Executive Summary

In response to a December 8, 2000, charge from the Director of the DOE Office of Science Dr. Mildred Dresselhaus (Appendix 1), the DOE Biological and Environmental Research Advisory Committee (BERAC) (Appendix 2) undertook an assessment of the current state of the Office of Biological and Environmental Research (BER) portfolio, including its recent accomplishments and potential. Where appropriate, specific recommendations are made as for directions and/or needs. The Office has three broad program elements that closely couple to DOE missions - life and biological sciences (that includes the genome program), environmental sciences and medical sciences. The BER portfolio includes such efforts as: developing novel uses for energy through research on advanced medical imaging technology and radiopharmaceuticals for diagnosis and treatment; creating new biologically based strategies for cleaning up environmental contamination at former weapons sites; understanding of global climate change needed to predict future energy needs and current impacts of energy use on the ecosystem; developing tools and resources to understand health risks from human exposures to energy-related by-products; and operation of user facilities, tools and resources for the broad biomedical and environmental scientific communities. BERAC finds that BER continues to fund cutting edge, high quality, peer-reviewed science consistent with, and guided by, the recommendations of this Advisory Committee. This research is highly relevant to DOE missions and also supports advances that are of broad importance to the health and well being of our Nation's citizens in a manner that is very complementary to that of the National Institutes of Health (NIH) and the National Science Foundation (NSF).

As articulated in the assessment that follows, the BER research programs require a broad range of specialized scientific facilities. These span a range from the traditional "Bricks and Mortar" facilities through widely distributed environmental field research sites. Included among these are the unique state-of-the-art beamlines and instrumentation to investigate macromolecular structures on the DOE-Basic Energy Sciences (BES) funded synchrotron sources, the Joint Genome Institute's (JGI) Production Sequencing Facility for high throughput DNA sequencing, the Environmental Molecular Sciences Laboratory (EMSL) at Pacific Northwest Laboratory, the new Laboratory for Comparative Genomics at the Oak Ridge National Laboratory (ORNL) (now under construction), and globally distributed facilities including Cloud and Radiation Testbeds for the Atmospheric Radiation Measurement (ARM) program, Free-Air Carbon Dioxide Enrichment facilities and the AmeriFlux Carbon Dioxide flux measurement sites. These facilities collectively serve more than 5000 researchers and provide truly unique resources that are an essential part of the Nation's scientific infrastructure.

Within the framework of this broad research portfolio comes the opportunity to address the next grand challenge in the biological and biomedical sciences that arises from understanding the sequence of the human (and many other) genomes. That is, to answer the question, "how do living things actually function and what factors - genetic, environmental, and others - influence life in positive as well as negative ways?" The researchers, tools and infrastructure supported by the BER program are uniquely

positioned to tackle this problem of enormous complexity that has the potential to profoundly influence our approaches to a range of questions from understanding the risks from low doses of radiation to developing new sources of energy to cleaning up our environment. This proposed new initiative, called “Genomes to Life” is described in detail (see http://www.DOEGenomestoLife.org) and here we simply emphasize the opportunity and how it will build on the strengths of many elements in the BER portfolio.

At the BERAC meeting in Washington, D.C. on December 11-12, 2000, Committee Members discussed the BER program elements, agreed unanimously, and voted upon the following statement as the explicit recommendation to come from this assessment:

“Based on scientific accomplishments, unique intellectual capital and resources, and the promise of new discovery in the BER portfolio (global change, environmental remediation, biomedical and genomics and structural biology research) summarized in this assessment, BERAC urges that DOE seek to:

- Double the budget for the DOE-BER program beginning in FY 2002, continuing for the next 5 years

and within this framework that:

- Increases be used to adequately support core capabilities and facility operations in addition to new initiatives

- $50M per year be allocated beginning in FY 2002 to the new initiative “Genomes to Life”

Further, BERAC lends its strong endorsement and support to the doubling of the DOE Office of Science budget over the next 5 years.”

Introduction

In the following sections, the different elements of the BER program portfolio are considered. In making this assessment, accomplishments were considered as well as future potential and impact within the particular field of science over the coming decade. Where possible, the programs were compared with other activities worldwide. It is important to note that a number of the missions of the BER program are carried out in close cooperation with other Offices in DOE, with other federal agencies, or in an even broader international context. The BERAC Committee recognizes that BER program staff play a crucial role in helping create and maintain these interfaces which are extremely important to leverage the BER investments and significantly extend the impact of BER funded research. In fact, BERAC emphasizes that part of the reason for the success of the program is the visionary leadership provided by program staff and its strong reliance on the principles of peer review. We strongly endorse this approach and stress its value in assuring the most effective utilization of federal research funding.

Genomics - the Human and Microbial Programs

The DOE-BER contribution to the human genome project and to genome science more broadly has been spectacular in spite of the reality that its resources were small compared to those of NIH and the United Kingdom's Wellcome Trust, the principal partners in the publicly funded effort. Not only did BER first have the foresight and vision to recognize the value of the challenge of this bold new venture (which culminated in perhaps one of the greatest accomplishments of the 20th century - the sequencing of the human genome), it developed key technologies necessary for success:

- High-speed capillary electrophoresis was initially developed with BER funding and is now the heart of the state-of-the-art sequencing instruments
- Key enzymes now used universally for DNA sequencing chemistries were engineered
- Key cloning strategies were developed and have been crucial in the assembly of large DNA molecules
- Methods for clone characterization were perfected
- Key gene-finding algorithms and database strategies were developed

In the sequence production phase of the human genome project, the BER has played a major and innovative role.

- Through the pooling of DOE resources in a unique way, the BER-funded JGI has made a major contribution to the human sequence, announced as a success last summer and published in February 2001
- It strongly supported high throughput sequencing of cDNAs – genes themselves

- It promoted and supported sequencing of the first microbial genome, and has provided support for more than one-third of the 70 or so microbial sequences now near completion
- It was a major player in completing the sequence of the genome of Drosophila (the fruit fly), a very important model species
- In addition DOE-BER has lead the way in developing some of the best approaches to scaling up for high throughput genomic initiatives. The JGI in close cooperation with other national laboratory and university groups will continue to be major contributors to the ongoing analysis of additional genomes for the next phase – Bringing the Genome to Life project

BERAC finds that through BER projects and research support, efforts are well along to developing key technologies for the next phase of the genome project that will focus on understanding the structure, function and higher-level organization of complex biological systems. Methodologies include very advanced mass spectrometric methods for proteome analysis, advanced computational methodologies and new approaches for imaging.

The genome effort has set a very substantial foundation for pursuit of specific DOE missions. The accumulated microbial genome sequences are the crucial raw material for taking advantage of biology to develop novel new methods for dealing with toxic clean up problems, with carbon sequestration and with global warming. In addition the genome information opens many opportunities for commercialization of biologically engineered new products in both a safe and economically effective manner.

Notable throughout these early years of genome science has been the close collaboration between the DOE and other federal agencies. The BER's JGI is one of the five laboratories – including three supported by NIH and the Sanger lab funded by the Wellcome Trust – that play major roles in the public human genome sequencing effort. The so-called "G5" group worked closely together to share ways to increase high throughput sequencing with a minimum of overlapping effort. This resulted in finishing of the human genome sequence ahead of schedule, helped specifically by the DOE effort. Cooperation on microbial genome sequencing with NSF, the U.S. Department of Agriculture (USDA) and NIH has maximized the resource value. The effort of each federal agency has been maximized through cooperative ventures and agreements. This has not always been easy, but the success is clear.

Overall, BERAC finds that the DOE genome effort is excellent science, providing a model for success of future DOE life science endeavors and serving DOE missions exceptionally well. It is world class and competitive with that of any other similar effort internationally. It takes advantage of the unique capabilities of the DOE laboratories and effectively engages academic science in pursuit of the broad programmatic goals established in partnership with other agencies. This program is indeed a model of success of which the whole DOE, indeed the whole Nation's scientific enterprise, should look for how to effectively manage a complex endeavor and to coordinate its efforts within a much broader National framework.

Structural Biology Program

The BER structural biology program has two major elements - user station development / operation and research. The former element is essential to making DOE's major national user facilities widely available to researchers in structural biology. The most important of these facilities are the Department's four synchrotron light sources and two neutron beam facilities. The latter program element focuses on research in instrumentation intended to improve the usefulness of these facilities and on experimental and computational structural biology projects that are enabling progress in mission areas within the BER program. The instrumentation research component places emphasis on new detectors, and provides funding essential to the development of the next generation of detectors beyond the charge-coupled detectors widely used today in synchrotron radiation (SR) x-ray crystallography. The experimental and computational research component was recently redirected. A new set of projects was initiated at the start of Fiscal Year 2001 that address questions relevant to the low-dose radiation research program or the Natural and Accelerated Bioremediation Research (NABIR) program (see section on bioremediation program). The structural biology program also provides funding for the Protein Data Bank in cooperation with the NIH and NSF. The remainder of this discussion will be devoted to the facilities-related portion of the program that accounts for three-fourths of the BER budget in structural biology in FY 2001.

Synchrotron radiation has enabled a remarkable evolution in structural molecular biology (SMB) techniques and science that utilize x-rays over the past 10 years. The availability of reliable and sustainable access to synchrotron beams, coupled with advances in beam lines and x-ray optics, detectors, computational power and software, have transformed SR-based SMB experiments from being a heroic effort limited to a few pioneers in the 1980's into a technique with great breadth and depth across a wide range of basic and applied biomedical sciences. BER has, and continues to play, a very central and pivotal role in designing, building and operating user facilities at all four of the DOE-BES operated synchrotron centers. Through these user facilities, scientists are provided the specialized infrastructure, training and support for their experiments (NIH and a few other private entities also provide such resources, but DOE-BER is the largest single supporter of these efforts).

The increased utilization, productivity and impact over the past decade have been nothing short of remarkable. Since 1993, the number of scientists using the four DOE synchrotrons for structural biology research has more than tripled (>2000 per year) and the productivity as measured by new results of protein structures has increased by at least seven-fold. Between January and November of 2000, results from the four DOE synchrotron facilities accounted for 51 percent of the world's total productivity in protein structure determination as judged by publications in seven high impact journals. Collectively, they set a world class standard.

These DOE-BER funded SR user facilities (infrastructure, resources, technology development and user support) are absolutely critical for addressing problems at the cutting edge of the biological sciences in this millennium. They are essential resources for forefront research in areas ranging from fundamental biology of the complex macromolecular machines of the cell to drug discovery enabled by study of structure of integral membrane proteins that are key targets for new drugs. These BER-operated user facilities provide the foundation upon which new initiatives in the post-sequence genome era like structural genomics will be based. They will have a direct and significant impact on BER initiatives and core research, including DNA repair and low dose radiation effects, microbial cell function, bioremediation and more broadly the new Genomes to Life initiative. It is essential that BER be provided the means to continue to effectively support the operation of these resources, expanding capacity as appropriate and needed and investing in instrumentation upgrades that are necessary to maximize productivity, advance capability and maintain international competitiveness.

The BER program has under development two experimental stations at DOE neutron facilities that will provide information complementary to that from the x-ray studies, notably the shape and composition of assemblies of biological macromolecules. In recent years, there has been only very limited access to such facilities in the United States, causing serious difficulties for the user community. The two new stations promise to offer capabilities equal to the best in the world and BER will remain the primary source of support in the U.S. making this technology available to the user community. It is important to recognize that budgetary resources need to be provided for operations when the new stations are completed.

Global Change Program

The DOE-BER program has a long history of making significant contributions to basic environmental research, including the improved understanding of energy related impacts on air quality, climate, and ecological systems. DOE is the third largest contributor to the U.S. Global Change Research Program (USGCRP) budget following the National Aeronautics and Space Administration (NASA) and NSF. It has taken the lead Federal role in several key areas. There is increasing concern about mankind causing changes in the climate system. BER has taken a leadership role in improving scientific knowledge about the carbon cycle, the role of clouds and radiation in the climate system, and in building state of art climate models that can be used for climate prediction. The Intergovernmental Panel on Climate Change (IPCC) recently released its Third Assessment Report. This assessment states that mankind is changing the earth system in many different ways and the changes will increase in the 21st century. These changes make it imperative that policy decisions about the environment must be based on credible scientific information and predictions. A complete, in depth review of the DOE Global Change program will be conducted in March 2001 by a subcommittee of BERAC in which a more detailed set of recommendations will be provided. The results of our assessment prepared for the current BERAC report are given below and provide a more general outlook for the detailed evaluation that will follow:

Facility Support. Environmental research requires facilities and interdisciplinary teams of scientists who are supported at DOE laboratories and universities. The tools required are computational resources, distributed field facilities for environmental process studies and observations of changes in environmental variables. The issue of support for building, operating, upgrading, and maintaining these facilities is a major problem for DOE's environmental research program because of the current need to rely on research funds to support it. In our judgement, this is a broad issue that must be addressed in the larger BER context.

Scientific Support. Listed below are several specific areas that BERAC has specifically considered where the BER program has had an important role and that we believe will need special emphasis over the next few years:

1. The DOE-BER has taken on a Federal and world leadership role in establishing unique capabilities to address the role of clouds and radiation on the climate system by designing and building an elaborate ground measurement system as part of the ARM program. There is one major site and two additional smaller measurement sites. The cloud and radiation measurements are especially important for understanding how the climate system responds to changes in radiation forcing due to an increasing concentration of greenhouse gases and aerosols in the atmosphere. Research from the ARM program has provided much deeper insights into the complex interactions between solar and terrestrial radiation and its interactions with clouds. This new information has led to improvements of radiative aspects of climate models. This measurement capability must be maintained and enhanced since no other such work is being done either in the U.S. or abroad. The unmanned aerial vehicle (UAV) program has given the DOE a unique capability to carry out measurements in conjunction with ARM that are a valuable addition to ground based and satellite measurements.

2. The DOE-BER has been a world leader in carbon cycle research and has taken the lead in quantifying the magnitude and variation of carbon uptake by terrestrial ecosystems. Because of the role that carbon dioxide plays as a climate change forcing variable, it is mandatory that we have a better understanding of the complete carbon cycle. This research builds the groundwork on which carbon related energy policies are based. As a result of DOE research over the last few years, there has been substantial improvement in our understanding of the sources and sinks of carbon both regionally and globally. Without such information, it will be impossible to arrive at scientifically sound evaluations of costs and benefits of alternative policy options for addressing the climate change problem. In a related aspect of environmental research, we recommend that the DOE continue to support research to develop approaches for enhancing carbon sequestration and disposal in terrestrial and ocean ecosystems and to understand their environmental consequences. Both the carbon cycle research and the carbon sequestration research must be regarded as high priority.

3. The DOE-BER has been a long-time leader in ecosystem research, especially in areas of how terrestrial organisms and ecosystems respond to changes in climate and atmospheric composition, and the role that biological and ecological processes play in controlling observed responses. The unique experimental research supported by this program has provided much improved understanding of how terrestrial ecosystems

respond to various environmental changes. In order to make progress in this area there must be an expansion of long-term, distributed field studies combined with well-calibrated measurement systems, as well as data archiving and retrieval systems. We strongly urge continuation and enhancements of this program within the DOE research program, including support for distributed field facilities necessary for such research.

4. The DOE-BER has become a Federal government leader in the development of state-of-the-art climate models focused on prediction of the climate system on time scales of decades to centuries. Using its computational capabilities vested in the national laboratories and the scientific expertise of these labs plus the academic community, new and improved climate models are being developed and used to estimate energy related impacts on the environment. This activity must be enhanced to take advantage of new developments in computational science, especially with regard to using new generation high-performance supercomputers. The recently released IPCC report states "Confidence in the ability of models to project future climate has increased." Also, DOE supported climate models have shown a global and regional pattern of global surface warming from the 1870's to the present that is close to the observed changes. These new generation models do not have artificial adjustments of fluxes and the models give realistic monsoon, El Nino-La Nina, and North Atlantic and Arctic Oscillations patterns. Thus the models are capable of reproducing much of the observed regional climate variability patterns. New research over the next 5 years will be conducted as a partnership with the Office of Science's "Scientific Discovery through Advanced Computing" plan that provides the computational resources. With increased national and international concern about climate change and the need to understand the climate system, this program must be retained at a high priority level.

5. The integrated assessment (IA) activities supported by DOE-BER are a small but important societal component of a comprehensive climate research program. The objective of IA is to evaluate interactions between all components of the climate system, including human socio-economic systems. Causes of climate change, such as increasing greenhouse gases, are analyzed to assess impacts on society and the environment such as the economic cost of reducing greenhouse gas emissions. More specifically, assessments are made of technological innovation and diffusion and its use with emphasis on carbon emissions, greenhouse gases other than carbon dioxide, carbon sinks and land use changes, and carbon sequestration. This program provides an important link between policy makers, climate science, and economics. DOE is the primary supporter of such vital and important activities within the federal USGCRP. The program supports research that allows policy analysts to answer questions such as: if action were to be taken to reduce anticipated climate change, what options would be most cost-effective? What benefits would be expected?

The DOE has been a research leader in the broad area of atmospheric processes that control the transport, transformation, and fate of energy related chemicals and particulate matter. These processes cover regional, national, and global aspects of air quality and climate change. The results have important implications to energy policies. This comprehensive program covers improving understanding of air pollution by sulfur and nitrogen oxides and tropospheric ozone. Dispersion of energy-related chemicals and particulates, and the developments of predictive models is a major component of the program. The national laboratories and the academic community are involved in the research. Special emphasis is on atmospheric chemistry and meteorology. Program accomplishments include improved UV measurements, radiative (solar and long-wave) measurements both of chemical compounds and aerosols, and measurement of air quality. This program is at the core of many of the energy related science issues found only in DOE.

Environmental Molecular Sciences Laboratory (EMSL)

The EMSL is still a rather young laboratory, dedicated only in October 1997. It is a National user facility funded and operated by BER. In its short lifetime, EMSL has had a significant impact by providing a unique suite of research tools to investigate molecular interactions of importance to DOE and the broader scientific user community. EMSL provides world-class research capabilities for conducting both experimental and theoretical fundamental investigations at the molecular to meso-scale. This work is highly relevant to DOE missions broadly and specifically within the purview of Office of Science interests. The featured research tools are precisely those needed to address major complex problems such as post-genomic biology, nanoscience, and technology and environmental sciences. EMSL also provides unique educational opportunities for students and postdoctoral fellows who comprise the next generation of researchers in the molecular sciences.

EMSL has made an impressive start, becoming well known to the science community. Its success rests on hiring good on-site scientists, acquiring and developing state-of-the-art instrumentation, and encouraging others to come use this facility. In spite of its somewhat remote location, EMSL receives high marks as a national user facility. It is a user-friendly laboratory, which is important, but it benefits primarily from providing ready access to a broad range of sophisticated research tools so critical in today's multidisciplinary approach to science. EMSL accomplishments of particular importance to BER and the broader community interests include:

- ***Molecular Science Computing Facility (MSCF)*** - providing high-performance, massively parallel computer systems and software supports research on chemical and biological systems, aerosol formation, subsurface science and regional climate models as well as critical support to EMSL experimental science
- ***Mass spectrometry*** - providing essential tools for characterizing proteomes, as described in the proposed new BER initiative, *Genomes to Life.* The systems approach taken by EMSL's mass spectrometry facility to address the problem of identifying and measuring the relative abundance of expressed proteins is orders of magnitude faster and orders of magnitude more sensitive than the most advanced mass spectrometry methods available commercially

- ***High Field Nuclear Magnetic Resonance (NMR) Facility*** - is the largest NMR facility of its kind in the U.S., and will be one of the first to receive a 900 MHz NMR (being delivered in mid-2001), the most powerful being built
- ***Bioinformatics*** - addressing/enhancing high throughput analytical approaches requiring real-time access to extensive libraries of data - e.g., in EMSL's proteomics by mass spectrometry effort
- ***Spectroscopic and surface analysis instrumentation*** - featuring scanning probe microscopies, ultrafast and nonlinear optical spectroscopies and probes, enabling investigation of nano-structures and their properties
- ***Instrumentation Development*** - fabricating one-of-a-kind instrumentation and extensively modifying existing instruments

The true measure of a laboratory is how it competes on the national and international level. Three examples of EMSL's leadership: (1) currently the most extensive suite of NMR instruments in the world, at least until the Japanese NMR "farm" in Yokohama comes on line. EMSL will have the highest field NMR as of this summer; (2) currently the highest resolution Fourier Transform mass spectrometer in existence, coupling this with a broad systems approach to the measurement of proteins; and (3) unique marriage of spectroscopic approaches, combining NMR with optical and laser spectroscopies to investigate cellular processes spatially and dynamically. In terms of weaknesses, EMSL suffers from a less-than-central location, making travel for on-site collaboration time consuming and expensive. And like other national labs, it must enforce some security levels that complicate interactions with foreign nationals.

EMSL has the opportunity to play an important role in where BER programs are heading. Tools that will be required for success in "big science" (e.g., high capacity computing, cutting edge spectroscopies, etc.) are currently in place or being developed at EMSL. For example, the 900 MHz NMR will provide enhanced resolution in addressing important problems in functional genomics (i.e., mechanisms of DNA damage recognition and repair). The massively parallel computer systems at EMSL will provide needed modeling capability for a wide range of BER (and international) interests, such as climate, aerosols, and biological structures. Leadership in mass spectrometry will be a key to unraveling the proteomics challenge. Automation of these methods, coupled with advances in bioinformatics being addressed in parallel to this effort, offers the opportunity for a major breakthrough in molecular biology. First demonstrated for the highly radiation resistant *Deinococcus radiodurans* microbe, this methodology can rapidly be expanded to microbial research of special interest to BER. With an expanded effort it can be extended to more complex proteomes, including human cells, with the potential of enormous benefit to human health.

EMSL is still a new lab without the aging infrastructure typical of many of the other DOE Office of Science facilities. Instrumentation typically has a 5-10 year lifetime, so replacement is not yet a critical budget need. However, there is one outstanding exception: the effective lifetime of large computer systems. Three-four years seems to be the outside time for obsolescence and the need to upgrade. Arguably the most advanced chemical sciences computing facility at the time EMSL was established, this part of the resource is no longer at the cutting edge and should be renewed very soon if EMSL is to sustain its leadership role as a molecular sciences user facility.

Bioremediation Research Program

DOE's environmental remediation research under BER is unique in that it is the only government program that focuses on basic research to underpin and advance the science needed for more effective cleanup of environmental pollutants, especially those resulting from past DOE activities. Remediation of environmental contaminants is among the most complex technical challenges facing society and requires basic research to provide the information to make wise decisions for solutions for other than the simplest problems. DOE's problems of mixed wastes in a variety of subsurface environments are among the most complex challenges. To attack this problem, DOE developed the Natural and Accelerated Bioremediation Research Program (NABIR) organized around seven fundamental research areas needed to meet the challenge.

In the past three years, the NABIR program has built a strong science base to understand the potential for bioremediation of metals and radionuclides. Many of those studies have been laboratory based, using contaminated sediments and soils from DOE sites. With the initiation of the Field Research Center at ORNL in 2000, the program can now move into an exciting new phase: Field scale hypothesis testing. The past difficulties of extrapolating data from bench-scale studies to field scale problems at DOE sites can be overcome by conducting controlled experiments at a uranium contaminated site in Bear Creek Valley, ORNL.

The Field Research Center represents a unique facility in remediation research where DOE and academic investigators with different expertise and from many locations can conduct integrated research on a complex problem as it occurs in nature. DOE's unique instrumentation and methodologies are also important for providing mechanistic understanding of the behavior of metals and radionuclides in their natural geological matrices.

Since the inception of the full program in 1997, the NABIR program has produced over 140 publications in peer reviewed journals including three in *Science*, and one in *Nature*. NABIR researchers have been invited to present their results at major meetings in the field including the American Society of Microbiology, the International Symposium on Subsurface Microbiology, and the International Society of Microbial Ecology, to name a few. The program has attracted many of the leaders in the field of environmental microbiology.

At DOE facilities, contaminants in groundwater are dominated by metals and radionuclides; more than 60 percent of the sites have these types of contaminants. Metals and radionuclides are also the largest class of contaminants in soils and sediments at DOE waste sites; they are found at about 40 percent of the sites surveyed. Common metal and radionuclide contaminants include uranium, technetium, plutonium, chromium and mercury. Bioremediation of these DOE relevant contaminants is the focus of NABIR research.

The NABIR program is carefully coordinated with science and technology programs of other agencies including the Environmental Protection Agency (EPA), Department of Defense, USDA, NSF, the Strategic Environmental Research and Development Program (SERDP) and others. This coordination occurs through the active participation of DOE program managers in the Interagency Working Group on Environmental Biotechnology and the Cleanup-Technical Thrust Area Working Group of SERDP. Furthermore, NABIR has a Science Advisory Subcommittee under BERAC that has representatives from the Office of Naval Research, EPA's Hazardous Substance Research Centers, and DOE's Environmental Management program. The NABIR program is unique among bioremediation research programs with its focus on metals and radionuclides. No other agency is addressing or plans to address the problem of radionuclide contamination.

Low Dose Radiation Research Program - Science Supporting Radiation Risk Policy

The Department of Energy has recently developed a basic science program, currently funded at $20.3 million in FY 2001, to support peer-reviewed research directed toward understanding the risks to people from exposure to low-dose, low-dose-rate, low-linear energy transfer (LET) radiation. The information generated by this program is intended to provide a scientific base that underpins the development of future radiation risk regulatory policy. This research is important since most of the projected non-medical, man-made radiation exposures over the next 100 years will be from waste clean-up and environmental isolation of materials associated with nuclear weapons production and will be in the form of low-LET radiation delivered at low doses and low dose-rates. In this program, low dose is defined as less than twice the occupational limit of 0.10 Gy or 10,000 mrem. This is, of course close to the limit of detection of biological change, but is much higher than the 300 mrem received annually from background and the level of exposure associated with radiation protection standards for the public.

The Low Dose Radiation Research Program builds on recent advances in both technology and biology. Application of new cellular and molecular biology techniques to the low dose problem represents a major highlight of the Program. Techniques such as gene sequencing, gene chip technology, modern DNA repair methodologies and other cellular and molecular approaches are being used to define the mechanisms involved in radiation-induced alterations after low-dose exposures.

After exposure to high levels of radiation or other environmental insults there is no question that diseases such as cancer can be produced. However, at occupational or environmental levels of concern for regulation, there is little direct evidence for adverse health effects from radiation exposure. Thus, scientists and regulators are required to extrapolate the effects observed at high doses to inferred effects at low doses. This is typically done using linear exposure-response models. The current research will develop information on the mechanisms of radiation-induced biological effects to support or refute these extrapolations and the risk estimates for low doses derived from them. Current research projects are focused on understanding the biological responses at low radiation doses and determining the role of early biological changes, such as alterations in gene expression, genomic instability and effects on neighboring cells, in the development of radiation-induced disease. Forty-six projects are funded by the program at universities (23 projects), research institutions (5 projects) and DOE National Laboratories (18 projects).

The major research areas funded in the program are: (1) Technology and Tool Development; (2) Biological Research; (3) Modeling; and (4) Communication.

One example of the use of new technology to address the low-dose problem has been the development of microbeams. Microbeams are being developed using low-LET radiation. Such machines will be useful in addressing the problems associated with understanding the biological effects of small numbers of cells and even specific regions within cells exposed to low doses of low-LET radiation.

Using new biological techniques, scientists in this program are now able to evaluate biological changes at levels of radiation exposure and biological organization that previously were not measurable. By increasing the understanding of the influence of low doses of radiation on human health risk, scientists may help determine if low doses of radiation pose a greater or lesser health risk than currently assumed. Such research may result in major paradigm shifts in radiation protection and biology.

An important part of this research is to determine if the initial damage induced by radiation is similar to or different from damage induced by normal endogenous processes or damage induced by high doses. The construction and use of gene chip technology, using radiation-induced genes involved in either DNA repair or cell death, has provided information on gene activation as a function of dose, dose rate and time after exposure. The research has demonstrated that many of the genes induced after high doses were different from those induced after low doses suggesting different mechanisms of action. Gene-chip studies provide additional data that suggest the need to reconsider the linear extrapolation of risk from high doses to the low dose region. Research on cell and matrix interactions have demonstrated that following radiation exposure the microenvironment can regulate cell phenotype and tissue function. It was suggested that the total response may not be the sum of the individual cellular responses and supports the tissue theory of cancer, which could impact the shape of the dose response curve at low doses.

For science to impact policy, it is necessary for the data to be evaluated and incorporated into understandable and validated models. As the models are developed, it is likewise important to convey the information and implications of the models to the decision-makers and regulators. This is being done through close interaction between the DOE and regulatory agencies such as the EPA and Nuclear Regulatory Commission. Research is needed to move from recognition of the hazardous nature of radiation (the ability to cause injury without regard to dose) to risk which takes into account exposure (dose). This is ultimately needed to address the question of "how low is low enough?" in remediation or clean up activities. The importance of relating these exposures to background levels of radiation and cancer is essential to put risk in perspective. Continued review of the dose-response relationships for the induction of biological changes at low doses is important in light of new data being developed in this program.

Communication, education and public outreach are important elements of this research program, since it is essential that scientific advances generated in this program be conveyed to the scientific community, policy makers and the general public in a timely manner. The program has developed an effective web site for exchange of information about the research program and about radiation in general. The web site (http://www.lowdose.org) has grown considerably in its first year of operation and is now receiving more than 60,000 hits per month from nearly 2000 unique visitors, respectable numbers given its narrow focus.

At this early stage of the program, what the science will tell us is unknown. The data may support the current standards or suggest that changes are required. All levels of exposure are of regulatory concern. However, if levels of exposure exist below which there is no evidence of biological damage these exposure levels may be used to help define areas that are below the level of regulatory action. On the other hand, the research may suggest that even stricter control of radiation exposure is required. Research may demonstrate that there are sub-populations sensitive to low doses of radiation or that low doses of radiation induce changes such as genomic instability that pre-dispose individuals to injury from other agents. Regardless of the research outcome, it is essential that the regulations for clean-up standards and appropriate radiation protection practices be founded on the best science possible. This represents the ultimate goals of the program.

The program has an advisory committee that is a subcommittee of the BERAC to provide independent scientific input. The program has effective links with other Federal radiation research programs as well as with similar programs internationally. The DOE Low Dose Radiation Research Program is unique in its focus and is considered the lead program in this area in the U.S. and internationally.

Overall, the program has gotten off to an excellent start and is funding a number of scientifically sound and important projects. It has issued two new solicitations that will result in the critical review and likely turnover of some of the projects that were initially funded as well as attracting new investigators to the program. On the recommendation of the program advisory committee, one of the new solicitations is for modeling pilot projects that should help strengthen this important component of the program considerably. Major effort will be directed to integrating the experimental and modeling efforts recognizing that models are a key bridge to regulatory analysis.

This is a strong and important research program that will make useful contributions to DOE's mission needs in environmental cleanup and worker and public protection from radiation risks. Moreover, it will help improve the science base for national debate on how to address potential risks of low-level exposure to radiation as well as other agents.

To have the greatest impact, it is essential that the program engage members of the regulatory community to better identify their needs that could be addressed by future research and to make them fully aware of the research that is being supported.

Molecular Nuclear Medicine Program

The BER Medical Sciences Nuclear Medicine Program carries out radiopharmaceutical and radiation detector imaging research that provides the scientific and technological foundation for the use of radioisotopes in a broad range of diagnostic and therapeutic applications. The BER Medical Sciences Nuclear Medicine Program laid the foundations for the establishment of nuclear medicine as a major clinical specialty. Major nuclear medicine program contributions include the establishment of: (1) technetium-99m-labeled pharmaceuticals, now the cornerstones of clinical nuclear medicine; (2) the radiopharmaceutical MIBG, a powerful tool to both visualize and treat deadly neuroblastoma tumors in children; (3) fluorine-18-deoxyglucose (FDG), the most widely used positron emission tomography (PET) radiotracer in PET metabolic imaging for clinical diagnosis; and (4) the gamma camera and the positron emission tomograph. Millions of nuclear medicine procedures are now performed annually throughout the world. As examples, nuclear medicine today routinely diagnoses cancer metastases, localizes infections, and assesses heart and lung performance.

New molecular radiotracers and biological MicroPET imaging technologies developed through the Nuclear Medicine Program are bringing revolutionary changes to molecular nuclear medicine: these high precision guiding tools permit previously unimaginable insights into brain and heart physiology and pathophysiology, providing improved diagnosis and treatment of patients with diverse illnesses such as cancer, Alzheimer's disease, and coronary artery disease. New fluorine-18-labeled guanine acyclonucleoside, deoxyuridine, and dopamine-receptor binding PET reporter probes have been developed to imaging gene expression in animals in real-time. The pioneering research on mapping dopamine brain biochemistry related to cocaine abuse, alcoholism, cigarette smoking and addiction treatment (published in *Time Magazine* and top scientific journals including *Nature*) is already influencing medical science around the world. The BER Nuclear Medicine Program is recognized for its research in the development and application of new radiotracers to understand the biology of neurological and psychiatric disorders, particularly addiction and aging, and for its research on imaging gene function in vivo.

BER developed the original detection systems for PET used today by more than 260 centers around the world. The Program has developed miniaturized PET devices to visualize the molecular biology of disease in living systems, such as human breast and prostate organs, as well as whole small animals. The new MicroPET, a small instrument with the extraordinary capacity for PET imaging of small animals, will be invaluable for tracking metabolic functions over a period of time in a living animal, enabling (for example) repeated experiments in the same animal without having to sacrifice the animal.

Advanced Imaging Technology

The development of radionuclides and radiopharmaceuticals that are useful in medicine is an essential mission of the DOE. This expertise in radiopharmaceuticals prompted BER supported engineers, physicists and computational scientists, primarily at the National Laboratories, to initiate programs to construct instrumentation to detect the distribution and localization of radiotracers within the body. BER programs have generated a remarkable list of technologies that have become the critical instrumentation in nuclear medicine worldwide. These include: the rectilinear scanner, the gamma camera, the CCD camera, the computational capacity to make cross-sectional imaging, and the PET and micro-PET imaging systems.

During the past two decades the DOE Laboratories have developed extraordinary expertise in other advanced imaging technologies including medical applications of synchrotron light sources, lasers, MRI detection systems using high field magnets and advanced multimodality biophotonic systems for disease detection. The BER laser program has been prominent nationally with the establishment of " Centers of Excellence in Laser Medicine", which are collaborative relationships between the National Laboratories and the University of California, Davis, City University of New York, The University of California, Irvine and the Sheppens Eye Research Institute in Boston.

The current program in innovative imaging technologies focuses on multi-intuitional, DOE Laboratory-University collaborations in developing technology that will have a "high impact" in biomedicine.

Research areas of exceptional merit that are ongoing in this program include the following:

1. Construction of an artificial retina. A collaboration between Johns Hopkins Medical Center and five National Laboratories is dedicated to the construction of a microelectronic implantable chip that would convert visual information into an electrical stimulation pattern that would be transmitted to retinal neurons. It is envisioned that this device would be of benefit to individuals suffering from the major causes of blindness in the United States.
2. Development of compact imaging devices for the early diagnosis of cancer. Investigators at Lawrence Berkeley National Laboratory, Thomas Jefferson National Laboratory, Oak Ridge National Laboratory and industrial partners are constructing a new generation of compact, high spatial resolution PET and SPECT cameras for more accurate diagnosis of cancer, particularly breast cancer.
3. Development of PET and MRI instrumentation capable of imaging an awake animal. The formidable challenge of performing functional images on moving animals necessitates that design of novel dipole magnets, fiber-optic arrays and the construction of algorithms to detect and correct for motion during image acquisition.

The advanced imaging technology program works closely with other Federal Agencies, especially the NIH and the NIH Clinical Center, to help coordinate and focus the research efforts at the National Laboratories. This includes interaction with the intramural and extramural research programs at NIH and participation on the the DOE/NIH Steering Committee that functions to rapidly exploit basic DOE technology through the intramural program of the NIH. The DOE is recognized as the Federal Agency with a primary mission in supporting the basic sciences of physics, chemistry, computation and engineering and it is widely acknowledged that many of the advances at the National Laboratories will have a significant impact on biomedicine.

Boron Neutron Capture Therapy (BNCT)

Boron Neutron Capture Therapy (BNCT) is an experimental approach to cancer therapy using neutron irradiation of sensitized tumor cells. BER funded Phase I clinical trials of BNCT have been completed successfully at both BNL and at the joint Harvard-MIT program. Each research center was able to define for its respective neutron beam an approximate upper limit for the neutron dose that can be safely administered to normal tissues. Intensive efforts are directed at completing the collection of follow-up data for scientific publications. The results of these trials will have a major impact on the design and execution of any future Phase I or Phase II trials.

BER has initiated steps for an orderly transfer of its clinical BNCT program to the National Cancer Institute (NCI). A series of meetings with NCI's radiation oncology staff and a joint DOE-NCI workshop have explored mechanisms for greater NIH support of both clinical and basic research involving BNCT. These actions respond directly to specific recommendations made by a BERAC subcommittee that was commissioned to review DOE's BNCT program (http://www.sc.doe.gov/ober/berac/bnctfnl1199.html) and again illustrate the responsiveness of BER program staff to recommendations coming from advisory and peer review.

BER continues to support boron compound development. Most BNCT researchers have identified the weak link in past and future clinical trials of BNCT as the lack of a superior non-toxic boron-containing compound with high tumor-seeking capability. BER is currently directing its BNCT research funding to this crucial issue.

Superior Neutron Source for Medical Applications. BNCT requires a suitable epithermal neutron beam to irradiate tumors that have been selectively sensitized to neutron radiation by enriched boron compounds. A landmark achievement in the development of a superior epithermal neutron beam has been achieved with DOE support at MIT in Boston with the world's first successful installation of a fission beam converter. The modification of the MIT reactor was designed to boost the reactor's externally directed beam intensity by more than one order of magnitude. Preliminary measurements are in close accord with design goals and demonstrate conclusively the feasibility of using fission beam converters for this purpose. The MIT reactor now features the best flux and beam composition characteristics available in the world for BNCT. It is the only U.S. facility currently suitable for clinical trials with cancer patients.

Appendix 1 – Charge letter from the Director of the DOE Office of Science

December 8, 2000

Dr. Keith O. Hodgson
Director, Stanford Synchrotron Radiation Laboratory
Department of Chemistry
Stanford University
Stanford, CA 94305

Dear Dr. Hodgson:

The Office of Science is currently developing its priorities for the FY 2002 budget. It is important that we do this with an understanding of the strengths of our current programs and of the role that they play in the broader scientific community. I would, therefore, like BERAC's views on several key questions regarding the BER program.

First, what is the overall quality of the BER program, its various subdiscipline areas, and its facilities, relative to the best-in-class science in the U.S. and internationally?

Second, how does the research and facilities funded by BER relate and contribute to Departmental mission needs?

Third, how does the BER program interface with and complement other programs across the Federal government? It would be very helpful if BERAC would provide specific examples of interagency interactions across the BER program, including an evaluation of the importance and success of these interactions.

Finally, how would BERAC prioritize the new scientific opportunities within the purview of the BER program?

At a minimum, please include the following programs (and any others that you think should be singled out) in your evaluation: genomics – human and microbial; structural biology; low dose radiation research; global change; bioremediation; molecular nuclear medicine; biomedical engineering; carbon sequestration; and the Environmental and Molecular Sciences Laboratory.

A letter report by early January would be most helpful.

Sincerely,

Mildred S. Dresselhaus
Director
Office of Science

Appendix 2 – BERAC Membership

Chair, BERAC
Dr. Keith O. Hodgson
Stanford University

Dr. Eugene W. Bierly
American Geophysical Union

Dr. David R. Burgess
Boston College

Dr. Carlos J. Bustamante
University of California, Berkeley

Curt I. Civin, M.D.
Johns Hopkins Hospital

Dr. Claire M. Fraser
The Institute for Genomic Research

Dr. Raymond F. Gesteland
University of Utah

Dr. Jonathan Greer
Abbott Laboratories

Dr. Richard E. Hallgren
American Meteorological Society

Dr. Williard W. Harrison
University of Florida

Dr. Leroy E. Hood
Institute for Systems Biology

Dr. Fern Y. Hunt
National Institute of Standards
and Technology

Dr. David A.L. Jenkins
Chartwood Resources Ltd.

Richard A. Lerner, M.D.
The Scripps Research Institute

Roger O. McClellan, DVM
Advisor, Toxicology and Human Health
Risk Analysis

Dr. Jill P. Mesirov
Whitehead Institute

Dr. James W. Mitchell
Lucent Technologies

Dr. Louis F. Pitelka
University of Maryland

Dr. Alan Rabson
National Cancer Institute

Dr. Janet L. Smith
Purdue University

Dr. Lisa Stubbs
Lawrence Livermore National Laboratory

Dr. James M. Tiedje
Michigan State University

Dr. Warren M. Washington
National Center for Atmospheric Research

Dr. Barbara J. Wold
California Institute of Technology