent location at the UC Davis Cancer Center. Work on this project will focus on determining the major specifications and architecture of the technical system, followed by completing a Full Design Report.

The Alveolar Lining Layer in the Lung

JACOB BASTACKY

The liquid layer lining the alveoli in the lung has been difficult to study because of its thinness, inaccessibility, and high water content. The electron microscope can magnify the alveolar lining sufficiently, but its vacuum requires that water be removed, and the attendant shrinkage and distortion of this highly hydrated layer makes analysis problematic.

With the advent of the low-temperature scanning electron microscope (LTSEM), the lung can be analyzed at magnifications of 10 to 10,000× with water preserved as ice in the frozen hydrated state. The native air-liquid interface in the alveoli thus can be imaged directly.

The proposed study will test several hypotheses:

- The surface lining layer is continuous over the entire alveolus and indeed over the entire alveolar duct portion of the respiratory zone. We will test this by examining microdissections of airways in frozen, hydrated rat lungs at high magnification;
- The contour of the surface is smooth. We will test this by applying surface roughness criteria to stereo images of hydrated alveoli; and
- All pores of Kohn are filled with alveolar lining material in normal lungs. We will test this by counting the number of open pores in hydrated, frozen alveoli. Studies will be extended to human normal and emphysematous lung.

We will also determine the thickness and volume of the aqueous subphase of the alveolar lining layer with photogrammetric methods from three-dimensional images made with the LTSEM.

Characterization of the alveolar lining layer is important in understanding the contribution of surface forces to the mechanics of respiration and for preventing and treating conditions that are disturbances of this layer, such as respiratory distress syndrome, pulmonary edema, and pneumonia.

Effects of Tobacco on Rat Lung Alveolar Lining Liquid
JACOB BASTACKY

We propose to test a new and sensitive indicator of the early changes that might be expected in response to tobacco smoke in the alveoli of the rat. The goal of this research is to determine the effect of tobacco smoke on the alveolar lining liquid layer in the lungs of rats. This fluid layer, considered to be a monolayer of surfactant floating on an aqueous subphase, is of critical importance to normal respiration in that it prevents alveoli from collapsing, regulates the air-blood diffusion distance, protects the thin alveolar septum, and provides a medium for intra-alveolar macrophages. Perturbations of this lining layer are seen in tobacco-related diseases such as respiratory failure and emphysema, the pulmonary edema and pneumonia that complicate them, as well as respiratory distress syndrome. Little is known, however, about this fluid compartment: the amount of fluid in the layer; its configuration, composition, and homogeneity; and its response to tobacco smoke. The alveolar lining layer has been difficult to study, since it is primarily composed of water, which must be removed for routine electron microscopy. We have developed techniques of low-temperature scanning electron microscopy, however, that allow us to study the lung with its water preserved at magnifications appropriate for imaging the alveolar lining layer. We freeze the lung as rapidly as possible in the living, physiologically controlled animal, and remove and examine a portion of this frozen lung in the low-temperature scanning electron microscope (LTSEM). Water is preserved as ice during this examination and can be imaged directly in the microscope. We use quantitative methods of stereometric surface analysis to measure quantitatively and accurately several important features that allow assessment of total volume, configuration and continuity of the alveolar lining layer in control and smoke-exposed rat lung.

This study will test several hypotheses:

- Exposure to tobacco smoke changes the amount and distribution of alveolar lining fluid as measured in individual alveoli;

- Intra-alveolar fluid can increase by small amounts without necessarily leading to complete flooding of each affected alveolus;

- In the early stages of edema caused by tobacco smoke, the alveolar lining layer remains continuous and the air-liquid interface remains smooth; and

- The interalveolar pores of Kohn remain filled with alveolar lining material and do not open under the influence of inhaled tobacco smoke.

Low-Temperature Scanning Electron Microscopy of the Lung

Subcontract from the Harvard School of Public Health

JACOB BASTACKY

This project uses techniques and instrumentation that have been developed at LBL for low-temperature scanning electron microscopy of lung. We will be studying airways in the frozen, hydrated state from lungs of animals that have been treated with physiologic and pharmacologic agents that cause airway constriction, airway relaxation, and airway secretion. The aim of the study is to increase understanding of the normal airway and the disease process of asthma. Low-temperature scanning electron microscopy preserves lung and airway water in place for analysis, facilitating these studies. For this study, one of the Harvard investigators will bring prepared samples of lung to LBL for scanning. We will then use our microscope and various preparatory equipment to produce photomicrographs of the samples.

Airway Obstruction and Liquid Layer Mobility Microscopy
Subcontract from Massachusetts Institute of Technology
JACOB BASTACKY

Lawrence Berkeley Laboratory will provide research for the microscopy component of a National Institutes of Health project awarded to Dr. Roger Kamm at MIT. The microscopy component of the project will include experimental design, sample preparation, freezing, cutting, transfer, fracturing, coating, imaging, surveying, recording, photographic processing, filing, photographic post-processing, measurements, data collection, data analysis, data interpretation as well as microscope maintenance, repair, modification, scheduling, instruction, and safety. Various systems of microscopy will be used, including low-temperature scanning electron microscopy, conventional scanning electron microscopy, x-ray microanalysis, and light microscopy.

Late Effects of Galactic Cosmic Radiation in the Canine Brain
KATHLEEN BRENNAN

Proper planning of manned missions to the moon and Mars depends on new information on the effects of long-term exposure to galactic cosmic rays and in particular to high-atomic-number charged (HZE) particles. The fluence of these particles is such that, during an extended mission outside the geomagnetosphere, on the average every biologic cell will be traversed by a few particles. Estimates of cell killing or transformation induction cannot be made from known data from previous studies using protons, neutrons, and Bevalac-accelerated HZE nuclei in rodents, dogs, and monkeys because experiments simulating expected exposures to heavier nuclei such as iron have not been undertaken.

Thus we propose a ground-based experiment to evaluate the health effects of HZE particles using protracted irradiation of the dog brain at a total fluence of 3×10^6 particles/cm^2 for nuclei of atomic number 3–26 for a 2-year mission. Approximately 3 particles will traverse each cell nucleus. We plan to use iron nuclei at 600 Mev/a.m.u. (150 KeV/mm) to irradiate the brain. Our experiment will use a total of 80 dogs, with 40 being exposed and 40 used as controls. Multiple exposures over 2–8 months will simulate low-dose-rate exposure during space travel. Endpoints will be changes in neurochemistry and neuroanatomy as measured by repetitive, non-invasive studies using high-resolution positron-emission tomography (PET) and high-resolution nuclear magnetic resonance (NMR) imaging and spectroscopy. We do not expect changes until over 3 years post-irradiation based on preliminary work from 15 dog studies using hemibrain irradiation with helium and neon ions. We will follow brain-mediated changes in the hematapoetic, musculoskeletal, and hormonal systems by clinical laboratory studies. The irradiations commenced in FY93 and will continue into FY94 with the long-term follow-up of 80 animals to be conducted for at least 12 years.

Cerebral Blood Flow Patterns in Alzheimer's Disease

THOMAS BUDINGER

The previous work on this project used positron emission tomography (PET) and single photon emission computed tomography (SPECT) to study the changes in regional cerebral blood flow and metabolism in Alzheimer's disease (AD). We propose to use PET to investigate the relationship between these perfusion abnormalities, cognitive deficits, and regional changes in dopamine metabolism in patients with AD and Parkinson's disease (PD), an illness associated with a dementia sharing clinical, pathological, and imaging characteristics with AD. While the striatal dopamine deficiency in PD is well established, evidence from PET and neuropsychological investigations also implicates the frontal lobes as an area affected by the disease. In AD, clinical and pathologic studies suggest a role for dopaminergic dysfunction in the pathophysiology of frontal lobe and extrapyramidal symptoms. The use of the dopamine metabolic tracer [^{18}F]-6-fluorodopa with high-resolution PET will allow the determination of the role of frontal lobe, putaminal, and caudate dopamine deficiency in the production of frontal lobe hypoperfusion and cognitive symptomatology in these diseases.

The study design entails the evaluation of PD and AD patients and controls, with specific reference to the presence of frontal lobe perfusion abnormalities, extrapyramidal symptoms, and frontal cognitive deficits. We will select all patients from a larger cohort enrolled in an ongoing longitudinal study of changes in blood flow using SPECT, who will receive continued clinical follow up with a view to ultimate autopsy correlation. We will use the PET-600 tomograph, which has a resolution of 2.6 mm, for all studies. Immediately following a study to evaluate regional blood flow using the tracer [^{122}I]-HIPDM (210-sec half-life), subjects will undergo a fluorodopa PET study. Quantitative analysis of the data will utilize an input function determined via an arterial catheter with an on-line technique, together with dynamic PET brain uptake data. We will use the blood and brain time-activity curves in conjunction with models for blood flow and dopamine metabolism to derive parameters describing regional cerebral blood flow and dopamine metabolism. The dopamine metabolic model will employ the known time course of significant metabolic products of the tracer in order to quantitate rate constants for transport and metabolism.

The major hypothesis is that putaminal abnormalities of dopamine metabolism will be related to the extrapyramidal symptoms seen in PD and AD subjects. In addition, we expect the frontal lobe perfusion deficits and cognitive deficits to be associated with diminished frontal lobe dopamine metabolism. Such studies will expand our understanding of the specific pattern of dopamine deficiency in these states and will relate neurotransmitter deficits to cognitive and blood flow abnormalities which have important implications for understanding the pathophysiology and potential treatments for both diseases.

Development of Radionuclides for Medical Imaging Purposes
THOMAS BUDINGER

Our objectives are to develop methods for the incorporation of short-lived radionuclides into biochemical substrates and to utilize these radiolabeled compounds in the investigation of physiological processes in normal and diseased states using non-invasive imaging techniques. We follow the distribution of these radiolabeled agents employing positron emission tomography (PET) and single photon emission computed tomography (SPECT).

Our approach is to investigate 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 as lipophilic complexes containing ^{68}Ga, ^{82}Rb, and ^{118}Sb. They remain to be fully exploited for blood flow measurements and other *in vivo* applications. Toward this goal, we are synthesizing and evaluating various chelating ligands which will form ^{68}Ga-complexes of overall zero and +1 net charge for use as brain and myocardial blood flow agents for PET. We are also attempting to synthesize complexes which will chelate $^{82}Rb^{+1}$ and form a neutral, lipophilic agent for PET brain blood flow studies. In contrast to metal ions eluted from generator systems, we can incorporate short-lived cyclotron-produced radionuclides such as ^{18}F, ^{11}C, and ^{15}O 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 adrenergic and cholinergic 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.

Human Brain and Heart Metabolism and Flow Measurements by Non-Invasive Techniques

THOMAS BUDINGER

This project focuses on the design and data analysis of advanced emission tomography and NMR systems which are beyond currently envisioned commercial implementation and on the application of new technologies for the study of atherosclerosis, heart disease, aging, mental disorders, and radiation effects. We are applying the joint approach of new technologies and experimental physiology to medical science problems using a team of physicists and research physicians devoted to development of quantitative methods of experimental medical science. In addition to the non-invasive methods of nuclear medicine, NMR, and autoradiography, we are using tracer studies *in vitro* and, most recently, synchrotron light source studies of elemental changes. The program has a major emphasis on mathematical modeling and statistical analyses. These instrument development programs have as an integral part technological transfer in collaboration with private industry.

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, the statistical basis of dynamic positron emission tomography (PET), clinical studies of a unique 2.6-mm-resolution PET instrument, tritium nuclear magnetic resonance (NMR) studies of carbohydrate metabolism, and use of soft x-rays for studies of calcium precipitation.

Proposed work includes perfection of our uniquely high resolution PET in studies of dementias, schizophrenia, heart disease, and tumor metabolism response to therapies. In addition, we will use advanced mathematical techniques to continue the development of algorithms for reconstruction of multidimensional image distributions and to enhance the quantitative aspects of medical science data analysis for the benefit of the national effort in molecular nuclear medicine.

A supplement to this activity was acquisition of a mini-cyclotron in 1991 in order to provide radiopharmaceuticals to LBL and to advance PET in the research and medical community

Quantitative Cardiovascular Research
THOMAS BUDINGER

Training in the methods of development of new technologies appropriate for instrumentation in emission tomography and nuclear magnetic resonance (NMR) includes education in basic physics and chemistry followed by participation in specific technological projects. Training in physiology and medical science includes the basic education in quantitative techniques followed by participation in or initiation of medical science investigative projects. The program envisions creating positions for three predoctoral and three postdoctoral researchers with backgrounds in physics, chemistry, mathematics, computer science, physiology, or medicine. The predoctoral trainees are selected from undergraduates in the University of California, Berkeley, and University of California, San Francisco programs in physics, computer science and electrical engineering, and bioengineering. We recruit postdoctoral candidates using advertisements in journals, notices at scientific meetings, and personal recruitment by the project director at scientific meetings.

Resources available include curriculum of the UC Berkeley and UC San Francisco campuses, the facilities associated with the Lawrence Berkeley Laboratory including two positron emission tomographs, two single photon emission tomographs, an NMR 0.5T whole body imaging system, 2.35T 40 centimeter spectroscopy system, and various NMR spectrometers up to 500 MHz for *in vitro* studies. Students have access to computers in the Information and Computing Sciences Division at LBL and on the campus. The project director has access to various machines, from dedicated architecture devices to the CRAY 2, Hypercube, and connection machines. Patient resources include neurological, neurosurgical, and cardiovascular diseased patients from UC San Francisco, Martinez Veterans Administration, UC Davis, Merritt-Peralta Hospitals, Alta Bates, and Herrick Hospital complexes.

Research projects include myocardial flow and metabolism studies by positron emission tomography (PET), tissue parenchymal perfusion development studies by NMR, and study of cerebral vascular disease using new radionuclides. Participants will also work on high-resolution detector development for multilayer PET, development of methods for tissue capillary perfusion in flow imaging using NMR techniques, and investigation of effects of very high fields on the cardiovascular system. We will also undertake the investigation of rapid field changes in the nervous system with respect to hazards of NMR, study of the metabolic pathway changes associated with exercise using ^{13}C NMR, studies of the metabolic pathways associated with hypoxia and ischemia using ^{13}C and ^{19}F compounds. We will also develop new algorithms for construction tomography, taking into account the variation and the point spread functions.

Research Medicine Applications of the Advanced Light Source

THOMAS BUDINGER AND THOMAS HAYES

This program deals with three categories of medical research experiments using existing synchrotron radiation facilities. The objective is to optimize methods of biologic x-ray microscopy at the Advanced Light Source (ALS) by execution of significant medical experiments in existing facilities and thereby provide new data as well as provide end-station facilities for completion of a national user facility. The program will study cellular metabolism, including the role of calcium deposit formation and dissolution in aging, oxidative stress, and pathological conditions of ischemia and hypoxia. An LBL and Brookhaven National Laboratory team recently demonstrated the unique microscopic capabilities of visualizing the distribution of 100-nm calcium-containing particles in stressed heart cells and in cerebral tissue sections from Alzheimer's disease patients. We can also study the microscopic architectural changes in calcium distribution in osteoporosis and the occurrence of calcium particles in arthritic cartilage in animal models in coordination with microscopic NMR. A second focus is the study of intracellular potassium and chlorine ion distribution at resolutions below 100 nm to evaluate basic questions regarding epilepsy and cardiac arrhythmias. The third study involves structural biology studies of cellular structural and electrolyte changes of tissues undergoing freezing and thawing. Cryopreservation and fundamental biology objectives are served by this project. We will study tissues which are known to survive $-196°$ for structural and electrolytic distribution changes during freezing and thawing.

These three goals are accompanied by technological development objectives involving imaging chambers for wet and frozen preparations 4 μm to 7 μm thick in collaboration with the work of Dr. Stephen Rothman. We will maintain cells in controlled chemical environments. These chambers will have environmental control for media, temperature, and gas saturation. The outcome of these methodological development studies will help set the stage for other users of the ALS x-ray microscope beamline(s).

Structural and Metabolic Properties of Human IDL Subspecies
HANNIA CAMPOS

Intermediate density lipoproteins (IDL) are considered transition products generated during lipolysis of very low density lipoproteins (VLDL) and have been associated with coronary artery disease (CAD). We have identified two major IDL subspecies of differing size, density, and composition. This study is designed to test whether levels and properties of potentially atherogenic cholesterol-enriched IDL subspecies are altered as a result of increased fat intake. Our specific objectives are:

- To determine differences in apoE, apoC, and esterified cholesterol content in IDL subspecies separated by immunoaffinity chromatography (using apoB and apoE antibodies) and by fast protein liquid chromatography;

- To determine differences in binding of isolated IDL subspecies to cell surface receptors on hepatocytes (HepG-2 cells); and

- To determine if increased fat intake affects levels or properties of one or both IDL subspecies.

Treatment of Cancer with Heavy Charged Particles
JOESPH CASTRO

This program project will continue research in the use of heavy charged particles such as helium and neon ions for treatment of human cancers.

The physical parameters of protons and helium ions permit precision charged-particle radiation therapy to be delivered, resulting in highly significant clinical advances in the treatment of tumors lying close to critical normal structures in the eye, orbit, skull base, paranasal sinuses, juxtaspinal axes, retroperitoneum or pelvis. Optimization of the use of these low linear energy transfer (LET) charged particles will continue, as LBL beam availability permits, through collaboration with other proton facilities in cooperative clinical trials.

Neon ions, in addition to their dose-localizing properties, offer greater biological effectiveness because of their high LET. We have seen clinical promise in neon ion preliminary trials in bone and soft tissue sarcoma, prostate cancer, salivary gland tumors, skull base tumors such as nasopharynx and paranasal sinus cancers, juxtaspinal tumors, and biliary tract tumors. Prospective trials are under way to determine whether dose localization alone (protons or helium ions) is comparable to dose localization combined with high-LET (neon ions) therapy. We are also comparing neon ions with megavoltage low-LET therapy in treatment of prostate tumors and glioblastoma of the brain.

We expect to achieve added clinical gains through further research and development of improved treatment delivery techniques, specifically implementation of dynamic conformal heavy charged-particle therapy. Potentially, highly significant improvement in high-LET charged-particle therapy will be possible through much improved conformation of the high-LET dose zone to the tumor, with sparing of normal tissues, both proximal and distal to the tumor. We intend to make improvements in treatment planning to implement this highly promising form of charged-particle therapy.

The goals of the program are to optimize low-LET dose-localization therapy with protons and helium ions and to study the application of high-LET beams such as neon ions in the treatment of human cancers.

Raster-Scanning Development for Three-Dimensional Conformal Therapy

WILLIAM CHU

This research will produce significant improvements in beam delivery technology, enabling us to realize the full clinical advantage of heavy charged-particle beams. Specifically, we will develop a raster-scanning beam-spreading system that allows modulation of the spread Bragg peak over the target volume for the implementation of three-dimensional (3D) conformal therapy. The system will not only improve the therapeutic efficacy of the delivered beams but will also increase the versatility of the beam-spreading system for varied clinical situations. To introduce the variable-modulation heavy charged-particle beams for therapy, we will develop new devices, as well as automated control and monitoring systems for safeguarding the patients treated using these devices. In particular, we will:

- Upgrade the power supply of the existing raster scanner magnets to allow modulation of the scanning speed;
- Develop and fabricate a variable collimator which automatically varies the size and shape of the radiation field;
- Develop and fabricate a large-area high-resolution ionization chamber to control and monitor the dose delivered by the raster-scanning system; and

- Integrate the raster scanner with adjustable scan speed, the variable collimator, and the large-area high-resolution ionization chamber into one working system capable of performing 3D conformal therapy. We will accomplish this through the development of control hardware and software and expand the treatment control system for the raster-scanning beam-spreading system to deliver radiation treatments ensuring accuracy, reliability, and patient safety.

The results of the project will provide important and timely transfer of advanced technology to the scientific and medical community, which is now attempting to implement in the clinical environment the heavy charged-particle radiotherapy developed in research institutions.

High-Resolution Positron Emission Tomography Detector Using Solid-State Phototronics
STEPHEN DERENZO

The overall objective of this project is to develop a new block detector module for multilayer, high-resolution positron emission tomography (PET) that provides high resolution over the entire imaging field, high maximum counting rates, and high sensitivity. The advantages over existing block detector designs is a smaller block size, which results in higher maximum coincident event rates, and individual coupling of scintillator crystals to position sensitive photodiodes, which improves the spatial resolution. Special features of this approach are:

- Individual readout of narrow, heavy-atom scintillation crystals for 2-mm spatial resolution, maximum efficiency, and high maximum event rates; and

- Position-sensitive solid-state photodetectors for identifying the crystal of interaction and measuring depth of interaction, thus reducing the position error that causes radial blurring.

This detector design is being developed for the quantitative measurement of tracer compounds with high spatial and temporal resolution to measure specific perfusion and metabolism. This project proposes only to do proof-of-principle studies culminating with testable images. No complete tomographs will be constructed. When completed, we will offer the design to potential collaborators in private industry (CTI, Inc. of Knoxville, TN has already shown interest in this design) who may incorporate it into complete scanners. We believe that the detector module proposed can be used to construct either of the following specific tomographs:

- A human brain imaging tomograph with 2-mm crystals and 2-mm resolution over the entire brain. This tomograph would permit the study of cortical and brain stem biochemistry with sufficient resolution to provide accurate quantitation in 4 x 4 x 5 mm^3 volumes.

- An animal tomograph with 1 mm crystals and 1–1.5 mm resolution. This system would be able to image small animals with unprecedented resolution and approach the goal of *in vivo* autoradiography, in which the animals are used as their own controls.

Improved Instrumentation for Positron Tomography

STEPHEN DERENZO

The objective of this project is the development of advanced detector concepts for the imaging of positron-labeled tracers in humans and animals with substantial improvements in spatial and temporal resolution. Our tomograph designs encircle the patient with multiple rings of detectors having good detection efficiency, good spatial resolution, and low dead time.

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 ultra-high resolution (≤ 2 mm) imaging of tracer compounds in the brain, we are developing a version of the above 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: systematically searching pure and doped heavy-atom compounds to find those exhibiting fast fluorescence; measuring the scintillation properties of optical crystals of promising compounds; and investigating scintillation mechanisms through the use of synchrotron radiation.

We are working with industry on the development of improved positron tomographs; silicon photodiodes; novel solid-state photodetectors; and 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.

Search for Ultra-Fast Heavy Atom Scintillators
STEPHEN DERENZO

The objective of this research is to discover new scintillators with very rapid emissions, high atomic number, high density, and high luminosity. Specifically, we seek a scintillator with the photopeak detection efficiency of BGO, the timing resolution of BaF_2, and the luminosity of NaI(Tl). Our ultimate goal is to improve substantially the capabilities of positron emission tomographs by providing high photopeak efficiency and good spatial resolution, the advantages of time-of-flight information, and good pulse height resolution for scatter rejection. In addition, single photon tomography and conventional nuclear medicine imaging would benefit from a scintillator having higher stopping power and less dead time than NaI(Tl).

While the general physical properties and theory of scintillators are known, there is no known method for predicting scintillation properties of crystals of specific compounds. Thus we have developed a method able to rapidly screen hundreds of available chemical compounds without the costly and time-consuming step of growing scintillation quality crystals. This method uses intense 500-ps bursts of 20- to 30-keV x-rays from a table-top pulsed x-ray generator (available at the Stanford Synchrotron Radiation Laboratory and the Brookhaven National Synchrotron Light Source) to measure the intensity, decay time, and emission spectrum of any fluorescent emissions from powdered samples. We will make our measurements using microchannel phototubes with 55-ps single photoelectron transit time jitter and sapphire faceplates which transmit from 140 nm (far UV) to 650 nm (red). We will place a monochrometer between the sample and the PMT to measure the fluorescence spectrum and the decay time of each spectral component. In a separate experiment, we propose to prepare thin crystals by vacuum evaporation to measure the relative light output and use positron coincidence timing to measure the fluorescence decay time with a resolution of 200 ps. Experiments to determine scintillation mechanisms include excitation by tuneable 6- to 60-eV VUV excitation and both photoelectron spectroscopy and time-resolved fluorescence spectroscopy.

Biokinetics of Strontium/Actinides
PATRICIA DURBIN

Our objective is to advance internal radiation dosimetry and radiation protection. Biokinetic models for the elements provide the means to calculate radiation dose rates and integral doses in the tissues in which they are deposited. These models and their validity depend on reliable measurements (biokinetic data) of initial element distribution and its retention over time in human tissues. Human data adequate for biokinetic modeling do not exist for the actinides, and it is necessary to rely on data from suitable laboratory animals. *Macaca*, a genus of Old World monkeys phylogenetically closely related to man, were the subjects of these experiments. Biokinetic data were obtained from the monkeys after injection of one of the following nuclides: ^{241}Am; 30 adult, 1 d to 6 y post-injection (p.i.); ^{238}Pu, 27 adolescent and adult, 2 d to 3 y p.i.; ^{237}Np, 2 adult, 4 d and 2 y p.i.; ^{90}Sr, 90 growing and adult, 1 d to 19.5 y p.i. Monkeys were managed individually. Radioanalysis of all bones (many subdivided), soft tissues, and excreta, and serial external counting achieved material balances $\geq$ 90% of the injected radioactivity. No live animals remain; we have radioanalyzed all samples; we are completing reduction and entry of numerical data into the computer archive; soft tissue and most sets of bone autoradiographs are complete. Analysis of the numerical data and autoradiographs will quantitatively describe the initial distributions and temporal changes of the study elements in a laboratory animal that is a developmentally, anatomically, and physiologically ideal substitute for man. We will analyze and publish the archived data from this project and will construct mechanistic models to serve as foundations for improved models of the study elements in man and other animals.

Biological Evaluation of New Actinide-Chelating Agents
PATRICIA DURBIN

Alpha-emitting actinides deposited in bone, liver, or lungs (if inhaled) induce cancer. Complexation by transferrin prevents excretion and effectuates deposition in target organs. The only known way to reduce cancer risk is by accelerating actinide excretion with chelating agents. The similar coordination properties of Pu(IV) and Fe(III) indicate that macromolecules containing four bidentate Fe(III)-binding groups should form excretable Pu(IV) complexes at pH 7 but spare essential divalent metals. Ligating groups of microbial iron-sequestering agents (siderophores)—catechol (CAM), hydroxamate (X), and hydroxypyridinone (HOPO)—are being incorporated into octadentate ligands. Molecular backbones are: aminoalkane (spermine, 3,4,3-LI); ethylenediamine (H); triethyleneamine (TREN); desferrioxamine (DFO) to which a fourth group is attached. Solubility and acidity of CAM are increased by additions to the benzene ring: sulfonate, CAM(S); carboxyl, CAM(C); methylamide, MeTAM. We evaluate ligands (injected or oral) in mice for promoting excretion of i.v.-injected $^{238}Pu(IV)$ and for acute toxicity using liver and kidney lesions as endpoints. Among ligands tested, seven promoted more Pu excretion than $CaNa_3$-DTPA at the standard dosage of 30 μmole kg^{-1} injected i.p.; nine given orally were superior to $CaNa_3$-DTPA; six left no Pu residue in kidneys (Pu complexes are stable at low pH); six that were tested at 1/10 to 1/3 the standard dosage were still effective for Pu removal, but $CaNa_3$-DTPA is not. Ten ligands and $CaNa_3$-DTPA were ranked for the following: a) Pu removal after injection, b) Pu removal after gavage, c) percent injected Pu left in kidneys. In order of combined ranking, ligands with better overall Pu removal than $CaNa_3$-DTPA are: 1) 3,4,3-LI(1,2-HOPO); 2) DFO-(1,2-HOPO); 3) 3,4,3-LIMeTAM; 4) 3,4,3-LICAM(S); 5) DFO-MeTAM; 6) 3,4,3-LICAM(C); 7) H(2,2)-MeTAM. Ligands 2, 4, 6 were tested for removal of $^{241}Am(III)$ and $^{237}Np(V)$; they promoted significantly more Np excretion than $CaNa_3$-DTPA, but were essentially ineffective for removing Am. Ligands 1, 3, 4, 5 were acutely toxic if injected at 1000 μmole kg^{-1}, which is 3,000 to 10,000 times their effective dosages. Planned research includes:

- Evaluation of new ligands for Pu removal (syntheses of new ligands containing MeTAM or low-toxicity 2-Me-(3,4-HOPO) are in progress);

- Evaluation or reevaluation of acute toxicity of effective ligands using a revised protocol (10 daily injections of 100 μmole kg^{-1}, which is 300 to 1000 times their effective dosages);

- Biokinetic studies, including GI absorption, of representative effective free ligands using colorimetry of their Fe(III) complexes or ^3H-labeling and, for some ligands, the ^{59}Fe-labeled ferric-ligand complexes; and

- Evaluation of HOPO ligands for removing Am(III) and Np(V).

Vascular and Blood Diseases
SHIRLEY EBBE

A goal of this project is to identify early and advanced vascular lesions in animals by their interaction with radioisotopically labeled substances. Recent work has focused on the tissues of mice during the first few days after irradiation (10.5 Gy, ^{60}Co), and the kidneys have shown an abnormality. ^{111}In-oxine, administered as such or as labeled platelets, accumulated in the kidneys in excess of that found in unirradiated controls; red cells, albumin, and transferrin did not. This mouse model may offer the possibility of detecting and modifying the early effects of radiation, which may, in turn, modify potentially lethal late renal effects.

Abnormalities of platelets, megakaryocytes, leukocytes, and lipids were found in rabbits with Watanabe heritable hyperlipidemia and a deficiency of receptors for low-density lipoprotein (LDL). The findings differed from earlier results in rabbits with dietary hypercholesterolemia (DHc), suggesting that the presence or absence of LDL receptors may affect megakaryocytopoiesis. We are analyzing megakaryocytes in DHc to further test this notion. Platelets from animals or human beings with hypercholesterolemia are commonly found to be hyperreactive to agonists *in vitro*, but it is not known if they are more reactive than normal *in vivo*. Experiments are under way with platelets from rabbits with DHc to determine their reactivity.

We have previously described compensated hypomegakaryocytic states. We have experiments in progress to determine if a superabundance of megakaryocytes can be produced by implanting excess bone and marrow from donor mice. We are seeking evidence for abnormalities of platelets, megakaryocytes, and total marrow mass. Others have found that in the genetic hypomegakaryocytic state of Sl/Sl^d mice, production of a growth factor is specifically defective. The effects of administration of this growth factor will be analyzed to determine the relationship between it and the abnormal megakaryocytopoiesis. It is also planned to determine the effects of extracellular matrix proteins on the production and growth of megakaryocytes in cultures of normal murine bone marrow and marrow from Sl/Sl^d mice.

Effects of Heavy-Particle Radiation

RICHARD LEVY

This project will investigate physical and biologic properties of heavy ions and cellular and metabolic responses in mammalian brain following irradiation, including regulatory control, cell and tissue kinetics, regional cerebral blood flow (rCBF) dynamics, and reaction of the brain to heavy-ion radiation injury. Heavy ions used as neuroscience probes can reveal cell and tissue reaction to radiation injury, including repair, dose-, dose-rate-, and time-dependent responses for induction of central nervous system damage. Our experimental approach includes physics research that examines beam quality, straggling, fragmentation, multiple scattering, and RBE/LET relationships; biophysics research that investigates effects of heavy ions on DNA damage and repair, on protein and lipid membranes under a variety of physical, biologic, and metabolic conditions; cell and tissue kinetics research that examines brain cell kinetic parameters using quantitative histology; nuclear medicine technology that explores anatomic, biochemical, metabolic, and rCBF responses using nuclear magnetic resonance and positron emission tomography.

We hope to characterize neuropathophysiologic responses, regulatory control, and tissue injury and repair in mammalian brain *in vivo*. The results will help with modifying and optimizing treatment strategies for human brain disorders, primarily late delayed radiation injury.

Our future directions include investigating the physical properties of heavy-ion beams. We will study beam quality and RBE/LET relationships for He, C, and Ne ions and cellular and metabolic response in brain following heavy-ion radiation injury and repair. We will investigate dynamics of brain cell proliferation and differentiation, including nucleic acid metabolism, processes of myelination, and homeostasis. We will also examine the pathophysiology, rCBF dynamics, and altered metabolism in irradiated human brain using NMR and PET scanning. We will explore the application of focused charged-particle beams for stereotactic radiosurgery of intracranial vascular and neoplastic disorders in humans. Finally, we will develop applications for heavy charged-particle research and initiate technology transfer for existing and new scientific initiatives in radiation oncology and radiation protection.

Heavy-Ion Radiosurgery
RICHARD LEVY

Our goal is to develop stereotactic heavy charged-particle Bragg peak radiosurgery for treatment of intracranial vascular disorders and brain tumors in humans. We will investigate cerebrovascular reaction to injury in human brain by applying nuclear medicine procedures (CT, NMR, PET imaging) to examine pathophysiologic and metabolic events following heavy-ion irradiation. We will also examine physical properties and beam quality of heavy ions for developing beam-delivery systems for nuclear medicine applications. We will establish RBE/LET, dose-effect, and dose-rate-effect relationships for different sites in human brain. This effort will allow us to modify and influence therapeutic strategies for nuclear medicine application through technology transfer to hospital-based facilities. This work exploits the superior physical and biologic properties of heavy-ion beams in brain compared with protons and photons. Their advantages include sharp lateral and distal borders, less scattering and range straggling for the same range in tissue, minimal dose beyond the target volume, improved dose distribution in Bragg peak, and improved peak-plateau RBE ratios.

We are using stereotactic neuro-imaging procedures (angiography, CT, NMR, PET) to determine the size, shape, location, and metabolic determinants of intracranial targets. We use three-dimensional (3D) conformal charged-particle treatment planning and dosimetry and precise subject immobilization to deliver optimal dose localizations and dose distributions within the brain. We are using nuclear medicine procedures (NMR, PET, Xe-CT) to investigate pathophysiologic and normal CNS tissue reactions to heavy-ion radiation injury.

We have irradiated and followed up over 450 research subjects (including 55 children) with intracranial vascular disorders, with 80–85% cured. We have correlated NMR and PET sequential studies in selected patients and examined adverse sequelae and brain injury mechanisms using nuclear medicine probes. We have conducted comparisons of different radiation types and irradiation geometries for optimal response.

In the future we plan to investigate research procedures with heavy charged particles and investigate the potential for the greater precision afforded by helium ion beams. We will improve advanced 3D conformal treatment planning. We will examine the efficacy of radiosurgery, especially treatment of very large intracranial targets and effects of fractionation, with reduced morbidity. We will study pathophysiologic brain tissue reaction to injury, altered rCBF dynamics, and tissue metabolism following heavy-ion irradiation. We also hope to engage in effective technology transfer to hospital-based programs, including those in development, such as proton beam cancer therapy, and new scientific initiatives, such as boron neutron capture therapy.

Cell and Molecular Biology of Lipoprotein Metabolism

TRUDY FORTE

This is an interdisciplinary training program in cellular, molecular, and biophysical aspects of lipid and lipoprotein metabolism and the process of atherogenesis. It will involve three postdoctoral trainees in the first year, increasing to four in the second year and five in the third and succeeding years. Trainees with a Ph.D., M.D./Ph.D., or M.D. degree are eligible for the program. We expect trainees to have a strong background in either cell and molecular biology, biochemistry, physiology or nutrition in order to be accepted into the program. The program strongly emphasizes "hands-on" bench work in the laboratory of the preceptor. Each trainee must develop a research hypothesis, draft a mini-grant proposal related to the proposed research, and present her or his research at monthly in-house seminars. In addition, trainees must participate in the weekly journal club and seminars related to their field; they are also expected to present their research at national meetings. Research training areas include:

- Molecular biology of transgenic mice using normal and mutant human apolipoprotein genes and studying their influence on the atherosclerosis;
- Cell biology of CHO cells transfected with apoHDL genes to study the intra- and extracellular origins of HDL and their role in reverse cholesterol transport;
- The major physical-chemical determinants of HDL structure using *in vitro* assembly approaches;
- Genetic regulation of IDL and LDL subpopulations;
- Biological oxidation and free radical formation in lipoproteins, cell membranes, and myocardial ischemia and the role of antioxidants in protecting such systems from oxidative stress;
- Development of new stable isotope techniques for the non-invasive measurement of ^{13}carbon and ^{15}nitrogen labeling patterns for intracellular lipids and proteins; and
- Protein and lipid organization in normal and various pathologic red cells.

Upon completion of training, trainees will be very knowledgeable in molecular and cell biology approaches to studying lipoproteins and will also be knowledgeable in physical-chemical methods for assessing lipoproteins and their role in atherogenesis.

Effect of Cigarette Smoke on High-Risk Lipoprotein Profiles
TRUDY FORTE

It is well known that cigarette smoking is an independent risk factor in cardiovascular disease. In heavy smokers, cigarette smoke (CS) gas phase is likely to be absorbed by the lung, thereby initiating CS-dependent oxidative damage to lipid-transporting particles, the plasma lipoproteins. Since lipoproteins are not homogeneous populations of particles but rather are heterogeneous with respect to size, density, lipid composition, and apolipoprotein content, it is likely that various lipoprotein subclasses will respond differently to CS oxidation as a function of their physical-chemical properties. Although never tested, it is possible that certain high-risk plasma lipid profiles which have been shown to predispose individuals to premature cardiovascular disease (e.g., small, dense pattern B LDL and hypertriglyceridemia) may be more susceptible to CS oxidation than normal lipid profiles. These "high-risk profiles" may become even more atherogenic after exposure to CS gas phase. In this program we address the question of whether some subclasses of plasma lipoproteins, especially those associated with high-risk profiles, are more susceptible to oxidative damage by CS than others. Since HDL are known to protect LDL from oxidative damage *in vitro*, we will also examine the question of whether this protective attribute resides with a specific subclass of the HDL, namely the HDL_{2b} subpopulation. In this project we will obtain plasma from subjects with high-risk lipoprotein profiles, including hypertriglyceridemia (elevated VLDL and IDL) and pattern B LDL and incubate the plasma with CS gas phase as a model for what may be occurring *in vivo*. We will use normolipemic plasma as a reference. We will determine the physical-chemical changes induced by CS in various lipoprotein fractions and compare them with control samples. Assays will include: measurement of lipid hydroperoxides, electrophoretic assessment of lipoprotein mobility based on particle charge and size, electrophoretic assessment of protein fragmentation and/or crosslinking, and measurement of lipoprotein composition and phospholipase A2-like activity. We will test the potential increased atherogenicity of specific lipoprotein subclasses, e.g., small dense pattern B LDL, resulting from CS exposure by their uptake and degradation in macrophages via the scavenger receptor. We will test the ability of HDL_{2b} to protect less dense lipoproteins from excessive damage from CS by plasma reconstitution studies wherein we will add known amounts of HDL_{2b} to CS incubations. The proposed studies will provide new insights into the pathophysiology of CS-modified lipoproteins.

Lipoprotein Methodology, Structure, and Function

TRUDY FORTE

The purpose of this program is to train postdoctoral fellows and graduate students in the investigation of lipoprotein structure and metabolism. Our major expectation is that the trainees will be able to pursue independent careers in arteriosclerosis research or related fields.

Postdoctoral trainees participating in this program are required to have backgrounds emphasizing biochemistry, physiology, nutrition, or biophysics. Training is carried out within the research framework of the Lipoprotein Group in Donner Laboratory, Lawrence Berkeley Laboratory, University of California, Berkeley. This group consists of four established investigators and represents combined expertise in the following basic areas of lipoprotein research:

- Development of methodologies for identification and quantification of lipoprotein subpopulations;
- Delineation of the origin, structure, and metabolic fate of HDL subpopulations;
- Delineation of metabolic interconversions and interrelationships of VLDL, IDL, and LDL subpopulations;
- Investigations on regulation of nascent lipoprotein production by cultured liver cells; and
- Identification of genetic and environmental factors which influence the expression of specific lipoprotein subclasses as they relate to dyslipoproteinemia.

Trainees are introduced to each of these areas of research by individual project directors and subsequently proceed to an in-depth research program in one of them. Weekly meetings of staff and trainees are held for discussion of current literature (Journal Club) relevant to their work. Formal Lipoprotein Research Seminars are held biweekly. At these seminars, staff and trainees describe their work in progress; on alternate weeks, a visiting scientist presents a seminar. Trainees are also encouraged to take advantage of the many resources, such as special seminars and courses, available on the Berkeley campus and nearby institutions such as the University of California Medical Center and the Gladstone Foundation.

Postdoctoral trainees entering the training program will have a Ph.D. or M.D. degree. Selection of trainees is based upon the following criteria: predoctoral training, thesis, statement of purpose by the applicant, experience, publications, letters of recommendation, and interviews. The proposed training program is aimed at preparing trainees for future positions such as: university teaching and/or research appointments, clinical research, research in Federal Laboratories or industry, or supervision of clinical laboratories. Predoctoral students are recruited mainly from the Graduate Group in Biophysics and

Medical Physics, which is situated within Donner Laboratory. Upon completion of their degrees, students are encouraged to seek postdoctoral training in outstanding institutions or to pursue further professional training in health-related areas.

The Lipoprotein Group occupies 4800 sq. ft. of laboratory space in Donner Laboratory, which is a biomedical research facility of the Lawrence Berkeley Laboratory located on the University of California campus. This laboratory houses the Department of Biophysics and Medical Physics and is also the site of a major part of the biomedical effort of the Lawrence Berkeley Laboratory operated under a contract with the Department of Energy (DOE). The Lipoprotein Group is the recipient of a National Heart, Lung, and Blood Institute Program Project Grant, thus providing "core" facilities and diverse research programs which constitute the basis for training students. Available "core" facilities include: preparative and analytic ultracentrifuges, computer facility, Gilford autoanalyzer, apolipoprotein isolation and purification technology, immunochemical techniques, and non-denaturing gradient gel electrophoresis technology. Highly specialized techniques for analyzing lipoprotein distribution, structure, and function are also available within the context of individual research programs. An excellent library and mechanical and electronic shops are also on the premises.

Environmental Pollutants and Oxidative Stress

TRUDY FORTE AND RONALD KRAUSS

In the last two decades, there has been a profound increase in energy utilization, which has been paralleled by a large increase in air pollutants. Such atmospheric pollutants represent a hazard to all biological systems. Major concerns have been raised by DOE and other organizations about the substantial increases in energy-related atmospheric CO_2, with its potential for a "greenhouse" effect, and about the accumulation of SO_x and NO_x, which are deleterious to biological systems because of acid rain formation. In addition to the aforementioned pollutants, there has also been an increase in ground ozone, which poses a health threat to humans in our rapidly expanding urban areas. Ozone, a strong oxidant, has been associated with increased risk of lung and cardiovascular diseases. In order to better understand the health effects of ozone, which predispose to premature atherosclerosis and in order to devise strategies to deal with this health problem, we propose to study the effects of ozone-generated oxidative stress on plasma lipoproteins. Previous work has implicated the oxidation of low-density lipoproteins (LDL) in the atherogenic process. Plasma lipoproteins are the major transport system for lipids (cholesterol and fatty acids) required for cell energy, growth, and membrane repair. These lipids are also primary targets for free radicals; the resulting oxidized lipids transported by lipoproteins have the potential not only to promote atherogenesis but to contribute to other health-related problems such as carcinogenesis and aging. Four approaches using *in vitro* systems will be used to assess the biological effects of ozone on lipoproteins:

- Address the question whether plasma from subjects with high-risk lipid profiles, i.e., hypertriglyceridemia, hypercholesteremia, and low-HDL cholesterol are at additional risk from oxidative stress of ozone;

- Determine whether oxidized lipoproteins transform macrophages into foam cells, thus initiating early steps in atherogenesis;

- Investigate whether specific HDL subspecies can protect susceptible lipoproteins against oxidative damage; and

- Test the ability of antioxidants such as vitamin E to ameliorate oxidative modification.

Prebeta-Migrating High-Density Lipoproteins in Plasma
BRIAN ISHIDA

The level of a subtraction of plasma high-density lipoproteins (HDL), termed prebeta-migrating HDL ($HDL_{prebeta}$), is elevated in several forms of dyslipoproteinemia. In man, $HDL_{prebeta}$ mass is correlated with hypercholesterolemia and with triglyceridemia. Elevated levels of $HDL_{prebeta}$ are also induced by the feeding of atherogenic diets in experimental animals. $HDL_{prebeta}$ has been operationally characterized as a small, spherical, very-high-density lipoprotein containing apolipoprotein AI (apoAI), cholesterol, and phospholipid. Hyperlipemic subjects generally display a trend toward decreased total HDL cholesterol (HDL-C) when $HDL_{prebeta}$ is elevated, suggesting a disequilibrium in the metabolic processing of the major HDL subfractions, HDL_2 and HDL_3.

Elevated levels of $HDL_{prebeta}$ are also induced by the feeding of atherogenic diets in experimental animals. In the mouse model of diet-induced atherosclerosis, a single gene known as *Ath-1* controls the level of HDL. In a particular inbred strain, C57BL/6, the diminished HDL results in atherosclerosis, mimicking the human findings. Hence mice of this strain and other strains resistant to diet-induced atherosclerosis (due to high levels of HDL-C) will be compared to identify the role of $HDL_{prebeta}$ in HDL cholesterol metabolism. Studies will include

C57BL/6 mice which are transgenic for the human form of apoAI and which have been "cured" of their inherent genetic predisposition to develop atherosclerosis.

The preliminary observations in man and in animals suggest the following as a working hypothesis: $HDL_{prebeta}$ particles (and related molecular forms) are lipoprotein intermediates which accumulate in pathological lipid states. These lipoproteins are transformed into "mature" HDL_2 and HDL_3 particles in plasma by enzymatic processing events. The transformation process is reversible, allowing for the generation of $HDL_{prebeta}$ particles. The plasma residence time may differ for $HDL_{prebeta}$ and for HDL_2 and HDL_3. Thus elevated levels of $HDL_{prebeta}$ represent a disequilibrium in the synthetic and degradation pathways of HDL. Control of the transformation process can be the basis of future therapeutic goals to reestablish a normal apoAI distribution in dyslipoproteinemias.

Alcohol and Memory: A Positron Emission Tomography Study

WILLIAM JAGUST

Chronic alcoholism is well known to affect cerebral function. Nevertheless, the nosology and pathophysiology of alcohol-related brain impairment syndromes remain confusing and incompletely understood. Classifications of such syndromes have characteristically distinguished Korsakoff's syndrome (KS), described as an amnestic disorder consequent to diencephalic pathology, from alcoholic dementia (AlcD), a global disturbance in cognition which is presumably due to diffuse cortical damage. However, the existence of AlcD as a distinct syndrome is controversial, and the overlap between KS and AlcD has become increasingly apparent, since KS patients show evidence of cortical impairment and AlcD patients show evidence of subcortical damage.

This project will apply the technique of positron emission tomography (PET), combined with careful clinical and neuropsychological characterization of patient groups, to the study of alcohol-related brain impairment syndromes. We will use the PET600 tomograph (2.6-mm resolution) with the glucose metabolic tracer 2-[^{18}F]-fluoro-2-deoxyglucose (FDG) to quantitate regional cerebral metabolic rates for glucose (rCMRglc), thus providing a measurement of regional brain function. The objective of the project is the definition of the brain regions which show impaired function in different alcoholic neurobehavioral syndromes in order to better classify these syndromes as well as understand the mechanisms underlying memory impairment in chronic alcoholism.

The study will include subjects from four groups: non-alcoholic controls, non-demented alcoholics, patients with AlcD, and patients with KS. All subjects will undergo a careful medical and neurological screening examination and will have a battery of cognitive tests designed to characterize and quantitate intellectual deficits. Evaluation of anterograde and retrograde memory, temporal discrimination, and release from proactive interference will be an important part of the test battery. All subjects will have PET-FDG studies as well as magnetic resonance imaging of brain structure. A particular feature of the study is the determination of rate constants for glucose transport and phosphorylation in a subset of patients from each group.

The core hypothesis of this project is the expectation that the relative metabolic impairment of cortical and diencephalic brain regions will define the clinical presentation of the alcoholic neurobehavioral syndromes and will be related to the specific character of memory disorders. This work will have important consequences for classification of the alcoholic neurobehavioral syndromes, which will allow further investigations in the field to proceed on a firmer footing. Characterization of the metabolic bases of these behavioral deficits will also provide important insights into the neural basis of memory function in humans.

Longitudinal Single Positron Emission Computed Tomography and Positron Emission Tomography Studies of Dementia
WILLIAM JAGUST

Positron emission tomography (PET) has increased understanding of Alzheimer's disease (AD) by demonstrating specific abnormalities of regional cerebral blood flow and metabolism. However, these studies have not generally been longitudinal and have been limited to small patient groups; thus questions remain regarding the progression of these changes over time and their relationship to neuropathological abnormalities and clinical progression of the disease. We propose to utilize the more practical and widely available technique of single photon emission computed tomography (SPECT) to follow a large cohort of patients with AD and Parkinson's disease (PD) in order to understand the evolution of regional blood flow changes, their relationship to neuropathology and clinical disease progression, and the relationship of the two diseases to each other.

The project will enroll 30 new AD patients and 20 new PD patients per year for the first three years and follow them with yearly SPECT studies and neuropsychological evaluations for the five years of the study. We will evaluate a total of 90 patients with AD and 60 patients with PD. A group of 26 AD patients is already enrolled in a preliminary study and will continue to be followed and augmented, assuring a long period of observation. We will utilize the blood flow tracer ^{123}I-N-isopropyl-p-iodoamphetamine (IMP) with the Cleon multidetector scanner for SPECT imaging. We will study a subset of twenty patients from each group using PET with the quantitative blood flow tracer ^{122}1-N,N,N'-trimethyl-N'-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine (HIPDM) in order to validate the SPECT studies.

A major hypothesis is that while patients with mild and moderate AD will show temporoparietal blood flow deficits (which will increase in severity as the disease progresses), severely demented patients will also show frontal lobe hypoperfusion. Patients with PD, on the other hand, are expected to demonstrate frontal deficits in early disease stages while a temporoparietal pattern of hypoperfusion will appear in some patients and predict the development of a severe dementia with Alzheimer neuropathological features. We expect these physiological abnormalities to correlate with both the cognitive abnormalities revealed on neuropsychological testing and with the regional histopathological abnormalities seen post-mortem. Of major potential clinical significance is the prospect that different perfusion patterns will identify different clinical subtypes, elucidating the pathophysiological mechanisms responsible for the clinical heterogeneity of these diseases.

Identification and Characterization of Patients with Familial Defective ApoB-100

RONALD KRAUSS

The major aim of this project will be to carry out detailed clinical and biochemical characterization of patients with familial defective apoB-100. All affected subjects and family members will undergo a thorough medical evaluation, with particular emphasis on detecting presence of xanthomas and clinical evidence for cardiovascular disease. Laboratory characterization will include quantitation of plasma total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, apoB, apoAI, and apoE. We will determine apoE isoform phenotype by isoelectric focusing. We will assess electrophoretic mobility of plasma lipoproteins by agarose electrophoresis. We will use analytic ultracentrifugation to measure mass of VLDL, IDL, LDL, and HDL, as well as subtractions of these lipoproteins. We will also assess distribution of major VLDL, IDL, LDL, and HDL subspecies, as well as mass of Lp(a), by non-denaturing gradient gel electrophoresis. In addition, we plan to isolate major lipoprotein classes and subclasses by preparative and density gradient ultracentrifugation and to analyze lipid and apoprotein composition of these fractions. Finally, we will use density gradient ultracentrifugation to achieve further purification of LDL particles containing defective apoB-100

Lipoprotein Subclasses: Structure, Origin, and Metabolism
RONALD KRAUSS

The principal aim of this program is to delineate the processes that give rise to the multiple subclasses of human plasma lipoproteins, thereby to better understand the influence of genetic and environmental factors on plasma lipid transport and the development of atherosclerosis. We will use a wide range of scientific disciplines and experimental approaches, including molecular genetics, metabolism, cell biology, biochemistry, and biophysics. The program is organized into three highly interactive projects and three core units which provide support services used by each of the projects. Project 1 is aimed at determining the influence of genetic and metabolic factors on the distribution and properties of human low-density lipoprotein (LDL) subclasses. We intend to investigate in detail the structural, metabolic, and genetic implications of recently demonstrated differences in glycosylation of apolipoprotein (apo) B across the LDL particle spectrum. We will also use primary hepatocyte cultures to further investigate the relationship of varying apoB glycosylation with LDL subclass formation and metabolism. In Project 2, we will investigate the *in vivo* origins of HDL subclasses, their structural and regulatory determinants, and their influence on lipoprotein metabolism and atherosclerosis in transgenic mice carrying the human genes for apoAI and apoAII, the major HDL protein constituents. We will employ cell culture systems in Project 3 to delineate the cellular origins of apo-specific HDL subpopulations, the role of these subpopulations in cholesterol uptake, and the influence of apoAI and apoAII gene expression on these processes. The Lipoprotein Analysis Core will provide standardized measurements of lipids, lipoproteins, and apolipoproteins for all projects and will also serve as a resource for specialized analytic and preparative procedures. The Cell Culture Core will maintain and provide monolayer cultures of cells as needed for specific projects and will provide conditioned media for isolation of lipoprotein products.

Plasma Lipoproteins in Coronary Artery Disease
RONALD KRAUSS

The major goal of this project is to determine the extent to which changes in plasma levels of specific lipoproteins, lipoprotein subspecies, and apolipoproteins are associated with quantitative changes in coronary atherosclerosis during the course of a controlled four-year risk-factor intervention program.

The study group consists of 300 patients admitted to Stanford University Medical Center for management of coronary artery disease (transluminal percutaneous coronary angioplasty, coronary artery bypass surgery, or medical treatment). We have carried out coronary angiography and computerized quantitation of non-bypassed or non-dilated coronary artery segments at baseline on all subjects and will repeat examination at four years following medical management (all subjects) and intensive multiple-risk-factor intervention (one-half of the subjects, randomly assigned) according to a protocol which is being carried out under separate funding at Stanford. The special intervention program at Stanford includes improved nutrition, weight reduction, increased aerobic exercise, stress management, and individualized treatment, including pharmacologic reduction of low-density lipoprotein cholesterol, elimination of cigarette use, and reduction of hypertension.

We performed initial lipoprotein analyses on all 300 subjects one to three weeks after medical stabilization, or six weeks after surgery, and analyses are being repeated annually during four years of follow-up. In addition, we will obtain pre-treatment samples on all subjects beginning HMG CoA reductase-inhibitor treatment. We will measure subtractions of plasma very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density (LDL), and high-density lipoprotein (HDL) by analytic ultracentrifugation with a computer-based quantitation procedure. We also measure LDL and HDL subspecies by high-resolution polyacrylamide gradient gel electrophoresis. We measure apolipoproteins (apo) AI, AII, and B in plasma and apoB in LDL by immunoassay. Analysis of lipid and lipoprotein measurements in relation to changes in coronary atherosclerosis will make it possible to identify those lipoprotein parameters most closely involved in the disease process. The results will also indicate whether detailed measurements of specific lipoprotein subclasses and apolipoproteins are more informative than conventional lipid measurements in predicting changes in coronary artery disease and in assessing the effects of strategies directed at its prevention and treatment.

Training Center for Clinical Management of Lipid Disorders

RONALD KRAUSS

Most efforts to educate physicians about lipid disorders, such as the National Cholesterol Education Program, have been targeted to all physicians, with emphasis on those providing primary care. Experience with such programs had indicated a gap in lipid practice between the community physician engaged in primary care and the lipid specialist practicing at a tertiary referral center. While the primary care physician can readily manage the majority of patients with high cholesterol or triglyceride levels, the remaining cases still exceed the capacity of the fifty or so regional lipid clinics in the U.S.

To fill this gap, we need to develop local community expertise in lipid disorders. The concept of the intermediate clinical lipid specialist has emerged—a physician who can establish a standard of practice as an opinion leader in large and small communities. A new training program in lipid disorders initiated by the American Heart Association (AHA) is intended to help meet this need.

Six regional lipid centers were chosen as AHA Training Centers for Clinical Management of Lipid Disorders on the basis of peer-reviewed competitive applications. Each center will provide in-depth education in pathophysiology, diagnosis, and management of a wide spectrum of lipoprotein disorders to approximately 80 physicians per year.

The Cholesterol Research Center at LBL is a key component of the AHA Training Center based at the Gladstone Foundation Laboratories. Dr. Ronald Krauss, Director of the Cholesterol Research Center, is Co-Director of the AHA Training Center Program with Dr. Robert Mahley of the Gladstone Foundation Laboratories. Researchers at LBL have developed unique lipoprotein analytical procedures and established the LBL Cholesterol Research Center as an outpatient clinical research facility to apply these procedures in the investigation of disease mechanisms. The information and technology developed at LBL will be made available to the medical community as a result of the AHA Training Center Program.

Brain N-Acetyl-L-Aspartic Acid in Dementia
POW KWO-ON-YUEN

The purpose of the study is to measure regional brain concentrations of N-acetyl-L-aspartic acid (NAA) in Alzheimer's disease (AD) in order to explore the use of quantitative determination of NAA as a method of studying cell loss. The proposed research will characterize the regional concentrations of NAA in post-mortem brain tissue of patients with AD.

NAA is a nominal constituent of neurons but not of other brain cells. We can readily quantitate it using *in vitro* and *in vivo* nuclear magnetic resonance (NMR) spectroscopy. Because of well-described neuronal loss, which is seen in AD, we expect regional NAA concentrations to reflect neuronal numbers and, in turn, the severity of dementia. Our specific aims are:

- To measure the regional concentrations of NAA in post-mortem brains of patients with AD and in non-demented controls;
- To study the association between regional brain NAA concentrations and neuronal cell counts in AD; and
- To investigate the association between regional brain NAA concentrations and the severity of dementia in AD.

Cortical and white matter tissue samples will be obtained from four preselected areas of autopsy brains from 30 patients with pathologically verified AD and 30 non-demented controls of comparable age group. The AD sample will consist of patients who have been clinically diagnosed and followed up yearly until death. We will excise brain tissue samples for NAA determination at autopsy, and the remaining brain will be fixed in formalin for subsequent pathological verification and neuronal cell counts of the areas immediately adjacent to those sampled for NAA analyses. The areas chosen will correspond to Brodmann areas 17, 9, 22, and 28, representing areas with increasing pathological predilection in Alzheimer's disease. We will quantitatively determine NAA using high-resolution proton NMR spectroscopy of excised tissues after perchloric acid extraction. We will perform cell counts on cresyl violet stained sections using a Quantimet 920 image analyzer.

While limited results of proton NMR spectra have been published on young subjects, such data on older individuals are currently lacking. In addition, the study of NAA and its relationship to age, to the presence of dementia, and to the severity of dementia has not been performed. We seek to demonstrate that the proton spectra from cortical tissue of patients with AD will be different from controls. We hypothesize that:

- Significantly reduced NAA concentrations will be observed from areas of maximal predilection in AD;
- These reductions will correlate with the degree of neuronal loss; and
- These reductions will parallel the clinical severity of the disease during life.

The experimental results will provide validated *in vitro* data to further the development of *in vivo* proton spectroscopic images of NAA as a means of quantitating neuronal loss in AD that can be extended to other degenerative diseases.

Biological Effects of Magnetic Fields
ROBERT LIBURDY

We are investigating mechanisms of interaction of ultrahigh intensity, ultrahigh frequency, and ultrafast switched magnetic fields with biological systems. We are employing exposure frequencies ranging from DC to GHz, and our research includes study of animal, tissue, and cellular systems. This research supports exposure guidelines for industrial, research, and medical environments. New biotechnologies based on the above magnetic field interactions have been developed, and advances have been made in drug delivery, high-pressure liquid chromatography (HPLC), and spectroscopy of living cells.

Studies at the cellular level indicate that rat lymphocytes when activated by mitogen to undergo signal transduction show decreased calcium influx during 60-minute treatment in static magnetic fields of 7.5 and 9.0 T, but not at 2.3 T Activated rat and human lymphocytes exposed to nuclear magnetic resonance (NMR) imaging fields (2.3 T DC; 1 T/sec, dB/dt; 100 Mhz, 64 uT, RF) show increased calcium influx; individual fields show no detectable effect. We are investigating field combinations, which appear to play an important role. Whole animal exposures to these NMR imaging fields lead to no effect on blood-brain permeability in the rat. We have set up two advanced fluorescence microscopy systems to perform quantitative photometry and digital imaging of cells during exposure to electric and magnetic fields. Technology transfer is evolving in two areas: microwave-triggered drug delivery from liposome vesicles which has potential for cancer therapy and pulsed-field HPLC, which separates large biopolymers such as DNA faster than pulsed-field gel electrophoresis.

Future bioeffects studies will focus on using fluorescent probes to quantitate, at the single-cell level, effects of electric and magnetic fields on lymphocyte signal transduction processes. We plan to perform the first single-cell measurements of $[Ca^{2+}]_i$ in lymphocytes exposed to static magnetic fields up to 9.0 T and to ultrafast switched magnetic fields up to 1000 T/s; both are being considered in advanced NMR imaging systems. In addition, we will follow biochemical markers of lymphocyte activation such as inositol phosphate production, protein kinase C activation, and subsequent DNA synthesis. We plan to pursue biotechnology transfer of microwave-triggered drug delivery and pulsed-field HPLC with industry.

Electromagnetic Field Effects on Cells

ROBERT LIBURDY

We are investigating the lymphocyte cell membrane as a direct, molecular-level site of interaction for extremely-low-frequency (ELF) electromagnetic fields. The hypothesis we are testing is that membrane signal-transduction processes are targets for ELF field interaction. We have found that ELF fields alter calcium-dependent signal transduction events and that this response is fundamentally linked to the ***biological state*** of the lymphocyte (i.e., lymphocyte mitogen activation). We have recently obtained evidence that the induced electric field, and not the applied magnetic field flux density, is the important field exposure parameter. This finding relates directly to interaction mechanisms and to guidance in setting human safety standards. Recently we have reported that sinusoidal 60-Hz fields alter calcium metabolism during signal transduction. This is a fundamental finding, since signal transduction at the cell surface is the first event in a cell's interactions with the environment. We observed that 60-Hz field exposures significantly increased calcium transport in thymic lymphocytes, and most recently $[Ca^{2+}]_i$, but only when these cells are exposed in the presence of the mitogen, *Concanavalin A*. This indicates that the ELF field acts as a *co-mitogen*; this is an important finding, since any agent that alters the process of mitogenesis can have a direct effect on the process of carcinogenesis. Future research will address a number of important biological and engineering questions:

- What is the dose response for the electric field metric?
- What is the temporal dependence of ELF exposure?
- Are there field effects on mitogen binding effects?
- Which signal transduction pathways are involved in the alteration of calcium signaling?
- Is there a membrane phase transition (temperature) dependence?
- What specific biological factors influence the ELF response?
- What is the role that animal age plays in the lymphocyte response to ELF fields?

To perform single-cell measurements quantitatively we have recently developed a fluorescence microscope spectrophotometer system for these studies. A five-laboratory consortium has been organized, termed the *ELF In Vitro Group*, to facilitate replication of important *in vitro* experiments. A first group study will be a calcium experiment based on findings in our laboratory.

High-Field Bioeffects—Lymphocyte Ca^{2+} Metabolism
ROBERT LIBURDY

We have shown that electromagnetic fields from a high-field nuclear magnetic resonance (NMR) imaging instrument (Static: 2.3 T; RF: 100 MHz; Gradient Field: 1.0 T/s at 1 mT; 60 min exposure at 37°C) enhance calcium transport *in vitro* in rat thymocytes and in human peripheral blood lymphocytes. Additional studies indicate that thymocytes from mature rats, compared with juvenile rats, respond more vigorously. Spectral analysis of the NMR gradient field indicates that extremely-low-frequency (ELF) components at 20, 40, and 60 Hz are prominent in the NMR imaging exposure. Independently, we show that a 60-Hz sinusoidal magnetic field can stimulate calcium transport in the rat thymocyte.

These findings demonstrate for the first time that high-field NMR signals can stimulate net calcium transport in the lymphocyte, particularly in the mature lymphocyte, and that non-thermal ELF components in the NMR gradient field may play a role in this response.

We will study rodent and human lymphocytes to:

- Determine whether the static, gradient, and/or RF field(s) contribute to this calcium response and then establish a threshold value;

- Characterize the age-dependence for rodent and human lymphocyte responses;

- Characterize the alteration of the following membrane signal transduction events (since calcium is an important second messenger): $[Ca^{2+}]_i$, inositol 1,4,5-triphosphate turnover, and protein kinase C activation; and

- Determine, importantly, whether subsequent DNA and protein synthesis is altered.

This research will carefully define lymphocyte responses to electromagnetic fields associated with high-field NMR. It should assist future design efforts for emerging high-field NMR systems.

Fluorodeoxyglucose Kinetics in Myocardium

ROBERT MARSHALL

The overall goal of this proposal is to use an isolated, isovolumic retrograde blood-perfused rabbit heart to evaluate the stability of the lumped constant in the ^{18}F-2-fluoro-deoxyglucose (FDG) tracer kinetic model and the ability of the model to accurately measure exogenous glucose metabolism under conditions of altered substrate supply, coronary blood flow, and mechanical workload. The FDG tracer kinetic model requires three different parameter measurements to estimate glucose consumption:

- The lumped constant;
- The rate constants describing exchange between the three compartments of the model; and
- Tissue ^{18}FDG content.

We will measure these three parameters in an *in vitro* preparation to evaluate their accuracy and reproducibility. Once these parameters are known, we will use the lumped constant, together with independently determined plasma glucose and FDG concentrations and the model-predicted tissue FDG-6-O_4, with the FDG operational equation to compute exogenous glucose consumption from a single measurement of tissue ^{18}F content. We will also evaluate two other methods of computing myocardial glucose consumption. We will compare the results of all three approaches to the Fick-determined glucose metabolic rate.

In the first project, we will investigate the possibility that 2-^{3}H-glucose can be used to assess the rate constants of glucose membrane transport and phosphorylation using the FDG model. We hypothesize that 2-^{3}H-glucose undergoes only membrane transport and phosphorylation in its labeled form because of the documented rapid exchange of ^{3}H-label in the 2 position with unlabeled cytoplasmic water during the hexose isomerase reaction. In the second and fourth projects, we will evaluate the stability of the lumped constant under conditions in which available evidence suggests its possible instability. In the second project, we will evaluate the lumped constant in the presence and absence of insulin in order to change the rate-limiting step in FDG extraction from the phosphorylation reaction to membrane transport. In the fourth project, we will determine the stability of the lumped constant under altered cardiac loading and blood flow conditions. The third and fifth projects will evaluate the ability of the model to accurately measure myocardial glucose consumption under conditions that are identical to those used for evaluation of the lumped constant. Completion of these projects should provide new information which might help in the use of FDG and positron emission tomography to quantify glucose utilization in patients.

Serotonin Uptake Inhibitor Ligands for PET Studies
CHESTER MATHIS

Positron emission tomography (PET) studies of cerebral receptors hold great promise in helping to identify the role of receptor defects in many diseases. To date, postsynaptic receptors have been the focus of PET investigations partly because appropriate radioligands are available. Studies of presynaptic binding sites can provide additional insight into the pathogenesis of certain diseases which result in the selective death of brain neurons and decreases in their axonal projections. This project proposes to develop presynaptic radioligands which bind to the serotonin re-uptake complex in the brain and, hence, will reflect the density of viable serotonin neurons *in vivo* for use in PET studies. The eventual long-term goal of this research is the application of these radioligands to PET studies of disorders such as Alzheimer's and Parkinson's diseases, which have been shown to involve serotonergic deficits. We anticipate that the radioligands developed in this work will assist in the understanding of the evolution and clinical progression of these diseases when used in concert with other radiopharmaceuticals in PET studies.

We will synthesize various cold (non-radioactive) chemical analogs of paroxetine, a serotonin presynaptic uptake site inhibitor. The analogs will contain fluorine in a position capable of rapid radiofluorination with high specific activity ^{18}F-fluoride (a short-lived positron emitter with a 110-min half-life). We will evaluate the binding characteristics of these compounds *in vitro* to determine their potential as radioligands for PET studies. We will radiolabel with tritium those compounds which demonstrate a high presynaptic serotonin uptake site affinity using *in vitro* competitive binding techniques. We will then use the tritium-labeled compound in further studies to assess other *in vitro* binding parameters, such as B_{max} and K_d, as well as to determine its *in vivo* whole body distribution, brain localization, pharmacological specificity, and metabolism in rats. As a next step, we will label with high specific activity ^{18}F those compounds displaying promising characteristics *in vitro* and in rat studies and utilize them in PET regional localization investigations in a monkey.

We will determine the presynaptic uptake site densities and dissociation binding constant for the agent in the monkey. We will compare PET studies in control monkeys and serotonergic neurotoxin-treated animals to determine the efficacy of the compound as a potential serotonin uptake site ligand for future PET investigations in humans.

Study of Scintillation Mechanisms for Positron Emission Tomography

WILLIAM MOSES

We will study the scintillation mechanisms of heavy-atom inorganic scintillators, with the ultimate goal of refining a theory to predict denser, faster, and more luminous scintillators for medical imaging instrumentation. Radionuclide imaging devices, such as positron emission tomography (PET) and single positron emission computed tomography (SPECT) imagers, are currently limited by the photon detectors, primarily the scintillator. If a scintillator with high density, fast decay time, and large light output were engineered, it would lead to PET and SPECT cameras capable of much finer spatial and temporal resolution, higher event rates, and improved quantitation.

Earlier work has attempted to discover such a scintillator with an empirical search, but despite finding two new scintillators, we feel that more theoretical understanding is necessary. Virtually all heavy-atom scintillators were discovered by empirical searches or by chance; sodium iodide (NaI[Tl]) is the only such scintillator that was designed and developed. Part of the reason for this paucity of theoretical guidance is that until recently, the dominant scintillation mechanism was thought to be a process that is extremely difficult to model. However, a new, ultra-fast scintillation mechanism was discovered and described a few years ago. This mechanism relies only on the relative positions of electron energy bands, so it should be able to predict the scintillation properties of a compound once its electron energy bands are known. If one alters the position of these bands by the addition of dopants, it may also be possible to enhance the scintillation properties of a compound.

The predictive power of this new theory has not yet been realized because experimental measurements of electron energy bands are needed before the theory can be applied to candidate compounds. We propose to use two standard synchrotron light source techniques, known as ultraviolet photoelectron emission spectroscopy and ultraviolet spectroscopy, to probe the energy bands of several newly discovered scintillators to determine their scintillation mechanisms. We also intend to investigate the effect of dopants on these energy bands, in hopes that the energy level shifts induced by these dopants will enhance the scintillation process and lead to the development of a new scintillator.

Apolipoprotein-Specific HDL and Cholesterol Transport
ALEX NICHOLS

Ultimate understanding of the anti-atherogenic role of plasma high density lipoproteins (HDL) depends, in large part, on an appreciation of how HDL structure and metabolism affect intravascular and extravascular cholesterol redistribution. Specificity of HDL metabolism and function is closely linked to their apolipoprotein composition, and two major apolipoprotein-specific populations have recently been described. We will investigate, by use of model and native lipoprotein particles, the physical-chemical and metabolic bases for speciation, remodeling, and function in cholesterol redistribution of nascent and plasma apolipoprotein-specific HDL populations. In view of the important linkages between triglyceride (TG) metabolism and plasma HDL, our research emphasizes understanding how lipolysis-derived products of metabolism of TG-rich particles influence nascent and plasma apolipoprotein-specific HDL metabolism and function in cholesterol transport. Since secretory pathways appear to enrich nascent HDL subpopulations in specific phospholipids, such as phosphatidylethanolamine (PE) and lysoPE, as well as other lipolysis-derived products, we will investigate their influence on structure and metabolism of the model nascent apolipoprotein-specific HDL subpopulations. We will perform reassembly of single and hybrid apolipoprotein analogs of nascent HDL mainly by the cholate-dialysis method. We will isolate apolipoprotein-specific model and plasma HDL particles by immunoaffinity chromatography and further fractionate them by FPLC or gel filtration chromatography. Purified preparations of lecithin:cholesterol acyltransferase, cholesteryl ester and phospholipid transfer proteins, and hepatic lipase will be used for *in vitro* metabolic studies. We will analyze control particles and conversion products using gradient gel electrophoresis, electron microscopy, circular dichroism, immunoassay of apoAI epitope exposure, apolipoprotein immunoassays, and lipid assays by gas-liquid chromatography and standard techniques. Our rationale for emphasizing the model system approach is that it provides ample, well-defined material, together with tight control of experimental variables, and has already proven highly informative in delineating origins of plasma apoAI without apoAII HDL subpopulations. Lastly, this work will provide new information on differential behavior of HDL particles at the cellular level. We will use the macrophage-like cell line THP-1 and primary human monocyte-derived macrophage cells to investigate compositional determinants of apolipoprotein-specific HDL in effecting cholesterol efflux from cholesterol-laden macrophage cells.

Hippocampal Metabolism in Schizophrenia

THOMAS NORDAHL

Recent data, obtained by magnetic resonance imaging (MRI), positron emission tomography (PET), electrophysiological methods, and post-mortem examination, suggest that there may be an abnormality in the anterior hippocampal region (including amygdala) in schizophrenia. Hippocampal involvement in schizophrenia is supported by findings indicating that lesions in or stimulation of the hippocampal region can cause symptoms typical of schizophrenia. There is evidence that antipsychotic agents, such as remoxipride and clozapine, may act upon the mesolimbic dopamine system, and this lends support to the notion that a functional hippocampal defect in patients with schizophrenia may be a causative factor in the typical symptoms of schizophrenia. Also, myelination of cortico-hippocampal relays occurs during late adolescence, generally the earliest time of onset of psychotic symptoms in patients with schizophrenia. Prefrontal decrease in regional cerebral metabolic rate of glucose (rCMRglc) measured by PET has been noted in some studies of chronic, medication-free patients. This could be related to a defect in the hippocampal region.

This project will use the high-resolution (2.6-mm) 600-crystal PET (PET-600) and the tracer [F-18]-2-fluoro-2-deoxyglucose (FDG) for the measurement of rCMRglc in schizophrenia. We will correlate rCMRglc in the hippocampal region with typical symptoms of schizophrenia in order to test the hypothesis that the hippocampal function is involved in producing these symptoms. We will also study the effects of two anti-psychotic agents, remoxipride and haloperidol, on hippocampal, limbic, and striatal glucose metabolism in schizophrenia.

A total of twenty-four normal subjects and twenty-four patients with schizophrenia will be studied over a four-year period. We plan to study twelve of the patients after a two-week medication-free period and again after six weeks of treatment with remoxipride. We will study the remaining twelve patients after two weeks free of medication and again after six weeks of treatment with haloperidol.

This project is focused on the investigation of hippocampal metabolism in schizophrenia, seeking to localize functional abnormalities. We will study the relationship of the anterior hippocampal region (including amygdala) and the striatal region rCMRglc with psychotic and motor symptoms of schizophrenia.

Multiple Scattering in Three-Dimensional Charged-Particle TMT Planning
PAULA PETTI

Since charged particles deposit most of their energy at the end of their range in a sharp Bragg peak, charged-particle radiotherapy is ideal for the treatment of deep-seated tumors or tumors situated near critical normal structures. In heterogeneous media, however, physical processes such as multiple scattering can cause significant deterioration of the Bragg peak and can compromise the dose-localizing potential of charged-particle beams. In the proposed investigations, we will use Monte Carlo techniques to study the multiple-scattering effects in simulated patient geometries, determine optimal beam-line configurations to minimize these effects, and devise a truly three-dimensional (3D) dose-calculation algorithm which reflects the degradation in the Bragg peak due to multiple scattering in heterogeneous media. To accomplish these goals, we will develop a charged-particle Monte Carlo code incorporating multiple scattering and fragmentation processes. In this code, we will represent any volume as a collection of small volume elements (voxels), allowing us to describe relatively complicated geometries. In particular, it will be possible to utilize CT data directly. We will verify the Monte Carlo code through benchmark measurements in simple phantoms. The ultimate goal of this research is to use calculated Monte Carlo data to develop and evaluate new, truly 3D, dose-calculation models for charged-particle radiotherapy.

Application of X-Ray Microscopy to Study Protein Secretion
STEPHEN ROTHMAN

Our biological research program seeks to establish common ground to study substantive biological problems with emerging x-ray microscope techniques and to develop the necessary tools to do so effectively. We have chosen our problems to be interesting in the broad biological sense, to technically advance the method for biological research, and yet have features amenable to study with a developing methodology. We have been working with colleagues at the National Synchrotron Light Source (NSLS), while at the same time aiming at more advanced capabilities at the Advanced Light Source (ALS) in Berkeley. Our initial experiments centered around an important proof-of-principle for the method: imaging biological samples in the native state (in physiological environments) at high resolution. We have also been able to make use of the elemental information provided by the method to obtain quantitative values for the protein content of single cellular organelles. Our success 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 focused our efforts on the central cellular processes of protein secretion and intracellular transport. Although widely studied by other methods, numerous uncertainties still remain, including difficulties in directly observing certain events. Importantly, the study of protein transport and secretion requires the native-state conditions that x-ray microscopy allows, and offers significant opportunities for spectroscopy and chemical identification and quantification. These processes are also a useful choice in that they involve spatial features that span the resolution capabilities of x-ray imaging. Recently, we have been able to carry out dynamic imaging at high resolution for the first time to our knowledge with any microscopy, and follow time-resolved changes, both morphologic and quantitative (chemical) within single subcellular biological structures. These observations depended on our development of a special environmental chamber (LBL Wet Cell) for the microscope. Our next steps include further observations on the secretion process, measuring ion fluxes and distribution, applying three-dimensional stereoscopic imaging, and examining new biological samples. This research program is not intended to cover the construction of an x-ray microscope at the ALS, but we expect to provide valuable input regarding its design from a biological perspective.

Development of NMR-Assisted Cryosurgery

BORIS RUBINSKY

The objective of this project is to develop the technique of nuclear magnetic resonance (NMR)-assisted cryosurgery and to demonstrate its effectiveness for creating a definable zone of necrosis in three typical organ tissues. Cryosurgery is a treatment in which cancerous tumors are frozen and then left *in situ* to be absorbed. It can be highly effective in treating solid tumors and can offer hope when other treatments are ineffective. However, the application of cryosurgery to deep body tissues is prevented by the inability to observe the transient, irregular shape of the frozen region during treatment and by an inability to know the exact relation between the frozen region and the destroyed tissue. The eventual goal of this project is to provide the cryosurgeon with the ability to plan optimal freezing protocols and then observe and modify the freezing process during the cryosurgical treatment of cancerous tumors.

The project will develop fast NMR imaging techniques for monitoring the extent of freezing in real time and in three dimensions. Gelatin phantoms, rabbits, and dogs will serve as experimental models. We intend to study brain, liver, and prostate tissues because cryosurgery could be used effectively in these three tissues. Special cryosurgical probes will be developed to satisfy the requirement that no metallic materials be used inside an NMR magnet bore. In order to establish the effectiveness of the NMR imaging to predict the extent of tissue destruction, we will evaluate post-cryosurgical changes in tissue viability over a period of hours to days after freezing using standard histologic and electron microscopic analytic techniques. We will correlate the results of these analyses with ^{1}H NMR images obtained during and after freezing. We will develop a mathematical model of the temperature distribution in both the frozen and unfrozen regions and solve it in three dimensions using the finite enthalpy technique. We will implement the model on a computer for the purpose of pre-treatment planning. We will also develop a model that computes temperature distribution using the boundary at the frozen region detected by NMR imaging for monitoring and controlling cryosurgical procedures.

Successful completion of this project will establish NMR imaging as an effective means of monitoring the cryosurgical freezing process and provide a basis for the clinical application of cryosurgery to solid tumors located in the brain or internal organs.

The Methyl Carbon Pathway in Psychosis
THORNTON SARGENT

Many of the hypotheses of the cause of schizophrenia have involved abnormalities of methyl carbon metabolism; this project is designed to examine the role of the methyl carbon pathway in schizophrenia and other psychoses. While dopaminergic systems are clearly involved in both schizophrenia and affective disorders, there is as yet no clear indication of a specific biochemical defect by which the genetic determinants are expressed. Based on previous work in our laboratory which indicates an abnormality in the methyl carbon pathway, we have designed this project to determine the site of abnormal methyl carbon oxidation in psychosis by administering specific ^{14}C-labeled pathway intermediates to patients *in vivo*. A defect in methyl metabolism could affect dopaminergic function by a number of mechanisms, such as a consequent inability of catechol-O-methyl transferase to inactivate dopamine or disturbance of receptors via a defect in membrane phospholipid methylation. It could also be the resultant effect of diversion of methyl groups to methylate an expanded pool of metabolites requiring methylation. Demonstration of a causative defect in psychoses would enable design of more effective therapeutic interventions to alleviate these chronic debilitating diseases. By administering radiolabeled metabolic intermediates to unmedicated patients under dietary control and measuring the expired $^{14}CO_2$ and the rate of appearance of ^{14}C in metabolites in plasma, a determination will be made as to the integrity of different metabolic steps in the methyl carbon pathway. If one or more specific metabolic defects are demonstrated in patients with schizophrenia, we will study patients with affective disorders at the end of the project to examine the possibility of a unitary cause of psychosis or of different methyl metabolism errors. We will examine the pathways in animals using labeled precursors, after pretreating the animals with selected inhibitors and loading doses of metabolites; ^{14}C in CO_2 and metabolites in plasma and in organs will be measured. We have developed high pressure liquid chromatography (HPLC) separations for pathway intermediates, and we will use a new Accelerator Mass Spectrometry (AMS) method for high sensitivity ^{14}C counting. We will use the data from the above observations to formulate an appropriate kinetic model that describes the methyl carbon pathway and to determine the range of rate constants associated with psychosis.

The Production and Characterization of apoAII Transgenic Mice

Subcontract from Harvard School of Public Health

JOSHUA SCHULTZ

The aim of this investigation is to construct genetically engineered transgenic C57BL/6 mice expressing high levels of a human apoAII gene and subsequently examine the role that transgenic apoAII plays in determining the structure of high-density lipoprotein (HDL) particles; affecting levels of HDL and other apolipoproteins; and protecting transgenic mice from atherosclerosis. These studies will provide an *in vivo* model system to test the hypothesis that the structure of HDL and the susceptibility to atherosclerosis can be directly influenced by changes in the plasma apoAII levels. In addition, such an approach should provide a means of determining molecular mechanisms underlying the origins, properties, and significance of HDL subclasses. Ultimately, the proposed research will allow us to assess the *in vivo* effect of increased plasma apoAII on the susceptibility to atherosclerosis in response to diet.

Role of Nutrients in Biosphere's Response to Global Change

SCOTT TAYLOR

Current models that predict an enhancement of plant productivity due to fossil-fuel-induced changes in the global climate are inadequate. To predict the response of the biosphere to elevations in atmospheric carbon dioxide and temperature levels, it is important that one identify and quantify all factors that influence the development and productivity of the various ecosystems. The current modeling schemes do not fully take into consideration the role nutrient availability plays in controlling both plant growth and photosynthetic capacity. In terrestrial plant communities limited nutrient availability, especially nitrogen or phosphorus deficiency, is quite common. The conclusion that plants will respond to an enriched CO_2 atmosphere with an increase in productivity is based in large part upon studies utilizing well-fertilized plants. A program investigating the role nutrient deficiencies play in mitigating a plant's response to climatic changes needs to be completed before valid predictive models of biosphere/climate interactions can be developed.

We propose to examine how nitrogen or phosphorus deficiency influences the response of various plant species to increases in ambient CO_2 and temperature. Using a variety of *in vivo* and biochemical techniques, we will measure photosynthetic CO_2 assimilation, photochemical activity, respiration, carbon partitioning and export, and growth parameters in plants grown under different phosphorus and nitrogen regimes and at differing temperature and CO_2 levels. With these data, we can utilize existing models of photosynthesis to identify the processes that are sensitive to both nutritional and environmental factors. We can also estimate the extent that nutrient availability regulates the response of plant ecosystems to climatic change.

Lipoprotein Subfractions and CHD during 25-Year Follow-Up
PAUL WILLIAMS

We plan to investigate the relationships of fatal and non-fatal coronary heart disease (CHD) to lipoprotein subfractions and other risk factors in a prospective epidemiologic study of 1961 men who were employed at Lawrence Livermore National Laboratory (LLNL) between 1954 and 1957. Prior to 1958, Dr. John Gofman and colleagues measured their plasma total cholesterol, blood pressure, height, weight, tobacco use, and the following lipoprotein mass concentrations determined by analytic ultracentrifugation: high-density lipoproteins of lesser density (HDL_2) and greater density (HDL_3), low-density lipoproteins (LDL), intermediate-density lipoproteins (IDL), and very-low-density lipoproteins (VLDL). Dr. Gofman used the same method of analytic ultracentrifugation to measure lipoprotein subfractions in 1954 as the Donner Laboratory currently uses for epidemiologic and metabolic research. After 10 years of follow-up, Dr. Gofman reported that high concentrations of LDL, IDL, and smaller VLDL of flotation rate S_f 20–100 and low concentrations of HDL_2 and HDL_3 predicted increased CHD risk.

The discovery of computer files containing the baseline lipoprotein subfraction and other risk factor data provides a unique opportunity to examine the relationship of lipoprotein subfraction concentrations to CHD in a prospective epidemiologic study. We plan to determine the vital status and history of CHD in this cohort through state and national mortality surveillance systems, public records, medical reports at LLNL, hospital records, autopsy reports, and telephone interviews with cohort members. A physician will examine all medical documents and assign endpoints according to international diagnostic criteria.

We will use these data to extend Dr. Gofman's initial study from 10 to 30 years of follow-up. We expect these additional years to produce 405 new cases of fatal and non-fatal CHD (from 38 reported by Gofman in 1966 to an expected 443 cases by 1986). We will use survival analysis to assess the independent contributions of specific lipoprotein subclasses to CHD while controlling for other risk factors, and to allow for censoring at different times during the follow-up period. Among the issues to be examined are:

- Do HDL_2 and HDL_3 show different relationships to CHD?
- Are relationships of lipoprotein subfractions to CHD independent of other established risk factors?
- Do measurement of lipoprotein subfraction concentrations offer significant improvement over total cholesterol in predicting a person's CHD risk?

Except for Dr. Gofman's earlier work, there are no prospective epidemiologic studies that examine the relationship of mass of HDL_2, HDL_3, LDL, IDL, and VLDL subfractions to CHD. We will collect information for the continued follow-up of the cohort as a resource for future epidemiologic studies.

Dynamic NMR Imaging with Stochastic Excitation

SAM WONG

The trend of biomedical nuclear magnetic resonance (NMR) imaging and spectroscopy is toward higher static field strengths (4 Tesla or above) to improve both signal-to-noise ratios and resolution. However, the peak radio frequency (RF) power required by conventional pulsed Fourier transform techniques becomes prohibitively high (e.g., 500 kW for ^{13}C spectroscopic imaging studies at 4 Tesla). An alternative technique, stochastic excitation, probes the sample with a noise-modulated RF signal and provides a reduction of the peak power by several orders of magnitude. Previous studies in our laboratory demonstrated the feasibility of spectroscopic imaging with stochastic excitation. This project will take advantage of the efficient spatial encoding and reduced peak power offered by techniques employing stochastic excitation for dynamic imaging studies.

The goal of this project is to develop stochastic excitation techniques for dynamic NMR imaging, where the parameters of the spin system vary due to motion, flow, diffusion, heating, or tracer kinetics. The velocity-imaging techniques developed will be useful for diagnosis of strokes, aterio-venous malformation, reduction of blood flow in the cerebral cortex associated with aging and Alzheimer's disease and other diseases related to the vasculature. The parameter tracking feature that is proposed may be used to study blood perfusion in the heart, the wash-in and wash-out of contrast enhancement agents and the uptake of NMR tracers, and may provide important diagnostic information about ischemic heart disease and metabolic diseases. We can use T_1 tracking and diffusion imaging to monitor power deposition during cancer treatment with laser and in NMR spectroscopic studies using high-power decoupling.

The overall framework of the project is built upon system theory, adaptive filtering theory, digital signal processing theory and stochastic system theory. Using a parametrized model of the dynamic systems, we will develop experimental techniques and post-processing algorithms to track the time variation of spin system parameters with a temporal resolution on the order of 0.01 to 0.1 ms. Compared with a temporal resolution on the order of 30 ms offered by conventional snapshot imaging techniques, the use of stochastic excitation for dynamic NMR imaging shows great promise.

LIFE SCIENCES DIVISION

Human Genome Center

The Life Sciences Division is the administrative home to the Human Genome Center, one of three DOE-designated centers for research aimed at ultimately mapping and sequencing the human genome. In line with the DOE's strategy for developing advanced tools for the effort before undertaking large-scale mapping or sequencing programs, the Center is the focus of related activities in several LBL divisions, including Engineering, Materials Sciences, Chemical Sciences, and Information and Computing Sciences, as well as Life Sciences.

Human Genome Center

THOMAS BRENNAN

We plan to produce very large high-density arrays of oligonucleotides for use in hybridization sequencing. These arrays of oligonucleotides are synthesized by massively parallel chemical reactions on glass plates. A surface tension wall separates each element in the array from its nearest neighbors. This mechanism carries out the synthetic reactions on a picoliter scale, delivering the specific nucleotides to each array element by arrays of piezoelectric pumps similar to an ink jet printer. A stable hydroxyalkyl group bound to the plate acts as the 5'-OH surrogate on which to initiate strand synthesis. This linker arm enables removal of purine and pyrimidine blocking groups without cleavage of the oligonucleotide from the support.

A relatively simple machine should be able to produce the full 1024×1024 array of 10-mers at the rate of one plate or 10^6 oligos per hour.

Fluorescent Detection of Biological Probes

JOSEPH M. JAKLEVIC

In all areas of the Human Genome Program—genetic mapping, physical mapping, and sequencing—the detection and sizing of DNA fragments and the identification of hybridization probes attached to them are of major importance. In many cases these operations are currently carried out using ethidium bromide UV fluorescence and probes with radioisotopic labels such as ^{32}P. The continued use of these reporters in the large volumes anticipated in the programs constitutes a serious environmental hazard and associated waste disposal problem. In the past, radioisotopic labels have been used because of their high sensitivity. With the advent of PCR (polymerase chain reaction) technology, new protocols have been developed in which sensitivity is less of an issue, making it possible to use alternative reporters such as fluorescent dyes, which are environmentally safer and offer new performance features. In particular, we will investigate the application of multiwavelength-emitting fluorescent labels in the genome program, both to determine optimized protocols for their use and to develop instrumentation to detect them in various media such as microliter plate wells, membranes, and gels. Once developed, the techniques will be applied directly to the program, replacing existing methods wherever applicable. Initially, we will employ fluorescent tags similar to those used in existing fluorescent sequencing machines, but we plan to investigate other labels, including dyes with long lifetimes. We are also studying other methodologies for fluorescent detection, such as evanescent wave excitation.

Large-Scale DNA Sequencing
MICHAEL PALAZZOLO AND CHRISTOPHE MARTIN

Despite recent advances, the capability to sequence at the level and at the cost required to meet the stated goals of the Human Genome Project has not yet been achieved. Even the most advanced groups are more than two orders of magnitude away from the efficiency required from point of view of finished sequence throughput. Specifically, it is now possible for a dedicated group to generate between 100 and 200 kb of finished sequence per year. Furthermore, the cost of obtaining this sequence (about $6.00/base) is at least an order of magnitude greater than the cost at which it is considered economically feasible to anticipate funding experiments aimed at elucidating the entire human sequence.

One of the major difficulties in large-scale sequencing is the gap that exists between the size of the mapping clone (the 40-kb cosmid, the 100-kb Pl, or the 200 kb-YAC) and the 450-base-pair (bp) stretch of DNA that can be routinely sequenced from a single priming site. Thus we are seeking means to inexpensively and rapidly create or identify sequencing priming sites every 450 bp in a large DNA fragment. We plan to use a series of molecular biological and molecular genetic procedures to efficiently deliver a set of non-overlapping templates to the automated sequencers in order to better approach the theoretical throughput of these machines.

Human Genome Center
JASPER RINE

The Lawrence Berkeley Laboratory Human Genome Center participates in the DOE initiative to map and sequence the entire human genome. The Center's current activities include efforts in biology, engineering, and computing science; all are focused on achieving one of the 5-year goals of the Human Genome Program. Biology projects include:

- Identification of a series of overlapping cloned fragments of DNA that covers 10 million base pairs, along with identification of expressed genes within this region;
- Development of genetic maps of high resolution for human chromosomes 19, 21, and 10;
- Evaluation of strategies for efficient physical mapping, with and without repetitive DNA sequences; and
- Formulation of a prototype large-scale sequencing strategy based on the use of intermediate-size clones of DNA that can be reduced readily to small subclones for sequencing without sacrificing knowledge of order.

Engineering support for these projects has led to the development of new robotics and image analysis systems and two new efforts in rapid sequencing, one by mass spectrometry and the other sequencing by hybridization. Engineering support will enable successful strategies to scale up to production level within a year. The computer science group develops software to address the bottleneck in the acquisition and analysis of data. In addition, it is concerned with the longer-range problems of sequence and clone assembly, database design and tools for efficiently changing schemes and interfaces, and accessing multiple, heterogeneous databases.

Human Genome Center
STEWART SCHERER

Yeast artificial chromosomes (YAC) are an efficient way to provide first coverage of large regions of contiguous DNA. Many of the human YAC clones in existing libraries contain unrelated pieces of DNA. We will undertake a series of experiments to define the origin of the artifactual clones and related issues on the stability and growth characteristics of the artificial chromosomes. Central to these experiments is the cloning of DNA fragments representing defined regions of the genome rather than random segments. We plan to examine the possibility of assembling large configs from the defined fragments. This use of defined fragments depends on the distribution of the short DNA sequences used to cleave the genomic DNA. We will initiate computer studies on the distribution of oligonucleotides in the genome. For these computational analyses, we will develop new tools that will be capable of rapidly analyzing 10 megabase DNA sequences which derive from sequencing of model genomes and pilot studies on the human genome. The computer studies will also be of value in designing the large numbers of DNA primers for PCR (polymerase chain reactions) used in many parts of the genome project.

STRUCTURAL BIOLOGY DIVISION

The Structural Biology Division emphasizes fundamental rather than developmental research. The biological research component is primarily focused on a long-term interest in two main themes which make up the Structural Biology Program. The first theme is understanding the molecular dynamics of photosynthesis. Investigators study various components that make up the photosynthetic-reaction center complexes in different organisms. This work involves understanding the kinetics of energy transfer and storage in plants, as well as cellular regulation of gene expression for the photosynthetic apparatus. The second theme is understanding the relationship between structure and function in nucleic acids. Researchers with chemical and biophysical expertise study both the primary and secondary structures that influence interactions with proteins and other nucleic acids. These interactions are important for regulating the functional activity of genes.

The fundamental chemistry of electronically excited molecules, a critical dimension of every photosynthetic energy storage process, is also an important area of research. Researchers in Structural Biology are studying ways to store photon energy and to develop systems that can trap and transfer photosynthetic energy.

Artificial Photosynthesis
MELVIN CALVIN AND JOHN OTVOS

This is a continuing basic science effort directed toward designing artificial systems, based on knowledge of green plant photosynthesis, for the utilization and storage of solar energy. Our approach involves the search for appropriate catalysts to channel the stored energy from the initial photoinduced charge separation process into the decomposition of water to hydrogen and oxygen. Work on the oxidation side continues to be the main focus of the program and involves synthesis and characterization of transition-metal macrocycles because of their promise as multielectron transfer agents.

Chemistry with Near-IR Photons
HEINZ FREI

Identifying chemistry that can be initiated by red and near-infrared (NIR) quanta is the main goal of this task. We focus on reactions that may lend a basis for new concepts or models for chemical storage of near infrared photons, for their conversion into electrical energy, and for product-specific synthesis of high-value chemicals. Emphasis is on the elucidation of elementary reaction steps, since insight gained therefrom allows us to identify most readily those chemical systems most promising for our objectives. Time-resolved emission and absorption spectroscopy are used for the study of redox chemistry in aqueous solution and in colloidal semiconductor systems. Controlled atom and group transfer reactions are explored in inert, cryogenic matrices by excitation of reactant pairs with red and near-infrared light. Reaction paths are mapped by trapping of short-lived transients and elucidation of their structure by FT-infrared spectroscopy. Study of the wavelength dependence of the photochemistry with cw dye lasers is used to obtain insight into the dynamics of these reactions. These detailed studies on the synthesis of organic building blocks in cryogenic matrices form the basis for our new effort of exploring controlled photochemical synthesis in room temperature hydrocarbon polymer and zeolite matrices.

Photosynthetic Membrane Structure and Photosynthetic Light Reactions
KENNETH SAUER

We are using both steady-state and time-resolved spectroscopies to investigate the excited-state relaxation of photosynthetic pigments and the trapping of excitation by the reaction centers. Time-resolved fluorescence measurements are made using the single-photon timing technique, and optical absorption transients are studied using a pulse-probe apparatus that can be used in either single-wavelength or two-wavelength configuration. The time resolution of the two instruments is about 15 ps and 1.5 ps, respectively. To improve the time resolution of the fluorescence relaxation measurements, we have recently applied the technique of fluorescence upconversion. Excitation transfer among chromophores with similar or identical absorption spectra is investigated using polarization spectroscopy, in either steady-state or time-resolved modes.

Our biological materials are derived from a variety of photosynthetic organisms. We have isolated and characterized intact complexes, such as phycobilisomes, Photosystem I complexes, and Photosystem II complexes containing reaction centers and the apparatus for oxygen evolution. We have also fractionated many of these complexes to isolate individual phycobiliproteins, reaction center core complexes, and light-harvesting chlorophyll proteins. Spectroscopic studies have been carried out over a wide range of temperatures, both to improve spectroscopic resolution and to investigate the strong temperature dependence of excited-state relaxation that occurs in some of the chlorophyll proteins.

Mutants generated in the laboratory of Prof. Donald Bryant at Penn State University have allowed us to investigate the role of specific polypeptides of the phycobilisome complex in controlling or channeling excitation transfer to make antenna components that are efficient in light collection. In the case of molecules like phycocyanin, where structural information is known from x-ray crystallography, the availability of site-specific mutants from Prof. Bryant enables us to determine the consequences of the removal of specific chromophores from the pigment protein and to determine the spectroscopic consequences of changes in amino acids in the chromophore binding pocket. Such studies are particularly valuable in connection with our theoretical calculations of excitation transfer dynamics in phycobiliproteins, which are designed to test the applicability of the Förster inductive resonance transfer and exciton coupling models to this class of photosynthetic antenna complexes where detailed structural information is uniquely available.

Mechanism of Water Oxidation and Oxygen Evolution

MELVIN P. KLEIN

Four successive photo-induced charge separations are involved in the oxidation of two water molecules to molecular oxygen by the membrane-bound oxygen-evolving complex associated with PS II. Five states, termed S_0 through S_4, have been proposed to stabilize oxidized intermediates of the complex, and many indirect observations indicate that a protein-bound manganese component is involved.

Studies using x-ray absorption techniques in our laboratory have provided information about the ligand structure and average oxidation state of manganese in dark-adapted photosynthetic membranes. Using recently developed stable PS II complexes containing decreased manganese-to-reaction center ratios, improved signal-to-noise has been obtained for the XAS measurements. Furthermore, the use of the photo-induced EPR signal rich in hyperfine structure routinely observable at low temperature in PS II preparations permits a more precise definition of the S-state of the sample being measured by x-ray spectroscopy.

The use of enriched PS II complexes allows a more sensitive determination of the x-ray absorption properties that are relevant to the structure and oxidation state of the Mn involved. We use the low-temperature EPR signal amplitude as an indication of the presence of the S_2 state. The x-ray spectra provide evidence for changes in oxidation state of the Mn associated with S-state advancement. They also indicate the nature of the ligands coordinated to the Mn atoms and to the presence of relatively short Mn-Mn distances in the photosynthetically active complexes.

stereochemical characterization of the adduct between the polynuclear photoreagent and the DNA allows for the separation of the various addition products on a chemically synthesized oligonucleotide. These modified DNA molecules have then been used for *in vitro* and *in vivo* assays of DNA excision repair and the mutagenesis associated with this process.

In the past year this laboratory has perfected the large-scale synthesis of psoralen-modified DNA oligonucleotides. These products are being used to determine the three-dimensional structure of the psoralen crosslink and the psoralen furan-side monoadduct using NMR in collaboration with David Wemmer. A crosslinked 8mer duplex has been crystallized, and the long-term goal is the determination of the x-ray crystal structure of this same oligo in collaboration with Johann Deisenhofer. In addition, *Escherichia coli* uvrA has been crystallized, and the x-ray structure of it and the co-crystal of uvrA and 8mer crosslink oligo are anticipated, again in collaboration with the Deisenhofer laboratory. Finally, the central feature of all of these studies has been the collaboration with the laboratory of Aziz Sancar of the University of North Carolina Medical School. The new emphasis has been the development of reliable assay systems, using our unusual substrates, for excision repair in human cells and cell-free extracts. This is the first step toward the isolation of the excision repair enzymes of humans. Already, there is an indication that while the *E. coli* repair excises a damaged fragment of twelve nucleotides, the human enzyme system excises a different sized fragment, suggesting that human or mammalian excision repair incorporates an entirely new class of enzymes.

Center for Biomolecular Design
PETER SCHULTZ, SUNG-HOU KIM, AND DAVID WEMMER

We have established at Lawrence Berkeley Laboratory a unique center of excellence, the Center for Biomolecular Design, that will bridge chemical science, biological science, and computer science by combining the expertise in LBL and the University of California-Berkeley. The Center will catalyze an interdisciplinary approach toward chemical biology and computational biology that merges a detailed understanding of biological systems with the ability to analyze and manipulate chemical structure. Our aim is to redesign the biological molecules to create new classes of novel biomolecular structures with applications to major problems in the medical, biological, and environmental sciences relevant to DOE missions.

Examples of new technologies that are emerging from interdisciplinary studies at LBL include designing and creating a new generation of biopolymers that have unique properties and redesigning natural proteins to create new properties. One example of the latter is catalytic antibodies tapping the tremendous diversity (> 10^{10} molecules) and specificity of the immune system to create "custom made" catalysts. These molecules may lead to restriction enzymes for proteins and sugars for novel therapeutic agents for destroying cancer cells, viruses, or even atherosclerotic plaques. Chimeric receptors have been constructed that "reprogram" the transmittal of information to cells. This research will aid in the therapy and understanding of disease, including memory dysfunction, and may ultimately lead to novel cellular-based sensory or memory devices. Proteins from organisms that function under extreme conditions of pressure, temperature, and pH (extremophiles) are being isolated and characterized. These proteins can be redesigned in order to create new proteins with new catalytic properties functioning under extreme conditions. Powerful methods have been developed making it possible to generate proteins that contain synthetic amino acids with novel properties not limited to the natural 20 amino acids. These activities reflect the tremendous chemical potential inherent in the complex architecture of biomolecules.

Structure and Function of Catalytic RNA

SUNG-HOU KIM, IGNACIO TINOCO, JOHN E. HEARST, AND DAVID WEMMER

This research is intended to identify the properties of a self-processing RNA molecule. The RNA itself is a 359-base-long satellite RNA of tobacco ringspot virus, which is an infectious agent of plants. The mechanism of autocatalysis is inherently different from that of any other self-processing RNA described, since the molecule is able to cleave and relegate one of its own phosphodiester bonds through a mechanism which appears similar to normal acid/base-catalyzed hydrolysis, but cleavage is at a single unique site in its sequence.

Specific aims toward understanding this phenomenon are:

- Determination of the minimum size necessary for this molecule to carry out the self-processing reaction.
- Production of large quantities of the minimum processing size RNA.
- Probing of the RNA with structural specific nucleases to identify structural regions.
- Reaction of the RNA with psoralen, which crosslinks at certain bases which are both sequence and structure specific, to identify structural regions.

- Nucleotide substitutions which will give altered base sequences to define both base-specific and structural requirements of the processing reaction.
- Attempts at growth of crystals for x-ray diffraction.
- Phylogenetic comparisons of related satellite RNAs, all of which are self-processing, which will allow structural predictions to be made based on conserved regions.
- Production of large quantities of slowly cleaving analogs and development of methods for incorporation of isotopic labels.
- NMR analysis of secondary and tertiary structure elements and determine their relationship to activity.

Biomolecular Structure Analysis by NMR
DAVID WEMMER

The objective of this task is to develop NMR (Nuclear Magnetic Resonance) methodology and carry out structural studies on appropriate models for biologically important molecules. We continue to use a combination of two-dimensional NMR experiments with distance-geometry and molecular-mechanics programs to define the molecular structures in solution and analyze many kinetic and thermodynamic aspects of the interactions between them. We will continue work on the DNA-binding domains of gd and TN3 resolvase in complex with their cognate DNA. We will begin NMR studies on another DNA binding protein, FUR, the ferric uptake regulator from *Escherichia coli*. The studies of the dimeric form of this protein, with a total molecular weight of about 30 kD, will require isotope labeling and 3D NMR, which will be initiated. We are also investigating the production, through cloning and expression, of active parts of transcriptional regulatory proteins. These systems will provide information about the molecular interactions, which are at a second level of gene regulation. We are also beginning to investigate the hydration of DNA in solution by measuring the extent of cross-relaxation between solvent protons and those on the DNA. Similar work will be carried out on RNA once the experimental techniques have been mastered. ^{1}H NMR will be used for determining the structures and conformations of protein cofactors, particularly bilin pigments from photosynthetic bacteria. We will continue efforts to apply new solid-state NMR techniques (together with the Pines group) in problems of biomolecular structure in ordered samples.

Genetics of Growth Control

JAMES C. BARTHOLOMEW

Our experiments are designed to investigate the genes coding for cellular factors participating in the control of DNA synthesis in human cells. We are using subtractive hybridization after infection of the cells with adeno SV40 constructs which code for T-antigens with different transformation potentials. The mutant T-antigen that we have characterized appears to be normal in all respects relative to wild-type T-antigen except in its ability to transform cells and to induce factors necessary for the initiation of DNA synthesis. These transformation-defective mutants are different from those reported by others in that they interact normally with anti-oncogene products such as Rb and p53. Our goal is to identify genes responsible for the initiation of DNA synthesis by taking advantage of the differential inducing activities of the mutant and wild-type T-antigens. We are also trying to determine if these genes are involved with transformation. The differential inducing activities of the T-antigens coupled with the power of subtractive hybridizations offer a unique opportunity to specifically identify the genes involved in the initiation of DNA synthesis. Our recent studies have focused on the involvement of phosphorylation of T-antigen in determining the phenotype of the mutant T-antigen. These studies indicate that the phosphorylation state of the T-antigen is controlling the activity relative to inducing cellular factors. In addition, we have been studying the elements of the episomal DNA that are required for long-term maintenance of the DNA in human cells. Understanding the role of these factors in controlling DNA synthesis is important to our understanding of the mechanism of malignant transformation.

Biophysical Chemistry

MELVIN P. KLEIN

Our work is directed toward an enhanced understanding of the bioenergetics and redox state of the cell and of important cellular constituents. Applications of physical techniques will continue to provide the means to these ends. We shall employ x-ray absorption spectroscopy (XAS) using synchrotron radiation to ascertain the oxidation state(s) of cellular sulfur, especially that of glutathione in the living cell. Preliminary results demonstrate that the precise energy and shapes of the sulfur x-ray absorption edge can distinguish among all of the oxidation states of sulfur and, in particular, among the three oxidation states of glutathione. This result has important consequences for understanding the cellular responses to oxidative insult and damage. Intimately involved in most redox-mediated pathways are the ubiquitous electron-transport proteins called the ferredoxins. Although structurally quite similar they exhibit a very large range of reducing potentials. The sulfur atoms are thought to provide the sites of variable electron density that in turn may be modulated by hydrogen bonding. The electron density at the sulfur components will be determined by observation of the sulfur x-ray absorption edges while hydrogen bonding will be determined by very high resolution electron paramagnetic resonance with electron-spin-echo spectroscopy and ENDOR. The Advanced Light Source will facilitate these investigations.

NATIONAL TRITIUM LABELING FACILITY

DAVID WEMMER AND PETER SCHULTZ

This is a national user facility both for carrying out research into the labeling of compounds to high specific activity with tritium and for providing a tritium-labeling service for other investigators throughout the country. This laboratory is moving toward the development of compounds and techniques to allow ^{3}H-NMR studies of biological macromolecules.

ENERGY SCIENCES

CHEMICAL SCIENCES DIVISION

The Division conducts research on chemical reaction mechanisms and dynamics in the gas and condensed phases, synthetic chemistry, actinide chemistry, homogeneous and heterogeneous catalysis, thermodynamics and phase equilibria, surface science, and atomic physics. The Division also hosts a major new LBL initiative in combustion dynamics.

Photochemistry of Materials in the Stratosphere

HAROLD S. JOHNSTON

This research is concerned with global atmospheric photochemical modeling and with experimental gas-phase photochemistry. In collaboration with Lawrence Livermore National Laboratory, theoretical studies are made of atmospheric transport, radiation balance, and photochemistry. One goal of the experimental work is to obtain optical and kinetic data in the laboratory that are needed by modelers of the atmosphere. Another goal is to measure the distribution of excess energy in the fragments produced after a molecule is broken apart by an energetic pulse of light. The experimental methods include laser flash photolysis, laser resonance absorption, resonance fluorescence, dispersed chemiluminescence from photolysis products, and infrared diode lasers. This research has applications to molecular dynamics, to problems of atmospheric ozone, and to problems of global change of trace gases in the atmosphere.

Selective Photochemistry

C. BRADLEY MOORE

The fundamental goal of this program is to understand the photophysics and photochemistry that occur following selective excitation of molecules and during the reactions of free radicals. Of particular interest are the chemical reactions of specifically excited states and the dynamics of energy transfer, both within a molecule and to surrounding molecules.

For low levels of vibrational excitation in small molecules, individual quantum states may be excited, enabling the measurement of reaction and energy-transfer rate constants for each quantum state. For larger or more highly excited molecules, it is usually not possible to excite single eigenstates. Instead, a number of eigenstates are excited simultaneously, and a redistribution of the initial vibrational excitation occurs. This process, known as intramolecular vibrational-energy redistribution (IVR), is extremely rapid and severely limits the realization of truly mode-specific unimolecular reactions. Advances in mode-specific chemistry will come from a more complete understanding of the IVR process and the parameters that control its efficiency. By being able to predict the rates of IVR and the path of vibrational-energy flow through a molecule, experiments can be designed utilizing molecular systems that maximize the possibilities for mode-specific effects. Studies designed to elucidate the coupling mechanisms and dominant pathways for IVR are currently under way on a number of model systems.

The rates and mechanisms of free-radical reactions, such as are important in combustion, are often best studied by flash kinetic spectroscopy using lasers for thermal heating, for photolyzing, and for spectroscopic probing. Reactions can be studied as a function of individual quantum states. A fundamental understanding of the rate constants and product distributions for these reactions is sought to serve as a basis for modeling combustion processes.

Actinide Chemistry
NORMAN M. EDELSTEIN

Development of new technological processes for the use, safe handling, storage, and disposal of actinide materials relies on the further understanding of basic actinide chemistry and the availability of a cadre of trained personnel. This research program is a comprehensive, multifaceted approach to the exploration of actinide chemistry and to the training of students. Research efforts include: synthetic organic and inorganic chemistry for the development of new chemical agents and materials; their chemical and physical elucidation through various characterization techniques; and thermodynamic and kinetic studies for the evaluation of complex formation. One aspect is the development and understanding of complexing agents that specifically and effectively sequester actinide ions. Such agents are intended for the decorporation of actinides in humans, in the environment, and in systems related to the nuclear fuel cycle. Extensive studies are underway to prepare organometallic and coordination compounds of the f-block elements that show the differences and similarities among the f-elements and between the f- and d- transition series elements. Optical and magnetic studies on actinides as isolated ions in ionic solids and in molecules provide information about electronic properties as a function of atomic number. A proposed new program is the construction of an actinide branch line and endstations at the Advanced Light Source in order to measure directly the electronic structure of actinide materials.

Physical Chemistry with Emphasis on Thermodynamic Properties
KENNETH S. PITZER

The purpose of this program is the discovery and development of methods of calculation of thermodynamic and related properties of important chemical systems by use of quantum and statistical mechanics, together with experimental measurements for key systems.

Primary emphasis is on ionized systems, electrolyte solutions, and plasmas, with particular attention to fluid-fluid phase equilibria and critical behavior. While the critical region has been carefully studied for pure fluids and mixtures of neutral molecules, there has been little attention to critical behavior for ionic systems. The alternating charge and long-range nature of ionic forces require a separate theoretical treatment. Recent contributions of this project have included treatments of the critical properties of pure ionic fluids and of NaCl at very high temperature in both steam and brine (liquid) phases. Liquid-salt/polar-solvent systems have also been discovered that have sufficiently moderate critical temperatures that measurements can be made of various properties, including conductance and critical exponents. Investigations of aqueous NaCl and other salts at high temperature and pressure are being carried out in collaboration with U.S.G.S., Menlo Park, CA. These systems, and especially $NaCl\text{-}H_2O$, are of both geological and industrial importance.

Molecular Interactions
WILLIAM A. LESTER, JR.

This research program is directed at extending fundamental knowledge of atoms and molecules, including their electronic structure, mutual interaction, collision dynamics, and interaction with radiation. The approach combines the use of *ab initio* methods—Hartree-Fock (HF), multiconfiguration HF, configuration interaction, and the recently developed quantum Monte Carlo (QMC)—to describe electronic structure, intermolecular interactions, and other properties, with various methods for characterizing inelastic and reactive collision processes and photodissociation dynamics. Present activity is focused on the development and application of the QMC method.

Theory of Atomic and Molecular Collision Processes
WILLIAM H. MILLER

This research is primarily involved with the development and application of theoretical methods and models for describing atomic and molecular collision processes and chemical reaction dynamics. Specific topics of interest have included the theory of inelastic and reactive scattering, collision processes involving electronically excited atoms or molecules, collisional ionization phenomena, statistical theories of chemical reactions, scattering of atoms and molecules from surfaces, and interactions of molecular systems with high-power laser radiation.

Most recently, research has focused on the development of theoretical methods for a first-principles treatment of dynamics in polyatomic molecular systems. The goal is to develop approaches that can utilize *ab initio* quantum chemical calculations of the potential energy surface (in the Born-Oppenheimer approximation) as direct input into the dynamical treatment, and thus, to as great an extent as possible, have a truly predictive theory.

The potential application of these methods is almost without limit. In this group hydrogen-atom transfer processes have been studied in a variety of systems. Other research groups have used these approaches to describe a variety of reactions that are relevant to the primary steps in combustion.

Crossed Molecular Beams
YUAN T. LEE

The major thrusts of this research project are to elucidate detailed dynamics of simple elementary reactions that are theoretically important and to unravel the mechanisms of complex chemical reactions or photochemical processes that play important roles in many macroscopic processes. Molecular beams of reactants are used to study individual encounters between molecules or to monitor photodissociation events in a collision-free environment. Most of the information is derived from measurement of the product's fragment energy and angular distributions.

Recent activities are centered on the mechanisms of elementary chemical reactions involving oxygen atoms with unsaturated hydrocarbons, the dynamics of endothermic substitution reactions, the dependence of the chemical reactivity of electronically excited atoms on the alignment of excited orbitals, the primary photochemical processes of polyatomic molecules, intramolecular energy transfer of chemically activated and locally excited molecules, the energetics of free radicals that are important to combustion processes, the infrared-absorption spectra of carbonium ions and hydrated hydronium ions, and bond-selective photodissociation through electric excitation.

High-Energy Atomic Physics
HARVEY GOULD

The goal of this program is to understand atomic collisions of relativistic ions and to test quantum electrodynamics (QED) in atoms of very high atomic number. These are new areas of research that involve physics that are not accessible at lower energies or with lower atomic number. Recent results include the first measurement of electron impact ionization of highly ionized very heavy ions (U^{88+}, U^{89+}, U^{90+}, and U^{91+}). This measurement was done by channeling relativistic uranium ions through Si single crystals. These and earlier experiments in this program have led to an understanding of relativistic heavy-ion/atom collisions that in most cases is now more complete than for nonrelativistic collisions. Present activities include measurement of screening-antiscreening effects in relativistic ionization and a precision (1.0%) measurement of the Lamb shift in uranium. Future experiments will attempt to observe a new capture mechanism—electron capture from the production of electron-positron pairs by the motional coulomb fields of relativistic nuclei passing within atomic distances of each other.

Atomic Physics
MICHAEL PRIOR

This program performs challenging studies of the structure and interactions of atomic systems in order to provide the most detailed description of their behavior and to stimulate theoretical understanding of the observed phenomena. Recent results include the first determination of magnetic substate population fractions following a double-electron-capture collision. This was done using C^{5+} and B^{4+} ion beams and He atom targets at collision velocities in the range of 0.25–0.50 atomic units. Strong variations of the population fractions with velocity were observed, and a marked difference was noted in the fractions for the two ions studied. The measurements are the most detailed challenge to date of theorists' abilities to reproduce this simple double-capture process.

In general our work emphasizes research topics which are best addressed with the unique tools and expertise available at LBL. Currently the program exploits the ability of state-of-the-art electron-cyclotron resonance (ECR) ion sources at LBL to produce intense, highly charged beams for conducting low-energy ion-atom and ion-ion collision studies. Current emphasis is upon multiple electron transfer phenomena and Auger electron spectroscopy. The program benefits substantially from collaborative efforts with colleagues from outside LBL.

Formation of Oxyacids of Sulfur from SO_2
ROBERT E. CONNICK

Stimulus for this research is the existence of acid rain. Coal-burning power plants produce sulfur dioxide, which is oxidized in air to form sulfuric acid, the principal component of acid rain. In most commercial flue-gas desulfurization processes, the sulfur dioxide is absorbed in an aqueous solution of low acidity, where it can be oxidized by O_2. Control of the rate of the oxidation reaction is of major importance to these processes. While recent research of the project has been concentrated on this reaction, investigation of the fundamental chemistry of species formed from sulfur dioxide and reactions of these species remains the primary goal. The oxidation-reduction chemistry of sulfur should be studied, particularly reactions between two oxidation states of the element, e.g., reactions involving HSO^3-, H^2S, S^8, and the polythionates.

Transition-Metal Catalyzed Conversion of CO, NO, H_2, and Organic Molecules to Fuels and Petrochemicals
ROBERT G. BERGMAN

The central objectives of this program are:

- Discovering new chemical reactions between organic compounds and organotransition metals;
- Understanding how these reactions work; and
- Examining the applicability of the new transformations to the preparation of potentially useful materials such as fuels, commodity chemicals, and fine chemicals.

In 1982 a major discovery of this project was the finding that certain iridium complexes undergo oxidative addition into the carbon-hydrogen bonds of saturated hydrocarbons (alkanes). This was the first example of this long-sought C-H activation reaction. Research carried out following this discovery has extended the C-H insertion reaction to rhodium and rhenium systems and provided information on its mechanism. Current work is aimed at detecting and studying directly the transient intermediates responsible for the critical C-H insertion step, understanding the thermodynamics of the transformation, determining whether C-H activation processes are feasible in multi-metallic systems, and developing methods for using C-H activation to convert alkanes into functionalized organic compounds.

Energy Transfer and Structural Studies of Molecules on Surfaces

CHARLES B. HARRIS

The goal of this research is to study the mechanisms that are responsible for the transfer of energy from the excited states of molecules to metal surfaces and to develop new laser techniques for probing molecule-surface interactions. The research program is both theoretical and experimental in character, and it includes nonlinear optical and picosecond laser techniques in addition to a variety of standard surface-science tools for characterizing molecule-surface interactions. Recent work has centered on the development of picosecond infrared lasers, the elucidation of the mechanism of surface-enhanced photochemistry, surface-enhanced photoelectron emission, the breakdown of classical dielectric response theory for explaining energy transfer from molecules to noble metal surfaces, and the development of new techniques for studying the dynamics of electrons at interfaces on femtosecond time scales. The results of this program have a direct bearing on high-speed technological devices and materials and on problems of general interest such as surface-enhanced photochemistry, the dynamics of surface photoemission, and the optical properties of thin films.

High-Energy Oxidizers and Delocalized-Electron Solids

NEIL BARTLETT

The main aim of this program is the synthesis and characterization of new materials that may have value in electrochemical applications. The synthetic work tests models and theories that correlate physical properties (such as electrical conductivity) with chemical composition and structure. The present emphasis is on the study of two-dimensional extended atomic networks, such as those derived from graphite, layer-form boron nitride, and their relatives. Electron oxidation of such materials (with accompanying intercalation to form salts) generates durable and conductive materials (some conducting better than aluminum). Chemical, stoichiometric, and structural requirements for the best conductivity are being defined. The layered materials can often be oxidized (and intercalated) electrochemically in a reversible process. Some of these materials may find uses in high-energy electrodes. Physical and chemical studies are being applied to such materials to determine the structure and bonding changes that accompany oxidation and reduction. Salts that are either proton conductors or fluoride-ion conductors and that are resistant to oxidation but are not metallic are being sought as solid electrolytes for use with the metallic layer-material salts.

Potentially Catalytic and Conducting Polyorganometallics
K. PETER C. VOLLHARDT

Soluble organotransition metal clusters have great potential as catalysts for known and new organic transformations and as building blocks for novel electronic materials. While much is known about how such clusters are assembled and disassembled, their chemistry is largely unpredictable and/or uncontrollable. This project constitutes an interdisciplinary approach to the designed construction of polymetallic arrays, anchored rigidly on novel π-ligands that enforce hitherto unprecedented metallic topologies. For this purpose, new synthetic organic methodology has been developed that allows the stepwise chemo-, regio- and loco- specific building-up of cluster-chains (i.e., the identity of the metal sequence in heterometallic systems). Many of their physical and chemical properties are unparalleled and include: extreme ligand deformations, highly strained metal-metal bonds, intramolecular fragment migrations, intrachain electron transfers, and thermally reversible photochemical storage processes.

Molecular Thermodynamics for Phase Equilibria in Mixtures
JOHN M. PRAUSNITZ

Phase equilibria are required for efficient design of large-scale separation processes (e.g., distillation and extraction) in the chemical and related industries. In this context, "efficient" refers to optimum use of raw materials and to conservation of energy. Since the variety of technologically important fluid mixtures is extremely large, it is not possible to obtain all desired equilibria from experiment. Therefore, the objective of this research is the development of molecular thermodynamics for interpretation and correlation of selected data that will yield reliable general predictions of phase equilibria for engineering. The correlations are expressed through semi-theoretical physico-chemical models in a form suitable for computer-aided design. Particular attention is given to those systems that are of interest in energy-related industries, especially those concerned with fossil fuels, aqueous salt solutions, and high-value chemicals produced by enzyme-catalyzed processes (biotechnology). Development of molecular thermodynamics calls for a combination of theoretical, computational, and experimental work. Further, it demands simultaneous awareness of progress in molecular science and of realistic requirements for engineering design.

Free-Radical Photochemistry

DANIEL M. NEUMARK

This research project is aimed at understanding the bond energetics, electronic spectroscopy, and photodissociation dynamics of reactive free radicals. These species play important roles in a wide variety of chemical processes, including atmospheric and combustion chemistry. Our research will result in a better understanding of the spectroscopy and reactivity of these species. We have developed a novel experimental scheme in which free radicals are generated by photodetachment of a mass-selected beam of negative ions. The radicals then undergo photodissociation, and the resulting fragments are detected and energy-analyzed. This very general technique has been applied to several small polyatomic free radicals. We plan to study unsaturated organometallic species and clusters of carbon and silicon in the near future.

EARTH SCIENCES DIVISION

Scientists and engineers of the Earth Sciences Division conduct research on a wide variety of topics relevant to the nation's energy development programs.

The Division's researchers investigate the physical and chemical properties and processes in the earth's crust, from the partially saturated, low-temperature near-surface environment to the high-temperature environments characteristic of regions where magmatic hydrothermal processes are active.

The Division's strengths in laboratory and field instrumentation, numerical modeling, and in situ *measurement allow investigation of the transport of mass and heat through geologic media. These studies include the analysis of the appropriate chemical reactions, and parallel laboratory and field investigations of the effects of temperature, pressure, stresses, pore fluids, and fractures on the elastic and electrical properties of rock masses. Studies concerned with rock behavior in the brittle and ductile crustal regimes drive the development of improved geomechemical and geophysical tools and techniques for mapping and characterizing heterogeneity in the subsurface.*

Three new Division efforts address problems in the discovery and recovery of petroleum, the application of isotope geochemistry to the study of geodynamic processes and earth history, and the development of borehole methods for high-resolution imaging of the subsurface using seismic and electromagnetic waves.

Mechanisms of Mobility Control with Foams

CLAYTON J. RADKE

Enhancing underground oil recovery is a crucial problem, since many domestic reservoirs are nearing depletion with standard production techniques. Modern enhanced-oil-recovery (EOR) practice is well developed in the area of dislodging trapped oil, namely by establishing ultralow tensions with exquisitely designed surfactant formulations. However, the need to maintain mobility control is not well practiced, even though the basic principles are understood. Current EOR processes, including steam flooding, hydrocarbon injection, CO_2 and N_2 flooding, alkaline flooding, and surfactant flooding, demand much improved mobility control. This work focuses on the use of gas-aqueous surfactant dispersions (referred to generally as "foams") as general mobility-control agents both in establishing macroscopic sweep efficiency and microscopic displacement efficiency and for a range of EOR processes. Initially, considerable effort was directed toward a fundamental understanding of how foams are generated and how they flow in porous media. Much of this work is now complete. The program is now directed toward applying the fundamental and mechanistic findings to modeling the foam displacement process and toward devising appropriate surfactant screening procedures for the design of effective chemical packages. The program has four research elements:

- Foam displacement modeling;
- Long-core foam displacement experiments;
- Measurements of thin film forces; and
- Dynamic tension and surface rheology studies.

Geothermal Technology Development
MARCELO LIPPMANN

The goal of this work is to determine geothermal reservoir parameters, to detect and characterize reservoir fractures and boundaries, and to identify and evaluate the importance of reservoir processes for their productive capacity and longevity under commercial exploitation. It encompasses field, theoretical, and laboratory projects to develop, improve, and validate the methods, models, and instrumentation needed to accomplish these goals. A geophysical segment of this program involves the development and testing of instrumentation, field techniques, and data processing and interpretation. A second focus of the program is to develop well-testing techniques, laboratory methods, and mathematical modeling codes to analyze and evaluate geothermal reservoirs. Under study are various reservoir engineering° methods of characterizing and simulating the dynamic behavior of liquid- and vapor-dominated systems under natural and exploitation conditions, with various fluid compositions and reservoir-rock conditions.

Thermodynamic Properties of Mixed Organic-Radionuclide Wastes
HEINO NITSCHE

Using laboratory research, this project seeks to provide fundamental knowledge of the basic chemical processes that occur between radionuclides and synthetic organic chemicals present in mixed organic-radionuclide wastes at DOE sites. This knowledge will provide an increased mechanistic understanding of organic-radionuclide mixtures that will then allow more accurate predictions of the processes that control contaminant mobilization and transport in the subsurface environment.

The project experimentally determines the thermodynamic and kinetic solution phenomena, such as complexation constants, speciation, and solubility of complexes and the nature of compounds that can form between the actinide elements plutonium and americium and selected hydrophilic and hydrophobic organic constituents of mixed organic-radionuclide wastes. The resulting data are necessary to predict and model the interaction and the mobility of co-contaminants and their maximum release concentrations in the subsurface. Existing data used as input for transport modeling are incomplete. Data are necessary for complexation, speciation, and solubility of most hydrophilic mixed organic-actinide waste complexes and compounds. This experimental program contributes to filling these gaps.

The results of this task support the Co-contaminant Chemistry Subprogram of DOE's Subsurface Science Program (SSP). It may provide possible pathways for manipulating the geochemistry to achieve remediation by either stabilizing or mobilizing contaminants in the subsurface.

Characterization of Natural Subsurface Heterogeneity

ERNEST L. MAJER

Characterization of *in situ* heterogeneity controlling subsurface processes is vital to predicting the behavior of natural systems for remediation purposes. Fundamentally, the interaction of the physical, chemical, and microbiological properties must be understood to determine relative effects of these heterogeneities as well as the scales at which each type of heterogeneity is important. This research involves a joint geophysical-hydrologic approach to characterizing and identifying the fundamental properties necessary to map heterogeneities that may control subsurface processes. Characterizing these properties is important for understanding and evaluating fluid and chemical transport in media at shallow toxic waste sites. The approach uses controlled small-scale field sites and supplementary laboratory information to characterize the properties that affect fluid flow and chemical transport so that they can be imaged with *in situ* characterization methods. Initial efforts have concentrated on defining the hierarchy of physical characteristics that control fluid flow and seismic properties by means of *in situ* application of high-resolution seismic imaging in dispersive and "fast path" environments. Data from controlled intermediate-scale lab and *in situ* soil block experiments are being used to determine the dominant physical characteristics of these environments.

In the future this work will interface with the other subprograms within the Subsurface Science Program (SSP) (such as Deep Microbiology, Biodegradation/Microbial Physiology, Geochemical Transport/Colloids, and Coupled Processes) to further examine the hypothesis that the physical heterogeneities have a significant effect on the chemical and microbial properties in the subsurface. In addition to the seismic methods, several other characterization methodologies will be used to define and characterize the natural subsurface physical heterogeneity at DOE sites where information has been gathered on the microbiological, physical, and chemical properties. Potential sites within the SSP are the GEMHEX experiments at Hanford/PNL, the New Mexico outcrop and borehole sites, the Melton Branch and soil block sites at ORNL, and the Georgetown site in South Carolina.

Innovative and modern computer simulation and visualization methods will then be used to analyze the effect of physical heterogeneities on the spatial distribution of the chemical and microbiological properties. The overall goal is to provide advanced methodology to collect and analyze prototype databases for evaluating the effect of natural heterogeneity on fluid flow and chemical transport in porous media.

Chemistry of Toxic Organic/Metal Ion (Radionuclide) Co-contaminants Involved in Subsurface Transport
DALE L. PERRY

Recent studies have shown that one of the most important mechanisms that affects toxic metal subsurface transport is that of organic complexation. Cobalt, uranium, lead, 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 practically non-existent. Virtually no experimental spectroscopic data using unique, state-of-the-science instrumental characterization techniques exist for these organic/metal ion mixtures.

This research will initially focus on the synthesis of organic/metal ion complexes involving cobalt, uranium, lead, and chromium with the multidentate chelating carboxylic acids diethylenetriaminepentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), and cyclohexanediaminetetraacetic acid (CDTA). Characterization tools include Auger, x-ray photoelectron, nuclear magnetic resonance, Fourier transform infrared, and Raman spectroscopies. These techniques are used both to study the chemistry and spectroscopy of the mixed contaminants and to devise new analytical approaches for their detection. This project also attempts to devise new analytical approaches for the detection of the mixed contaminants in soil and groundwater. Later studies will address binuclear metal complexes involving the metals mentioned above.

The data derived from this research will provide an extremely critical experimental chemical base for modeling the hydrologic transport of co-contaminant organic/metal ion species in subsoils and groundwater.

Fundamental Geosciences Program
THOMAS V. MCEVILLY

This is a multidisciplinary program in fundamental research to further the scientific basis for many energy-related technologies, including safe disposal of radioactive and toxic chemical wastes, exploitation of geothermal energy, and development of petroleum and strategic-mineral resources. Researchers at LBL are among the leading investigators in the areas of subsurface imaging of the structure and dynamics of the earth's deep crust and the mechanisms by which lithospheric processes influence energy resources; the chemistry and physics of geological materials at high temperatures and pressures; and coupled processes occurring in complex dynamic fractured rock formations.

Geological and geochemical studies focus on the properties of magmas and electrolytes, the generation and migration of petroleum compounds, the occurrence of abiogenic methane, and the interactions between minerals and groundwaters. Geohydrology research at LBL includes studies of the physical behavior of fluid-saturated rock, the dynamics of subsurface reservoirs, and the mechanisms associated with chemical transport and fracture-flow phenomena. Geophysicists are developing methodologies and instruments to image crustal structure, measure elastic anisotropy in geological formations, and track the movement of toxic chemical contaminant plumes in underground aquifers. Other geophysical research employs new computational codes to measure fracture properties in subsurface reservoirs and map hydrofractures at well sites.

LBL/Industry Heterogeneous Reservoir Performance Definition Project
ERNEST L. MAJER

We have organized a cooperative research program between LBL and both CONOCO and British Petroleum (BP) that focuses on the characterization of heterogeneous reservoirs. Both CONOCO and BP already have characterization efforts under way at several test facilities. The new program is intended to enhance these efforts through the participation of DOE/LBL.

LBL personnel are working cooperatively with both exploration and development departments to design integrated geophysical and hydrologic investigation procedures and analysis techniques. The companies (CONOCO and BP) are providing access to the field sites and to the data collected at these sites. LBL, under

DOE funding, is helping to design the investigations, perform some of the characterization experiments, and analyze the data in an effort to integrate the various geophysical and hydrologic methods at a few well-calibrated and well-characterized sites. The results of this cooperation will allow techniques that were developed for waste storage and geothermal energy to be adapted for use in heterogeneous and fractured reservoirs.

The goal of this work is to demonstrate the combined use of state-of-the-art technology in fluid flow modeling and geophysical imaging in an interdisciplinary approach for predicting the behavior of heterogeneous petroleum reservoirs. The product of this work will be improved interpretational and predictive methods that will be used by the petroleum industry to enhance recovery from existing and new reservoirs. This effort will also provide feedback that will optimize improvements and refinements in geophysical methods.

Electrical and Electromagnetic Methods for Reservoir Description and Process Monitoring

KI H. LEE

Exploration for hydrocarbons and the subsequent development of a reservoir depends on a description of the structure and properties of the rocks. Electrical conductivity has a direct relationship to reservoir properties, since the conductivity of rocks is controlled by the pore fluids. The correct understanding of reservoir properties is essential for drilling wells and subsequent reservoir management through process monitoring. This research is part of a coordinated multilaboratory (LBL, LLNL and SNL) EM program to improve the understanding of the relationships between electrical conductivity and the various enhanced oil recovery processes. We have two main objectives. The first is to continue developing reliable forward and inversion/imaging schemes essential for mapping and monitoring subsurface electrical conductivity. Research activities include t-k domain finite difference 3-D modeling, Born inversion of cylindrically symmetric media using borehole EM data, and wave-field analysis of EM fields for tomographic applications. The second objective is to improve the scale model facilities at LBL and conduct time-domain EM experiments valuable in assisting in experimental design by assessing practical instrumentation problems. In conjunction with the development of reliable forward and inversion/imaging schemes, the scale model experiment will be an essential tool for achieving our ultimate objective of monitoring the processes of existing reservoirs.

Analytic Performance Assessment
THOMAS H. PIGFORD

The objective of this task is to develop analytical techniques (models) for predicting the long-term performance of geologic repositories for high-level radioactive waste. We specialize in developing mathematical models to predict the transport of heat, fluids, and radionuclides through geologic media. The work includes overall systems analysis, far-field transport of liquid and gases in porous fractured media, and near-field mass transfer from buried waste solids. The work of the group is now focused on performance assessment of a geologic repository in partially saturated tuff. Our role is primarily to attack new technical issues fundamental to the performance of a geologic repository for high-level and defense waste. This will aid the resolution of performance-assessment issues for the Yucca Mountain Project. Current work includes:

- Release and transport of gaseous C-14 in unsaturated tuff
- Transport of radioactive colloids
- Transport of gases and radionuclides through partly failed waste containers
- Release of radionuclides from waste packages in a tuff repository
- Accelerated transport of radionuclides by heat-pipe effects

To provide an early determination of site suitability, the DOE will use sensitivity analysis to evaluate Potentially Adverse Conditions (10 CFR 60.122) for Yucca Mountain. The Potentially Adverse Conditions include volcanic activity, faulting, induced hydrologic changes, and geochemical changes. Our analytical techniques are particularly effective for sensitivity analysis. We will assist DOE in its analysis of Potentially Adverse Conditions.

A critical need is to unify the approach to waste-package performance assessment taken by various DOE contractors. The simplistic model of release rate limited by water flow rate and solubility contrasts sharply with the more mechanistic analyses of release by diffusion and convection. Both types of model incorporate simplifying and unrealistic assumptions about the partly failed container and are necessarily conservative. The work underway, together with new container failure predictions from the University of Minnesota, promises more realistic and more defensible predictions of waste package performance at Yucca Mountain.

ENERGY & ENVIRONMENT DIVISION

The Energy & Environment Division (EED) of Lawrence Berkeley Laboratory was formed in the early 1970s in response to national concerns over energy and the environment. Over the longer term, the nation must use energy efficiently and must develop new energy sources, especially since oil imports are a large and growing fraction of the trade deficit. Concerns over the health, environmental, and global climate impacts of energy use are increasing. Energy consumption plays an important role in determining the nation's international industrial competitiveness. The Division conducts research that will help the nation address these concerns.

The Division's major research areas are: energy conversion and storage (advanced batteries and fuel cells, solar and fossil fuel conversion, biotechnology, and materials for energy applications); environmental research (atmospheric and biospheric effects of combustion, combustion processes, and ecological systems); building sciences (advanced electrical lighting, windows, daylight, building energy-use measurement, computer simulation and prediction, building-data compilation and analysis, and indoor air quality); and policy analysis (energy conservation by energy utilities, international energy use, environmental policy analysis, and appliance efficiency standards).

The Division continues to develop new and expanded research areas. EED leads LBL's considerably enhanced research program on indoor radon. In response to the growing concern over global warming from carbon dioxide and other "greenhouse" gases, EED is increasing its activities in environmental research (e.g., cloud dynamics, impact on ecosystems) and analysis (e.g., potential for reducing emissions through energy efficiency, and projected energy use in developing countries). A long-term effort to develop advanced computer-based methods for designing buildings—methods which would readily permit incorporation of energy efficiency measures—is underway. A research program on energy efficiency addressing the needs of California has been established.

EED scientists have received numerous awards and national recognition for their accomplishments in the fields of energy conservation, environmental science, and technology transfer.

Synthetic Data Testing of PRISM Software
ALAN MEIER

Bonneville Power Administration uses PRISM to estimate weather-normalized energy use and energy savings from thermal envelope improvements in homes. The model has never been fully validated. LBL will test PRISM by creating synthetic monitored data using the DOE-2 building simulation model. Various prototypes will be simulated to identify building characteristics (insulation levels, orientations, thermal mass) and occupancy patterns (thermostat settings, internal gains, etc.) that lead to inaccurate PRISM predictions of normalized annual consumption.

Long-Term Energy Use Related to Global Warming
JAYANT SATHAYE AND LEON SCHIPPER

This project will continue work that assists the U.S. Environmental Protection Agency (EPA) in the assessment of the environmental effects of global climate change and the choices the international community may need to consider to both adapt to and limit potential global warming. LBL will continue to assist in characterizing technology and improving projections of scenarios of global energy use. This will be achieved through an end-use-oriented approach relying on a network of international contacts in all major energy-consuming developing countries. Workshops will be organized and convened for this purpose. Scenarios will be considered, and implementation strategies will be developed.

Since forests are one of the major sinks for absorbing carbon dioxide, this project is being expanded for the next two fiscal years to include data collection and analysis on deforestation and the possible policy avenues for reducing it in the tropical countries. The project will also include a workshop with participants from several countries, to be held in conjunction with a tropical forestry meeting in Sao Paulo, a series of case studies for individual countries, and the development of a network of experts on forestry-related issues.

This project will also continue work to:

- Determine recent trends in efficiency and the structure of OECD energy demand;
- Extend the analysis to selected Comecon countries; and
- Examine these trends extrapolated well into the next century.

These findings will be used to reassess the long-term scenarios and policy recommendations currently under discussion at the EPA.

Conservation Verification Protocols
ALAN MEIER

As part of the Acid Rain Provisions in the Clean Air Act, utilities will be given credits for reduced pollutant output due to energy conservation activities that they initiate. To qualify for these credits, the utilities must verify that these energy-savings programs indeed have worked. The U.S. Environmental Protection Agency (EPA) must now establish protocols for acceptable verification procedures. LBL will develop those protocols with particular emphasis on measurement and evaluation techniques.

Integrated Resource Planning

MARK D. LEVINE

The DOE IRP project at LBL has four program elements:

- *Planning Processes* Development of processes for the preparation of integrated resource plans for electric and gas utilities and the provision of guidance to utilities, regulators, and consumer groups with involvement of entities such as PMAs, NARUC, AGA, EPRI and public and private utilities.

- *Regulatory Analysis/Studies* Development and analysis of regulatory policies that remove barriers to competition and ensure a level playing field in the implementation of demand-side management options, renewable supply options, and traditional supply options by electric utilities. These policies include competitive bidding, changes in rate-of-return regulation, transmission issues, and appropriate ways to incorporate externalities in utility résumé planning and acquisition.

- *Demand-Side Management (DSM)* Testing and evaluation of technologies and programs to reduce and shape energy services by monitoring, validating, and disseminating data on electric and gas utility conservation and load-management programs. LBL's DSM activities are organized into three broad categories: a) information for end-use resource characterization, b) DSM technology assessment, and c) DSM program experience.

- *Technical Assistance and Technology Transfer* Technical assistance to state regulatory staff and utilities through participation and organization of seminars, workshops, and conferences.

Thermal Energy Distribution in Buildings
MARK MODERA

Improving the efficiency of Thermal Energy Distribution (TED) systems in buildings can have potentially dramatic impacts on building-sector energy use. This large potential stems from the facts that a clear majority of the space-conditioning energy for buildings passes through distribution systems and that efficiency improvements in these systems have significantly lagged behind improvements in the efficiency of energy-conversion equipment. Therefore, research aimed at improving distribution systems has the potential to greatly enhance building energy efficiency during the next decade. This is particularly true for residences, although commercial buildings also offer significant room for improvement.

The purposes of this project are to develop and enhance the tools necessary for evaluating thermal energy distribution performance in the laboratory, in the field, and within building energy simulation software, as well as to develop and test new and existing technologies for improving that performance. The tools to be developed include standardized laboratory and field efficiency-measurement protocols, field diagnostic tools, and usable distribution-simulation software. The technologies to be developed and tested include retrofit technologies (such as *in situ* duct-sealing systems and internal-pressure balancing retrofits) as well as new-construction technologies. Some of the new-construction technologies to be examined include zone-conditioning systems, self-contained duct systems, and hydronic/refrigerant distribution systems for residences, as well as alternative cooling technologies (e.g., radiant cooling, cold-air distribution, and occupant-controlled cooling) for commercial buildings.

Recent Developments in the Wholesale Private Power Industry
EDWARD P. KAHN

The private power industry represents one of the major pathways for the development of new electric generating capacity. It is expected that approximately half the new capacity built in the next decade will be of this kind. To understand the evolving trends in this segment of the power supply system, it is useful to construct a database. This project builds on previous work by LBL on the private power industry over the past six years. The project will assemble data of three distinct types on the private power industry. First, the power purchase contracts between developers and electric utilities will be collected and categorized. Second, the finances of the private power industry will be studied by collecting public documents, including bond prospectuses.

Third, regulatory policy will be categorized by analyzing decisions affecting private power, including avoided-cost methodologies and competitive bidding protocols. Analytic studies will be performed using these data, in consultation with DOE project managers.

Separations by Reversible Chemical Association
C. JUDSON KING

Carboxylic acids, alcohols, glycols, and related polar organic substances are attractive for manufacture from biomass by fermentation; however, they must be recovered from highly complex and dilute solutions. Separations involving these and related substances (e.g., phenols) are also needed for many large-volume industrial processing and waste streams in the petrochemical and chemical industries and elsewhere. Separations based upon reversible chemical association promise better selectivity and lower energy consumption than do alternative approaches.

The general objectives of the project are: to develop novel and effective methods of separation based upon reversible complexation or association with organic agents; to obtain fundamental insight into pertinent phase equilibrium and rate properties; to develop rational selection criteria for complexation reagents; to develop suitable methods for regeneration and process integration; and to define the most attractive applications.

This work emphasizes solvent extraction and the use of solid sorbents. We are currently carrying out research that involves recovery of carboxylic acids, including at $pH > pK_a$; separations in which favorable equilibrium for recovery of a solute is achieved by removal of another, minor component, which is typically water; and separations of diols, polyols, sugars, etc., by complexation with functional groups such as boronates and phenols.

Energy Structures and Evolution
MARK D. LEVINE, JAYANT SATHAYE AND LEON SCHIPPER

This work consists of three separate tasks:

- *Energy in China* This effort consists of the compilation of statistical data on China's energy system and use of these data to analyze energy issues.

- *Assessment of energy issues in developing countries* This task assesses the role of energy end-use efficiency in LDC energy demand growth; and

- *Russia energy futures* In this task we will develop a set of energy demand scenarios for 1995 and 2005 based on alternative U.S. and Soviet views of the structure of the Soviet economy and the pace of economic reform.

Progress in Home Energy Conservation
LEON SCHIPPER

The LBL effort to analyze residential and service sector energy use will continue its comparison of the results of major energy conservation programs with observed changes in structure and intensity of the housing stock. Where possible we will extend the analysis to commercial buildings as well. This review will lead to the evaluation of the results of a number of energy conservation programs and to the analysis of factors that have determined their success or failure, taking into consideration the applicability of the foreign experience to U.S. conservation policy. A separate analysis will extend our analysis of the changes in energy use and conservation since the fall in oil prices, emphasizing the clear presentation of trends in the energy-related properties of the housing and equipment stock, the changes in unit energy consumption (as measured by yearly surveys in each country), and total changes in residential energy use as well as energy conservation activities. We will also compare the dynamics of penetration of conservation technologies in electric appliances to establish which technologies have reached (or are reaching) acceptance level. Additionally, we will update our user-friendly database on residential energy demand to allow interfacing with DOE modeling and forecasting.

The outputs of the study will permit both the continuous monitoring of the evolution of demand and the assessment of the impact of energy conservation measures.

Greenhouse Gas Emissions: Policy Studies
MARK D. LEVINE

The increasing concentration of CO_2 and other greenhouse gases has raised concern in the scientific community about the issue of global climate change. The anticipated increase in the use of energy around the world will further exacerbate this problem. The U.S. Department of Energy is interested in developing a comprehensive understanding of the factors that govern the release of greenhouse gases, particularly those produced by combustion of fossil fuels. A better understanding of current sources and trends is essential in projecting future emissions and in formulating and evaluating candidate mitigation policies. LBL will address the following:

- Global energy demand with an emphasis on LDCs;
- China as a contributor to global CO_2 and other greenhouse emissions;
- Assessment of physical impacts of climate change;
- Energy conservation and forecasts for energy use in U.S. buildings; and
- Other policy analyses.

Dilute Engine Combustion
ROBERT F. SAWYER AND RALPH GRIEF

Dilute engine combustion, achieved through obtained excess air induction, exhaust gas recirculation, or residual retention, holds the promise of improved efficiency, extended fuel tolerance, and reduced emissions. Understanding the fundamental processes that limit dilute combustion under engine conditions is essential to the development and improvement of dilute combustion engines. We are studying three aspects of the combustion:

- Inlet and in-cylinder flows and fuel-air mixing;
- Flame propagation, including the effects of in-cylinder mixing; and
- Wall heat transfer, including flame quenching.

Our latest work also focuses on hydrocarbon pollutant formation. For this research, we are using a unique transparent-walled piston engine simulator which provides full optical access to the flow and combustion processes, a valve flow simulator, and a constant-volume cell with optical and instrumentation ports.

Experimental studies include the visualization and quantification of intake flows, in-cylinder mixing of fuel and air, and combustion processes. Flame propagation rates, inflammation rates, energy release rates, and time- and space-dependent heat transfer rates are measured. Particle imaging velocimetry (PIV) provides mapping for velocity fields. Planar fluorescent imaging is planned to observe hydrocarbon formation processes. Theoretical models aid in the interpretation of experimental observations and contribute to comprehensive engine models.

Appliance Efficiency Performance Standards
JAMES E. MCMAHON

The objective of this project is to support the U.S. Department of Energy's (DOE) legislatively mandated analysis of energy efficiency standards for consumer products. During FY92, LBL provided technical support and analysis for a Notice of Proposed Rulemaking for nine products. LBL also analyzed potential policies for improving lighting efficiency in buildings. LBL reviewed and responded to comments on the Notice of Proposed Rulemaking for nine products. In FY92 and FY93, we will complete data collection and analysis of standards for a final rulemaking on nine products, including room air conditioners, mobile home furnaces, clothes washers, kitchen ranges and ovens, water heaters, pool heaters, fluorescent lamp ballasts, television sets, and direct heating equipment. In FY93, LBL is providing technical support and analysis for a Notice of Proposed Rulemaking (updates) for three products: central air conditioners and heat pumps, furnaces, and refrigerator/freezers and freezers. In FY94, LBL will prepare a final analysis of the updated standards for those three products. Our latest work will provide a continuing and improved analytic basis for DOE to draw upon in support of its rulemaking activities. We will conduct research in four broad areas: engineering analysis; consumer choice; manufacturer impacts; and integrated assessment of impacts and standards, including the effects on electric utilities and the environment. LBL will perform the overall project management function for DOE in support of the analysis of appliance standards.

Infrared Opacification of Aerogels
ARLON J. HUNT

The goal of this work is to develop advanced material processing methods to make new aerogel-based materials using sol-gel processing and supercritical drying techniques. The primary challenge is to develop new forms of aerogel with improved thermal properties for a cost-effective high-performance alternative to conventional CFC blown plastic foam insulators. These foams, used in refrigerators, water heaters, and industrial plants are a major source of the atmospheric CFCs responsible for stratospheric ozone depletion. Aerogel, already a high-performance insulator, is improved by adding nanostructured phases to increase the thermal resistance by reducing radiative heat transfer. Compounds are added during sol-gel processing to absorb and scatter infrared radiation responsible for radiative heat transfer within the aerogel. LBL is developing techniques to produce opacified aerogel. In related work, we are exploring aerogel processing techniques for improved magnetic materials. A nanostructured composite is formed by creating extremely small metallic particles in silica aerogel. This composite has strong paramagnetic properties useful in devices for paramagnetic cooling. These new processing techniques promise a whole new range of materials and applications arising from the unique characteristics of their nanostructures.

Fast-Track Development of Energy-Related Design Software

STEPHEN E. SELKOWITZ AND WILLIAM L. CARROLL

In this project, we will undertake a short, intensive effort to develop an energy-related design tool for the wide market of building designers. We will use DOE-2, an energy simulation program developed at LBL, as a foundation, adding new features and capabilities. The DOE-2 program provides detailed, accurate estimates of energy performance in buildings. DOE-2 is operational, well-validated, has comprehensive analysis capabilities, and is continuously maintained and enhanced. We will convert DOE-2 from a batch-oriented, "difficult-to-use" energy simulation tool to a versatile interactive tool that could be used to determine design strategies in buildings that optimize energy performance. Once such a tool is developed and embodies energy-efficient design guidance capabilities, we hope to achieve widespread distribution and use of the tool as a major strategy to extend the impact of DOE-supported research programs in building energy efficiency to a much wider audience. Such a tool could also be used for developing and evaluating federal facilities energy management or utility demand-side management programs.

Finding the High-Radon Houses: A Design Study

ANTHONY V. NERO

A design will be 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 having indoor radon concentrations above 20 pCi/l—corresponding to the occupational radiation dose limit—are located. For this purpose, area-dependent correlations will be examined between ranking indices derived from the *a priori* information on soil/geological, structural, and meteorological factors and on monitoring data acquired in various ways, which will then serve as the basis for developing estimates of the concentration distribution at various geographic scales. In addition, we will design approaches for developing the needed *a priori* information from various areas and for conducting monitoring surveys to ascertain concentrations in a sample of houses.

This project will be carried out jointly with the U.S. Geological Survey, which, with other support, will participate in developing the overall design and will carry out geological assessments in demonstration areas selected together with LBL. During the second year, an additional contractor will be added for conducting surveys in the demonstration areas. The two-year effort will determine the feasibility and design for a national program to find the high-radon houses.

Forecasting Demand and Efficiency in the U.S. Energy System
MARK D. LEVINE

This project involves an initial effort to improve and apply models to analyze and forecast energy demand and energy efficiency in the U.S. energy system. The long-term objective is to establish an analytic capability to assess impacts of different R&D and technology development strategies, government programs, and policies on U.S. energy demand growth. LBL will perform work in three of the four major end-use sectors (all except transportation). For residential buildings, we will develop forecasts and perform sensitivity analyses to compare our model results with those of the National Energy Strategy and other exercises. For the commercial sector, we will gather data and test and improve forecasting models. For the industrial sector, we will complete work on a simplified forecasting model and use the model to produce forecasts. The project also involves working with SERI and Pacific Northwest Laboratory to design an overall analysis effort.

Removal of H_2S Using Metal Salts
SCOTT LYNN

This project consists of three studies. The first is a three-step process for scrubbing H_2S from hot coal gas at the adiabatic saturation temperature (about 400 F at 35 atm). First, a copper sulfate solution absorbs H_2S, forming a slurry of CuS. Second, CuS is oxidized to elemental sulfur by ferric ion, regenerating the $CuSO_4$ and forming ferrous ion, Fe^{+3}. Third, air regenerates the Fe^{+3}, completing the cycle. Research to date has determined the kinetics of the first step, and the investigation of the second step is under way.

The second study is of the sorption of H_2S from high-temperature coal gas (1500 to 1800°F) in a moving bed of small grains of limestone that would serve simultaneously as a filter. Calculations have determined both the conditions of temperature, pressure, and gas composition necessary for nearly complete sorption of H_2S and the parameters required to ensure effective filtration of solid particulates. Experimental work has determined that CaS, which does not sinter in this temperature range in an inert atmosphere, does sinter when CO_2 is present. Conditions that allow high conversion of the limestone in spite of the sintering phenomenon are now being sought. A computer simulation completed in FY91 is used to evaluate the relative merits of the cleanup systems for different types of gasifiers.

The third study, an outgrowth of the second, is exploring a novel, emissionless method of converting H_2S to elemental sulfur and synthesis gas or hydrogen. The water-gas-shift reaction is used to increase substantially the conversion of H_2S relative to what can be obtained in simple thermal splitting, and may prove to be a substantial improvement over conventional Claus technology.

Additive Effects on Scrubber Chemistry

SHIH-GER CHANG

Wet limestone systems have been widely used for the control of SO_2 emissions from coal-fired power plants. However, these systems are incapable of removing NO because of its low solubility in aqueous solutions. One of the objectives of this project is to develop new additives for use in wet limestone systems such that NO_x can be simultaneously removed in an efficient and cost-effective manner. Current research efforts are directed toward investigating two approaches for promoting the dissolution of NO. One approach involves the development of metal chelates for absorption of NO in solution. The other approach involves the development of oxidants for selective oxidation of NO to the more soluble NO_2. After dissolution, NO may be converted to other nitrogen species which should be harmless to the environment.

Another objective is to develop cost-effective ways for disposal of wastes from various types of advanced scrubbing systems. Catalysts for conversion of SO_2 and H_2S in a waste gas stream to elemental sulfur will be developed so that the cost-effectiveness of NOXSO, CuO, Cansolv, and Wellman-Lord/Tungs processes can be improved. Also, the most economic method of treating nitrogen-sulfur compounds formed in a wet scrubbing system, such as the LBL PhoSNOX process, will be determined.

Gas-Filled Panel Insulation for Refrigerator/Freezers

DARIUSH ARASTEH

CFC blown foams are used as thermal insulation in many building and appliance applications. International efforts to curtail the use of CFCs will result in the use of blown foams with poorer insulation capabilities. Lawrence Berkeley Laboratory is carrying out a research program aimed at developing gas-filled panels (GFPs), a completely CFC-free method of insulation, for use in applications where CFC-blown foams are currently used. Gas-filled panels have R-values up to twice those of conventional CFC-blown foam insulation.

Current research objectives are aimed at developing suitable prototypes for use in conjunction with non-CFC-blown foams in refrigerator/freezers (R/F). The technology base developed for this application will aid the use of GFPs in building shells, refrigerated transport, airplane insulation, vehicle insulation, and other niche applications. Research tasks include collaborative efforts with component suppliers to develop and analyze appropriate gas barrier materials and to develop cost-effective baffle structures. Other tasks include the production of prototypes for use and testing in prototype R/F applications as well as for independent thermal testing by Oak Ridge National Laboratory (ORNL).

Advanced Electrode Research
ELTON J. CAIRNS

The aims of this project are to study processes in electrodes used in high-performance aqueous, molten-salt, and solid-electrolyte systems and to investigate practical means for improving their performance and lifetime. Systems of current interest include ambient-temperature rechargeable cells with zinc electrodes, rechargeable high-temperature cells, and direct-methanol fuel cells. We are studying phenomena that limit the life and performance of these cells, including realistic operating conditions. Improvements to electrodes are proposed and investigated.

Existing Buildings Efficiency Research
RICHARD C. DIAMOND

Most of the current building stock will still be in use in the year 2010. The potential energy savings in existing buildings has a greater potential payback to the U.S. Department of Energy than in new construction. In existing buildings it is necessary to be able to directly measure system, subsystem, and component performance and from that performance infer characteristics that indicate how performance can be most efficiently improved.

The purpose of this project is to develop tools necessary for ascertaining energy-saving potential, achieving savings, evaluating retrofits in existing buildings, and developing new retrofit technologies. These tools include diagnostic instrumentation, audit tools, analytical methods, and implementation guides.

Lack of technical ability is not the only barrier to improving the efficiency of existing buildings. Many non-technical barriers, including behavioral, institutional, and informational, exist and must be overcome for potential improvements to be realized.

Infiltration, Ventilation, and Indoor Air Quality

JOAN M. DAISEY AND MAX SHERMAN

Approximately thirteen quads of energy is 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 the U.S. Department of Energy (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 (IAQ) and occupant health, comfort, and productivity.

The purpose of this project is to develop and disseminate the information and technology needed to achieve this goal through research on the relationships between building energy usage, ventilation and infiltration, IAQ, and human factors (e.g., health, comfort, productivity).

The research employs a combination of modeling, laboratory experiments, and field studies. Research on building tightness and air leakage yields technologies for measuring and modeling infiltration and reducing excess infiltration. Advanced techniques of heating, ventilating, and air conditioning that are simultaneously energy efficient and effective in maintaining indoor air quality and comfort are developed and evaluated. Methods for reducing energy use by thermal distribution systems are developed. Indoor pollutant concentrations and source strengths and their dependence on ventilation and building characteristics are investigated, providing information needed for energy-efficient control of indoor air quality. Factors that cause the occupants of large buildings to have building-related health symptoms are also being investigated because they are estimated to cost billions of dollars annually through illness and lost productivity and because they lead to increased ventilation and energy use.

Performance Calculations for Buildings
FREDERICK C. WINKELMANN

The LBL Simulation Research Group (SRG) provides the architectural, engineering, and research communities with accurate, well-validated computer programs to assist in the design of energy-efficient cost-effective buildings. SRG's work includes development and maintenance of the current-generation benchmark program, DOE-2, and research leading to the development of next-generation building-performance calculation tools.

SRG will continue to document, support, and distribute the current version of DOE-2. Research will also be performed to advance the state of the art in building-performance simulation to ensure that adequate analysis tools exist as the complexity of building designs increases. This work will continue development of the Simulation Problem Analysis and Research Kernel (SPARK), a modular simulation environment that will allow researchers to efficiently create customized models for detailed analysis of building components, systems, and subsystems. We will also develop a next-generation version of DOE-2 that will be much easier to use by the average architect or engineer than the current version. The new program will provide built-in design guidance and, by incorporating SPARK methods, will be able to simulate future HVAC technologies.

Windows and Daylighting
STEPHEN E. SELKOWITZ

Windows are responsible for more than 5% of national energy consumption. Lawrence Berkeley Laboratory is carrying out a comprehensive program aimed at bringing about substantial energy savings in this area by:

- Developing advanced energy-efficient window materials and systems;
- Characterizing the properties of fenestration components and systems and their performance in buildings; and
- Carrying out investigations that provide the community of fenestration users with information on the impact of energy-efficient fenestration on people and the environment.

The program supports research in three areas:

- Advanced materials research to develop switchable glazings, superwindows, and other highly efficient fenestration systems;

- Calculational tools and experimental facilities for characterizing and rating fenestration system properties and complex energy-related interactions between fenestration systems and buildings; and

- Advanced design tools to determine impacts of fenestrations and enable their optimal use in the building industry.

With one-of-a-kind experimental facilities, broad calculational capability, and wide technical contacts and credibility within the fenestration industry, it is a program unique in the U.S., with its results directed toward improving U.S. energy efficiency and enhancing the long-term viability of the fenestration industry.

Lighting Technology
SAMUEL M. BERMAN

Lighting energy use accounts for 25% of national electrical consumption. Lawrence Berkeley Laboratory is carrying out a comprehensive program aimed at bringing about substantial energy savings in this area by:

- Supporting a wide range of both short- and long-term research of new energy-efficient lighting systems; and

- Carrying out investigations that provide the community of lighting users with information on the impact of advanced lighting technologies on people, machinery, and the environment.

The program supports research and development leading to energy-efficient use of lighting. This includes efforts to develop more efficient light sources and to manage lighting energy use more effectively. In addition, a series of studies is being conducted that relates lighting to visibility, health, and productivity to assure lighting users that adopting energy-efficient systems will have positive effects on productivity.

The lighting program combines the facilities and staff of LBL with those of the University of California School of Optometry on the Berkeley campus and the School of Medicine in San Francisco (UCSF). This interdisciplinary program encourages innovation in the industry and accelerates the societal benefits obtainable from a more cost-effective and efficient lighting economy. This comprehensive program is unique in the United States.

Electrochromic Window Technology
STEPHEN E. SELKOWITZ

We will develop electronically switchable electrochromic glazings suitable for a variety of building types. Electrochromic technology is the most promising method for the dynamic control of solar energy and daylight in architectural glazing. This technology will be a key element in the smart window/smart building technology of the future, aimed at minimizing energy consumption and peak demand while improving comfort and productivity.

Our technical approach is to develop electrochromic device component layers using materials and processes that can be used by industry as commercially viable production processes. Currently we are developing device components of inorganic and polymeric materials for use on glass and plastic substrates. We have developed unique ion-storage polymers that can be used with many electrochromic coatings to reduce device complexity and produce a lower-cost device.

With industry partners we are scaling up devices for use as windows and investigating alternative materials for device components. Our research emphasizes improving the optical performance and durability of successive generations of prototype devices to meet market needs. We are testing and modeling these devices and devices made by others to quantify their energy-saving potential.

Turbulent Combustion
LAWRENCE TALBOT AND ROBERT K. CHENG

Turbulence enhances combustion rate and affects other combustion processes such as ignition, extinction, and the rates of pollutant formation. To obtain a better fundamental understanding of the complex coupling between turbulence and chemical reactions, laboratory-scale premixed and non-premixed turbulent flames with idealized flow geometries amenable to theoretical analysis are studied experimentally using laser diagnostics. A theoretical study of premixed turbulent flames using the vortex dynamics method is also being carried out. These investigations are directed toward developing turbulent combustion theories and numerical models capable of predicting combustor performance and pollutant-formation characteristics.

The three laboratory premixed flame configurations are: a flame stabilized in a stagnation flow; a freely propagating flame stabilized by weak swirl; and a rod-stabilized v-flame.

Current emphasis is on developing methods to characterize the effects of combustion heat release on the turbulent flow field and to determine the mean reaction rate and the flame speed based on scalars and velocity statistics obtained at a point. We also wish to characterize scales and flame structures determined by a two-dimensional (2D) laser tomography technique. The interpretation of the 2D flame structures are guided by the results of three-dimensional direct numerical simulations of Ashurst. The results are used to validate the predictions of a deterministic theoretical simulation of premixed turbulent flames developed by us and predictions obtained by a statistical model developed by Bray and Libby.

Combustion Chemistry

NANCY J. BROWN

Combustion processes are governed by chemical kinetics, energy transfer, transport, fluid mechanics, and the complex interactions among these factors. In all chemical changes, the pathways for energy movement and the competition among the pathways determine reaction rates, product yields, and product-state energy distributions. Understanding the fundamental chemical processes offers the possibility of optimizing combustion processes.

Recent research has been concerned with the application of functional sensitivity analysis to determine the relationship between dynamic observables and the potential energy surface structure. This provides an understanding of how different regions of the potential play a part in controlling the dynamics and thereby influence the eventual outcome of calculated observables. Functional sensitivity analysis has been applied to classical dynamics studies of energy transfer and to quantum mechanical studies of reactive scattering. Functional sensitivity analysis can be used to identify regions of configuration space of highest sensitivity so that quantum chemists will calculate a high density of *ab initio* points in those regions. The sensitivities can be used in guiding the improvement of the potential surface to improve agreement between theory and experiment. A second portion of the effort is concerned with modeling combustion chemistry, with particular emphasis on the use of sensitivity analysis.

Electrode Surface Layers
FRANK MCLARNON

The structure, composition, and mode of formation of surface layers on electrodes used in rechargeable batteries and fuel cells are determined by *in situ* and *ex situ* characterization techniques that are sensitive to surface composition and microtopography. The primary objective is to identify film properties that improve the rechargeability, cycle-life performance, specific power, specific energy, stability, and energy efficiency of electrochemical cells.

Building Energy Data, Modeling, and Analysis
MARK D. LEVINE

The objective of the proposed work is to support the analytic efforts of the Office of Building Technologies (OBT) of the Assistant Secretary for Conservation and Renewable Energy (CE), U.S. Department of Energy (DOE). The project will principally involve a compilation and documentation of data needed for improved end-use forecasting in the residential sector; an update of measured energy-savings data for new buildings (BECA-A); continued development of residential forecasting tools for OBT use; an assessment of the impact of utility-sponsored energy-efficiency programs; continued analysis of international appliance-efficiency trends; an international assessment of programs and policies to promote efficiency; and continued LBL support for the National Energy Strategy and related analyses. FY93 efforts are expanding the residential efforts into the commercial sectors.

Thin Film Coatings for Automotive Glass
MICHAEL D. RUBIN

The purpose of this work will be to develop thin-film materials for automobile windows that will control solar heat gain, and to analyze the effects of these coatings on fuel consumption and coolant requirements. Reduced load on the air conditioner will directly reduce fuel consumption. Reduced peak loads will lower the CFC coolant capacity of the air conditioner or allow alternative cycles. We will develop, in collaboration with industry, a spectrally selective solar control film that is durable enough to be used on the side or rear windows of an automobile. Two separate pathways to this goal will be pursued: coatings based on intrinsically selective materials and coatings based on a microstructural effect. Taking advantage of the laminated structure of the windshield, we will develop an electrochromic device that uses a polymer ion-conducting layer. We will continue to assist industry with the development of angle-selective microstructures. Modeling efforts to quantify general savings of energy and coolants will be completed. An industry standard for further specific calculations will be established.

Repetitively Pulsed Laser Material Interaction

RICHARD E. RUSSO

The repetitively pulsed laser material interaction represents a powerful approach for direct solid-sample chemical analysis. However, the explosive sampling interaction is not fundamentally understood. This research program employs several experimental techniques to monitor the interaction, the results of which are used to describe the fundamental mechanisms. Atomic emission spectroscopy (AES), acoustic monitoring, and optical probe laser beam deflection are utilized to resolve the time-dependent components of the interaction. By injecting the laser-sampled species into an inductively coupled plasma (ICP), we simultaneously study emission intensity due to changes in the laser material interaction and determine parameters that influence this technique for chemical analysis. The work emphasizes the use of a repetitively pulsed laser material interaction for producing *steady-state* emission intensity in the ICP. For chemical analysis, *steady-state* laser sampling provides improved accuracy and precision over transient sampling.

A 125-MHz bandwidth piezoelectric sensor is used to study the character and propagation of acoustic waves induced in the material by pulsed laser radiation. Changes in the acoustic response as a function of laser power and material properties are studied to indicate the existence and time dependence for mechanisms of heating, melting, vaporization, and ablation. Optical probe beam deflection is employed to monitor the region adjacent to the solid surface illuminated by the laser beam to determine heat transfer mechanisms, the onset of material removal, and the formation of a laser-initiated surface plasma. Fundamental mechanisms describing the explosive laser material interaction will be characterized by drawing correlations between these acoustic, deflection, and atomic emission data.

Characterization of Airborne Radon Concentrations

ASHOK J. GADGIL AND RICHARD G. SEXTRO

This project investigates the sources of indoor radon and characterizes factors affecting exposure to indoor radon progeny. Indoor radon provides more than half of the total radiological dose to the general population. Human exposure to indoor radon progeny can be more effectively controlled or reduced with a better understanding of the processes that determine radon entry into dwellings and the factors that control the fate of radon progeny. These factors include the mechanisms of radon entry and various transformation and removal mechanisms for radon progeny (such as attachment to indoor aerosols, deposition on indoor surfaces, and removal by ventilation). This project aims at gaining an understanding of these factors, through experiments and analytical and numerical modeling. In addition, this project investigates methods to characterize mechanisms of radon entry in houses, which would lead to a better understanding of human exposure to radon, and improved strategies to reduce the harmful effects of the exposure to radon progeny in the general population.

Experimental and Theoretical Investigations of Radon Availability
RICHARD G. SEXTRO, HAROLD A. WOLLENBERG, T. N. NARASIMHAN, AND WILLIAM J. FISK

Pressure-driven flow of radon-bearing soil gas is responsible for radon entry into buildings, at least those with elevated indoor concentrations. The behavior of the building-sod system is complex, due both to the interactive nature of this system and the heterogeneous nature of both the soils and the building substructure. The objective of this study is two-fold: to experimentally examine radon migration through soils and into small, identically constructed structures with controlled leakage characteristics and controlled pressure differences between the structure interior and the soil; and to develop and validate models of radon migration through soils and into dwellings that deal more effectively with heterogeneous sod structures and soil environmental conditions (soil moisture, temperature, and changes in surface conditions).

For the experimental portion of the study, several small structures will be constructed in field locations with different soil properties. Two structures have been fabricated at the first site. Experiments are being conducted with continuous data collection done by means of a computer-based data-logging system. Changes in radon entry rate at each experimental site will also be studied as a function of steady-state and time-varying applied differential pressures, as environmental parameters change, and as a function of size and location of penetrations to the soil.

The modeling effort involves the modification, validation, and use of state-of-the-art steady-state and transient numerical models of soil gas and radon transport. The models account for advective and diffusive transport, heterogeneous soil conditions, and detailed features of the substructure. Model verification experiments are being conducted. At the same time the models can be used to provide information to guide the experiments.

Air Pollutant Exposures in Buildings
ANTHONY V. NERO AND JOAN M. DAISEY

The purpose of this work is to advance scientific understanding of human exposures to, and health risks from, indoor air pollutants. A specific focus is the influence of reductions in ventilation and other technologies intended to decrease energy use in buildings. The baseline effort, however, includes modeling and assessment of current indoor concentrations and their health effects, utilizing available information on the parameters determining indoor concentration and epidemiological toxicological data indicating the adverse health effects of indoor pollutants. A major focus of the effort, development of a functional exposure model, will serve as the primary basis for examining major pollutant classes.

We are studying a variety of pollutant sources, including combustion emissions, radon, and organic carcinogens, irritants, and neurotoxins. Work on combustion emissions focuses on estimation of exposures in the context of this modeling approach. Work on radon is aimed at estimating the distribution of indoor concentrations and its dependence on underlying physical parameters, time-activity patterns, and population mobility to the distribution of personal lifetime exposures. Currently, a major activity is the development of an analytical approach for using monitoring and physical data jointly to yield a topology of indoor radon for the U.S. as a basis for identifying the high-radon areas. Research on organic pollutants is directed toward assembling, integrating, and assessing existing measurements of indoor concentrations of carcinogens, irritants and neurotoxins.

Indoor concentrations are modeled wherever possible to supplement this work and to further develop and validate models. Some work has begun on development of new biologically based methods for risk assessment.

Fuel Conservation Policy Studies
MARK D. LEVINE

The objective of the proposed work is to estimate the energy savings of several incentive-based ('feebate') programs to achieve improved light-duty-vehicle fuel efficiency. The project will include:

- Overview of approaches to 'feebates' to increase auto fuel economy;
- Development of a methodology for analyzing 'feebate' approaches;

- Data gathering and model enhancement to apply methodology; and
- Application of the model to estimate costs and fuel savings, resulting in the application of alternative 'feebate' approaches to increasing auto fuel economy.

Cloud Optical Properties
TIHOMIR NOVAKOV

The objective of this project is to quantitate, under field and laboratory conditions, the effects of atmospheric aerosols on optical properties of clouds. The field component of this project is performed at the El Yunque peak in Puerto Rico, a site that is frequently in clouds and characterized by seasonal changes in the aerosol composition and concentration. This enables us to distinguish between effects of anthropogenic (combustion-produced), biogenic, and natural mineral aerosols. The principal field research tool is a newly developed nephelometer that measures in real time the integrated cloud back-scattering coefficient (a quantity directly related to the thin cloud albedo). These measurements are complemented by monitoring cloud drop concentration, size distribution, and liquid water content. Aerosol measurements include collection and analyses of total and interstitial aerosols, aerosol number concentration, and cloud condensation nuclei concentration. Results from these field studies are used to design laboratory simulation experiments to identify the physics and chemistry of dominant importance in modifying the optical properties of clouds, with special emphasis on enhanced absorption of soot-associated clouds. A complementary activity is the development of a global soot emission inventory to be used in global circulation models.

Aerosol and Cloud Chemistry
TIHOMIR NOVAKOV

The overall objective of this project is to study, under laboratory conditions, the chemical interactions of gaseous pollutants with subsaturated aerosols and cloud drops nucleated on these particles. The motivation for these studies stems from the fact that most studies on aqueous atmospheric chemical processes were based on experiments with bulk solutions. In the atmosphere the aqueous systems are in a dispersed state, such as clouds and fogs. It is therefore of interest to conduct systematic studies to assess possible differences between dispersed and bulk aqueous systems. If such differences are found, then the treatment of specific reactions in atmospheric chemistry models will have to be modified appropriately. Our past results indicate that significant differences between such systems exist for SO_2 + NH_3 + H_2O and NO_2 + H_2O reactions. The approach to this study involves the use of a newly modified cloud/aerosol chamber.

Integration of Passive Solar Technologies

WILLIAM L. CARROLL

The overall goals of this continuing work are to better understand the effectiveness of solar strategies in commercial buildings and to provide improved design information that allows integration of the most effective solar and conservation techniques into U.S. buildings. This work consists of two tasks.

The first task concludes U.S. involvement in support of the IEA Task XI atrium research, with further research and technology transfer needs in this area to be defined as part of the effort.

The second task continues support for the development of design guidelines for commercial buildings in collaboration with the Passive Solar Industries Council and the National Renewable Energy Laboratory (NREL). Based on these guidelines, a computer tool will be implemented that allows full integration of passive technologies appropriate for commercial buildings with conventional and emerging energy efficiency technologies. LBL will provide relevant information from various sources, including the passive experimental buildings program completed several years ago, the integration studies carried out in international collaborations, and research carried out at LBL on specific passive technologies.

Modeling Light Scattering from Non-Spherical Organisms in the Ocean

ARLON J. HUNT

This work will investigate the polarized-light-scattering properties of picoplankton and bacteria in the ocean. This investigation will include both experimental measurements and theoretical modeling. The angular-dependence of the Mueller scattering matrix will be measured on several microorganisms. These data will be compared with predictions made using light-scattering theory based on the first Born approximation and the coupled-dipole approximation. The range of applicability and utility of these two methods will be evaluated, and the effects of oriented particles on the nature of light propagation in the ocean will be studied.

Modeling Radon Entry into Florida Homes
RICHARD G. SEXTRO

The EPA needs to have a simplified model capable of predicting average radon concentrations in new homes as a function of easily determinable building and soil parameters. The purpose of this project is to combine the skills of building modelers (in the Energy Performance of Buildings Group) and the radon modelers (in the Radon Group) to develop a simplified physical model of radon concentration. The approach would be to simplify exact analytical models of the physical processes to isolate the physically important and practically determinable parameters. Detailed simulations using COMIS, DOE-2, and the STAR models will be used along with measured data to validate the simplified model. The first application of the results of this expanded effort will be to support the Florida Radon Research Project.

Initiatives to Reduce Greenhouse Gas Emission from Developing Countries
Subcontract for the U.S. Agency for International Development (AID)
JAYANT SATHAYE AND MARK D. LEVINE

The overall purpose of this project is to conduct a series of studies to improve the efficiency with which energy is used and/or to promote the use of fuels that would reduce greenhouse gas emissions from developing countries. LBL will survey, analyze, and prepare studies adequate for implementation of programs to improve appliance and lighting efficiency in urban households; assess the performance of the electric power sector; evaluate mechanisms to increase the efficiency of the transport sector; and promote programs to increase the penetration of energy-efficient equipment.

Each of the studies will involve workshops, training programs, and the development of an information base on energy use in these countries. Under AID's new mandate the LBL activities will focus on one or more key countries. These include the Philippines, Indonesia, India, Brazil, Mexico, and Zaire.

Impact Evaluation of the Energy Edge Program
RICHARD C. DIAMOND AND ALAN MEIER

This is the continuation of an existing Bonneville Power Administration funded project to evaluate the impact of the Energy Edge project and to assess technical performance and cost-effectiveness of 28 new commercial buildings in the Pacific Northwest designed to perform 30% better than required by the Model Conservation Standards. LBL compiles and analyzes data (collected by other contractors) on building performance, cost-effectiveness, and comparisons with predicted values, and examines potential for a regionwide program modeled after this pilot project. LBL also provides technical assistance in analyses of field-monitored data and in comparisons of monitored and DOE-2 simulated results.

Efficient Lighting for Naval Ships, Phase IV

RUDOLPH VERDERBER

During Phase III of this project, we developed an effective emergency lighting system that was installed in a small area on board a naval ship for testing. It has proved to be a vast improvement over the Navy's existing system, which consists of incandescent lamps scattered about the ship. These incandescent lamps provide minimum visibility and require considerable maintenance.

We plan to develop an emergency lighting system that can be used with the present lighting system on board Navy ships. The new system is a battery pack that will be integrated into the existing fluorescent lamps, thus providing sufficient lighting to carry out virtually all of the required assignments. The total number of emergency lamps will be reduced fivefold, thereby reducing the maintenance schedule.

We also plan to use RADIANCE, LBL's lighting simulation software, for the design of lighting on board ships, and explore the use of the more efficient T-8 fluorescent lamp to be used in place of the T-12 fluorescent lamp.

Heterogeneous Reactions of NO_2 in Dispersed Aqueous Systems

TIHOMIR NOVAKOV

The objective of this project is to perform laboratory studies of heterogeneous reactions of NO_2 and nitric acid with subsaturated aerosols and cloud drops nucleated on these particles. The proposed research is aimed at providing experimental explanations for our observation that the aqueous reactions of NO_2 are faster and fundamentally different in dispersed and bulk water systems. Specifically, we propose to test two working hypotheses formulated to explain these findings. The first hypothesis is that the differences are due to an intrinsic, possibly surface-chemical, property of high surface-to-volume aqueous systems. The second is that the uptake of NO_2 and its conversion to nitrate ion in a dispersed system are strongly enhanced by trace amounts of nitric acid adsorbed on subsaturated aerosols, cloud drops, and aerosol particles that serve as cloud condensation nuclei.

Dynamics of Wrinkled Laminar Flames in Microgravity and Zero-Gravity Environments
ROBERT K. CHENG

Although the performance of most turbulent combustion systems is not influenced by gravity, open idealized laboratory burners which have been developed for fundamental studies of turbulence-combustion interactions are more susceptible to the effects of gravity. Without the constraints of the burner walls, the flame is free to interact with the ambient air and the steady-state aerodynamics flowfield is determined by the coupling between gravity and flame geometry. Because detailed statistical data of velocity and scalars obtained from these burners have been used extensively for validating current theoretical and numerical models which do not consider the effects of gravity, the applications of the conclusions drawn from these comparisons may be limited.

The overall objective of this program is to investigate experimentally the flowfield and the dynamics and burning rate of low-Reynolds-number premixed turbulent flames in microgravity environments. These experiments are designed to be conducted on board the NASA KC-135 aircraft, which simulates reduced gravity by flying a parabolic trajectory. Due to the inherent experimental constraints on board, the diagnostics will be limited to several types of laser-based flow visualization. Detailed information will be sought from complementary ground-based experiments performed in +g and -g environments.

Spectroscopic Investigations of Actinides
RICHARD E. RUSSO

Developing spectroscopic techniques for the detection and identification of radioactive species in various environments constitutes a joint research effort between LBL and the Nuclear Chemistry Division at Lawrence Livermore National Laboratory. For this project, we employ state-of-the-art laser analytical methods for ultrasensitive monitoring of radionuclide chemistry. Components of the project include photothermal spectroscopies for monitoring non-radiative absorption behavior in aqueous samples, the use of optical fibers with these techniques for remote spectro-chemical studies, identification of surface oxidation species and dissolution behavior of radionuclide fuels, and application of spectroscopic techniques to replace existing chemical procedures for waste minimization. All studies conducted at LBL are performed with analog rare earth species (models for the radionuclides) to avoid handling hazardous materials.

Technical Assistance for the Advanced Customer Technology Test for Energy Efficiency (ACT²)

WILLIAM L. CARROLL

Pacific Gas and Electric Company has begun a program, Advanced Customer Technology Test for Energy Efficiency (ACT²), to substantiate the savings performance of selected technologies integrated into building or industrial/agricultural systems. The objective of this program is to provide scientific field test information on maximum energy savings possible by using modern high-efficiency end-use technologies in integrated packages acceptable to PG&E's customers.

In addition to providing general input and advice as requested by PGE, LBL will provide technical maintenance in more specific areas:

- Participation in the ACT² Steering Committee;
- Participation in technical advisory committees;
- Assistance in identifying candidate technologies and combinations of technologies for inclusion in the ACT² field tests;
- Review and critique of such technical documents as project plans and design plans;
- Monitoring and analysis of data; and
- Project evaluation.

Methane Activation Chemistry

RICHARD FISH

This project will focus on the following areas of research: the kinetics of the oxidation reactions with Mn and Fe clusters to order in substrate, oxidant, and catalyst; the identification and spectroscopic characterization of intermediate oxidants such as iron and manganese oxo, iron peroxo, etc.; the study of oxygen activation, since any practical application with these catalysts would use O_2 as the monooxygen transfer reagent; the delineation of the effect of temperature, pressure, oxidant, etc., on methanol formation; and the evaluation of new metal clusters that will act as superior catalysts for methane activation. For example, we are now attempting to synthesize new ruthenium clusters for C_2-C_3 activation.

Lighting Quality Assessment
RUDOLPH VERDERBER

Cal Trans wishes to evaluate a lighting installation with regard to the lighting quantity and quality. A portion of the building has been retrofitted with high-quality fluorescent luminaires to improve illumination. They want to find a way to objectively measure the lighting quality and compare the results with the illumination in the space that has not been altered. If an objective measurement can be achieved, it will be possible to set a standard for future lighting installations. We propose to use technologies developed at LBL for measuring lighting quality, which include using the luminance mapper, the 3x demagnifier, and contrast measurement. This will be a valuable field test of these techniques and could be a basis for their general use.

Issues in Integrated Planning in New York
EDWARD P. KAHN AND CHARLES GOLDMAN

In this project, LBL will provide technical and analytical assistance to the New York Public Service Commission (PSC) in evaluating the state's integrated resource planning process. We will focus on three major areas:

- Case studies of the integrated bidding programs of two New York utilities (Consolidated Edison and Niagara Mohawk);
- Evaluation of the relationship of the demand-side management (DSM) bidding program to the other core DSM programs offered by these two utilities; and
- Analysis of design and monitoring issues involved in the Orange and Rockland and Niagara Mohawk incentive rate proposals.

For bidding programs, the analysis will focus on the relationship between the utility's bidding program and its integrated resource plan, a comparison of the bid evaluation process, and design issues which affect the relative competitiveness of demand-side resources. In the second task, we will conduct a preliminary assessment of selected DSM programs sponsored by the two utilities. In the third task, we will analyze rate incentive plans from the utility's strategic perspective and examine how the PUC could structure its monitoring activities to simultaneously prevent inappropriate strategies by utilities and minimize the PSC's monitoring burden. This work will complement LBL's Least Cost Utility Planning Project and is being co-funded by DOE.

Toxic Volatile Organic Compounds in Environmental Tobacco Smoke

JOAN M. DAISEY

We will measure emission rates of selected candidate volatile organic compounds (VOC) for environmental tobacco smoke (ETS) using a room-sized environmental chamber. The specific objectives are to:

- Determine the emission rates of selected N-nitrosamines, aldehydes, and other VOC (including 1,3-butadiene) for ETS in a room-sized environmental chamber under controlled conditions which simulate real-world settings;
- Estimate the range and variability of the emission rates among a subset of cigarette brands which have the largest market share in California; and
- Investigate the effect of aging on ETS emission rates of 1,3-butadiene.

The proposed research will provide emission rate data for a number of candidate VOC and for many other toxic VOC which can be used to model the exposures of the California population. The research will also provide information on the effects of aging on the emission rates for 1,3-butadiene, a highly reactive compound. Since ETS is a major source of exposure for many candidate VOC, these data, when used in exposure models or with indoor or personal measurements of nicotine, will provide the means to assess the relative significance of ETS and other sources of these compounds and to set priorities for reducing exposures.

Hemoglobin Conversion to Pro-Oxidants by Cigarette Smoke

ROLF MEHLHORN

We will test the hypothesis that cigarette smoke degrades hemoglobin to iron complexes that catalyze free radical formation. We will examine the leakage of such complexes from the erythrocyte (which would be a mechanism of chronic vascular damage). Since the tar fraction of cigarette smoke is known to contain readily oxidizable molecules, we will examine their autoxidation by iron complexes. ESR assays will be applied to blood in gas-permeable tubing to detect elusive free radicals and transient oxidative processes in intact erythrocytes while they are being exposed to cigarette smoke. We will also examine the synergistic effects of ozone. Effects of oxygen tension will be studied by comparing hypoxic and normoxic cells. We will seek evidence that vitamin C deficiency accelerates hemoglobin degradation. Possible amplification of hemoglobin degradation by oxidants from activated neutrophils will be examined with a photochemical model system, which will allow us to treat erythrocytes with oxidants similar to those generated by neutrophils while they are being exposed to cigarette smoke.

Soil-Gas Transport: A Mechanism of Indoor Exposures to Volatile Organic Compounds
JOAN M. DAISEY

There is some evidence that pressure-driven flow of soil gases into residences is a major pathway of exposure to volatile organic compounds (VOC) for populations living near hazardous waste sites and landfills. However, the significance of the VOC soil-gas transport pathway is not known and is difficult to estimate based on currently available information. We will conduct research to:

- Advance our fundamental understanding of the nature of soil-gas transport of VOC into residences as an exposure pathway for populations living around hazardous waste sites and landfills;
- Evaluate the significance of this exposure pathway relative to other VOC exposure pathways for subjects living in houses around several sites; and
- Develop methods to estimate the contributions of contaminated soil gases to indoor air VOC exposures in occupied houses.

Advective and diffusive flows of VOC in soil columns and the sorption and desorption of VOC will be investigated in the laboratory under controlled conditions and compared with data from field experiments. Field experiments will be conducted to investigate advective flows of VOC and radon in soil gases into unoccupied houses located near hazardous waste sites. Temporal and spatial variations in indoor concentrations of soil-gas VOC will be investigated and compared with those for radon. Major factors influencing soil-gas transport of VOC into houses will be identified. The contributions of soil-gas VOC to indoor exposures will be compared with VOC exposures from other pathways.

Energy, Economics, and Climate Policy
LEON SCHIPPER

Economic analysis plays an important role in the debate over the appropriate policy response to the global climate change. On a conceptual level, economic evaluation techniques have been proposed as a means of achieving an "optimal" balance between the costs and benefits of greenhouse gas (GHG) emissions abatement. On an empirical level, research has focused on characterizing the likely effects of climate change and the potential impacts of emissions abatement on the macroeconomy. These issues are closely linked: both areas of research emphasize the use of aggregate models of the interrelationships between GHG emissions and the economy. This research will investigate the utility of macroeconomic models in the evaluation of the positive and normative issues relating to climate policy, with a special focus on energy use. Areas of particular emphasis will include:

- Analysis of the conceptual and empirical foundations of aggregate energy-economy models and their relationship to detailed technological studies of energy use, including discussion of the top-down, bottom-up controversy;

- Examination of the issues of economic efficiency, uncertainty, and equity between present and future generations and between geographical regions as they relate to the choice of climate policy criteria; and

- Estimation of energy conservation potential in an Eastern Bloc country.

Assessment of Estimated Energy Savings Used in Consumers Power Company's Demand-Side Management Programs

EDWARD L. VINE

LBL will assist the Michigan Public Service Commission (PSC) in assessing the reasonableness of engineering estimates developed by the Consumers Power Company as part of its demand-side management (DSM) programs, and in developing engineering estimates of savings for certain measures in those programs. This work will involve a critical review and assessment of the detailed assumptions, building energy engineering calculations, and resultant savings estimates from selected energy-efficiency measures currently being promoted in the Consumers Power Company's energy-efficiency programs, as well as developing estimates for new measures being proposed for inclusion in its programs. The specific measures to be analyzed will be determined by the Michigan PSC and Consumers Power.

Concentration of Pollutants Database
GREGORY TRAYNOR

Exposure to indoor air pollution has become recognized as a major component of total population exposures to air pollutants. In response to this, the U.S. Department of Energy, the Gas Research Institute and the Electric Power Research Institute have cofunded the development of a "Concentration of Indoor Pollutants (CIP) Database" to assist researchers, policymakers, and others in finding research articles relevant to their area of concern. We will continue to update the CIP Database, with a new release scheduled in three years. (Note that the International Conference on Indoor Air is held every three years.)

Infiltration Model Improvement
MAX SHERMAN

The LBL infiltration model is the most widely used method of predicting infiltration and ventilation rates in residential buildings. The LBL model home remained substantially unchanged since its completion in 1980 and incorporation into the 1981 ASHRAE Handbook of Fundamentals. During the intervening years, research has shown that in certain regimes the model can significantly overestimate the infiltration.

The purpose of this project is to make sufficiently detailed measurements on a carefully selected sample of houses to improve the accuracy of the following assumptions:

- The effect of leakage distribution, including the split between floor and ceiling and the impact of non-uniform wall leakage
- The appropriate pressure coefficients to use for the floor and ceiling for buildings containing attics and crawlspaces;
- Quantification of the terrain and shielding effects on wind-induced ventilation; and
- The superposition of stack, wind, and mechanical ventilation, including kitchen fans, bath fans, and designed ventilation systems.

This expansion will allow another set of homes to be measured and analyzed.

Application of Aquatic Ecological Hazard Assessment to Hazardous Waste Management

SUSAN ANDERSON

The ongoing goal of our Superfund program project has been to develop the application of genetic toxicology in ecological risk assessment. The specific aims of this project are threefold. The first specific aim is to develop our short-term mutagenesis test using the nematode *C. elegans* for application to soil sediment exposures. To date we have primarily worked with standard chemicals rather than native samples. Our second specific aim will be to evaluate the consequences of chronic, low-level multigeneration exposures to arsenic using two invertebrate species with varied life history strategies. The purpose of this research will not only be to evaluate the multigeneration effects of a widely distributed genotoxic substance, but also to determine whether the varied reproductive strategies of the two organisms are an important factor in determining population-level responses. The third specific aim will be to develop population models to evaluate the relative significance of life history parameters that may impart sensitivity to genotoxic substances on populations of organisms. An additional goal will be to explore possibilities for collaboration with molecular biologists to evaluate the chemical-specific nature of mutations in the nematode genome.

Energy-Efficient Systems for Thermal Energy Distributions

MARK MODERA

In this research project, we will employ numerical modeling, simulations of buildings and HVAC systems, and laboratory and field experimentation to investigate the energy performance and, in some cases, impact on the indoor environment of four aspects or methods of distributing thermal energy in buildings. The four components of this research are as follows:

- Indoor environmental conditions and energy implications associated with the supply of cold ventilation air to rooms;
- Heating, cooling, and ventilation using systems that permit individual control;
- Residential duct leakage and methods of sealing ducts; and
- The use of additives to aqueous solutions to reduce pumping power and energy.

This research will be performed jointly by LBL's Indoor Environment Program, University of California at Berkeley's School of Architecture, Cal State Riverside with Ed Sowell, and University of California at San Diego with Stan Middleman.

Integrated Analysis of Energy-Efficiency Improvements and Air Quality Emissions
MARK D. LEVINE

The objective of this project is to evaluate the potential effects of three novel energy-efficiency techniques on improving the air quality in the South Coast Air Basin. The project will emphasize two major themes: effects of load-shaping options within the residential, commercial, industrial, and transportation sectors on the reduction of air emissions; and effects of trees and surface albedo changes on smog formation. The overall approach is to develop a spatially based, computerized system for integration of important, but disparate data, including various energy-efficiency improvements, energy end-uses, air-quality emissions, emission-control strategies, and economic costs and benefits. Several analytical elements are proposed to develop the critical engineering and economic linkages between energy-efficiency strategies and air quality. This multiyear project consists of six integrated study elements:

- Load-shape scenario development and analysis (LBL);
- Economic valuation of emission reductions (Cal State Fullerton);
- Tree and albedo studies: tree types and amount of planting, biogenic emissions from trees, and cooling effects of trees and albedo changes (University of California at Los Angeles, LBL);
- Meteorological modeling (LBL, University of California at Davis);
- Air-quality modeling (Sonoma Technology); and
- Integrated database development (LBL).

The integrated database will be organized into a GIS format that provides spatial and temporal presentation of data on land use, air-quality emissions, end-use emissions, and other important variables. The results (in graphical, numerical, and written formats) will consider benefit/cost tradeoffs between energy-efficiency improvements and air quality in the South Coast Air Basin.

California Utility Database on Monitored Performance of Efficient End-Use Technologies
ALAN MEIER

This project builds on past work under the BECA, LCUP, and Appliance Standards Support projects to develop and test the concept of a data compilation, analysis, documentation, and dissemination activity concerning the measured performance and cost-effectiveness of energy end-use technologies. For the initial two years of the project, it is proposed that costs be shared by DOE/LCUP and the California Institute for Energy Efficiency (CIEE). It will focus initially on compiling and analyzing existing data from past field tests and demonstrations sponsored by the California utilities participating in CIEE. Results will be reviewed for data quality and consistency, documented, and organized in an easily accessed, public-domain electronic database for use by CIEE-sponsor utilities, public agencies, researchers, and other interested parties. A second purpose of the two-year effort will be to establish a common framework for future field data collection, analysis, and reporting of end-use efficiency monitoring and demonstration projects in California and, as appropriate, in other states.

Design of a Phase II Study of Sick Building Syndrome
WILLIAM J. FISK AND JOAN M. DAISEY

We propose to design a Phase II study of the sick building syndrome (SBS) that builds upon a recently completed investigation of occupant symptoms and environmental conditions in 12 office buildings in the San Francisco area. The Phase II design will also capitalize on the most recent research findings on the causes of SBS. Issues to be considered in the study design include: selection of optimal study populations; collection of more detailed symptom data; and improved sampling of volatile organic compounds. In addition, we will develop new hypotheses about the causes of SBS and identify methods to test these hypotheses. These hypotheses will relate to several factors that have correlated positively with SBS symptoms, including:

- The generation of pollutants in HVAC systems;
- The concentration of dust of biologic origin;
- The quantity of high-surface-area materials;

- The concentration of specific microbiological organisms; and
- The quality of ventilation system maintenance and building cleaning.

Spectrally Selective Glazings for Residential Retrofits
MICHAEL D. RUBIN AND DARIUSH ARASTEH

This project will assess the potential for developing spectrally selective single glazings for residential retrofit applications. Spectrally selective glazings are coated glazings which transmit solar radiation primarily in the visible portion of the solar spectrum and reflect most of the solar infrared; the result is a visually clear glazing with significantly reduced (10–40%) solar gains. Because of their susceptibility to moisture, the focus of spectrally selective glazings has been for use in insulated glass units (double glazing). However, for many existing residences, especially in cooling-dominated climates, selective glazings can only be a practical retrofit option if they are available as single glazing. This project will evaluate the potential energy savings available from spectrally selective single-glazing residential retrofits, identify suitable commercially available (or easily commercialized) selective glazing products, and define the obstacles to directly producing durable, spectrally selective glazings and spectrally selective, uncoated glass. Results of this project will help utilities make informed decisions about rebates for energy efficient window retrofits.

Integrated Estimation of Commercial Load-Shapes and Energy-Use Intensities
HASHEM AKBARI

The California Institute for Energy Efficiency (CIEE) granted funding for an exploratory project to validate an integrated load-shape (LS) and energy-use intensity (EUI) model, the End-use Disaggregation Algorithm (EDA). In the CIEE-sponsored project, we have envisioned using the Southern California Edison Company (SCE) end-use data for the validation purpose. The measured end-use data will be used for validation and refinement of EDA to extract end-use load profiles from the 15-minute (or hourly) whole-building electric load. Since such a model fully utilizes the information contained in the existing measured data, it will be extremely useful to utilities to obtain reliable end-use data without having to perform very expensive submetering projects.

This project is intended to facilitate the transfer and analysis of the SCE's submetered end-use data to the CIEE-sponsored project. The objectives of the project are: to obtain, analyze, and characterize metered end-use load data collected by SCE, and to use these and other data to refine and validate the EDA developed by LBL.

Energy-Efficient, Low NO_x and CO Burners for Residential and Small Industrial Gas Appliances

NANCY J. BROWN AND GREGORY W. TRAYNOR

This project will lead to improved understanding of the physical and chemical processes controlling the formation and fate of oxides of nitrogen and carbon monoxide in premixed combustion as it occurs in residential and small industrial appliance burners. The research will evaluate the impact of new low-polluting residential gas appliances on reducing outdoor air pollution levels. The burners of these appliances, of which there are millions, produce flames which are distinct from large furnace flames in that residential and small industrial appliance flames are usually laminar, premixed, and are in close contact with a heat-transfer surface.

The primary air pollutant produced by natural gas appliances has been considered to be nitric oxide. Recent studies indicate that other oxides of nitrogen may be produced in significant amounts and may contribute importantly to both indoor and outdoor pollution. We propose to measure these compounds under controlled conditions using new techniques to learn how and why these compounds are formed in gas appliances. Modeling studies will complement the lab studies.

Alternative to Compressive Cooling in California Transition Zones

Y. JOE HUANG

This is a California Institute for Energy Efficiency (CIEE) multiyear project involving, in addition to LBL, UC Berkeley, UC Davis, and Cal Poly Pomona. The overall objective of the project is to demonstrate that, with proper design of the building shell and equipment and smart control strategies, typical residential buildings in California transition climate zones can maintain indoor comfort without relying on compressor air conditioning.

The first-year tasks are to:

- Understand the climate and cooling load characteristics of houses in the California transition climates;

- Conduct a scoping study of the effectiveness of alternative cooling strategies to meet these cooling loads based on the current state of knowledge;

- Develop or improve analysis tools to predict the cooling effectiveness and comfort criteria produced by alternative cooling strategies such as natural and forced ventilation, evaporative cooling, and night storage using building thermal mass; and

- Identify the sociological, institutional, and industry barriers that might hamper public acceptance of these alternative strategies.

LBL will coordinate the overall effort, and will lead in Tasks 1 and 2 and parts of Task 3. Once a sound technical understanding of the project has been developed, along with the design requirements associated with these alternative cooling strategies, the following years will be devoted to establishing collaborative efforts with architects, builders, and utility companies to design and construct houses that utilize these cooling strategies, and to assess their performance market acceptability.

Genotoxic Polar Organics in Airborne Particles
JOAN M. DAISEY

Polar organic matter accounts for 30 to 60% of the organic-solvent extractable matter in airborne particles and 30 to 50% of the direct-acting mutagenic activity in the Ames bioassay with TA-98. More significantly, this fraction has been shown to transform mammalian cells *in vitro*. Thus there is reason to suspect that polar organic compounds may be of significance to human health. Little is known, however, about the chemical composition of this fraction.

We propose to identify the major organic classes and specific compounds in the polar organic fraction. A newly developed and highly sensitive bioassay, the Microscreen, will be used to focus on the most genotoxic subfractions and compounds. The polar organic matter will be fractionated by semi-preparative high-performance liquid chromatography (HPLC). Subfractions will be characterized with the Microscreen bioassay using Fourier-transform infrared spectrometry with chemical class tests which employ fluorigenic labeling for greater sensitivity. A number of mass spectrometric methods, suitable for polar organic compounds, will be used for class characterization and compound identification. These include direct-insertion probe distillation with electron impact (EI) and chemical ionization (CI) (positive and negative modes), fast atom bombardment, HPLC/mass spectrometry, and preparation of volatile derivatives followed by gas chromatography/mass spectrometry (EI and CI).

Environmental Tobacco Smoke: Physico-Chemical Properties
JOAN M. DAISEY

Exposure to environmental tobacco smoke (ETS) in indoor environments poses one of the greatest environmental health risks to the general population. Relationships between exposure, dose and risk of lung cancer, however, are not well understood for this complex mixture. The National Research Council has recommended that the physical and chemical properties of mixtures of radon and ETS be characterized to provide a better understanding of the relationships between exposure, dose, and risk ETS.

We will conduct research to:

- Develop an integrated sampler to effectively separate and collect gaseous and particulate phases of selected ETS components;
- Characterize the physical and chemical properties of selected components under varying conditions of ventilation and aging; and
- Investigate reactions of amines and NO_x in ETS to form carcinogenic N-nitrosamines.

Rechargeable Zinc Batteries
ELTON J. CAIRNS

The Zn/air and Zn/NiOOH batteries provide an active energy-storage option for electric vehicles. The purpose of this project is to provide the technology base to support the development of secondary Zn batteries for electric vehicles. Lawrence Berkeley Laboratory (LBL) will provide technical support to the U.S. Department of Energy (DOE)/OPS for the development of secondary Zn batteries for electric vehicle applications.

Assessment of Estimated Energy Savings Used in California Utility Demand-Side Management Programs
EDWARD L. VINE

LBL will assist the California Public Utilities Commission's Division Ratepayer Advocates (DRA) in assessing the reasonableness of engineering estimates developed by the major California utilities as part of their demand-side management (DSM) programs. This work will involve a critical review and assessment of the detailed assumptions, building-energy engineering calculations, and resultant savings estimates from energy-efficiency measures currently being promoted in the energy-efficiency programs of the four major California investor-owned utilities, as well as new measures being proposed by the utilities for inclusion in their programs.

The specific measures to be analyzed will be determined by DRA, and the work will be conducted in two phases. In the first phase, it is expected that most of the measures (technologies) to be assessed will be those that affect the following end-uses:

- Electric lighting (residential and non-residential);
- Electric air conditioning (residential and non-residential);
- Industrial electric motors; and
- Industrial gas processes.

Measures to be analyzed in the second phase will be determined near the end of the first phase.

Thermal Performance of Fluorescent Lamps
RUDY VERDERBER AND FRANCIS RUBINSTEIN

The purpose of this project is to conduct research on improving the energy efficiency of fluorescent lighting systems by reducing lamp wall temperatures to the optimally efficient point. Techniques to be investigated in this research include: developing a prototype lamp incorporating an internal Peltier device to reduce cold spot temperatures; devising advanced heat-sinking methods to conduct heat away from lamps and into the cooler plenum; and venting warm air within the fixture housing into the plenum via natural convection or forced air flow. This work will focus on standard four-foot fluorescent lamps and compact fluorescent applications.

Energy Use in Denmark from an International Perspective
LEON SCHIPPER

This is work by the Lawrence Berkeley Laboratory for the Danish Board of Energy (Energistyrelsen) to provide a new perspective on the flexibility of energy demand through: a thorough historical analysis of the structure of energy demand in Denmark; comparison of that structure with that in Scandinavia, W. Germany, the United States, and, where appropriate, other OECD countries; analysis, in light of these findings, of developments in energy use since 1973 to determine how much energy has been saved since that time and how permanent those savings are; understanding of the relationship between lifestyle and energy demand; and construction of a series of scenarios of future energy demand that reflect different perceptions about both energy savings and lifestyles.

Wetland Ecotoxicology of the San Francisco Bay
SUSAN ANDERSON

This project will evaluate toxicity in marsh ecosystems of San Francisco Bay using aquatic toxicity tests and selected genotoxicity tests. Approximately 6–8 marsh sites will be evaluated for toxicity, and attempts will be made to determine the substances causing detrimental effects. At selected sites, the sensitivity of newly developed genotoxicity tests will be compared with that of existing short-term chronic tests. This will be the first evaluation of the sensitivity of these tests under field conditions. We also hope to link ecotoxicological testing approaches to improved management of marsh enhancement projects.

Energy Use in Sweden from an International Perspective
LEON SCHIPPER

This is work by the Lawrence Berkeley Laboratory for the Swedish National Energy Board (Statens Energtiverk) to provide a new perspective on the flexibility of energy demand through: a thorough historical analysis of the structure of energy demand in Sweden; comparison of that structure with that in Scandinavia, W. Germany, the United States, and, where appropriate, other OECD countries; analysis, in light of these findings, of developments in energy use since 1973 to determine how much energy has been saved since that time and how permanent those savings are; understanding of the relationship between lifestyle and energy demand; and construction of a series of scenarios of future energy demand that reflect different perceptions about both energy savings and lifestyles.

Bioremediation of Heavy-Metal-Containing Wastes
ROLF MEHLHORN

Working jointly with investigators at the Savannah River Site, we will develop a microalgal process for the concentration and disposal/recovery of heavy metal pollutants. We would target mixed wastes containing a variety of metal ions and organically complexed heavy metals. A multistage scheme is envisioned, involving both processed algal biomass (inert cells) and immobilized living algae. This research will optimize the processing (de-ionizing, controlled denaturation) of algal biomass (prior to its use for water treatment) to maximize the selective sequestration of cationic heavy metals and organic metal complexes, while minimizing decomposition of biopolymers during the metal ion removal. The project will also identify optimal conditions for treating the waters with living algae. The product of this research will be a biological heavy metal filtration system suitable for *in situ* treatment of contaminated wastestreams.

Applied and Exploratory Research on Lithium/Polymer-Electrolyte Batteries
ELTON J. CAIRNS

Thin-film, solid-state batteries based on the use of polymeric lithium-ion conducting electrolytes exhibit several characteristics that suggest their potential for use as a high-performance power source in electric vehicles. DOE and the United States Advanced Battery Consortium (USABC) have recently signed a cooperative research and development agreement (CRADA) to accelerate the development of batteries for use in electric vehicles, and lithium/polymer batteries are among the systems being considered by the USABC. LBL will carry out applied and exploratory research to address fundamental life-limiting and performance-limiting processes. Tasks include studies of interfacial phenomena, mathematical modeling of transport phenomena, development of new polymeric electrolyte materials, characterization of manganese dioxide and carbonaceous electrode materials, and identification of strategies for overcharge and overdischarge protection.

Improved Techniques for Sediment Toxicity Assessment
SUSAN ANDERSON

To adequately manage the disposal of dredged materials into aquatic ecosystems, there is a need to identify those sediments which contain toxic substances at levels that may pose a threat to aquatic life. This information is used to make decisions on how dredging operations might be conducted and to determine suitable disposal options for dredged materials. It is widely accepted that chemical testing alone cannot be used to predict the effects of chemical mixtures or the effects of chemicals distributed in complex media such as sediment. Consequently, biological toxicity testing is used to complement chemical assessments to determine whether dredged sediments may pose a threat to aquatic life. However, existing sediment toxicity tests have two major deficiencies. First, they are subject to positive interferences attributable to factors that are not easily controlled, such as sediment grain size. Secondly, they do not assess sublethal effects of contaminant exposure. This research will consist of a detailed assessment of potential positive interferences and the development of new sublethal toxicity testing techniques. In addition, we will employ the new test techniques to evaluate improved methods for toxicity reduction, such as bioassay-directed fractionation.

MATERIALS SCIENCES DIVISION

The Materials Sciences Division (MSD) is made up of three closely linked research centers

- **THE CENTER FOR ADVANCED MATERIALS**
- **THE NATIONAL CENTER FOR ELECTRON MICROSCOPY**
- **THE CENTER FOR X-RAY OPTICS**

In addition, MSD supports the work of a number of multidisciplinary groups doing fundamental research in the materials sciences as part of the

- **DEPARTMENT OF PHYSICS, CHEMISTRY AND THE MATERIALS SCIENCES**

CENTER FOR ADVANCED MATERIALS (CAM)

CAM does fundamental research in areas of materials science that U.S. industry has identified as critical to its international competitiveness. CAM programs involve active participation of industry in the form of research collaborations; exchange of staff; Industrial Advisory Boards; and targeted, industry-funded projects. CAM continues the Lawrence Berkeley Laboratory and Materials Sciences Division tradition of science education by working closely with the University of California at Berkeley in training students and postdoctoral fellows to become the next generation of materials scientists and engineers.

CAM focuses its research on seven interdisciplinary research program areas: Ceramic Science, Electronic Materials, High-Performance Metals, High-T_c Superconductivity, Polymers and Composites, Surface Science and Catalysis, and Enzymatic Synthesis of Materials. Each program is supported by an Industrial Advisory Board, which meets annually to advise on research directions and industrial needs.

CERAMIC SCIENCE PROGRAM

LUTGARD C. DE JONGHE, PROGRAM LEADER

Experimental research on the processing of ceramics and composites, model studies, and the mechanical properties of such materials.

LUTGARD DE JONGHE, ROWLAND M. CANNON, ANDREAS GLAESER, ROBERT O. RITCHIE, AND GARETH THOMAS

The processing science of ceramics prepared from powder compacts is developed in an iterative program which examines pore evolution and interaction in model systems; establishes and verifies experimentally constitutive relationships for densification, damage development, and microstructural evolution in terms of practical parameters; prepares ceramic bodies of improved uniformity from single-phase powders, and from novel coated ceramic powders; characterizes microstructures and microchemistry; and evaluates the mechanical properties, including toughness and fatigue, of the materials that have been produced.

Single-phase high-temperature ceramics, as well as particulate composites prepared from coated powders, are studied. Processing parameters are identified that, based on constitutive relationships, optimize the homogeneity of the fabricated ceramic bodies to significantly improve their mechanical performance, especially under constant or cyclic load, and temperatures ranging from ambient to over 1400°C.

Loading dilatometry from fundamental densification studies, surface analytical methods (including ESCA, SIMS, Auger spectroscopy), and electron microscopy are used to characterize powders and sintered ceramics, while mechanical testing of fracture toughness, creep, and fatigue are used in experimental evaluation.

Model studies form another part of this program. Numerous properties of ceramics depend strongly on microstructure, necessitating control of microstructural characteristics developed during processing. This research program focuses on improving our understanding of processes which dictate the microstructural changes occurring during processing and utilization. Microstructure development in model compacts formed from an "ideal," nominally monodispersed, chemically synthesized titania powder is being examined by applying transmission electron microscopy to ultramicrotomed sections of heat-treated compacts. The effects of crystallization, polymorphic phase transformations, and particle substructure on microstructural evolution are being studied. A broad range of model experiments utilizing photolithographically introduced, microdesigned intragranular or intergranular pore/flaw structures have been developed and applied to studies of the kinetics of interfacial processes. Phenomena amenable to study include pore–grain boundary separation, pore coarsening or elimination, faceting (surface energy anisotropy), and high-temperature crack healing. Future work will focus on further development and exploitation of this lithographic method and an extension of the method to fundamental studies of ceramic-metal and ceramic-ceramic interfaces and their evolution during joining processes.

Another aspect of the CAM Ceramics Program concerns interfaces and interconnects. Key features of interfacial adhesion being studied include: basic decohesion mechanisms;

microstructures that yield more robust interfacial bonds under sustained and cyclic loading; and thin-film microstructures, stress states, and spalling. The results pertain to fabrication and reliability of microelectronic interconnects and packages and other technologies, such as protective coatings; these are being collaboratively investigated with industrial groups.

ELECTRONIC MATERIALS PROGRAM

Eugene E. Haller, Program Leader

Synthesis and characterization of advanced semiconductor materials systems, electronic and structural properties, contacts, and fundamental dopant incorporation questions.

EUGENE E. HALLER, EDITH D. BOURRET, ZUZANNA LILIENTAL-WEBER, WLADYSLAW WALUKIEWICZ, JACK WASHBURN, EICKE R. WEBER, AND KIN MAN YU

Research in the Electronic Materials Program (EMAT) at LBL concentrates on an improved understanding of the materials science of artificially structured semiconductor and semiconductor/metal systems. Basic studies concentrate on the relationships between synthesis and processing conditions and the properties of semiconductor materials, as modified by the resulting structural and electronic imperfections. Projects include the synthesis and study of heterointerfaces between highly dissimilar materials in order to understand mechanisms of interface formation and the defect structures resulting from lattice mismatch and differences in ionicity and electrochemical potential. The structure and stability of defects and interfaces are studied by advanced characterization techniques. Atomic resolution microscopes at the National Center for Electron Microscopy, scanning tunneling microscopy, and advanced x-ray techniques utilizing synchrotron radiation provide structural information. Optical spectroscopies ranging from the near UV to the far infrared region of the electromagnetic spectrum, electron paramagnetic resonance spectroscopy, and electrical transport measurements give the complementary electronic properties. Theoretical and experimental work on the effects of atomic-scale diffusion and the differences between solid solubility limits of dopants and the maximum concentration of free carriers is pursued. Novel types of processing methods designed to increase the electrically active fraction of dopants are explored, including annealing under large hydrostatic pressures and with tunable synchrotron radiation. Progress in this area is applicable to the design of advanced photovoltaic energy conversion devices and of a large variety of sensors used in energy-conversion processes.

Another element of the EMAT program involves Organo-Metallic Vapor-Phase Epitaxy (OMVPE) of II-VI compound semiconductors from single-molecule precursors and OMVPE of wide-band-gap II-VI compound semiconductors. One part of this project pursues the synthesis of II-VI compound semiconductors based on the use of low-toxicity single-molecule precursors containing both the metallic elements and the chalcogen in an OMVPE environment. Chemical synthesis of the new precursors is being studied as well as their surface decomposition reactions, optical stability, and absorption characteristics for photo-assisted growth and photo-chemical processing. The synthesized epitaxial films are being characterized for structural, electrical, and optical properties.

HIGH-PERFORMANCE METALS PROGRAM

John W. Morris, Jr., Program Leader

Studies of light alloys, metal forming, alloy theory, and mechanical properties of metals and alloys.

JOHN W. MORRIS, JR., ROBERT O. RITCHIE, AND GARETH THOMAS

This research program addresses the science of metallic materials for advanced energy needs. It is focused on a class of materials that can be called *functionally unstable materials*. These are metals and alloys whose properties are strongly affected by microstructural instabilities that occur during processing or service. The program includes basic research on interesting examples of functional instability, including:

- Unusual microstructures generated by structural, ordering, or coarsening instabilities;
- Exceptional mechanical behavior induced by structural instabilities under load, such as transformation toughening and recrystallization-induced superplasticity; and
- The behavioral effects of microstructural instabilities that are induced or enhanced by electromagnetic fields, such as magnetomechanical effects and electromigration.

The program also addresses the general theory of microstructural instabilities and how they may be manipulated and controlled to enhance material properties. This research interacts with a number of applied research projects that are funded from sources outside DOE's Office of Basic Energy Science and are done in collaboration with industry, including Sandia and Lawrence

Livermore National Laboratory; other divisions of LBL; other federal agencies, including the Naval Air Development Center; and other branches of the DOE, including the Office of Magnetic Fusion energy.

The High-Performance Metals Program also investigates the mechanical behavior of materials. The objective is to examine, from both macroscopic and microscopic perspectives, the mechanics and micromechanisms of subcritical and critical crack growth in engineering ceramics, metals, and the interfaces separating them. Current emphasis is devoted to:

- Defining the role of crack-tip shielding in influencing the cryogenic toughness and fatigue-crack growth (long- and small-crack) behavior of advanced alloys;

- Examining the mechanics and mechanisms of the cyclically-induced propagation of long and small cracks in ceramic materials;

- Developing extrinsic methods for toughening ceramic/metal interfaces; and

- Identifying mechanisms of fatigue and environmentally assisted crack growth along such interfaces (in collaboration with R. M. Cannon).

Characterization of crack-growth behavior and microscopic failure mechanisms is achieved through the use of advanced mechanical test methods, fracture mechanics, electron microscopy, surface-chemistry analysis, and quantitative fractography. The aim of the work is to develop a mechanistic understanding of fracture processes in order to provide guidelines for improved life prediction and the design of superior fracture-critical materials.

Structural alloys and weldments for high-field magnets constitute another element of the program. This project is supported by the DOE's Office of Energy Fusion and is concerned with the development of structural materials for high-field super-conducting magnets for magnetic fusion energy. The structures problem is due to the combination of the high magnetic field and the cryogenic temperature in the operating environment of the magnet, which results in high imposed stresses under conditions in which structural materials are often susceptible to mechanical failure. This research studies mechanical phenomena that are peculiar to the magnet environment and may lead to failure in operation, including specifically the influence of low temperature and magnetic fields on fracture toughness and fatigue-crack propagation. The research is done in collaboration with other national laboratories in the U.S. and abroad.

Part of the research program is concerned with the metallurgical mechanisms that govern friction and wear in the processing and engineering use of metals and alloys. Microstructural and profilometric studies are used to reveal the mechanisms of friction and wear. Knowledge of these mechanisms is used to develop improved predictive models of friction and wear and to suggest metallurgical changes that may create new alloys or metallurgical coatings with exceptional frictional and wear properties.

The microstructure, properties, and alloy design of advanced inorganic materials is a multicomponent, multidisciplinary project within the High-Performance Metals program. It involves fundamental quantitative studies of the structure-processing-property relationships in technologically significant materials critical to energy and conservation. All tasks involve characterization of both structure and composition at the highest levels of spatial (transmission electron microscopy) resolutions. Specific materials studied in this research include: high-temperature structural ceramics such as Si_3N_4, and mullite; and magnetic materials such as ceramics, recording thin films, nanostructured composites and permanent rare-earth magnetics. The overall objectives are to understand structure-property relations so as to design new materials (or to better utilize existing materials and processing routes for industrial practice) and to achieve both materials and energy conservation.

HIGH-T_C SUPERCONDUCTIVITY PROGRAM

Alex Zettl, Program Leader

Basic science of synthesis and characterization, ceramic processing, electron microscopy and thin films, and devices using these thin films

ALEX ZETTL, MARVIN L. COHEN, JOHN CLARKE, NORMAN E. PHILLIPS, PAUL L. RICHARDS, PETER Y. YU, YUEN-RON SHEN, AND EICKE R. WEBER

The High-T_c Superconductivity Program consists of three projects: Basic Science, Thin Films and Thin-Film Devices, and Electron Microscopy. The shared goal of all four projects is to advance the fundamental understanding of the new high-critical-temperature superconductors by both experimental and theoretical investigations and to build the base of knowledge necessary for their applications.

The basic science component includes theory, measurement of physical properties, and synthesis. Theoretical work includes fundamental microscopic calculations, phenomenological calculations, and computations of oxygen ordering in $YBa_2Cu_3O_7$. Physical properties measured encompass a wide variety of transport, electrodynamic, and thermodynamic properties, including resistivity as a function of crystallographic direction, pressure, frequency, etc.; electrodynamic response from zero frequency to above 10^{13} Hz; the superconducting energy gap with tunneling and far-infrared spectroscopies; specific heat; and the oxygen isotope effect. The thin-film component includes research on the fabrication of thin films and the relation of their electrical properties (such as noise) to fabrication conditions, and on the development of devices such as bolometers, flux transformers, and SQUIDs. The electron microscopy research features atomic-resolution imaging of cations, which enables defects, grain boundary structure, and composition to be analyzed and related to synthesis conditions and to physical properties. More generally, the electron microscopy research also includes both crystal structures and microstructure determinations.

One element of the High-T_c research is concerned with the microwave-frequency transport and magnetic properties of the high-temperature superconductors. Primary attention is currently being given to the microwave properties of high quality films in the Y-Ba-Cu-O system, with emphasis on critical behavior and hysteretic loss processes at high microwave power levels. Applications are to microwave transmission lines, delay lines, resonators, and antennas that utilize high-temperature superconductors.

The advent of high-transition-temperature (T_c) superconductors has led to the development of magnetometers operating at liquid nitrogen temperatures (77 K), and the sensitivity of these devices has now improved to the point where they are of interest for practical applications. The magnetometers consist of two components: a SQUID (Superconducting QUantum Interference Device) and a superconducting flux transformer. The flux transformer consists of a single-turn pickup loop connected to a smaller, multiturn coil that, in turn, is magnetically coupled to the SQUID; the purpose of the transformer is to enhance the magnetic field sensitivity of the SQUID. The sensitivity of the magnetometer made to date is 30 fT Hz^{-12} at frequencies above the 1/f noise (f is the measurement frequency) that dominates at frequencies up to about 1 kHz. Further reduction in 1/f noise is expected in the near future. The sensitivity is now sufficient to enable one to obtain "magnetocardiograms." Other potential applications include geophysics and non-destructive evaluation.

POLYMERS AND COMPOSITES PROGRAM
Morton M. Denn, Program Leader

Anisotropic polymeric materials, polymer/surface interactions.

MORTON M. DENN, ARUP CHAKRABORTY, SUSAN MULLER, BRUCE NOVAK, JEFFREY REIMER, AND DOROS THEODOROU

These projects focus on polymer synthesis and the development of a sound scientific basis for the prediction and control of microstructure during the melt processing and use of high-performance polymeric materials, particularly structure in the neighborhood of an interface. The program emphasizes two highly integrated project areas: heterogeneous polymeric materials and polymer/surface interactions. The former project emphasizes anisotropic liquids, particularly liquid crystalline polymers and blends, using rheology, nuclear magnetic resonance (NMR), thermal analysis, flow analysis, synthesis, and structural theory to elucidate how orientation and stress develop during shaping. The way in which the multiphasic nature of the polymer melt can affect macroscopic orientation and orientation rates is of particular concern.

Polymer synthesis focuses on unique, light-weight, composite materials that are formed from the intimate combination of organic and inorganic structures. Properties that can be designed into these materials include liquid crystallinity, low density, impact resistance, high strength, high modulus, electrical conductivity, and, finally, piezoelectric, ferroelectric, and electro-optic properties.

Catalysts for the living polymerization of helical, rodlike polyisocyanates are also being developed, along with new routes into liquid-crystalline block copolymers and organic-inorganic composite materials. The latter project is concerned with the theory of polymer conformation and stress state near an interface as a means of defining the influence of surface interactions on orientation and stress—in the bulk, in blends, and in thin films—and hence on properties. A complementary experimental program utilizes a variety of spectroscopic techniques to probe chain/surface interactions at a molecular and macroscopic level. The development of computational methods for predicting structure development and the onset of dynamical instabilities is an integral component of both project areas.

ENZYMATIC SYNTHESIS OF MATERIALS PROGRAM
Mark Alper, Program Leader

Engineering of enzymes for the synthesis of novel materials and thin films based on biological membranes.

MARK ALPER JACK F. KIRSCH, BRUCE NOVAK, PETER SCHULTZ, AND DANIEL E. KOSHLAND

This project, supported by the Division of Materials Sciences and also by the Division of Structural Biology, is focused on the synthesis of materials with novel and important properties through the use of naturally occurring, engineered, and "created" enzymes. Research involves the development of techniques to isolate and engineer enzymes, synthesize designed substrates for those enzymes, characterize the materials produced, and develop predictive structure-function relationships for them. The underlying premise is that the extraordinary substrate and reaction specificity that enzymes exhibit, their ability to catalyze reactions at room temperature with rate enhancements up to 10^{16}, and the newly found ability to engineer them for desired reactions will allow their use to produce valuable materials that cannot be synthesized in any other way.

Current work involves the synthesis of novel polysaccharides and polyamides through natural, engineered, and synthetic enzymes; the enzymatic synthesis of "non-biological" polymers with linkages not found in nature; the synthesis of materials with structures that can serve as a framework for the alignment and orientation of functional groups; and the design and synthesis of thin films for surface modifications and sensor development.

SURFACE SCIENCE AND CATALYSIS (SSC) PROGRAM
Gabor A. Somorjai, Program Leader

Atomic and molecular level understanding of surface and interface processes, heterogenous catalysis, surface structure and bonding, coatings, adhesion, lubrication and the development of surface science instrumentation.

GABOR A. SOMORJAI, ALEXIS T. BELL, HEINZ HEINEMANN, MIQUEL SALMERON, MICHEL A. VAN HOVE, AND YUEN-RON SHEN

There are two major aims of our studies of surfaces:

- To determine the atomic surface structure and chemical bonding of metals, adsorbed organic monolayers, oxides and sulfides; and

- To apply this knowledge to understand, on the molecular level, important macroscopic surface phenomena, heterogeneous catalysis, friction, lubrication, and the formation of hard coatings.

Low-energy electron-diffraction surface cystallography and scanning tunneling microscopy are developed and utilized to investigate the structure of surfaces and of adsorbed monolayers of atoms and molecules on the atomic scale.

The Surface Structure Database (SSD) contains the over 600 surface structures which have been determined since the inception of surface crystallography around 1970. It updates a first database which we published in 1987 (SCIS), both in electronic and book form, in collaboration with Imperial College in London and is being prepared in collaboration with Oregon State University and the Fritz Haber Institute in Berlin.

Single-crystal metals (Pt, Fe, Cu, Re, Mo, Rh, Pd), oxides (CuO, FeO, V_2O_5) and sulfides (MoS_2, ReS, CoS) are prepared and utilized as model catalysts to explore the surface science of catalyzed reactions that are important in chemical energy conversion. These include selective hydrocarbon conversion to produce clean fuels and chemicals, the reduction of nitrogen oxides, and the synthesis of methanol. The roles of additives, such as other metals, oxides, electron donors, and acceptors, are being explored.

The project on Catalytic Hydrogenation of Carbon Monoxide (supported by the Chemical Sciences Division) develops an understanding of the fundamental processes involved in catalytic conversion of carbon monoxide and hydrogen to gaseous and liquid fuels. Attention is focused on defining the factors that limit catalyst activity, selectivity, and resistance to poisoning, and on the relationship between catalyst composition/structure and performance. To meet these objectives, a variety of surface diagnostic techniques (LEED, AES, XPS, EELS, IRS, NMR, TPD) are used to characterize supported and unsupported catalysts before, during, and after reaction. The information thus obtained is combined with detailed studies of reaction kinetics to elucidate reaction mechanisms and the influence of modifications in catalyst composition and/or structure on the elementary reactions involved in carbon monoxide hydrogenation.

Fundamental studies of the mechanism of catalytic reactions with catalysts effective in the gasification of carbon solids is another component of the SSC Program. This project is supported by the Office of Fossil Energy through the Morgantown Energy Technology Center. Two tasks are under investigation:

- Catalytic gasification of chars, coal, and petroleum coke with steam at relatively low temperatures (approximately 600°C); and

- Methane conversion to CO and H_2 or higher-molecular-weight hydrocarbons by partial oxidation in the presence of oxygen and steam.

The work has attracted industrial interest and is now the subject of a Cooperative Research and Development Agreement (CRADA) between DOE, LBL, and Orion ACT.

The conversion of ethane and of propane to higher olefin hydrocarbons is work supported through the Office of Fossil Energy through the Pittsburgh Energy Technology Center. The objective of the work is to activate C_2 and C_3 paraffins by means of catalysts that have been shown to participate in the oxidative coupling of methane and to attempt to convert the C_2 and C_3 paraffins to higher-molecular-weight olefins. This is of particular importance in coal liquefaction, where C_2 and C_3 paraffins are produced as gaseous by-products of hydrocarbon liquids. Attempts are being made to convert C_2 and C_3 olefins, which are readily produced by catalytic oxidative dehydrogenation, to higher-molecular-weight hydrocarbons in a single step, overall process.

The goal of developing theoretical models that could be used to assist in the design of metal and zeolite catalysts is also part of the Surface Science and Catalysis Program. Quantum-mechanical calculations are carried out of the atomic-scale structure and catalytic properties of zeolites and mono- and bimetallic surfaces and of the interactions of small organic molecules with catalytically active sites in zeolites and at metallic surfaces. Molecular dynamics are used to determine diffusion coefficients for molecules sorbed in zeolites, and dynamically corrected transition-state theory is used to describe the dynamics of desorption and reactive processes for both metals and zeolites. The results of all calculations are validated by comparison with experimental measurements. The ultimate goal of this project is to assemble and integrate the individual elements of theory needed to describe the overall behavior of complete reaction networks.

Mechanical properties of surfaces, including hardness, friction, and lubrication are explored on the molecular level using atomic force microscopes and the scanning tunneling microscope. The physical-chemical characteristics of diamond films deposited from a microwave plasma are studied as a function of film thickness. The role of monolayers (S atoms, organic molecules) in reducing friction on metal surfaces is also explored.

Finally, the SCC Program has a project for developing new surface science instrumentation. These include the scanning tunneling microscope and atomic force microscope for a variety of studies, including: the atomic-level understanding of friction and wear, the effect of adsorbate binding on surfaces, and reactions at the liquid-solid interface. In addition, surface-sensitive electromagnetic radiation (SFG, SHG, laser Raman, and NMR) and electron- and ion-scattering spectroscopies (LEED, HREELS, XPS, AES, ISS, and SIMS) are developed for use in studies of, for example, chemisorbed molecules (S, C, CH_2CH_2, etc.) and of atomically thin layers of oxides such as FeO, TiO_2, and ZrO_2, on metal single crystals (Pt, Re, Rh, Mo, and others).

NATIONAL CENTER FOR ELECTRON MICROSCOPY (NCEM)

A national, user-oriented resource for transmission electron microscopy, NCEM was established in 1985. Presently available microscopes include a 1-MeV Atomic Resolution Microscope (ARM) for ultra-high-resolution imaging (resolution 0.16 nm direct, 0.14 nm with processing), a 1.5-MeV high-voltage electron microscope (HVEM) (resolution 0.4 nm) designed for dynamic *in situ* studies, a 200-keV analytical electron microscope for EDS and EELS spectroscopy, and a 200-keV high-resolution instrument (resolution 0.24 nm). A comprehensive computing facility networks the microscopes, allowing on-line image analysis and enhancement at the microscope and simulation at computer workstations, as well as quantification of microanalytical spectra. Further user support is provided by continuing software and instrument development. Other support facilities include photographic dark rooms, optical diffraction, and specimen preparation laboratories. Future plans call for a major upgrade of the Center instrumentation. New microscope acquisitions would include a Quantitative Sub-Ångstrom Microscope (QSAM) and a Magnetic Materials Microscope (MMM), and improvements would be made in the capabilities and speed of computing. Compatibility of the Center activities with the overall DOE electron microscopy and materials science goals will continue to be emphasized.

Crystallography of Microstructures
ULRICH DAHMEN

This program is aimed at understanding the fundamental features that underlie the evolution of microstructures in solids by applying crystallographic techniques to the analysis of topology and defects in crystalline materials. Many microstructures possess a degree of order that reflects crystallographic relationships with precursor or parent phases. Such relationships are put to use both analytically, to examine the structure of defects, and synthetically, to produce new and unique microstructures with defect configurations reflecting composite symmetries. The goal is to understand and ultimately gain control of the structure and distribution of defects such as inclusions, grain boundaries, domain walls, and dislocations. Because of the scale and nature of such microstructures, electron microscopy is an integral part of these investigations, as an analytical tool as well as a subject of technique development. Detailed characterization of the atomic structure of interfaces through extensive use of conventional, *in situ*, and atomic resolution microscopy, in tandem with computer image simulations, allows critical testing of theoretical models.

Solid-State Phase-Transformation Mechanisms
KENNETH H. WESTMACOTT

This research is directed toward understanding the structural factors that govern phase changes and phase stability. From such knowledge, first-principles alloy design for specific service applications is possible. A variety of electron-optical techniques, especially high-voltage electron microscopy (HVEM) and high-resolution electron microscopy, are used to infer the atomic rearrangements that occur when a product phase precipitates from the parent matrix. Since accommodation of a new phase of disparate size or crystal structure must involve deformation, the role of lattice defects in transformations is a focus of this work. This approach has been successful in identifying the specific defects associated with several classes of transformations characterized by different transformation strains. It has been possible to predict precipitate morphologies (growth directions, habit planes, orientation relationships, etc.) from first principles for several model alloy systems. Extension of these principles to more complex alloys and to the prediction of deposited-film microstructures and defects has demonstrated the generality of the concepts. New directions stemming from this research will include microstructure control and design from first principles.

Thin-Film Structures and Coatings
KANNAN M. KRISHNAN

The goals of this research are the synthesis and characterization of atomically engineered thin films with novel magnetic, optical, and mechanical properties. Focus is on magnetic ultrathin multilayers and films and low-pressure deposition of diamond on ceramic substrates. Fundamental investigations of new phenomena will be stressed, as well as the development, control, and optimization of microstructures to achieve enhanced properties. In addition to synthesis and property measurement, development of nanoscale spectroscopic, imaging, and diffraction methods at the appropriate level of resolution, with either electron or photon probes, will be critical to the success of these investigations and hence will be an integral part of these research projects.

Of current interest in this program are the synthesis and understanding of ultrathin magnetic nanostructures, development of a new ferromagnetic thin film with perpendicular anisotropy and potential for semiconductor-magnetic device integration, electronic structure changes associated with magnetic and chemical transitions in binary transition metal alloys, and the low-pressure deposition of diamond coatings on ceramic substrates. In the latter case, questions pertaining to the early stages of nucleation of diamond, the structure of the substrate/film interface, and factors affecting the adhesion and surface profile of the films are being addressed.

Structure and Properties of Transformation Interfaces
RONALD GRONSKY

The goal of this research program is to achieve a detailed understanding of the elementary role of interfaces in materials, using techniques of high-resolution transmission electron microscopy to probe the structure and composition of interfaces in both homogeneous and heterogeneous systems, and to relate the results to theoretical predictions. Microstructural information obtained in this way is then used to explain the macroscopic behavior (intergranular fracture, segregation, grain boundary precipitation, interdiffusion, delamination, short-circuit diffusion) so often attributed in general terms to the presence of interfaces in materials. This understanding is sought at the atomic level.

Emphasis is currently given to interfaces in the high-T_C superconducting materials, metallic contacts to semiconductors, and multilayer x-ray optics of the type to be used in the Advanced Light Source (ALS) and Advanced Photon Source (APS).

CENTER FOR X-RAY OPTICS (CXRO)
DAVID ATTWOOD AND JAMES UNDERWOOD

The Center for X-ray Optics has made considerable progress in setting up core programs to address national needs in the technical areas of efficient and high-precision transport, focusing and spectroscopic analysis of electromagnetic radiation in the x-ray and ultraviolet regions of the spectrum, and the utilization of these subsystems in high-flux applications. Progress in the physical, chemical, and life sciences will be enhanced by the broad availability of these new components, which can provide high spectral and spatial resolution with high throughput efficiency. Specific technical projects include fabrication of diffractive structures of improved resolution and efficiency; deposition of interference coatings on curved substrates; investigation of additional material combinations for improved performance in specified spectral ranges; and construction of various advanced imaging techniques based on these components.

Demonstration projects will be performed with collaborators from industry, universities, and other national laboratories to illustrate new scientific capabilities based on these new technologies. Particular attention will be given to demonstrations of high-spatial/high-spectral-resolution studies in the areas of thin films, surfaces, and material interfaces at existing and next-generation synchrotron facilities. We will continue participating in the development of short-wavelength, partially coherent radiation sources, including undulators, x-ray lasers, and free-electron lasers, efforts that are essential to establishing proper balance in the developing programs and to permit proper allocation of scarce resources.

Biological X-ray Microscopy Resource Center
DAVID ATTWOOD

Experimental facilities for a biological microscopy resource center are to be built at LBL's Advanced Light Source (ALS), a unique source of high-brightness, partially coherent soft x-rays especially well suited for biological microscopy. X-ray generation is based on undulator radiation from 1.5 GeV electrons traversing a periodic magnet structure at the ALS. Beamline optics and a monochromator will provide tunable, narrow-band radiation to two complementary microscopes: an imaging x-ray microscope (IXRM) and a scanning x-ray microscope (SXRM). Both microscopes will use high-resolution Fresnel x-ray zone plate lenses. The imaging microscope will operate in a real image-forming mode, recording the entire image at the highest possible spatial resolution and in the shortest possible exposure time. The scanning microscope, which forms an image on a pixel-by-pixel basis, does so with minimal radiation dose and a spatial resolution far beyond that of visible light microscopy.

Both microscopes are to serve a broad biological community from across the country, including university, national laboratory, and industrial researchers. It is anticipated that they will have wide ranging interests which span the life sciences. The resource center will include a large component of research and development associated with these newly developing tools, but will allocate a large portion of available time for collaborative research with external users and will address issues of user access, training, and assistance with the specialized instrumentation and software. Laboratories will also be available for sample preparation and characterization near the microscope facilities. An educational program for user training, including written materials, demonstrations, and occasional workshops, will be developed.

To help guide these activities, an external advisory committee will be formed with scientific and geographical breadth. The committee will advise on issues of major resource allocation, use of available beam time, peer review, and other issues deemed important to the success of a life sciences resource center.

Both microscopes will be compatible with sample chambers for near-native-state imaging, include user-friendly features, and be flexible in construction so as to permit inclusion of new features and developments as they become available. Visible light pre-alignment and sample viewing will be built into the system to minimize radiation exposure, to provide pre-and post-irradiation optical viewing, and to maximize efficient use of beamline operating time.

Coherent Optics Beamline
DAVID ATTWOOD

A coherent soft x-ray optics beamline will maximize use of the high brightness and partial coherence of undulator radiation at LBL's Advanced Light Source (ALS). New studies in the materials, physical, and life sciences will be conducted utilizing techniques never before attempted at x-ray wavelengths. Advanced imaging and analytic methodologies based on coherent projection (holographic) techniques would be pursued, with spatial resolutions of order 100 Å. Non-linear materials and atomic physics studies based on various multiphoton techniques would benefit from zone plate focusing of soft x-rays (20-50 Å wavelength) to x-ray intensities of order 109 Watts/cm^2. Atomic-resolution imaging with elemental specificity would be explored using a combination of scanning tunneling microscopies and focused tunable x-rays. A wide variety of other new and yet-undiscovered techniques could be pursued with this unique capability, available only in the U.S.

DEPARTMENT OF PHYSICS, CHEMISTRY AND THE MATERIALS SCIENCES (PCM)

In addition to its three research centers, the Materials Sciences Division supports a wide variety of research projects. These multidisciplinary projects of the Department of Physics, Chemistry and the Materials Sciences include:

Solid State Physics: Theory and Experimentation; Materials Research at the Advanced Light Source; Advanced Characterization; Electrochemistry; Alloy Theory; and *Materials Synthesis.*

SOLID-STATE PHYSICS: THEORY AND EXPERIMENTATION

Femtosecond Dynamics in Condensed Matter

CHARLES V. SHANK

Our research program is directed toward advancing the state of the art in femtosecond laser pulse generation and measurement, and applying these techniques to study ultrafast processes in solid-state materials and molecular systems. We have developed a unique laser facility with the capability for generating femtosecond pulses of only a few optical cycles covering the spectral region from 400 to 900 nm. This provides a means for investigating ultrafast dynamics in a wide range of materials, with applications in solid-state physics, chemistry, and biology. Our work in semiconductors has focused on the scattering and dephasing dynamics of highly nonequilibrium electron-hole plasmas which are optically excited by femtosecond pulses. Such investigations provide important information about the fundamental processes which influence the behavior of carriers under nonequilibrium conditions. We are extending this work to investigate the effects of quantum confinement on the carrier dynamics using quantum well structures and, more recently, semiconductor nanocrystals (~40 Å diam.) which are composed of fewer than 1000 atoms. The nanocrystals have unique electronic properties, owing to the strong confinement of the exciton and the molecular nature of the particles. Our research on molecular systems includes studies of the dynamic interactions between molecules and their solvent environments, as well as the response of molecules following impulsive optical excitation. In newly developed molecules such as C_{60}, measurements of coherent vibrational excitation provide information about the fundamental properties of the molecule and may contribute to our understanding of the superconducting properties of C_{60} molecular crystals.

Quantum Theory of Materials: Theoretical Studies of the Electronic Properties of Solid Surfaces
LEO M. FALICOV

The purpose of this program is to study properties of solid surfaces. In particular, the interest is in determining:

- Structural properties of surfaces, namely the organization and arrangement of atomic constituents at equilibrium;
- Constitutional properties of the surface, in particular the segregation properties of alloys at the surface as a function of crystal structure, surface orientation, nominal chemical composition, and temperature;
- Electronic structure of surfaces, in particular electron states and electron densities in the neighborhood of the surface;
- Vibronic properties of surfaces;
- Magnetic properties of surfaces, both in magnetic solids (ferromagnetic and antiferromagnetic) and in nonmagnetic solids that may develop a magnetic surface layer; and
- Chemical properties of solids—in particular their catalytic properties—as they are related to all the basic physical properties listed above.

Theoretical Solid-State Physics
MARVIN L. COHEN

Some of the focus of the theoretical work is to foster and maintain collaborations with the experimental programs at LBL in high-temperature superconductivity. In other areas the theoretical activity ranges from the development of new theoretical tools and approaches to materials development. In the latter category is the exploration of the use of high pressures for creating new systems and the theoretical analyses of data related to existing novel systems.

Surface, Chemisorption, and Theory of Solids
STEVEN G. LOUIE

The purpose of this work is to further basic understanding of the electronic and structural properties of solids and materials systems, such as surfaces and interfaces. First-principles quantum-mechanical calculations are carried out on realistic systems so that a microscopic understanding of material properties may be obtained. The research effort encompasses the study of bulk materials, surfaces, chemisorption systems, and interfaces and the formulation and development of new theoretical techniques for calculating ground-state and excited-state properties. Current projects include work on surface atomic and electronic structures, structure and vibrational properties of solids, electronic excitation spectra of solids, solid-solid phase transformations, and properties of semiconductor quantum wells and quantum dots.

Quantum-Size Effects in Semiconductor Nanostructures
DANIEL S. CHEMLA

The objective of this program is to explore the physical properties of low-dimensional materials, i.e., material systems whose sizes are intermediate between that of atoms/molecules and that of bulk solids. Because of quantum-mechanical size effects, the properties of such systems are strongly size dependent and neither like those of atoms nor those of macroscopic solids. They open new avenues for unprecedented experiments, further testing the limits of our understanding of condensed-matter physics.

Because of the availability of high-quality, well-controlled semiconductor nanostructures, these are the systems on which we concentrate our investigations of Quantum Size Effects. The research emphasizes the study of optical transitions, collective excitations and dynamics in ultrathin, quasi-2D layers, using time-resolved tunable ultrashort pulse-laser spectroscopy. In the future, the program will be extended further to systems of lower dimensionality, such as quasi-1D quantum wires and quasi-0D quantum boxes.

Electron Transport in Nanostructures
PAUL L. MCEUEN

The goal of this research program is to understand the transport properties of electrons confined within nanostructured materials. Since these systems are on the order of the fermi wavelength in size, single-electron charging and quantum confinement can dramatically influence electron transport. Understanding and controlling these quantum processes may lead to new classes of materials with carefully tailored electronic properties.

Currently, we are studying submicron semiconductor structures fabricated using electron beam lithography. In the future, we will explore new fabrication techniques that promise even smaller structures. These measurements will directly probe electron propagation on picosecond time scales, yielding new information about quantum transport processes.

Superconductivity, Superconducting Devices, and 1/f Noise
JOHN CLARKE

DC Superconducting QUantum Interference Devices (SQUIDs) based on a niobium technology are applied to a wide variety of applications, including geophysics, nuclear magnetic resonance, and the study of noise in high-transition-temperature (T_C) superconductors. Measurements on high-T_C superconductors, such as YBaCuO, BiCaSrCuO, or TlCaBaCuO, yield information concerning the dependence of the low-frequency magnetic flux noise on temperature and the microstructure of the materials, and they guide the design of devices operating at liquid nitrogen temperatures. Measurements of voltage noise at the resistive transition of superconductors yield information on the nature of the transition and are used to design superconducting bolometers. Sensitive SQUID amplifiers involving a tuned input circuit and a novel Q-spoiler are used to detect nuclear magnetic and nuclear quadrupole resonance in the frequency range of 20-50 MHz. This system is used to study magnetic resonance of surface layers. SQUIDs with superconducting input circuits are able to detect zero-field nuclear magnetic resonance or nuclear quadrupole resonance at frequencies as low as 20 kHz in organic and amorphous materials. These data provide information on the magnetic fields and electric-field gradients at the active nuclei. Submicron tunnel junctions are being investigated at ultralow temperatures to test new theories of macroscopic quantum phenomena, such as Bloch oscillations.

Dynamical Processes of Individual Nanoscale Materials
JOSEPH ORENSTEIN

The goal of this research is to develop new tools for the characterization and modeling of nanoscale materials and their interactions. Materials science in the 1990s and beyond will emphasize large-scale assemblies of artificially prepared nanostructures. A critical step in this program is the ability to characterize and model the properties of individual nanoscale structures, rather than the properties of an ensemble. To date, measurements of the properties of individual nanoscale structures have been largely confined to dc electrical transport. These measurements alone are not sufficient to characterize these materials. In our laboratory, we extend characterization techniques beyond dc electrical transport. The first stage of this project is to develop tools to measure the dynamical conductivity of individual nanoscale structures. In subsequent work, we will extend our techniques to magnetic and vibrational properties as well.

MATERIALS RESEARCH AT THE ADVANCED LIGHT SOURCE (ALS)

Studies of the Metal/Solution Interface with X-Rays

PHILIP N. ROSS

A new method for the determination of the *in situ* structure at metal/solution interfaces has been developed. The method utilizes the phenomenon of total reflection of x-rays from metal surfaces at glancing incidence and analysis of Bragg reflection parallel and perpendicular to the reflecting plane to obtain complete structural characterization of the interfacial region. Scattering calculations suggest it should be possible to obtain a determination of the structure of the solution side (the ionic double layer) as well as the metal side of the interface by this method. Proof-of-principle experiments have been conducted on the 54-pole wiggler beamline at SSRL. Initial experiments are directed towards the study of:

- The electrolytic growth of thin (< 100 nm) metal epilayers and the elucidation of dislocation creation and propagation; and

- The study of the electrolytic reconstruction of metal surfaces and the understanding of solvated ion-metal interaction that causes this phenomenon (related to the more familiar reconstruction of the (100) faces of Au, Pt, and Ir in UHV).

Future experiments are planned for the ALS, where the unique high brightness of this source is very advantageous for the glancing incidence geometry in these experiments.

Surface, Interface, and Nanostructure Studies Using Synchrotron Radiation in Combination with Other Probes

CHARLES S. FADLEY

The techniques of photoelectron diffraction and photoelectron holography have been further developed by this project as unique probes of near-surface atomic structures. Photoelectron diffraction has been applied to a variety of systems, including metal and oxide overlayers on semiconductors (e.g., Ag on Si and SiO_x on Si), surface phase transitions (e.g., surface disordering transitions on Ge), and spin-polarized photelectron diffraction from magnetic materials (e.g., high-temperature short-range order in a high-temperature Gd). The use of photelectron holography for the direct determination of three-dimensional atomic images near surfaces has also been advanced for the case of adsorbates and thin overlayers, with images for S on Ni being the best determined from experimental data to date. The application of holography to magnetic spin order has also been studied theoretically. The use of scanning tunneling microscopy as a complementary surface structure probe has also continued, and unique instrumentation combining photoelectron diffraction/holography and scanning tunneling microscopy on a synchrotron radiation beamline is being developed.

Picometer-Scale Structure of Interfaces from Synchrotron Radiation
MICHEL A. VAN HOVE, CHARLES S. FADLEY, AND PHILIP N. ROSS

This research attempts to unravel the picometer-scale structure (0.01 Å) of solid/solid, solid/liquid, and related interfaces using synchrotron radiation at LBL's Advanced Light Source. The focus is on the atomic-scale structure of practical metal/semiconductor, metal/metal, and metal/liquid interfaces. Experimental data from synchrotron-based interface-sensitive techniques are interpreted with new theoretical approaches developed within this project. The techniques include photoelectron diffraction, forward focusing of electrons, electron holography, and near-edge x-ray absorption fine structure.

Stimulated Desorption of Halogens
JORY A. YARMOFF

The interaction of radiation with surfaces is studied via desorption induced by electronic transitions (DIET) techniques. The Advanced Light Source at Lawrence Berkeley Laboratory will be utilized for the DIET studies. Of particular interest are the types of chemical systems that are important in the processing of semiconductor devices. Synchrotron-radiation-based techniques are employed, including soft x-ray photoemission and photon-stimulated desorption, at the National Synchrotron Light Source at Brookhaven National Laboratory and at MAXLAB in Lund, Sweden. From investigations of a number of halogen-semiconductor systems, including work on XeF^2/Si, a model of the halogen etching process of semiconductor surfaces has been developed. In addition, a system to be used for studies of radiation-induced surface damage via electron-stimulated desorption has been constructed in laboratories at the University of California, Riverside.

ADVANCED CHARACTERIZATION

Interfacial Materials and Processes

JOHN D. PORTER

Metal/liquid interfaces are of immense technological importance, but relatively little is known about their structure, properties, or dynamics at the molecular level. Compared with the present state of surface science in ultra-high vacuum (UHV), surface science in condensed media is still in a primitive state. Recent critical advances in interface synthesis and physical characterization form the basis of this research program, which addresses the disparity between UHV and condensed-phase state-of-the-art in two ways:

- Ultra-low-defect single-crystal metal surfaces will be prepared and characterized *in situ* and will be used as *de facto* standards for the development of new techniques; and

- High-resolution structural and spectroscopic methods well suited to the study of interfaces *in situ* will be developed.

The new methods to be developed are AFM/STM, simultaneous atomic force and scanning tunneling microscopy, which will allow deconvolution of topographic (structural) and electronic (bonding) effects with atomic resolution, and PTS, photoelectron tunneling spectroscopy, in which a macroscopic metal/liquid/metal tunneling junction is used in conjunction with a high-brightness photon source to probe valence and core-level electronic structure at the interface.

Nonlinear Excitations in Solid-State Systems

CARSON D. JEFFRIES

The central objectives of this program are to experimentally study nonlinear phenomena in solid-state systems and to develop models that can explain and predict the observed behavior. Previous work focused on spin waves and plasma waves. Present emphasis is on the novel nonlinear electrodynamics exhibited by high-temperature superconductors of the copper oxide type. The origin of the nonlinearities lies in the microstructures of these ceramic materials, which contain superconducting grains in contact through weak links. Observed generic behavior includes: very-high-order odd harmonic generation in zero dc field; even harmonics in nonzero field; and, at high harmonics and high pump power, very sharp power dips periodic in the dc field, due to flux quantization. Models are developed that semiquantitatively explain the observed behavior and help characterize the material. This work has a bearing on the problem of high critical currents in high magnetic fields, as well as on the origin of the superconductivity.

Low-Temperature Properties of Materials
NORMAN E. PHILLIPS

Measurements of low-temperature properties, particularly specific heats, are made to further the understanding of materials' properties and behavior. Measurements are made from 5 mK to above 100 K and at pressures to 20 kbar and in magnetic fields to 9 T. The current emphasis is on high-T_c superconductors and on heavy-fermion compounds, particularly heavy-fermion superconductors. Related work is carried out on the temperature scale in the region below 1 K, where it is not well established.

The objective is to obtain information that contributes to the fundamental understanding of condensed-matter systems, thereby providing a basis for testing theories and models and in turn contributing to the goal of predicting the properties of materials from their chemical and physical structure. The choice of materials for study has changed over the years. Prior to the discovery of high-T_c superconductors, the emphasis had been on heavy-fermion compounds. Currently, and for the immediate future, the emphasis is on high-T_c superconductors, both for their potential technical importance and because their superconductivity may result from a new mechanism, the understanding of which would itself be important in understanding the phenomenon of superconductivity more generally. However, work on heavy-fermion compounds, particularly heavy-fermion superconductors, will be continued because their superconductivity almost certainly results from a non-BCS mechanism, and these materials are prototypical examples of highly correlated electron systems. Their superconductivity may be related to that in the high-T_c materials, and, in any case, it is of great interest in connection with understanding the fundamental electron-electron interactions that can produce superconductivity.

Experimental Solid-State Physics and Quantum Electronics
YUEN-RON SHEN

The objective of this program is to further basic understanding of laser interaction with matter and to develop and apply modern optical techniques to materials science research. Emphasis is on nonlinear optical effects and techniques. Both theoretical and experimental investigations are being conducted. Recent work is mainly on the development of second-order nonlinear optical methods for surface and interface studies. Infrared-visible sum-frequency generation is demonstrated to be an extremely powerful and versatile tool for surface-vibrational spectroscopic studies. It is unique in its ability to probe surface molecules of a neat liquid. Optical second harmonic diffraction from laser-induced monolayer gratings of adsorbates is used to study anisotropic surface diffusion. Two independent diffusion channels are clearly identified for the first time in a heterogeneous surface-diffusion process, CO on Ni (110). These techniques will be further developed and applied to other problems of interest to the surface science community. Other nonlinear optical effects, such as resonant second-harmonic generation and doubly resonant difference-frequency photon echoes, will be investigated and their potential applications explored.

Time-Resolved Spectroscopies in Solids
PETER Y. YU

The object of this program is to understand ultrafast relaxation processes that occur when electrons in solids are excited either electrically or optically. Picosecond and subpicosecond laser pulses are used to excite energetic electrons in semiconductors such as GaAs. Using spectroscopic techniques, such as emission and inelastic light scattering, the dynamical properties of the excited hot electrons, and the lattice vibration they excite, are excited. The effects of defects and stress on the properties of electrons in solids are investigated by applying pressure to samples inside a diamond anvil cell. The optical properties of heterostructures, such as GaAs films grown on Si by molecular-beam epitaxy, are also studied.

Nuclear Magnetic Resonance (NMR)
ALEXANDER PINES

The nuclear magnetic resonance (NMR) program has two complementary directions. The first is the development of new concepts and techniques in NMR in order to extend its applicability to a wider range of problems and materials. Such a program demands a study of the interaction of nuclear spins with each other and with other degrees of freedom, such as molecular rotations, and requires the development of new theoretical approaches and experimental methods. Such methods entail a substantial effort in the design and fabrication of next-generation NMR equipment. Some developments currently under way in this direction are zero-field NMR, imaging of materials and flow, superconducting quantum interference device (SQUID) detectors for high-sensitivity, high-temperature NMR of silicates and glasses, optical polarization of gases and selective polarization of surfaces, and the double-rotation technique (DOR) for line-narrowing spectra of quadrupolar nuclei.

The second direction is the application of novel NMR methods and instrumentation to materials research problems in collaboration with other programs at LBL, as well as with outside laboratories. In fact, the new DOR technique is already being used to study silicates and catalysts, and the optical-pumping technique is being used to study the surfaces of polymers. This program addresses a national need for a model effort to implement the rapid development and transfer of NMR technology to laboratories in industry and other organizations

Far-Infrared Spectroscopy
PAUL L. RICHARDS

In this project, improved types of infrared sources, spectrometers, and detectors are being developed. Moveover, improved infrared techniques are being used to do experiments in areas of fundamental and applied infrared physics, where their impact is expected to be large. Infrared experiments in progress include: direct measurements of the absorptivity of the new high-T_C superconductors at far-infrared and submillimeter wavelengths, measurements of the infrared spectra of one-dimensional conductors, and measurements of the heat capacity of monolayers of adsorbates on metal films. Developments in infrared technology include: development of thin-film high-T_C superconducting bolometers for detecting x-ray, infrared, and microwave radiation, development of superconducting thin-film quasiparticle detectors and mixers for near-millimeter wavelengths that approach quantum limited sensitivity, and development of low-T_C superconducting microbolometers for detection of infrared and millimeter waves.

ELECTROCHEMISTRY

Electrochemical Energy Storage
ROLF H. MULLER, CHARLES W. TOBIAS, PHILIP N. ROSS, JAMES W. EVANS, LUTGARD C. DE JONGHE, AND JOHN NEWMAN

The overall aim of the program is to improve energy efficiency, lower capital cost, and increase material yield of electrochemical-cell processes employed for the reversible conversion of energy in galvanic cells. These goals are pursued in eight partially interdependent projects.

Surface Morphology of Metals in Electrodeposition: Role of electric-field and solution-side mass transport in the electrocrystallization of metals; mechanism of initiation, growth, and propagation of surface imperfections; development of surface textures.

Engineering Analysis of Electrolytic Gas Evolution: Characterization of the physical processes involved in the evolution of gases at electrodes, with emphasis on their effects on ohmic resistance and mass transport.

Surface Layers on Battery Materials: Structural and chemical transformation of surface layers on galvanic cell materials during change of valence (charge and discharge). Corrosion layers and protective, ionically conducting thin films on reactive metals. Control of corrosion of battery-plate materials by surface modification.

Analysis and Simulation of Electrochemical Systems: Development of mathematical models to predict the behavior of electrochemical systems and to identify important process parameters; experimental verification of the models.

Electrode Kinetics and Electrocatalysis: Oxygen reduction with new catalysts and carbon black corrosion during oxygen evolution.

Electrochemical Properties of Solid Electrolytes: Electrochemical behavior of polymeric separators for intermediate temperature sodium cells.

Advanced Electrode Research: Processes in electrodes for aqueous and molten salt electrolyte systems.

Electrical and Electrochemical Behavior of Particulate Electrodes: Electronic conduction and metal dissolution/deposition in particulate electrodes.

Electrochemical Processes: Novel approaches are explored, and the relevant theoretical framework is established for the control of composition and phase structure in the electrodeposition of alloys, with emphasis on magnetic materials.

Chemistry and Materials Problems in Energy-Production Technologies

DONALD R. OLANDER

The principal emphasis in this program is on the high-temperature properties and processes involving nuclear materials and other advanced materials. Motivated by the need for fundamental understanding of materials behavior during severe core damage accidents in light-water reactors, the thermodynamics of refractory oxides are investigated experimentally and developed theoretically. High-temperature vacuum vaporizations with mass spectrometric detection constitute the experimental aspects of the nuclear ceramics studies. Thermal gravimetric apparatus is used to investigate the oxidation and volatilization of UO_2 in steam. The same equipment is applied to determine the vapor pressure and oxidation kinetics of the C_{60} and C_{70} fullerenes. Modeling of moving-boundary effects on combined volume and grain boundary diffusion is part of the program. This project is relevant to fission product release from nuclear fuels during simultaneous grain growth. A modulated molecular beam-mass spectrometic detection apparatus is used to study gas-solid reactions, including etching of silicon carbide by atomic hydrogen and by fluorine-oxygen compounds.

MATERIALS SYNTHESIS

Synthesis of Novel Solids
ANGELICA M. STACY

The goal of this research is to synthesize advanced materials with novel properties. Current work is focused on rare-earth transition-metal phosphides. Rare-earth compounds have attracted attention because they exhibit cooperative phenomena, including valence fluctuations, heavy fermion superconductivity, and unusual types of magnetic ordering. These cooperative phenomena are difficult to model and remain a challenge to our understanding of condensed matter. The goals are to synthesize and characterize new classes of rare-earth transition-metal phosphides that exhibit cooperative phenomena (especially superconductivity). Such synthetic studies will lead to numerous new classes of materials with novel magnetic and electronic properties.

Nanocrystal Precursors
PAUL ALIVISATOS

In materials physics and chemistry the preparation of sub-micrometer artificially engineered semiconductor structures with new properties is a major goal. The electronic and optical properties of "quantum dots" or semiconductor crystallites that are small in comparison with bulk electron delocalization lengths (10 to 100 Å) are the subject of extensive investigations. Comparably sized crystallites of metals, inert gases, and molecular crystals all melt at temperatures well below the bulk melting point. Unlike these classes of materials, the bonding in semiconductors is highly directional and covalent. It is thus of interest from both theoretical and practical points of view to determine the melting temperature of semiconductor nanocrystals. Using temperature-dependent electron diffraction, we have demonstrated for the first time a large depression in melting temperature as size decreases for nanocrystals of a semiconductor. We find a decrease in melting temperature in clusters of the direct band-gap semiconductor CdS, comparable with the depression observed in gold clusters, and as large as 1000 K for the smallest crystallites studied.

The marked reduction in melting temperature for semiconductor nanocrystals has several important implications. First, the optimum annealing temperature for preparation of high-quality defect-free nanocrystals can be expected to be a small fraction of the bulk annealing temperature. Second, the ability to fuse nanocrystals to form a film at relatively modest temperatures indicates that nanocrystals may provide a new low-temperature route to thin-film growth. Finally, as the dimension of active domains is reduced to the nanometer length scale, the thermal stability of the new devices may be limited.

Synthesis of Novel Fullerene-Based Materials

ALEX ZETTL, MARVIN L. COHEN, JOEL M. HAWKINS, AND YUEN-RON SHEN

Fullerene carbon clusters and the related molecular solids formed from these clusters are new materials with unique properties. Although pure C_X fullerene structures and those doped with other atoms are extremely interesting in themselves, it is probable that future applications will come predominantly from *modified* fullerene structures.

This project focuses on the synthesis, characterization, physical understanding, and potential applications of modified fullerenes. Pristine and doped materials are made via arc formation, novel chemistry routes, monolayer formation, doping, and intercalation. Theory is used to compare the total energies of various structural configurations to determine potentially low-energy structures. Characterization involves a wide variety of probes including: nuclear magnetic resonance, x-ray, linear and nonlinear optics, magneto-optics, ac and dc magnetization, transport and superconducting properties, photoemission, elasticity, internal friction, and measurements of thermal properties.

Part of our goal is to prepare novel materials from discretely functionalized fullerenes. We are studying the osmylation of C_{60} and other organic reactions of fullerenes in order to synthesize pure and well-characterized fullerene derivatives. These derivatives serve as monomers for the preparation of novel fullerene-based films and polymers. Mono- and bisosmylated C_{60} show structural and bonding characteristics similar to those found in C_{60}. We plan to see how these properties translate into well-defined new materials.

ALLOY THEORY

Local Atomic Configurations in Solid Solutions

DIDIER R. DE FONTAINE

This investigation is concerned with ordering phenomena in alloys, and the recent emphasis has been on long-period ordered superstructures (modulated structures) in binary f.c.c. alloys. Two systems have been studied in detail: Cu-Pd and Ag-Mg. Structural observations have been carried out using the Atomic Resolution Microscope at LBL's National Center for Electron Microscopy (NCEM), and the nature of the periodic antiphase boundaries present in these alloys has been characterized. In addition, a systematic investigation of long- and short-range order in Cu-Pd has been undertaken using *in situ* variation of temperature and radiation dose in the High-Voltage Electron Microscope at NCEM. Other work on the Cu-Pd system, using standard electron microscopy techniques, is directed toward clarification of the equilibrium phase diagram. Concerning the theoretical aspect of this project, a statistical mechanics model for modulated structures in alloys has been proposed and solved within the mean field approximation. Results show agreement with some real systems. Moreover, the mechanism governing the distinction between sharp and diffuse antiphase boundaries has been elucidated. New work will focus on the nature of ordered structures in the technologically important Al-Ti system and related ternaries.

GENERAL SCIENCES

ACCELERATOR & FUSION RESEARCH DIVISION

Major efforts in the Accelerator and Fusion Research Division (AFRD) include:

- *Investigations in magnetic and inertial-confinement fusion.*
- *Design and operation of the Advanced Light Source, a state-of-the-art synchrotron-radiation facility.*
- *Theoretical studies of accelerator phenomena and characteristics.*
- *Research and development in support of the Superconducting Super Collider (SSC) and other high-energy accelerators.*

The physics and technology of beams of ions, electrons, and photons provide a common theme in these diverse research areas. Within and in parallel with the broad research areas outlined in this section, AFRD conducts many individual projects that offer opportunities for technology transfer and industrial cooperation.

Magnetic Fusion Energy and Related Research

WILLIAM S. COOPER III

Since 1975 LBL has participated in the national magnetic fusion program, primarily as a leading developer of neutral-beam systems for major experiments such as those at Princeton Plasma Physics Laboratory and GA Technologies in San Diego. These experiments, unlike the self-sustaining reactors of the future, typically run for only a fraction of a second (at most a few seconds) and thus require an influx of energy to heat the plasma with every pulse. Energetic neutral beams—usually either hydrogen or deuterium atoms—continue to be the method of choice for supplying this energy in most of today's large experiments. Historically, then, our efforts have been directed toward the development of sources of either positive or negative ions, systems for accelerating and transporting these ions, and means of efficiently neutralizing the ions to produce the required neutral atoms.

Currently, our work in these same areas has a much broader base. Ongoing efforts focus on negative-ion systems for the much larger fusion experiments of the future, such as the proposed International Thermonuclear Experimental Reactor (ITER), for industrial application (perhaps including ion implantation in semiconductors), and for defense. The interest in negative ions is based mainly on the fact that, at high energies (as needed, for example, to penetrate the larger plasma volumes of future fusion experiments or reactors), positive ions cannot be efficiently neutralized.

Negative-Ion-Based Neutral-Beam Research. Whether neutral beams begin as positive or negative ions is, in principle, unimportant, but the practical differences are considerable. On the one hand, high current densities are easier to generate with positive ions. In addition, injecting negative ions into an accelerator is complicated by the presence of like-charged electrons, and the ease with which negative ions can be stripped of their excess electrons makes pumping requirements exceedingly stringent. Only positive-ion systems have been developed thus far. On the other hand, at higher energies—such as those needed for larger fusion experiments and for many accelerator applications—only negative ions can be efficiently neutralized. Accordingly, our work now concentrates on negative ions—on generating higher currents from sources, on novel transport schemes, and on efficient neutralization scenarios. A particularly active area of ongoing research is source development, where we are especially encouraged by continuing progress in coaxing high currents from experimental volume-production sources and by our growing theoretical understanding of them. We also have a leading effort in the development and application of metal-vapor vacuum arc (MEVVA) ion sources and related technologies. We also continue to explore the many possible applications of lanthanum hexaboride cathodes as long-lived electron emitters.

Fusion Diagnostics and Theoretical Studies. Concurrent with the design and testing of neutral-beam systems, work continues on developing a noninterfering, on-line diagnostic technique for burning-plasma experiments. Another effort grounded in our interest in atomic and molecular physics is our theoretical study of the physics of negative-ion sources, a study which underlies and parallels our source-development efforts. Basic theoretical plasma-physics research also continues, with the goal of providing a better and broader understanding of processes and interactions that occur in plasmas.

Superconducting Magnets

CLYDE E. TAYLOR

One of the principal efforts of the magnet group has been the development of magnets for the SSC. Following up on our successful basic design of collider dipoles for the SSC, we designed the collider quadrupoles and conducted an intensive, highly interactive program to teach industrial companies how to build these magnets. As our SSC program moves through this technology transfer stage, we are turning our R&D toward stronger and more efficient magnets for the accelerators of the future.

We are also collaborating with industry and with academic researchers to produce superconducting cable with a higher critical current density than is now available. Concurrently, we are carrying out research aimed at a basic understanding of high-current-density accelerator magnets and the materials used in them. These include superconducting cryogenic and superconducting high T_c materials. The study of high T_c materials represents a more exploratory area of research.

Heavy-Ion Fusion Accelerator Research

ROGER BANGERTER

The Heavy-Ion Fusion Accelerator Research (HIFAR) program is studying the physics and technology of the heavy-ion induction linac, gathering knowledge for a sensible future decision on proceeding with inertial-fusion power development. A specific accelerator technology, the multiple-beam linear induction accelerator, is being studied from the viewpoints of physics, technology, and economic feasibility.

Because a heavy-ion fusion driver will require ion beams at unprecedentedly high currents with good optical quality, the HIFAR program is following a multiple approach to extend understanding of accelerator and beam physics well beyond the present state of the art.

This program includes
Scaled experiments such as:

- The Single Beam Transport Experiment (SBTE), which established the practical current limits of ion-beam transport in a strong-focusing channel;
- The four-beam induction accelerator (MBE-4), which modeled current amplification and longitudinal beam control in the electrostatically focused section of a fusion driver;
- The proposed Induction Linac System Experiment (ILSE), which will examine in a scaled way (and in some parameters at full scale) most of the beam manipulations required in a driver;

Theory and analysis that expand our physics understanding of multiple, space-charge-dominated ion beams and of the potential costs of accelerator drivers for inertial fusion; and

Engineering R&D to be able to produce accelerator technology at the proper scale and cost for a fusion driver.

Exploratory Studies and Accelerator Physics
SWAPAN CHATTOPADHYAY

Exploratory research is directed toward extending the frontiers of accelerator theory and technology as the basis for future novel accelerators and their applications. These efforts include creating new computer codes that evaluate various intensity-dependent beam-dynamical effects and lead to optimized designs. These codes will provide three-dimensional electromagnetic properties of complicated accelerator structures. This work also concentrates on fundamental research in low-emittance, high-brightness storage rings, novel free-electron lasers, and new methods of acceleration. These efforts led in the past to the successful paper design of an unprecedentedly high-brilliance coherent x-ray facility, development of the accelerator-physics optimization code ZAP, the electromagnetic field code COMET, infrared FEL, etc.

Several AFRD physicists from this same group form the core of the Accelerator Physics support group for the Advanced Light Source project. The primary activity of this core group is to provide accelerator-physics support to the basic design, parametric and beam-dynamical studies, accelerator systems performance, specification, and evaluation for the Advanced Light Source during all phases of preconstruction, construction, and commissioning of this facility. Efforts are divided into:

- Subsystems, such as injection (linac plus booster) and the main storage ring.

- Functions, such as accelerator modeling for the computer control system for the whole facility, impedance inventory and control, feedback systems, magnet quality assurance.

Theoretical studies focus on lattice considerations, dynamic aperture limitations due to undulators, various coherent instability and lifetime issues, impedance studies, and some beam instrumentation.

We are now participating in the launch of two major initiatives. One is the proposed Combustion Dynamics Facility (CDF), being pursued jointly with Sandia National Laboratories. A wide variety of challenging problems in pure and applied chemical dynamics can be addressed using beams of infrared light, synchrotron radiation in the VUV and soft x-ray regions, and optical lasers. The required beam qualities generally include high intensity, high wavelength resolution, short pulses, and synchronization capabilities. The CDF at LBL will have at its heart a tunable infrared free-electron laser, or IRFEL, with the characteristics mentioned above. Other prominent features will include two ALS beamlines, a variety of lasers, and state-of-the-art molecular-beam machines.

The other initiative is the proposed B factory at Stanford Linear Accelerator Facility (SLAC). B mesons and their rare decays are extremely interesting to high-energy physicists. For example, they can study CP (charge-parity) symmetry-breaking, and other challenging problems. This joint LBL/SLAC/Caltech proposal involves an unusual "asymmetric" collider scheme, with electrons at 9 GeV colliding with positrons at 3.1 GeV, reaching a resonance where pairs are produced copiously. The results of the collision would move in the laboratory frame of reference, giving some spatial and temporal separation to make detection easier. This scheme would save a great deal of construction money by using the existing high-energy Positron-Electron Project (PEP) storage ring, with a number of modifications. The lower-energy positron ring would go in the PEP tunnel as well.

The Beam Signal Electronics Section does developmental work on the many devices in an accelerator that detect small signals that reveal the beam's behavior, and on other devices that direct small corrective forces to the beam. Such devices are employed in the technique of stochastic beam cooling, which involves detecting deviations of single particles from the mean position and velocity of the beam, then applying corrective impulses to the same particles at a position downstream. We have developed and tested components for the stochastic cooling of antiprotons in the Tevatron collider project at Fermilab. We are also pursuing improvements in this technology, as well as new applications. A disruptive electromagnetic interaction can arise when a particle beam passes near some structure, as in an accelerator. The measurement of such interactions, called the beam-coupling impedance, and the development of device designs with reduced effects are also subjects of study. And we are performing R&D aimed at the many challenges on the luminosity frontier of high-energy physics, such as B-meson "factories" based on electron-positron collider rings.

Two-Beam Accelerator: The two-beam accelerator (TBA) concept, it is generally agreed, is a leading candidate for a configuration capable of producing electron energies in the teravolt range for future linear colliders. It exploits the higher accelerating gradients achievable when the operating frequency is increased. The total microwave power required in such a collider would be on the order of a terawatt. In the TBA, this would be produced in a long, low-energy (5-20 MeV), high-current (1-3 kA) induction accelerator system located alongside the high-gradient accelerator.

AFRD's Collider Physics Group is performing theoretical and experimental studies on two approaches for generating the required microwave power using the low-energy beam. The first combines the technology of the free-electron laser (FEL): kiloampere induction accelerator units, oversized waveguide and couplers operating at millimeter wavelengths, and traveling-wave (TW) linear accelerator structures. A collaboration with LLNL has resulted in achieving a 35-GHz single-mode FEL peak output of 1.8 GW with over 40% efficiency. Also, we have demonstrated an accelerating gradient of 180 MV/m in a 35-GHz TW test structure. A new 10-cm-long high-quality accelerator section will be tested soon and is expected to achieve a gradient in the 300- to 500-MV/m range.

The second approach, which is the focus of most of our present work, is a relativistic klystron version of a TBA. It involves the technology of high-current relativistic bunched beams, their reacceleration in induction units, and standing-wave cavities or TW accelerator sections functioning as microwave output couplers.

ADVANCED LIGHT SOURCE (ALS)

The Advanced Light Source promises to be one of the most significant Department of Energy national user facilities, and is one of the first in a new generation of dedicated synchrotron light sources. Work on the ALS began in December 1986, and the coordinated efforts of several design and development teams and construction crews have resulted in exceeding the formal project milestones of 50 mA of stored beam by April 1, 1993. Most recently the ring stored 400 mA with 1 hour life at 100 mA.

This facility is based on an electron storage ring designed to accommodate long magnetic insertion devices (known as "wigglers" and "undulators") that enhance production of synchrotron radiation. The undulators will provide photon beams of unprecedented brightness in the extreme-ultraviolet and soft-x-ray regions of the spectrum, whereas the wigglers and the bending magnets will contribute high-quality broadband radiation reaching into the hard-x-ray region.

Chemistry and surface science can benefit from its ultraviolet light, and the proposed Combustion Dynamics Facility counts a pair of ALS beamlines among its key components. Higher-energy photons, in the soft x-ray region, are useful for thin-film and interface studies, atomic physics research, studies of living cells, and industrial applications such as high-resolution characterization of integrated circuits. Hard x-rays from wigglers can be used for structural studies of crystallized viruses and proteins and for elemental probes of materials.

The scientific program has progressed from expressions of interest to formal beamline proposals, while a number of biotechnology, pharmaceutical and semiconductor companies are exploring technology transfer options.

NUCLEAR SCIENCE DIVISION

The principal objective of nuclear science research at Lawrence Berkeley Laboratory is the experimental and theoretical investigation of heavy-ion-induced nuclear reactions at all energies, with a focus on understanding nuclei and nuclear matter under extreme conditions. Complementary programs are carried out in light-ion nuclear science, in nuclear data evaluation, and in the development of advanced instrumentation. Experimental research programs are centered at the LBL 88-Inch Cyclotron, the CERN Super Proton Synchrotron (SPS) and the BNL Alternating Gradient Synchrotron (AGS). In addition, the Nuclear Science Division is collaborating in the Sudbury Neutrino Observatory (SNO) and is planning for a future at the Relativistic Heavy Ion Collider (RHIC) now under construction at BNL.

The Nuclear Science Division (NSD) enjoys a close relationship with the University of California at Berkeley Many NSD staff have faculty appointments in the Berkeley campus Chemistry and Physics Departments. Graduate students (from both UCB and many other universities) use LBL facilities to carry out their thesis research.

NSD operates the 88-Inch Cyclotron as a National Facility User in support of U.S. Department of Energy programs in basic nuclear science. The central component is a sector-focused, variable-energy cyclotron with an Electron-Cyclotron Resonance (ECR) ion source that is currently being upgraded by the addition of an Advanced ECR high-charge-state ion source. This versatile combination of the ECR source and cyclotron makes a reliable and cost-effective accelerator producing beams of both light ions (protons and deuterons) and heavy ions (helium to uranium). The Cyclotron also provides beams for the application of nuclear techniques to other areas of research, including biology and medicine, atomic physics, and the study of cosmic-ray damage to satellite electronic components.

Heavy Ion Physics

T. JAMES M. SYMONS

This project covers basic physics investigations with heavy ions at the 88-Inch Cyclotron, CERN and BNL. It supports developments in instrumentation, provides collaboration with visiting researchers, trains graduate students, and stimulates the development of accelerators and facilities.

Experimental heavy ion research at the 88-inch Cyclotron focuses primarily on the spectroscopy of high-spin states of nuclei, the search for and study of unusual transuranium isotopes and elements, the study of exotic nuclei far from the line of stability, and the investigation of heavy-ion reaction mechanisms over a wide range of energies. The research is aided by an impressive arsenal of detectors. A new detector array, Gammasphere, which will be the premier facility of the United States nuclear structure community, is now under construction at the 88-Inch Cyclotron, with first operation planned in 1993. Looking to the future, an R&D effort is being carried out in support of the proposed Isospin Laboratory, a national radioactive beam facility.

Experiments being carried out at the CERN Super Proton Synchrotron (SPS) and at BNL extend the heavy ion investigations to ultrarelativistic energies and search for evidence of quark-gluon plasma formation. In addition to looking ahead to participation in the new lead beam program at CERN, the NSD is also planning for a future at the Relativistic Heavy Ion Collider (RHIC) now being constructed at BNL. LBL is leading the STAR (Solenoidal Tracker At RHIC) collaboration in a recently approved experiment to study particle and jet production at Relativistic Heavy Ion Collider RHIC.

Low-Energy Physics
T. JAMES M. SYMONS

This project covers basic physics investigations with light ions (proton through ^{4}He, including polarized protons and deuterons) at the 88-Inch Cyclotron as well as some non-accelerator-based low-energy physics studies. In addition, it supports developments in instrumentation, provides collaboration with visiting researchers, trains graduate students, and stimulates the development of accelerators and facilities.

Studies of light nuclei far from stability utilize light ion beams and the on-line mass analyzer RAMA. Searches are conducted for nuclei near the proton and neutron drip lines that may decay by new or exotic radioactivities. Spin-polarization events in nuclear reactions are studied in collaboration with outside users, making use of the excellent polarized proton and deuteron beams from the 88-Inch Cyclotron. Experiments designed to test the basic symmetry properties of the nuclear interaction are also carried out.

A broad program in nuclear astrophysics has been established. This program has expanded to include significant participation in the Sudbury Neutrino Observatory (SNO) collaboration in its exciting project to detect solar and supernova neutrinos.

In 1991 a new group was formed to study weak interactions. While continuing several collaborative projects, this group is also starting a new project to measure the beta-decay asymmetry of ^{21}Na in order to investigate charge-changing weak currents.

Nuclear Theory
MIKLOS GYULASSY

The goal of the nuclear theory program at LBL is to develop precise theoretical tools and methods necessary for the proper analysis and interpretation of experiments involving atomic nuclei. These include nuclear reactions at low to ultrarelativistic energies, and lepton-nucleus and hadron-nucleus reactions. In addition, the program aims at adding breadth to the Division's overall nuclear research program by concentrated efforts in nuclear astrophysics, macroscopic nuclear models, QCD and hadrodynamic theories of ultradense matter and phase transitions, order-to-chaos transition in nuclei, and selected DOE research and development projects such as neurocomputing methods for pattern recognition.

The theory group conducts an ambitious visitor program to cover a broad range of additional theoretical topics. The group also provides an important focal point for developing postdoctoral fellows and university-based visitors to interact with senior theorists in a broad intellectual environment, and with direct access to nuclear experimentalists working at the frontier of this science.

Isotopes Project
EDGARDO BROWNE-MORENO AND RICHARD B. FIRESTONE

The Isotopes Project evaluates nuclear structure and radioactive decay data and also develops standard methodology for the analysis of nuclear data. From 1940 to 1978, the Isotopes Project produced seven editions of the *Table of Isotopes,* and in 1986 it published the first edition of the *Table of Radioactive Isotopes.* Since 1978, the group has coordinated its evaluation efforts with the U.S. Nuclear Data Network (USNDN) and the IAEA International Nuclear Data Committee Network of Nuclear Structure and Decay Data Evaluation (INDC/NSDD) to prepare the Evaluated Nuclear Structure Data File (ENSDF). The group is currently responsible for the evaluation of about 50 mass chains, preparation of an 8th edition of the *Table of Isotopes,* and development of a modern, computerized search and retrieval system for the ENSDF file.

In addition to serving a broad user community, the Isotopes Project plays an active role in promoting the science of nuclear data evaluation. The group maintains an extensive library with comprehensive bibliographical data, reprints, and the major nuclear physics journals. The Isotopes Project encourages the basic and applied nuclear science communities to take advantage of its resources and expertise in the field of nuclear structure and radioactive decay data.

Chemistry of Heaviest Elements
DARLEANE C. HOFFMAN

Determination of the fundamental chemical properties of the heaviest elements at the furthest reaches of the periodic table is of particular interest in determining the architecture of the periodic table. It is also important in assessing the influence of relativistic effects in these heaviest elements, and throughout the periodic table. A program to investigate some of the most fundamental chemical properties of elements 102 through 106 is being undertaken. The actinide series ends with Lr (103), and the change in chemical properties in going to the transactinide elements Rf (104), Ha (105), and 106 is especially important. Relativistic effects have been predicted to become increasingly prominent for the higher Z elements, and possible observable effects include anomalous trends in ionic radii and stabilization of different oxidation states relative to the lighter homologs. These properties can be investigated for the elements from 102 through 106, even with the small numbers of short-lived atoms which can be produced. This program includes determining or confirming the most stable oxidation state for each of these elements and exploring the range and stability of other oxidation states in aqueous solution. Detailed comparisons of transactinide chemical properties with those of the homologous elements are being made by studying the formation and stability of anionic complexes in aqueous solution. Gas-phase chemical separation procedures are also being used for the study of the chemical properties of the transactinide elements. Efforts will continue to try to produce and identify new, longer-lived isotopes of the heaviest elements, which will permit more detailed studies of their chemical properties.

88-INCH CYCLOTRON
CLAUDE M. LYNEIS

The 88-Inch Cyclotron at the Lawrence Berkeley Laboratory is operated as a national user facility in support of U.S. Department of Energy programs in basic nuclear science. The central component is a sector-focused, variable-energy cyclotron with an Electron-Cyclotron Resonance (ECR) ion source that is currently being upgraded by the addition of an Advanced ECR high-charge-state ion source. This versatile combination is expected to produce heavy-ion beams from helium to neon with energies up to 32.5 MeV/nucleon. For heavier ions, the maximum energy per nucleon decreases with increasing mass. Typical ions and maximum energy (MeV/nucleon) are expected to be argon (22), krypton (12), xenon (8), and bismuth (5). Most metallic ions and all other gaseous ions between the above examples have either been accelerated or can be developed as needed, with energies high enough for nuclear physics studies. Light ions—p, d, ^{3}He and ^{4}He—are produced up to total energies of 55, 65, 135, and 130 MeV, respectively. Polarized protons and deuterons at intensities of up to 0.5 microampere are also available.

The research program at the Cyclotron is conducted by scientists from many institutions, in addition to those from LBL and the University of California at Berkeley. It also plays an important role in the education and training of young scientists at the undergraduate, graduate, and postdoctoral stages of their careers. During FY 1991 the Cyclotron was used by 120 scientists from 18 institutions.

The research done at the 88-Inch Cyclotron cuts across many of the subfields of nuclear science. This research is defined by the interests of the scientists who choose to make use of this national facility and by the capabilities of the accelerator. A dominant theme in these programs is the power of heavy ion collisions in producing nuclei in extreme states, whether of excitation energy, isospin, or angular momentum. The ECR ion source, the first of its kind to operate in the United States, has had a profound effect on the capability of the Cyclotron, and the initial testing of the AECR source indicates that it meets the expectations for improved performance. New beam species, higher energies, and vastly increased reliability have combined with new detection systems, such as the High Energy Resolution Array (HERA), to produce a very exciting atmosphere for research, a fact reflected in the many proposals for experiments and consequent demand for beam-time. Written proposals for experiments in nuclear science are evaluated by a Program Advisory Committee on the basis of the science proposed.

The 88-Inch Cyclotron also provides a crucial service to organizations involved in the engineering and development of advanced systems for the U.S. space program. It is the major source of heavy-ion beams (worldwide) for the testing of computer chips and other solid-state components, such as charge-coupled devices (CCDs). As such, it fulfills an important national (and regional) need. In addition, an atomic physics program uses the high-intensity, highly charged, low-energy beams from the ECR ion sources to conduct novel studies of atomic structure and collision phenomena. The work provides insight into basic physics questions and has relevance to the understanding of processes operating in fusion or advanced laser plasmas.

PHYSICS DIVISION

The Physics Division conducts research primarily in experimental and theoretical particle physics and in the related area of particle astrophysics. The principal objective of particle physics is to understand the world at its deepest, most fundamental level. As the scale of the objects studied becomes ever smaller, the energy of collision necessary to study them grows correspondingly higher. Thus, particle physics is also called high-energy physics. The largest accelerator in the world, the Superconducting Super Collider, is now being built in Texas and will be the dominant force in particle physics in the next century. LBL will play a major role in developing detectors for the SSC over the next 10 years. In the meantime, physics research at the Tevatron, today's highest-energy accelerator, will continue with the Collider Detector Facility (CDF) and the D-zero Detector.

The SSC and the Tevatron are colliders that use proton beams to reach the highest possible energies. Other colliders use beams of electrons and positrons and thus offer a more precise means for the study of particle physics, albeit at lower energies. LBL researchers use such a collider at the Positron-Electron Project (PEP), located at the Stanford Linear Accelerator Center (SLAC). LBL is also involved with SLAC and other labs in a proposal to convert PEP to a so-called Asymmetric B Factory for the copious production of B mesons, which contain the heaviest known quark, the bottom, or b, quark. This exciting new possibility could become a reality by the mid-1990s.

LBL has also played a leading role in the emergence of a new field, particle astrophysics, at the boundary of particle physics and cosmology. The division is involved in several important experiments in collaboration with the Center for Particle Astrophysics, an NSF Center for Science and Technology that has been established on the Berkeley campus.

As we have progressed in our understanding of the basic constituents of nature and the fundamental forces that govern them, the techniques we use in our explorations have become increasingly challenging. New technologies are constantly being developed, many of which have found wide applications outside particle physics proper. LBL remains a leading developer of these technologies, in the areas of both accelerator design and particle detector development.

Within the Physics Division, we also have the Mathematics Department, which develops analytical and numerical methods for a wide range of engineering and physics problems.

EXPERIMENTAL PHYSICS RESEARCH

The SDC Detector

GEORGE H. TRILLING (SPOKESMAN)

The Solenoidal Detector Collaboration (SDC) is proposing a major detector facility for the Superconducting Super Collider (SSC). With over 80 institutions collaborating worldwide and with more than 500 physicists involved, it is one of the major physics research undertakings in the world. The detector aims to study a very broad range of physics phenomena at the SSC, both expected and unexpected. The detector, weighing 40,000 tons and containing trackers, calorimeters, a superconducting magnet, a muon filter, and massive electronic systems, must obtain nearly complete information on collisions of interest in an environment where 100,000,000 interactions occur each second. The required technological innovations are being developed in an allied R&D program that involves both university and industrial collaborators.

The CDF Detector
WILLIAM CARITHERS, JR. (SPOKESMAN)

The Collider Detector Facility (CDF) operates at the Tevatron collider at Fermilab at the highest energies now available, nearly 2 TeV. The LBL group has built calorimeters and electronics, and, more recently, has developed the SVX chip to read out an ultrahigh-precision vertex detector. This detector uses silicon strips to detect and measure the passage of charged particles. The precision of this device allows experimenters to distinguish closely spaced vertices, the points at which particles are produced. This device is presently in operation during the current run and should greatly enhance the search for the top quark, the only particle yet undiscovered among the known three generations of fermions. The silicon vertex detector will also permit the study of B physics by detecting the vertices of B-meson decays occurring at a distance from the primary vertex where the collision occurred.

D-Zero Detector
RONALD MADARAS (SPOKESMAN)

The D-zero detector is a new detector that is operating at the Fermilab Tevatron collider. It is primarily a calorimetric detector based on a hermetic liquid argon-uranium calorimeter. LBL has built both the vertex tracking chamber and the end-cap electromagnetic calorimeter. The D-zero detector, with very good electron and muon identification capabilities and superb calorimetry, will bring new power to searches for new phenomena and to the precise measurements of Standard Model parameters, such as the ratio of the masses of the Z^0 and $W^{\pm}$ bosons. LBL is also designing a silicon vertex chamber as an upgrade to the present detector.

The Time Projection Chamber (TPC)
MICHAEL RONAN (SPOKESMAN)

LBL operates the TPC detector at the PEP e^+e^- collider at Stanford. The detector is based on an innovative idea developed at LBL 15 years ago. A central tracking detector contains a 10-

atm drift volume with parallel electric and magnetic fields. The ionization produced by particles traversing this volume is measured to give the track position, curvature, and specific ionization with unparalleled detail. The technique, pioneered at LBL, is now used at several leading accelerators: the CDF detector at the Tevatron, the TOPAZ detector at the TRISTAN collider in Japan, and the ALEPH and DELPHI detectors at the LEP collider in Switzerland. The TPC detector has been used to study $e+e^-$ annihilations into hadrons and leptons, and it has specific features for the study of γ-γ collisions produced when both the positron and the electron shed bremsstrahlung photons, which then collide.

PARTICLE ASTROPHYSICS RESEARCH

The observed expansion of the universe, the distribution of elements that we observe, and the 3-K microwave background radiation all point to an unimaginably violent initial explosion that we call the Big Bang. The Big Bang cosmology postulates that the universe began in a small volume of space at extraordinary energy densities. The particle interactions we study in earthly accelerator laboratories are necessary to describe the evolution of the universe from these high energies to its present condition. However, at sufficiently early times in the expansion, the collision energies far exceeded those attainable in earth-bound accelerators. Stable massive particles might have been produced at those early times, and, if weakly interacting, might still be rattling around in the universe as relics of this early era. Just such particles are postulated to explain our greatest cosmological puzzle: The motion of galaxies and clusters of galaxies requires 10 times more matter than we actually see in the stars. This missing matter, or "dark matter," could be in the form of particles too massive to be produced in today's accelerators and thus very difficult to detect. Puzzles such as this are the focus of research in particle astrophysics. The Physics Division has three major programs in this field

Detection of Dark-Matter Particles

BERNARD SADOULET (SPOKESMAN)

New technologies employing low-noise silicon detection and cryogenic detection are being developed to detect the very low-level signals that might be produced by massive particles colliding with nuclei. In particular, the cryogenic detectors use phonons, or sound waves, produced when massive particles collide with nuclei in crystal detectors.

Measuring the Density of the Universe
RICHARD MULLER (SPOKESMAN)

By using supernova explosions, we can measure enormous distances in the universe. The comparison of distances measured this way with red shifts due to the expanding universe would measure the "deceleration" parameter. This parameter tells us whether the universe will expand forever or eventually stop and begin to contract. It is also intimately connected to the model of the earliest times after the Big Bang. This program in the Division measures nearby supernovae with a small automated telescope that observes several hundred galaxies per night, and distant supernovae with large telescopes based in Australia.

Study of the 3-K Microwave Background Radiation
GEORGE SMOOT (SPOKESMAN)

Researchers in the Division have developed radiometers aboard the Cosmic Background Explorer (COBE) satellite to measure fluctuations of the 3-K microwave background radiation. These fluctuations, or anisotropies, are related to the formation of galaxies. The matter fluctuations necessary to "seed" the formation of galaxies should be reflected in the anisotropies of the 3-K microwave background radiation. Data collected by the COBE satellite show fluctuations in background radiation on the order of 6 parts per million. These ripples, around 100 million light years across, confirm theoretical predictions made almost 30 years ago, and bolster the "Big Bang" theory of the universe's origin. The satellite observations are supplemented by balloon-based observations of the spectrum, as well as by observations carried out at the South Pole.

THEORETICAL RESEARCH

The Physics Division has one of the largest theoretical groups in the U.S. in areas of research related to particle physics and particle astrophysics. This effort is necessary to interpret results of the experimental program, as well as to develop the abstract models that might explain particles and particle interactions at their most fundamental level. The research ranges over a vast territory, from the explanation of current measurements to theories of quantum gravity that are relevant to the earliest moments of the universe and that we will never verify directly.

TECHNOLOGY R&D

The challenges of the SSC, with 20 times the energy of present machines (40 TeV) and 1000 times the event rate, require the development of new technologies. This R&D program is carried out in collaboration with universities and industries. The technologies being developed at LBL include the following.

Silicon Pixel Detector
DAVID NYGREN (SPOKESMAN)

With up to 10,000 elements per square centimeter, silicon pixel detectors will allow tracking even in the core of dense particle jets produced at the SSC. Each of the 10,000 elements will have enough "intelligence" to retain the data while signaling that it has detected a particle.

Integrated Detector and Detector Electronics
DAVID NYGREN (SPOKESMAN)

Researchers in the Division have developed the technology to place electronics in the same high-resistivity silicon that contains detector elements. This technology will eliminate the need to microbond the myriad detector elements to their electronic readout.

Warm-Liquid Calorimetry
MORRIS PRIPSTEIN (SPOKESMAN)

Liquid ionization calorimetry has typically been done with liquid argon. However, the use of cryogenic liquids is problematic, since it requires cryostats that interfere with complete coverage. The use of organic liquids at room temperature would greatly simplify the design. A calorimeter using organic liquids TMP and TMS is currently being tested.

Amorphous Silicon Detector
VICTOR PEREZ-MENDEZ (SPOKESMAN)

A program in the Division aims at developing economical detectors to cover large areas by using hydrogenated amorphous silicon. These detectors would have a wide range of application beyond particle physics. This research is being pursued in collaboration with industry.

Fast Electronics
MICHAEL LEVI (SPOKESMAN)

The fast electronics research program aims at developing the necessary electronics to acquire data from the SSC. The analog data, acquired at a rate of 100,000,000 events per second, must be preserved until a decision is made on the collisions of interest, usually a few per second. This decision is typically made within a few microseconds. The division is developing the general electronic architecture, as well as the electronic chips, to which detector elements will be connected.

Radiation Damage to Wire Chambers
JOHN KADYK (SPOKESMAN)

Extensive studies of radiation damage to gas wire chambers are being carried out, with the goals of understanding the fundamental causes and finding ways of avoiding or preventing the wire aging process. The work emphasizes the design of wire chamber systems which can operate in the intense radiation environment of these detectors without suffering appreciable radiation damage.

MATHEMATICS RESEARCH
ALEXANDRE CHORIN AND PAUL CONCUS

The mathematics research program focuses on the development of numerical and analytical methods and their application to the most challenging problems in physics and engineering. A central goal is the construction of mathematically sound, computationally efficient, and physically realistic models that can lead to fundamental scientific understanding. Investigations that began within the Division have been at the frontiers of such topics as vortex methods, random choice techniques, high-resolution methods in gas dynamics, front propagation techniques, and lattice and polymeric models in turbulence.

The three most active areas of current interest are particle and vortex methods, free-surface problems, and parallel processing. Efforts in the first of these areas include an analysis of superfluid turbulence by vortex methods, modeling of the turbulent boundary layer, vortex renormalization, rapid implementation of particle methods, and numerical studies of engineering flows and suspensions. In the second area, we are active in developing algorithms for following free-surface problems. We are using these techniques to study problems in differential geometry, combustion, flow in porous media, solidification, relativity, fluid instability, and capillarity. In the third area, we are developing software on a massively-parallel processor for solving problems of two-dimensional, viscous, incompressible fluid flow in arbitrary geometries and for scientific visualization. Other areas of activity include numerical linear algebra, finite difference methods in fluid mechanics, Monte Carlo methods, and labor-partitioning schemes for multiprocessors.

OPERATIONS

ENGINEERING DIVISION

An Engineering Division staff of some 700 persons serves as a scientific and technical resource to the Laboratory's major research facilities and programs. An essential component of this engineering effort goes into research on advanced engineering and instrumentation techniques. The Laboratory's research programs rely heavily upon the Division's electronics and mechanical expertise. This expertise includes engineering hardware and software designs, project management, technical support, and prototype shops fabrication.

The Division has developed and nurtured expertise unique to the support of research in the fields of atomic and nuclear physics. Engineering technologies conceived and developed for beam magnets, particle detectors, and nuclear instrumentation have contributed significantly to the success of many Laboratory research programs and are keystones to the future for major research facilities, such as the Advanced Light Source (ALS), and for proposed research in the General Sciences, Biosciences, and Energy Sciences programs of the Laboratory.

Magnet technologies developed by LBL's mechanical engineering personnel have been instrumental in the evolution, worldwide, of today's "new generation" of high-intensity Synchrotron Light Sources and Free Electron Lasers. Mechanical engineering support has also been essential in developing the proof-of-concept superconducting magnets for the Superconducting Super Collider (SSC) accelerator.

Semiconductor detectors of unique design, purity, and volume achievable nowhere else, and instrumentation which achieves the finest resolution yet, are the forte of LBL's electronics engineering personnel. In addition to supporting LBL research programs, this electronics engineering capability has become a resource to universities and agencies throughout the nation for one-of-a-kind semiconductor detector systems. Through publications and direct interactions, many of the concepts developed here have subsequently been adopted and applied by industry.

Large detector systems for high-energy physics and nuclear science are supported by both electronics and mechanical engineering. This is an area where LBL engineering has become a national and even an international resource. The TPC, or Time Projection Chamber, invented by an LBL physicist, was one of the first of these large-volume detector systems. Since the successful construction of this first TPC detector, LBL engineers have collaborated in the construction of follow-on TPC's in Japan, Europe, and the United States.

The Integrated Circuit Design Group within the Engineering Division supports all major detector projects in high-energy physics and nuclear science. High-performance, custom integrated circuits are being designed for detectors for the SSC, the Relativistic Heavy Ion Collider (RHIC) at Brookhaven National Laboratory (BNL), the Collider Detector Facility (CDF), D-Zero Detector and CERN. The group has designed high-speed, low-noise amplifiers, switched-capacitor memories, silicon-detector strips, and pixels instrumentation using CMOS, BIMOS, Bipolar, and GaAs technologies. The work of this group has helped push detector technology to a new level.

LBL has recently entered into a major initiative in the area of instrumentation for biological research as part of the larger Human Genome Program. The Engineering Division is playing a lead role in designing automated procedures for many repetitive biological protocols in addition to participating in the development of advanced instrumentation for biotechnology. This is a rapidly growing field likely to become an important component of the Division's responsibilities in the future.

LBL engineering participated in the design and construction of the Keck Observatory Primary Mirror Support System for the Keck Telescope, the world's largest optical astronomical telescope. Its segmented mirror (36 segments) is 10 m in diameter. Support system design at LBL was composed of mechanical support, active support elements, position sensors, and computers and software to control the mirror. It has performed within design specifications and is a demonstration of how the multidisciplinary engineering effort at LBL can solve difficult problems. LBL will be participating in the design effort for the Keck II telescope.

The Division operates various shop facilities which support the above work as well as supplying technical support directly to the research divisions.

Application of Permanent Magnets
KLAUS HALBACH AND ROSS D. SCHLUETER

It has become more and more important in recent years to produce strong magnetic fields in working volumes that have at least one very small linear dimension. Examples are magnetic lenses in particle accelerators and particle-beam transport systems, and wigglers and undulators for the production of electromagnetic radiation. Unfortunately, the fields obtainable with electromagnets become weaker as magnetically important dimensions become smaller. The reasons for this are practical limits on the current density in coils due to cooling limitations, combined with the saturation properties of soft magnetic materials. Since this current-density limitation does not exist for permanent magnet systems, they will always produce larger fields when critical dimensions are smaller than a value determined by the nature of the wanted field distribution. Using an undulator or wiggler as an example, we find that permanent-magnet insertion devices will generally perform better when the period is below 30 cm. For the case of a quadrupole, the critical aperture radius is on the order of 1 cm.

It is the purpose of this project to bring the permanent-magnet devices developed so far to maturity with regard to field quality and reliability (e.g., it is desirable to have a guarantee that one can cycle an adjustable-strength permanent-magnet quadrupole between two extreme gradients at least 10,000 times). Field quality will be particularly important for the insertion devices needed for the next generation of synchrotron light sources. Consequently, the effect of construction and material tolerances on field quality is being investigated, and improved construction methods are being developed.

In addition, work is proceeding to incorporate permanent-magnet materials into electromagnets in order to make it possible to produce fields with permanent-magnet-assisted electromagnets of the same strength that permanent magnets produce. This work is particularly important for tapered undulators in free-electron lasers, where one needs the combination of permanent-magnet strength and electromagnet variability. In many applications of undulator-produced synchrotron radiation, extremely accurate positioning of the center of the synchrotron radiation pattern is necessary. In order to position the electron beam with corresponding accuracy, one needs to be able to measure its position with equal accuracy. An effort is underway to develop a better understanding of beam position monitors, providing a tool for both better analysis and design of such devices.

SSC Low-Energy Booster Prototype Quadrupole Fabrication

ROBERT FULTON AND MICHAEL MORRISON

LBL's experience in the development and building of specialty electromagnets is being drawn upon to produce a prototype quadrupole magnet for the SSC Low-Energy Booster ring. The magnetic design of this water-cooled copper conductor magnet was developed by LBL Engineering Division personnel. When fabricated, this prototype will validate the SSC's detailed design of the magnet, allow for the design of the required fixturing and act as a test of the planned production and assembly methods.

Semiconductor X-Ray Detectors for Synchrotrons

JOSEPH M. JAKLEVIC

This project focuses on the development of new semiconductor detectors specifically designed for synchrotron applications. Our approach combines existing expertise in semiconductor device fabrication, x-ray analytical measurements, and synchrotron radiation experimentation, and includes a close collaboration with LBL experimenters in the biosciences and in materials research. A primary goal of this effort is the realization of specialized spectrometers which are capable of exploiting the unique properties of synchrotron radiation sources. Initial studies focus on the development of semiconductor detector systems optimized for low-energy photon detection and on detector arrays. An array detector optimized for energy resolution at high count rates is being developed for fluorescence in Extended X-ray Absorption Fine Structure Spectroscopy (EXAFS) applications. An alternative to the array, employing a novel, large-area, low-capacitance design, is also being developed for high-rate fluorescence applications; the latter device is being targeted for application in x-ray microprobe experiments. A comparison of the fundamental differences between Si(Li) and Ge surface barrier x-ray detectors has been completed, and will facilitate the selection of such devices for x-ray fluorescence applications. Much of the work has been, and will continue to be, undertaken in a collaborative mode with synchrotron radiation experimenters who will be able to effectively exploit the new technology for specific applications.

Semiconductor Radiation-Detector Technology
JOSEPH M. JAKLEVIC

The project is designed to perform research and development directed toward the design of radiation detectors and associated pulse-processing electronics. Particular emphasis is placed on semiconductor detector spectrometer systems for use in a variety of applications. The work includes basic detector material studies, development of improved semiconductor devices, and the design of specialized electronic signal-processing techniques. Previous activities in this project have helped establish the foundation for modern detector technology. Recent work has emphasized the importance of radiation damage in semiconductor spectrometers and improved methods for pulse shaping applicable to large-volume gamma-ray detectors. Ongoing studies include the development of noninjecting contacts for segmented detectors, investigations of alternative materials, and fabrication techniques for room temperature detectors and the characterization of silicon drift detectors.

Advanced Detectors for Mass Spectrometry
JOSEPH M. JAKLEVIC, W. HENRY BENNER, AND JOSEPH E. KATZ

The application of mass spectrometry to the separation of macromolecules is currently limited in the maximum size which can be efficiently measured. Future developments directed toward DNA mapping and sequencing using mass spectrometry are seriously affected by this limitation. Although there exist methods for mobilizing and accelerating intact, charged molecular species with a mass of 200,000 daltons, conventional ion detectors are inefficient for these large ions. These detectors rely primarily on the multiplication of secondary electrons generated by high velocity impact of the primary molecular ion—a process which becomes less efficient for heavier molecular ions. We propose to investigate the fundamental parameters which limit the use of secondary electron emission for the efficient detection of large ions, with the goal of extending this approach to the limits of applicability. In addition, we will explore alternative methods for the efficient detection of large molecules. These include hybrid detectors in which the primary ion is used to produce secondary, smaller ions through collision cascades, cryogenic bolometric devices in which the energy of the ion is determined directly without reference to ionization processes, and semiconductor diode detectors in which the thermal spike generated by the heavy-ion impulse is electronically measured. Feasibility studies will be undertaken in each case followed by practical implementation and testing where appropriate. The long-term goal of the project is the design of a mass spectrometer capable of efficient operation in the mass range above 100,000 daltons and optimized for the measurement of large DNA fragments.

High-Energy Physics and Nuclear Science Particle Detectors

RICHARD LAPIERRE, RICHARD C. JARED, ALLAN ARTHUR, AND WILLIAM EDWARDS

The Engineering Division, in support of and in collaboration with the Nuclear Science and Physics Divisions, is heavily involved in large detector projects. Collaborations include a 90,000-channel TPC for CERN, a 150,000-channel TPC for STAR at Brookhaven National Laboratory (BNL) and the Solenoidal Detector Collaboration (SDC) Detector for the Superconducting Super Collider (SSC). LBL Engineering has been involved in these detectors since their inception. We are currently involved in several subsystems, including: Silicon Vertex Tracking and its associated electronics (SDC and STAR), Scintillator Calorimetry and its electronics (SDC), a large TPC and its highly integrated electronics (STAR), and a new large-bore (5-m diam), very thin, superconducting solenoid (STAR). All of these detector systems incorporate unique integrated circuits developed by Engineering's IC design group.

Double-Beta Decay in ^{76}Ge and Dark Matter Detection

ALAN R. SMITH

This project involves the operation of a very low-background detector facility 700 feet under rock at the Oroville Power Dam. The detector array is surrounded by an active scintillation shield to reject scattered gamma rays and a 15-ton lead shield to reduce gamma rays from the walls of the cavern.

Our early experiments focused on detection of rare decays of ^{76}Ge nuclei (in germanium detectors) with simultaneous emission of two electrons and no neutrinos. This experiment has set a lower limit of 10^{24} years for the half-life of the process—a result that can be interpreted in terms of a Majorana neutrino mass less than 1 eV.

The same system is now being used to detect rare collisions of potential dark matter particles and thereby determine the constitution of dark matter in the universe or to eliminate theoretical particles that have been postulated to exist.

Lung Density Determination by Compton Scatter
BILLY LOO

A technique is being explored and tested that uses a radioactive source to irradiate a cylindrical "pipe" of the lung and a small germanium detector with adequate energy resolution to observe the scattered radiation and determine the origin of each scattered photon. Since the scattering rate is proportional to density, this will permit a fast measurement of the density-depth profile of the lung. An instrument based on this principle has been designed and built and is being tested in studies of pulmonary edema.

Application of Statistically Based Algorithms to Emission Tomography
JORGE LLACER

The objective of this research project is the development, evaluation, and initial application of image-reconstruction algorithms for emission tomography based on the knowledge of the statistics of the emission and detection processes and the "a priori" statistical, medical, and perceptual knowledge available at the time of the reconstruction. The work uses as a foundation the results of Maximum Likelihood Estimator (MLE) reconstructions, using the concept of "feasibility" as a necessary condition for image acceptability; a stopping rule based on likelihood cross-validation; and preliminary work on Bayesian methods of reconstruction using Vision Response Functions as the basis for representation of prior knowledge. The research includes work on the following main areas:

- Carrying out critical evaluations of MLE reconstructions from real patient data in Positron Emission Tomography (PET) by means of receiver operating characteristics (ROC) analysis in order to ascertain the diagnostic benefits of the MLE methodology.

- Developing methods of representing anatomical prior knowledge by means of Vision Response Functions (VRFs), which are derived from the way the first level of neurons behind the human retina records information.

- Finding iterative algorithms for the solution of the tomographic reconstruction problem, with Bayesian terms incorporating VRFs.

- Evaluation of the images obtained by Bayesian VRF methods, both analytically and statistically in a clinical environment.

Keck II Active Mirror Control System
RICHARD C. JARED

LBL is undertaking the design of the Keck II Active Mirror Control System (AMCS). This sister to the 10-Meter Keck Telescope will be mounted next to the existing telescope on Mauna Kea, Hawaii. The engineering is a followthrough of the earlier effort in support of a University of California proposal to build a 10-meter-diameter optical telescope and the design and construction of the first Keck Telescope Primary Mirror Support System. The AMCS will control the attitude of each of the 36 segments of the 10-meter primary mirror so as to maintain the desired overall shape of the mirror.

Analysis and Control of Computer Network Congestion
VAN JACOBSON

This project involves both research into the dynamics of computer network performance and the development of applications using the IP protocol over ESNET, and supports DOE's mission to provide fast, simple access to supercomputers and computer communications for DOE scientists and the U.S. scientific community generally.

In the past, there was some conjecture that traffic in wide-area networks would be "random" and thus uncontrollable. Our work has demonstrated that this is not the case: traffic fluctuations are predictable, and large networks have substantial "self-organizing" traffic structure both in time and location. Based on this observation, we developed several network protocol enhancements to minimize congestive behavior. These enhancements have been widely adopted.

Similarly, in the context of today's emerging high-speed networks, there is conjecture about both the adequacy of existing protocols like TCP/IP to inter-operate fast enough to support leading-edge applications and the nature of congestion at internet gateways. These two issues, of course, are intimately related.

The work focuses on extending our earlier modeling and analysis from the endpoints to the interior systems and gateways of the network. In particular, we are developing models and controls to allow a gateway to dynamically estimate its available bandwidth and delay parameters and to allocate resources among different classes of traffic based on administratively determined policies. In addition, since there is some concern that advances in high-speed networking technology may make existing transport protocols, and thus existing congestion control schemes, obsolete, we will analyze whether existing protocols are adequate for future networking technology and, if not, what areas need to be improved. As a major application and demonstration of this research, we are implementing video conferencing using the IP protocol over ESNET.

ENVIRONMENT, HEALTH & SAFETY DIVISION

The Environment, Health and Safety (EH&S) Division is made up of three Departments providing EH&S support to the programmatic divisions at the Laboratory. The Environment Department includes the Site Restoration, Waste Management, and Environmental Protection Groups; the Health Department includes the Medical, Industrial Hygiene, Bioassay and Dosimetry, and Radiation Assessment Groups; and the Safety Department includes the Occupational Safety and Emergency Services Groups. LBL's potential EH&S risks are those characteristic of accelerator operations, shops, a diversity of laboratories for chemical, biological, materials science and technology development, and other facilities support operations. Hazards arise from both radiological and nonradiological activities, and the EH&S Division is equipped to address all areas. The Division monitors air, groundwater, and effluents for both radiation and chemical sources and discharges. EH&S Departments are staffed with both professional and technical experts in their areas of responsibility. The EH&S Division is committed to making the Laboratory a model research and development organization that integrates workplace safety and environmental stewardship with its scientific activities. Laboratory operations will at all times be performed within Laboratory EH&S policies and procedures, developed to comply fully with existing, proposed, and anticipated DOE Orders, Federal laws and regulations, and applicable state and local regulations.

Neutron Monitor for Dose-Equivalent Measurements with a Sensitivity Range from Thermal Neutrons to 1-GeV Neutrons

RAI-KO S. SUN

This project uses low-energy neutrons (with energy levels below 50 MeV) and high-energy neutrons (with energy levels from 100 to 800 Mev) to test a modified Andersson-Braun-type neutron remmeter. A remmeter is an instrument used to measure neutron dose equivalent over a specified energy spectrum. A remmeter is composed of an empirically designed boron sleeve and a proportional counter that uses boron trifluoride as the counting gas, all surrounded by an eight-inch polyethylene cylinder as a moderator. Monoenergetic neutron beams produced by accelerators are used to radiate the moderated BF_3 counter, which produces an approximate tissue-equivalent neutron radiation dose. Current remmeters are only tissue-equivalent to neutron energies of approximately 15 MeV. The limitation of current remmeters, which do not measure dose equivalents above the 15-MeV range, is a significant issue at high-energy accelerators.

The theoretical response of the moderated detector as a function of neutron energy is obtained by means of Monte Carlo calculations, using LAHET and MCNP codes from Los Alamos

National Laboratory. A neutron spectrometer system called "Muffins" was used to determine the detailed neutron spectral and spatial distributional information of the high-energy accelerator beams with energies beyond 100 MeV.

Theoretical Monte Carlo calculations by Birattari et al., using FLUKE and MORSE Monte Carlo codes, predicted that inserting a lead sleeve in a polyethylene moderator would extend its sensitivity range from thermal energies to 400 Mev. We have constructed an Andersson-Braun-type neutron detector with a one-centimeter layer of lead inserted into an otherwise hydrogenous (mostly polyethylene) moderator. The eventual design began with a modification of the Andersson-Braun moderator and a neutron response curve obtained as a function of changing the geometric dimensions and/or materials, using the LAHET and MCNP codes. In the experimental design of the moderator, a cylindrical layer was added to make it easy to change the lead/polyethylene dimensions. The experimental results of this design will be compared with the theoretical results, and adjustments will then be made for a revised design.

The initial response of the experimental detector was studied at two neutron energies: 400-Mev (Au ions at 400 MeV/amu on an Al target) and 1050-MeV (1050 MeV/amu deuterons on a polyethylene target). The results were quite close to the Monte Carlo calculations carried out with the LAHET and MCNP codes for the LBL model. The results are expressed as a relative ratio between standard and lead-modified Andersson-Braun moderators. The initial low-energy neutron-beam experiments were conducted at the 88-Inch Cyclotron, using a 40-MeV proton beam on a lithium target. The latter experiments, conducted in the Cave 4C facility at the 88-Inch Cyclotron, showed a good correlation with the expected ratio of the two moderators.

These studies are particularly significant in verifying the utility of Monte Carlo methods for simulation of a neutron remmeter and, therefore, in the design of new neutron detectors. This will be especially useful when remmeters will have to be modified to accommodate the new dose-response functions recommended by ICRP and ICRU. The development of this extended range remmeter will result in a valuable instrument for Health Physics, Nuclear Science, and High-Energy Physics, and the technology would be available for transfer to the private sector.

INFORMATION & COMPUTING SCIENCES DIVISION

The Information and Computing Sciences Division (ICSD) operates the Laboratory's central computer facilities, its libraries, its telephone and networking systems, its software analysis and training program, its workstation support group, and its technical publishing facilities. The Division also offers writing, editing, word processing, illustrating, photography and conference coordination services to the Laboratory.

Beyond this essential support activity, the Division conducts several leading-edge research programs investigating and developing new data-management techniques suitable for scientific and statistical applications, and developing distributed computing systems to handle the increasing complexity of scientific computation.

The Division has been very active in formulating and supporting the Federal High Performance Computing Program. The Division's role is to promote collaboration among laboratories, universities, and the computing industry in the development of modern scientific software. The software, designed to improve the productivity of scientists, will use high-performance workstations and network connections to powerful computing resources.

The Division is also developing a data-management system for the Human Genome Center that will provide a uniform means of data access and analysis. Ultimately, a sophisticated program must be created for comparing physical map data from different sources and reconciling these with genetic and restriction maps.

The Comprehensive Epidemiologic Data Resource program (CEDR) will integrate and broaden access to the Department of Energy's (DOE) epidemiologic and occupational health information. It is envisioned that CEDR will include health and mortality data on individual DOE workers, as well as census and mortality data on a wide variety of geographic areas. The Division is playing a lead role in developing user requirements and specifying longer-term computer components for CEDR.

The Division is expanding its expertise and technology base in software engineering, adding a capacity to build industrial-grade software and providing a review service for software developed by other groups at the Laboratory. The Advanced Development Group is currently developing software for the SSC Magnet Test Laboratory using advanced software engineering techniques. The distributed data acquisition kernel of this software, a "software bus," is available to all groups at the Laboratory wishing to use it.

A new Imaging Group has been formed to aid Laboratory scientists in devising a variety of techniques to enhance and analyze images with the computer.

Comprehensive Epidemiologic Data Resource
HARVARD HOLMES AND ARIE SHOSHANI

As part of an effort to integrate and broaden access to its epidemiologic and occupational health information, the DOE has established a Comprehensive Epidemiologic Data Resource (CEDR). LBL is playing a lead role in developing user requirements, building a rapid-prototype interim system (pre-CEDR), examining critical data-management issues, and specifying high-level system-design alternatives for CEDR.

As currently envisioned, CEDR will include health and mortality data on individual DOE workers as well as census and mortality data on a wide variety of geographic areas. In the future, CEDR may also serve as the repository for ongoing DOE worker health surveillance and individual-level community epidemiologic data.

The first data available through CEDR are the analysis files from the DOE Health and Mortality studies (about 20 studies) and the intermediate files upon which those studies were based (about 400 MBytes of data). These studies explore the relationships between occupational radiation exposures and mortality outcomes. The datasets have information about individuals' demographic characteristics, radiation exposures, and cause of death. These data are accessed electronically from the CEDR machine located at LBL. Comprehensive on-line documentation is provided to assist users in selecting and understanding datasets of interest.

Printed documentation, tapes, and diskettes of data can be provided.

Information Analysis Techniques: Data-Management Research
ARIE SHOSHANI

The purpose of the Scientific Database Management Research Program is to develop data-management techniques suited to scientific and statistical applications. Because scientific and statistical applications have different requirements from conventional commercial Database Management System applications, new techniques are required to effectively support these applications. The research program is composed of two types of activities: first, the analysis of scientific and statistical data-management applications to identify special requirements and, second, efforts to develop methods that meet these special requirements.

Such requirements arise from the structure and semantics of the data (e.g., sparse multidimensional tables, temporal data) and the operations that need to be performed over them (e.g., transposition, aggregation, random sampling, proximity searches). Accordingly, the research program has proceeded to develop new techniques for the efficient storage organization of the data, new algorithms to access and manipulate the data efficiently, and new data-modeling methods to capture the semantics of scientific data.

Specific research topics have recently included: random sampling from relational databases, temporal data modeling and access methods, optimization of multidimensional storage structures, distributed query optimization, parallel I/O optimization, conceptual database design tools, and translation tools for commercial relational systems.

Populations at Risk to Environmental Pollution (PAREP)

DEANE W. MERRILL AND STEVE SELVIN

The PAREP project focuses on the collection, analysis, and interpretation of data pertaining to relationships between human health and environmental pollution. A major focus of the effort is the development of statistical and computational techniques for the analysis of ecologic summary data, especially small-area geographic data. The availability and completeness of ecologic summary data, together with these techniques, make them useful for quickly investigating alleged departures from expected disease rates, for generating etiologic hypotheses, and for planning clinical trials, case control, or cohort studies.

The PAREP project database forms an important and integral part of the Socio-Economic Environmental Demographic Information System (SEEDIS), which provides access to large quantities of socio-economic data, population counts, environmental data, and other relevant information, along with the tools to integrate, analyze, and display data. SEEDIS now contains the most complete existing collection of on-line numeric data for public-health research. The data from SEEDIS, including new 1990 Census data, are being incorporated into CEDR (described above).

Current research includes the comparison of distance vs. relative risk measures for the analysis of health effects and the further development of the density-equalizing transformation (DEMP) for identification of disease clusters.

High Performance Data Acquisition

DENNIS HALL

The goal of the High Performance Data Acquisition effort is to demonstrate the feasibility of using high-performance, commercial data switches and backplanes in particle detectors. This would significantly reduce the amount of special purpose hardware needed in both the SSC-SDC and the RHIC-STAR detectors. Such usage, if feasible, would represent a major step toward the construction of practical supercomputers that use local area network technology as a backplane. It would also move DOE data-acquisition systems toward higher-performance, more-reliable, lower-cost designs.

Of particular interest are the "event builder" subsystems in these detectors. The task of the event builder is to merge m bytes of fragmented event data from each of n front-end crates into an unfragmented block of event data (containing mn bytes) at a sustained rate of r events per second. Approximate design goals for m, n, and r and desired aggregate bandwidth (mnr) for the two detectors are as follows:

Detector	m (crates)	n (bytes/crate)	r (events/sec)	mnr (bytes/sec)
SSC-SDC	400	2,500	1,000	10^9
RHIC-STAR	20	200,000	10	4×10^7

The principal collaborator for SSC-SDC is Michael Levi. The commercial technologies to be investigated are Fibre Channel, VME enhancements, MCA, and FutureBits+. A test bed will be constructed and the relevant performance parameters measured.

Supercomputer Access Tools

DENNIS HALL AND WILLIAM JOHNSTON

The goal of the Supercomputer Access Tools effort is to increase the research potential of high-performance computing available to Energy Research (ER) scientists. The magnetic field measurements system (MFM) developed during FY 1991 was used to measure SSC quadrupole magnets at LBL and to measure model SSC dipole magnets at Fermilab. Collaborations with industry continue to be explored.

The "software bus" developed for interconnecting MFM software components was selected for feasibility studies that would use a gigabit network for the SSC-SDC and RHIC-STAR "event builders".

Collaborations on detector systems led to a realization that the bus could be used not only as a tool for interconnecting high-performance distributed systems, but also as a principle for organizing and controlling the massive efforts that build particle detector data-analysis software. A major focus of the FY 1993 effort will be extension of the software bus to the domain of particle detector data-analysis software. The principal scientific collaborator for this effort will be Douglas Olson of LBL's Nuclear Science Division.

The LBL distributed video movie system (SCRY) was used as a testbed to investigate new, higher-speed paradigms for IPC, while the University of New Mexico's Khoros system is being investigated as an iconic program builder interface for software bus based imaging and visualization systems. High-speed 3D segmentation and visualization algorithms are also being developed as prototype gigabit network applications.

This effort links directly with the DOE High Performance Computing and Communications program (HPCC).

SUBJECT INDEX

PRINCIPAL INVESTIGATOR INDEX

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