Environmental Contamination, Biotechnology, and the Law: The Impact of Emerging Genomic Information: Summary of a Forum

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Environmental Contamination, Biotechnology, and the Law: The Impact of Emerging Genomic Information

Summary of a Forum Held at the
National Academy of Sciences
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By
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PLANNING GROUP FOR THE FORUM ON ENVIRONMENTAL CONTAMINATION, BIOTECHNOLOGY, AND THE LAW: THE IMPACT OF EMERGING GENOMIC INFORMATION

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BOARD ON LIFE SCIENCES

Background

In 1993, the National Research Council's (NRC) Board on Life Sciences (formerly named the Board on Biology) established a series of forums to explore various topics related to the field of biotechnology. The purpose of these forums is to foster open communication among scientists, policy-makers, and others involved in biotechnology-related research, development, and commercialization. The neutral setting offered by the NRC is intended to promote mutual understanding among government, industry, and academe and to help develop imaginative approaches to problem-solving. The objective of the forums is to illuminate issues, not to resolve them. The forums cannot provide advice or recommendations to any government agency or other organization. Summaries of forums are prohibited from reaching conclusions or recommendations, but instead are intended to reflect the variety of opinions expressed by the speakers.

The first forum, held in 1996, focused on intellectual-property rights issues related to plant biotechnology. Other forums have focused on issues related to developing an agricultural genome project, privacy in biomedical and clinical research, and the field of bioinformatics.

On August 16, 2000, the Board on Life Sciences held a forum on "Environmental Contamination, Biotechnology, and the Law: The Impact of Emerging Genomic Information." The purpose of the forum was to explore the legal implications of current and developing biotechnology approaches to evaluating potential human health and environmental effects caused by exposure to environmental contaminants and to cleaning up contaminated areas. The forum brought together scientists from academe, government, and industry and members of the

legal community, including lawyers and judges, to discuss the interface between the use of those approaches and the legal system.

NRC staff was assisted in planning the forum by Frederick R. Anderson, of Cadwalader, Wickersham & Taft, Washington, DC; Donald R. Mattison, of the March of Dimes Birth Defects Foundation, White Plains, New York; Charles O'Melia, of Johns Hopkins University, Baltimore, Maryland; and Margaret N. Strand, of Oppenheimer, Wolff, Donnelly & Bayh, Washington, DC. The planning group suggested topics and speakers and provided comments on drafts of the forum agenda; they did not participate in the preparation of the forum summary.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the forum charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: David L. Eaton, of University of Washington, Seattle, Washington; Sidney Green, of Howard University, Washington, DC; Richard A. Merrill, of University of Virginia School of Law, Charlottesville, Virginia; and Margaret N. Strand, of Oppenheimer, Wolff, Donnelly & Bayh, Washington, DC.

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by Raymond L. White, of DNA Sciences, Inc., Fremont, California. Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author and the institution.

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Introduction: Genomics, Environment, and Health

On June 26, 2000, two independent groups of scientists announced that they had completed the first draft of the entire sequence of the human genome, identifying the sequence of every human gene and its location on the chromosomes, except for some minor gaps that should be filled in within the next year or two. That accomplishment received widespread attention in the popular media and has been hailed—rightly—as a landmark in human history and the beginning of a new era in understanding the human body and mind.

More broadly, however, this milestone in the Human Genome Project is but one step in a biologic revolution that is likely to transform many sectors of human life. Over the next decade or so, researchers will assemble the genomes of most of the organisms important to humankind, from crop plants and farm animals to disease-causing viruses and bacteria, and of a number of organisms used mainly in research. The information contained in these genomes might give scientists, physicians, and others tools they need to improve the human condition in various ways. Some of the applications are well known and have been discussed at length in the mass media. It might be possible, for example, to treat and eventually wipe out many genetic diseases, such as cystic fibrosis and Huntington disease. Farmers using genetically engineered crops might be able to grow more nutritious food in greater quantity, at lower cost, and with less damage to the surrounding environment than is possible now. And pharmaceutical companies might be able to design more-effective vaccines and drugs for the treatment of infectious diseases.

There is at least one other application of genomic information, less well known, whose implications are potentially equally profound, and it warrants

equal attention. For decades, physicians and researchers have known that environmental contaminants—radioactive wastes, heavy metals, toxic chemicals, and so on—play a role in human diseases, including cancers, neurodegenerative disorders, and birth defects. But the threat posed by these contaminants has proved complex and difficult to resolve. On the environmental side, for instance, cleaning up contamination is often frustrating and expensive, especially when the contaminants are spread through many square miles of ground and in large underground aquifers, as in large-scale contaminated sites. On the human-health side, how a person's body responds to an environmental insult depends heavily on the person's genes, and there is some degree of variation from person to person in vulnerability to environmental contaminants. That variability complicates the analysis, treatment, and prevention of environmentally triggered diseases, and scientists often find it difficult to answer even such seemingly simple questions as whether a cluster of cancers in one small geographic area occurred by chance or was caused by exposure to some environmental carcinogen.

The coming flood of genomic information could change all that. Environmental cleanup, for example, might be greatly aided by the ability to genetically engineer plants and bacteria to remove some contaminants from soil and water. On the medical front, researchers believe that having the complete human genome to work with might help them understand how environmental contaminants lead to cancers and other diseases and to figure out why some people are more susceptible than others. Ultimately, both prevention and treatment could be transformed by the insights that stem from genomic information.

The genomic revolution can also be expected to have ramifications outside science and medicine. It might have consequences, for example, for the court system, where citizens and corporations go to determine who has been harmed by environmental contamination, who is at fault, and how much compensation is owed for the harm. Judges and juries are already straining to comprehend the scientific evidence in some cases; how will they respond to a deluge of new, complex information that they must digest to reach a verdict? The new, more complete genomic information that is coming will once again raise the issue of genetic discrimination in hiring decisions and health insurance. Should the government, for instance, allow companies to use information about a person's susceptibilities to environmental contaminants in hiring and insurance decisions? And how might the new genomic information change how people think of disease? If it becomes possible to trace the development of a disease from the first environmental insult through each of the intermediate stages to the point where it can be identified as a recognizable syndrome, then disease might come to be seen not in terms of black and white or off and on, but as one end of a spectrum.

Because of the importance of this complex set of issues, and because they have seldom been analyzed as a whole instead of as separate pieces, on August 16, 2000, the National Academies' Board on Life Sciences held a one-day forum, "Environmental Contamination, Biotechnology, and the Law: The Impact

of Emerging Genomic Information." Sixteen speakers, representing the scientific and legal professions, gave presentations ranging from a primer on science in the courts to detailed descriptions of how genomic information can be applied in bioremediation. The forum agenda and biographical information on the speakers can be found in appendixes A and B, respectively. Discussion periods and question-and-answer sessions allowed the invited speakers and audience members to exchange ideas and information and to flesh out some of the topics introduced in the talks.

The following is a summary and synthesis of the information presented at the forum. It is divided into three sections covering health, environmental cleanup, and legal issues. Each section can be read independently, but the third will make more sense if the reader is at least familiar with the subjects in the first and second.

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Forum Summary

GENOMICS AND ENVIRONMENTAL HEALTH

Doctors and public-health officials face a host of complex diseases that have both environmental and genetic components: cancers, pulmonary diseases, neurodegenerative disorders, autoimmune diseases, birth defects, and many others. As Richard Sharp, a biomedical ethicist at the National Institute of Environmental Health Sciences (NIEHS), stated, they are diseases in which "genetics loads the gun, but the environment pulls the trigger." To deal with them effectively, it will be necessary not only to have a good idea of which environmental agents can cause cancers or other diseases, but also to understand how and why different versions of genes alter a person's response to the environment, making the person more or less susceptible to developing the disease.

The genomic revolution promises to make that understanding a reality. It will allow doctors to understand environmental diseases in far greater detail than ever before possible, and that in turn will make possible great improvements in the diagnosis, treatment, and prevention of these diseases.

To think about the role of genetics in disease, Sharp said, it is helpful to distinguish among three broad types of genetic influence. "First, there are what we might call disease genes. These are genes that are associated with disease in many different environments and in nearly all people who possess the particular alleles [particular versions of genes]. They are rare genes, and they include those associated with Huntington disease and phenylketonuria (PKU). If you have one of these genes and you live long enough, you are eventually going to develop symptoms associated with the disease."

The second type of gene that influences disease, Sharp said, might be called a susceptibility gene: "genes that, when they contain specific alterations, substantially increase a person's likelihood of developing an associated disease." In other words, susceptibility genes confer a higher than normal risk of some pathologic condition. These genes are fairly predictive of future disease states.

Finally, there are sensitivity genes, which are of most interest to researchers studying environmentally triggered diseases. Different people have slightly different versions of these genes, and some versions make a person more vulnerable to adverse environmental exposures than others. "These are genes that geneticists refer to as 'less penetrant,' meaning that they are less predictive of a person's overall risks," Sharp explained. That doesn't mean, however, that they are less important than the other types of genes. "Although a single genetic mutation in one of these alleles might not be highly predictive of a person's overall risks of disease," Sharp said, "if you take them together, they may combine in ways that are synergistic and actually help you look into the future." Furthermore, because sensitivity genes are far more common in most groups of people than either disease genes or susceptibility genes, they end up playing a large role in the development of diseases in a population as a whole.

According to William Suk, of NIEHS, as researchers have studied environmental diseases in increasing detail, they have discovered that the diseases are typically quite complex, and this complexity makes the task of understanding how they develop much more difficult. "These complex diseases are polygenic, for instance. They require the interaction of two or more genes and therefore an understanding of how these genes work."

"The environmental contribution is equally complex," Suk noted. "It is increasingly obvious as we look at environmental exposures that they don't occur as a single isolated event. Instead, they happen over time. For the most part, except when we talk about occupational exposures, they are usually low level, chronic, and in the form of complex mixtures. It is not a single chemical at a single time." Sometimes, a bacterium, virus, or other infective agent plays a role. The upshot, Suk said, is that "you are dealing with levels of complexity that need to be creatively teased apart."

Many researchers today are working to do just that, Sharp said. "Much of what is going on in biomedical research is trying to sort through what the genetic influences are and how the genes influence how we respond to environmental exposures. If we think about the general pathway from harmful environmental exposure to disease, we know that all sorts of biochemical pathways are implicated in the process. Some are involved in the distribution or metabolism of toxicants. Others are involved in the repair of associated genomic damage. Still others are involved in various signal-transduction pathways."

It is in trying to map out these details that the flood of genomic information will come into play. Not only will scientists have access to all the genes in the human genome; they will also have information about the functions of the proteins that the various genes encode.

One way the information will be useful—and, indeed, is already being used—is in the discovery of which genes are affected by various environmental toxicants. Researchers in the new field of toxicogenomics seek to "use genetic or genomic resources to identify potential environmental toxicants and their mechanisms of action" explained Paul Locke, deputy director of the Pew Environmental Health Commission at Johns Hopkins School of Public Health and a senior researcher at the Environmental Law Institute. In particular, he said, toxicogenomics researchers are interested in identifying characteristic patterns of gene expression that are elicited by various toxicants. When a person is exposed to a chemical in the environment, cells in the body respond by switching on some genes and switching off others, thus altering which proteins are produced by the cells. The on-off pattern of the various genes is different for different toxicants, and characterizing these patterns will give researchers a starting point for understanding what changes take place in a cell exposed to a particular toxicant. In addition, potential signatures showing which chemicals are involved can be studied.

In this research, scientists are greatly aided by a tool called a gene chip or DNA chip. As Locke explained, each chip contains an array of hundreds or thousands of short strands of DNA, each of which acts as a probe for a specific gene. To test which genes are active in a cell, a researcher collects the cell's messenger RNA (the molecules generated by active genes to serve as templates for building proteins) and then creates cDNA (complementary DNA) from the messenger RNA. At the same time, the cDNA is tagged with some sort of fluorescent or radioactive molecule so that its presence can be easily detected. "The cDNA sticks to a specific probe on the chip, and its presence is picked up," Locke said. "That creates what scientists hope will be characteristic patterns." On the gene chip, one sees an array of small dots, each corresponding to a particular gene and each producing a signal or not, depending on whether the gene was turned on or off in the cell. Thus, reading the pattern of gene expression in a cell becomes a matter of scanning an array of dots—something that a machine can do quickly and accurately.

NIEHS has developed a gene chip that can look at 12,000 human genes simultaneously, Sharp said. In the future, it might be possible to put all 100,000 or so human genes on one chip.

"With such tools, the Environmental Genome Project at NIEHS is looking for the human genes that respond to various environmental exposures," Suk said. Once the genes are discovered, it should be possible to piece together the biochemical pathways that lead from an environmental exposure to the development of cancers or other disease. And from there, Suk said, "researchers can go after the real prize: an understanding of the wide variation in individual susceptibility to these environmental exposures. Different versions of a gene will respond in subtly different ways to environmental stimuli, and the particular collection of alleles in a person's genome will determine how likely a toxicant is to lead to disease."

"Understanding of the collections of genes that respond to various environmental exposures and knowledge of which versions of those genes make a person most susceptible to disease will help doctors and public-health specialists in a variety of ways," Sharp said. First is primary prevention—getting people to stop smoking, for example. This simple step decreases a person's risk of lung cancer by about a factor of 20, Sharp noted, but doctors often have difficulty making the case to their patients, who feel that lung cancer won't happen to them. "Now, if your doctor could test you for certain alleles, certain genes that predispose you to the harmful effects of the carcinogens found in cigarette smoke, then that doctor could use that information to personalize your particular risk," Sharp said. "So, instead of saying to you, 'Look, you should quit smoking because smoking is bad,' now your doctor could say, 'You have these genes and because you have these genes, you are especially at risk.' It helps to make that risk more personal, more real. I think that it can have a dramatic effect on how we think about those risks and in getting people to change their behaviors to avoid harmful environments." It is possible that the converse of that example may be true as well. Smokers who find out they have genes that may make them relatively resistant to one tobacco related disease, for example, lung cancer, may use their "genetic protection" as a justification to continue smoking, even though there may be other adverse health effects from tobacco smoke.

"In terms of secondary prevention," Sharp added, "the development of diagnostic tools will allow us to sort through what is going wrong when a person has symptoms associated with a given disease." Looking at the pattern of gene expression in a patient's cells, for example, might someday make it possible to tell what environmental agents the patient has been exposed to and how far along and in what ways the disease has progressed.

Finally, Sharp said, doctors should eventually be able to prescribe individualized drug treatments based on a patient's genetic makeup. "The sensitivity genes that play a role in the metabolism of different environmental exposures are often the same genes that are implicated in the metabolism of pharmaceutical agents," he explained. "So, if a particular allele is associated with an adverse event in response to a particular drug, you might screen a patient for the presence of that allele before dosing. You might adjust dosages accordingly, or you might avoid a particular therapeutic regimen altogether."

GENOMICS AND CLEANING THE ENVIRONMENT

The flood of genomic information now under way should help to prevent some of the exposures that can trigger environmental diseases. By genetically engineering plants and microorganisms for use in bioremediation, scientists hope to be able to remove or neutralize many of the worst environmental toxicants that threaten human health.

"The problem is hazardous waste that is contaminating our land and our

Box 1
A New Concept of Disease

New genetic techniques will soon allow doctors and researchers to observe the progression of a complex disease from initial environmental exposure through the early biologic responses of the cells in the body to the disease's final stages. And this capability, John Groopman, of Johns Hopkins University, told the forum, will transform how society thinks of disease and who has a disease.

Traditionally, Groopman noted, disease has always been seen as an either-or situation: either one has a disease, or one doesn't. And for those who did have a disease, doctors developed classifications to describe how far along it was. "In the case of cancers, for example, there are well established stages. There is stage 1, stage 2, stage 3, based on 100 years of pathology principles as to how something looks morphologically, whether it has metastasized, whether it has moved around the body, and the like." In short, doctors have described and conceptualized cancers and other diseases according to the information available to them, from physical examinations and blood tests to tissue pathology and MRIs.

But soon doctors will have a wealth of new data on disease, Groopman said. "What is arising now, as a direct result of the Human Genome Project, is that we are developing a whole panoply of early detection markers," and the consequence will be that disease will no longer be seen in the traditional discrete way as yes or no, diseased or healthy.

"We are going to be on a continuum where a person will have biomarkers of disease state for some outcome. It might be cardiovascular disease because I am overweight. It might be skin cancer because I was exposed to the sun. These early detection markers are going to place me and many of you in this room on this continuum of ultimate disease risk."

"One of the greatest challenges that we have in dealing with this particular unanticipated outcome of the Human Genome Project is that we are going to have molecular diagnostic techniques that are now for the first time going to identify some high-risk people within the healthy population. Not high risk just because you carry some sort of predisposing factor, such as BRCA1 or BRCA2, but because you have an early-stage disease. That in itself might not kill you. It might not even have to be clinically managed. But we are entering this phase where we are all going to be placed on a continuous process going from what we used to think of as being healthy and normal through what was always a step function of clinical diagnosis to the point where we are going to be at these additional types of levels."

In short, doctors will be able to examine some people who have no sign of a disease that traditional tests could pick out and know that those people have taken steps toward the development of that disease. A patient might have been exposed to some environmental toxicant, for instance, which triggered changes in the biochemical pathways in some cells. It might take several more steps before the disease actually appears—and perhaps it will never appear—but the signs are there. And that, Groopman said, will raise all sorts of social issues that must be addressed.

"As you start to place people as 15% along the process of developing clinical disease, how do we handle that? How do we handle the fact that every one of us is going to be staged in this fashion and the possibility that we will carry around a card that has the gene expression profile of our disease state at a given time? This is not fantasy. I submit that this is only a few years off, and I also submit that we are

fighting last year's battle in terms of some of the genomic issues that have been raised this morning. Without too much of a crystal ball, we can look ahead a few years to where many companies are going to have these types of markers available, and anyone is going to be able to submit a blood sample and get a whole spectrum of information."

"That information could be used as a basis for decisions in hiring, health insurance, and so on; and in general the situation will pose challenges that we as a society are not yet prepared to face," Groopman said. "Yet it is coming, and doctors, medical ethicists, and others should be considering how it should be handled."

water," said Bob Burlage, of Oak Ridge National Laboratory (ORNL). Much of that hazardous waste has been generated by the Department of Defense and the Department of Energy (DOE) and its predecessor, the Atomic Energy Commission, he noted. "We are not talking about your typical little spill. That is easily taken care of by cheap, easy methods. We are talking about some sites that have cubic miles of contaminated ground and groundwater. The contaminants get into the ground, they start to move, and you lose track of them. How do you get them back? How do you remediate that? Furthermore, you can have a mixture of contaminants. It is never just one thing down there. It is always a mix of all sorts of things: radionuclides, heavy metals, organics, acids, and explosives."

One approach to remediation of heavy metals is phytoextraction, the use of plants to remove metals from contaminated soil. "It is applicable to soil contaminated with a variety of metals," said Mitch Lasat, an American Association for the Advancement of Science fellow working on phytoremediation issues at the Environmental Protection Agency (EPA). "This type of contamination usually results from mining and manufacturing operations."

Phytoremediation takes advantage of the fact that many metals—such as copper, zinc, and nickel—are actually plant micronutrients, Lasat explained. To extract metals from contaminated soil, "special plants are grown—plants that have the ability to absorb these metals in their roots. The most important part of this process is metal translocation from the root to the shoot. At maturity, the aboveground shoot biomass is harvested, and accumulated metal is removed, leaving behind cleaned-out soil."

Phytoremediation is less expensive than other methods of dealing with metal contaminants, such as fixation or soil extraction, and it is friendly to the ecosystem. Its major weakness is that, in most cases, each plant pulls a relatively small amount of metal from the soil, and this has limited the applicability of the approach. A potential solution to that limitation appeared with the discovery of metal-hyperaccumulative plants, which can both accumulate large amounts of metals and tolerate large amounts in their tissues. "Probably the best known

metal hyperaccumulator," Lasat said, "is *Thlaspi caerulescens* (common name, alpine pennycress). *T. caervlescens*, a short-lived perennial weed, is a zinc and cadmium hyperaccumulator that has been shown to accumulate up to 4% zinc in shoots on a dry-weight basis. Clearly, hyperaccumulators are very attractive for soil remediation. However, there is a drawback: most metal hyperaccumulators are small and slow-growing. Because they are small, their direct use for soil restoration is impossible."

The idea, then, is to find out what makes plants like *T. caerulescens* accumulate so much metal and engineer that trait into other, larger plants. That demands modern genetic techniques for analyzing *T. caerulescens* and then genetically engineering other plants to have the same hyperaccumulating capacity. Lasat has been pursuing that strategy. First, he cloned ZNT1, the gene coding for the protein that transports zinc in the roots of *T. caerulescens*. He studied a closely related species, *T. arvense*, that is not a zinc accumulator, and he found that it has the same zinc-transporter gene. *T. arvense*, the nonaccumulator, makes much less of the protein than does *T. caerulescens*. In the terminology of molecular biology, the zinc-transporter gene is overexpressed in the hyperaccumulating plants, and this leads to the production of extra amounts of protein. The additional amount of the zinc-transporting protein causes *T. caerulescens* to accumulate zinc, and as hypothesized, allows *T. caerulescens* to tolerate zinc concentrations that would be toxic to other plants.

The next step, Lasat said, is to investigate this zinc-tolerance mechanism of *T. caerulescens* because "the molecular regulation of this mechanism must be understood and controlled if one day we are to improve plants for environmental restoration. In the final phase, once we have the genes, we hope to use biotechnology to transfer them from hyperaccumulators like *T. caerulescens* to the species of interest." That would provide a safe, cost-effective way of removing zinc and possibly, cadmium from contaminated soil. Furthermore, by using similar genetic techniques, it should be possible to create an array of plants that can extract many metal contaminants from soil in a similar way.

Plants are convenient for bioremediation in that they bring contaminants to the soil surface, where they can be harvested and disposed of. But plants have serious limitations as well. They cannot, for instance, reach contaminants any farther below the surface than their root systems extend—generally no more than a few feet.

Bacteria have a number of characteristics that make them promising for bioremediation. They can migrate through the soil to wherever the contaminants are. Under the proper conditions, they can multiply rapidly; even though each individual organism is quite small, they can generate large enough populations to clean up significant amounts of contaminants. Although they will not move the contaminants above the surface for disposal, a number of bacteria will chemically degrade some of the contaminants, changing them into substances that are less dangerous. *Pseudomonas putida*, for instance, "has great versatility for organic compounds," Burlage said. And in the case of metals, which cannot be

degraded, bacteria can chemically transform them into less toxic forms. "Geobacters change the oxidation state of a number of metals, including uranium and technetium," Burlage noted.

Furthermore, bacteria can survive in a wide range of conditions, many of which would be fatal to plants or animals. "One microorganism can live at 3%C below freezing," said Dan Drell of DOE. "Another lives in a hot spring at about 116%C." Some bacteria have been found 8,000 ft below the surface of the ocean, where the pressure is about 230 atmospheres. "The Great Salt Lake and the Dead Sea support microbial life," Drell added, "and a microorganism was recently found in some acid mine drainage that had a pH of 0.5"—comparable with that of strong sulfuric acid.

Perhaps the most astonishing bacterium in this context is *Deinococcus radiodurans*, which can tolerate up to 6,500 grays of direct radiation. A gray is equivalent to 1 joule of energy absorbed by 1 kilogram of body mass. Burlage compared the radiation sensitivity of *D. radiodurans* with that of humans. "For a typical person, if you get around 10 grays, you are probably dead. In comparison, *Deinococcus* can easily take 3,000 grays, and it will just repair itself. It is extraordinary."

"We would like to know which genes are involved in that [*Deinococcus*] repair mechanism," Burlage said. "We would like to be able to borrow some of those genes to work in some places that have high radiation, but we don't know how yet." The genome of *D. radiodurans* has been mapped out, he noted, and researchers are now looking for the genes that allow it to survive such intense radiation. The task facing bioremediation specialists is to learn how to mix and match various useful bacterial traits to produce genetically engineered bacteria that can clean up collections of hazardous waste.

"More generally, there is a long list of characteristics that researchers would like to be able to engineer into bacteria for the purpose of bioremediation," Burlage said. At the top of that list are genes for proteins that reduce metal atoms—that is, add electrons so that the metal is less reactive—or that lead to products that sequester metal atoms. "Plenty of microorganisms have such genes," said Suk. "Studies show that microorganisms will sequester and accumulate vast quantities of metals. This has been done for survival purposes. In some cases, they had to do it to survive in the environmental mixture in which they live." Bacteria that accumulate metals in this way could neutralize many of the toxic metals in hazardous-waste sites.

Researchers are also looking for dehalogenation genes—that is, genes for proteins that will remove a halogen atom, such as fluorine or chlorine, from a chemical compound. Examples of halogenated compounds include polychlorinated biphenyls and polybrominated biphenyls, which were used extensively in transformers and have leaked into the soil for many years. Certain solvents, such as trichloroethylene, are also common contaminants of groundwater. Dehalogenation is an important way of neutralizing a number of toxic chemicals.

"Also," Burlage said, "because we are often dealing with sites that are way below the surface, we have to get those bacteria there. A lot of the bacteria that we work with are not conducive to transport. Some of them will stick to the first thing they encounter. They will stick to the lip of the well. But you need to be able to transport them in a manner in which they can reach the contamination site. In contrast, they can't be flushed out too easily. If they can, you are going to flush them right through. They also must be able to reach the small pores in the soil, because that is where a lot of contamination is. Particles can have crevices that are far smaller than the bacteria themselves. How do you get the bacteria into those crevices? If you can't do that, then you are going to have contaminants leaching out for years, even after you have declared the site clear."

After the bacteria reach the contamination, they have to survive long enough to do the job. "The deep subsurface is very oxygen-poor," Burlage said, so the bacteria must be able to live and multiply with little or no oxygen. "Basically, the bacteria have to survive until the job gets done. At that point, we hope they will die or at least not cause any further problems."

Researchers have already engineered a number of microorganisms for use in bioremediation. Phil Sayre, of EPA, described a bacterium native to Florida that had been genetically engineered to degrade chlorinated solvents, such as trichloroethylene and dichloroethylene. It was used in a cleanup effort at Dover Air Force Base in Delaware and was surprisingly effective. "Most people thought that you could not establish a nonindigenous bacterium," Sayre said. "You can't take a bacterium from Florida and expect it to compete in a subsurface with a bacterium from Dover. In fact, this one did, and it did because it had—at least we theorize that it had—a unique ecologic advantage. It could use the chlorinated solvents in the subsurface as a food source, which other microorganisms couldn't do. That gave a selective advantage. It used the chlorinated solvents, grew, and degraded the chlorinated solvents."

Sayre also described a field test of a genetically engineered bacterium, *Pseudomonas fluorescens*, strain HK44, in 1996. "The idea was to take soils amended with particular polynuclear aromatic hydrocarbons (PAHs), compounds commonly found in refined petroleum products and known to be carcinogenic and toxic in other ways, and test them in some contained systems at the ORNL site in Tennessee. The goal was to determine whether *P. fluorescens* HK44 could degrade these PAHs and also be used as a biomonitor or a bioindicator of their presence." The bacterium was given two sets of genes. One was for the partial degradation of PAHs; the other made the microorganism produce a signal in the presence of contaminants. In the field tests, the bacteria successfully degraded the PAHs and also produced a signal when contaminants were present. Beyond that, it behaved exactly as one would hope with respect to its survival, Sayre said. "In nonsterile soil—in the presence of other microorganisms—it established itself fine but decreased after about 6 months, particularly in the absence of contaminants. That is pretty much what you would want it to do. The

bacteria stays around while the contaminants are there and in the absence of contaminants, they decrease in number, although they don't disappear."

So far, Sayre said, EPA has approved testing of several genetically engineered microorganisms for bioremediation. "We have seen applications for a number of different kinds of pollutants, such as PAHs, PCBs, and trichloroethylene. However, they have all been field tests. There has been no application of recombinant microorganisms for full-scale bioremediation."

Ultimately, Sayre suggested, the most important use of bioengineered microorganisms could actually be as biosensors, such as the *Pseudomonas* that produced a signal in the presence of contaminants, rather than in bioremediation itself. "You would be able to detect contaminants in a much less expensive fashion than through exhaustive chemical analysis," he said. Furthermore, because the engineered microorganisms would respond only to contaminants that were bioavailable—that is, can be absorbed and used by a living organism—they would give a much more accurate reading than the traditional chemical tests, which detect all forms of a contaminant, bioavailable or not.

LEGAL IMPLICATIONS

Over the last several decades, environmental contamination has spawned an increasing amount of litigation in the US court system. Some of the lawsuits have been aimed at stopping practices by corporations or government agencies that were seen as threatening to the environment. Others were torts, seeking redress for damages claimed to have been caused by environmental contamination.

Such litigation has often pushed the legal system to its limits, as judges or juries are asked to make decisions based on science that is complex and uncertain. With the wealth of new genomic information and techniques that will become available over the next few years, the legal system is almost certain to find itself straining to answer questions that not even scientists can agree on.

"Trying cases in court that involve scientific issues is never a simple matter," said Richard Levie, of ADR Associates in Washington, DC, a retired associate judge of the Superior Court of the District of Columbia. A large part of the difficulty, he said, "is that science and law are different entities."

"One of the fundamental problems in this interplay between law and science is that we speak different languages," he said. "We approach problems differently. We think differently. We analyze differently, and the difficulty occurs not when you are in a scientific meeting, but when you walk into the courtroom, because then you are playing in our ballpark and you have to adapt your language, your thinking, and your communication to the courtroom."

"In science you have a constantly evolving process. You are always examining and re-examining and looking for what is going on. In the law, we are required to seek certainty. In science, you are dealing with the concept of replication and testing of hypotheses. In a courtroom, in a legal context, it is an

Box 2
Do Environmental Mutagens Cause Cancers?

For decades, researchers studying cancers have assumed that some chemicals in the environment cause cancers by inducing mutations in the body's cells. The idea is that the chemicals are taken into cells, metabolized by various enzymes, and transformed into a wide array of other chemicals, which then act to increase the likelihood that mutations will occur in a cell's DNA. Mutations set the cell on the path to unchecked growth. "That was once known as the genetic toxicology paradigm at MIT, and we used it in teaching for many years," said Bill Thilly, director of Massachusetts Institute of Technology's Center for Environmental Health Sciences. "There was never any direct test of it, however."

Thilly said that research from his laboratory suggests that what everyone assumed about the environmental influence on cancer rates may not be true. Although the environment does influence the risk of developing cancers, it may not cause mutations in the cells.

Mutations in a cell's DNA do play a major role in the development of cancers, Thilly said. "We know that genetic changes lead to cancers. For instance, in the case of most sporadic colon cancers, we know that the adenomatous polyposis coli gene (APC) must be mutated and both good copies lost in order to get colon cancer." In other words, researchers know that there must be mutations in the DNA for cancers to get their start. "It is widely believed, although no one has ever demonstrated it, that genetic changes are necessary in the second stage, called promotion, when a small preneoplastic colony starts to grow."

And, Thilly said, "environmental factors do influence cancer risk." One of the best examples is the history of breast cancer in women of Japanese descent in the United States. Throughout the last century, women in Japan had much lower rates of breast cancer than women in the United States, but women of Japanese descent whose ancestors moved to the United States two or three generations earlier had breast cancer rates much closer to the American average. Clearly, environmental differences account for the difference in cancer rates, although, as Thilly noted, it is difficult to know whether something in American culture increases cancer risk or something in Japanese culture decreases cancer risk.

To account for the various factors in cancer, Thilly has taken a two-pronged approach. First, he has accumulated a tremendous amount of data for statistical analysis. "We have gathered all the available data in the United States, all recorded national mortality data from 1900—with regard to cancers, infectious diseases, and other causes of death. We have assembled all the death certificates in Massachusetts and six other states since 1969 and analyzed them. We also have all the available Japanese mortality data in our computer files."

With those historical data, Thilly was able to calculate the percentage of the population at lifetime risk for any given cancer. "That is an abstract fraction at risk," he said, "the people who would die of that cancer if they couldn't die of any other form of disease. In other words, if you are not at essential risk, you cannot get that cancer." Thilly stated that the calculation depends on the observation that as time goes on and people die from, say, lung cancer, the percentage of the population at risk for lung cancer will go down because those people are not replaced.

The percentage of the population at lifetime risk depends on both genetic susceptibility and environmental factors, Thilly's research showed. For example, as

the percentage of cigarette smokers in the United States rose steadily throughout much of the 20th century and then began to decline, the percentage of the population at lifetime risk for lung cancer went up and down in an almost identical pattern with a lag period of about 2 decades. Thilly calculated that at least 94% of smokers are at lifetime risk for lung cancer.

"In contrast with lung cancer, however, most other cancers have not become more of a threat over time," Thilly said. "If you look at other big cancer killers—cancer of the breast, colon, and prostate—my laboratory discovered that there has been no change in the primary fraction at risk in the population in the last 120 or so years." That implies, he said, that there have been no changes in the environment that have caused these cancers to threaten a larger percentage of people than they did a century ago. "It is always possible that some risk went up when another risk went down as a function of history," he noted, but Ockham's Razor suggests that the more likely hypothesis is that the environment's contribution to cancer rates has been stable over the last century.

That doesn't mean that the environment plays no role, Thilly noted. Long-term historical data show that the primary risk of various cancers rose steadily from the time of the Industrial Revolution to the early part of the 20th century, when they leveled off. So primary cancer risks are higher now than they were in the preindustrial era. "But the data do not indicate any specific effect of any chemical exposures that have taken place since the mass introduction of chemicals and pesticides in our country, which started in the late 19th century in some areas and then spread across the country by the end of World War II."

Besides analyzing the percentage of the population at essential risk, Thilly used his data set to calculate mutation rates over time. "The first mutations giving rise to a cancer are called initiation mutations. With our mathematical model, we are able to calculate the rates of these mutations." When the analysis is applied to colon cancer, it finds that mutation rates in the colon have remained historically constant. That would be expected, given that colon-cancer rates have not increased over the last century. The finding that mutation rates in the lung have not increased appreciably was unexpected. "There was less than a twofold increase in the calculated rate of mutation in smokers relative to nonsmokers," he said. "That change would not be biologically significant. It certainly would have no effect that could be observed in the marked increase in lung cancer. So it appears that the effect of cigarette-smoking on the lung is not an effect on mutation rates in the lung."

That conclusion is reinforced by the second prong of Thilly's research. "My laboratory has been responsible for developing technology that allows us to see the pattern of mutations directly in a human organ sample or to study the kinds and patterns of mutations that are caused by chemicals in human cells grown in the laboratory." In this case, we studied bronchial epithelial cells from which lung cancers arise. We have studied the mitochondrial DNA from persons who smoked and didn't smoke, including three pairs of identical twins discordant for cigarette use. We found no significant differences between the smokers and the nonsmokers. Similar work on mutations in the nuclei of bronchial epithelial cells has to date found no differences between smokers and nonsmokers, he said.

How does smoking cause lung cancer, if not by causing genetic mutations? Thilly suggested three main mechanisms: smoking increases the number of biochemical pathways in the cell that can lead to cancers; it increases the growth rate of adenomas, the precancer colonies; and it increases the primary fraction of the population at risk for lung cancer.

adversarial process. On the scientific side, it is consensus. On the legal side, it is controversy. One at a time, the experts will get up and give their opinions, and the opposing attorneys will do everything they can to tear them apart for lack of qualifications or by challenging their methods and conclusions. The keystone to our system of law is that the adversarial process will produce the truth through the use of competing experts and through the use of cross examination."

One of the results of the difference in approaches is what Levie termed "legal leapfrog." It derives not from science or the law, but from the interplay between them. "It starts with a scientific pronouncement—some scientists publish a study. They have done research, and they believe that exposure to A results in B, whether it be disease or injury. Not long thereafter, a series of lawsuits based on that scientific pronouncement will be filed. The existence of the lawsuits will generate more scientific study regarding the original pronouncement. The further studies will lead to new scientific pronouncements, not infrequently reaching different results." That was the case, for instance, with the anti-nausea drug Bendectin in the early 1980s. Some preliminary studies suggested a connection between Bendectin, which was prescribed for pregnant women and birth defects. "That led to a spate of lawsuits," Levie recounted. "A number of them resulted in significant verdicts for the plaintiffs. "Over the next decade or so, there were numerous studies of the effect of Bendectin, and ultimately the conclusion was that Bendectin does not cause birth defects, at least not with a frequency that would lead to a finding of causation in court. That wreaked havoc on the legal system because when you go to trial you are asking a judge or a jury to make a decision based on that little snapshot, a given level of scientific study at that time. The legal system is not well equipped to roll back the clock years later, when new scientific studies suggest that the original verdicts might have been in error from a scientific point of view." A similar pattern of events unfolded in the litigation over silicon breast implants and their supposed connection with diseases of connective tissue, Levie noted.

The coming genomic revolution will put even more pressure on the legal system, Levie predicted. "Genetic research is going to lead to more issues coming to court that will be related to both research and the practical application of results of the research. When I think about the interplay between science and law, particularly genetics and law, it is scary. It is scary because it is going to be difficult for judges and it is going to be difficult for juries."

Forum speakers identified two ways in particular in which genomic research will probably affect and be affected by the legal system. First, Susan Poulter, of the University of Utah College of Law, argued that the new genomic information will probably be misused in legal cases unless people—both scientists and those in the legal system—think carefully ahead of time about what it means and how it should be applied. "I am going to talk mainly about toxic-injury litigation," she said, "because that is where I think there is the most potential for the use, and unfortunately, for the misuse of genetic-testing information in the courtroom."

In the so-called "toxic tort" cases—that is, when people allege that they have been injured by some toxic substance—a general paradigm for proving causation has been developed in case law, Poulter said. "First of all, the plaintiff needs to show general causation." That is, there must be scientific evidence, usually epidemiologic, that the substance in question can cause the disease. "The person has to prove exposure to the substance or radiation in question and has to have some medical testimony about the diagnosis. Then, usually by inference, the plaintiff's witness must link the exposure and the general causation information to the case." This sort of case is almost always probabilistic, she noted. It is impossible to prove to a certainty that the exposure in question caused the disease, so the plaintiff argues simply that there is a good probability that the exposure was to blame.

"As doctors and researchers learn more about the interplay between genes and environment in the development of disease, this knowledge will affect toxic-tort cases in a number of ways," Poulter said. "There may be exposure or causation markers. Toxic substances or radiation might alter DNA in a way that is specific to that particular type of exposure." If so, testing for such markers could prove whether a person had been exposed to a particular environmental toxicant.

"One of the ways that genetic information is starting to be used in litigation is in assessing life expectancy of a victim. For example, if someone has been in an automobile accident and needs custodial care for the rest of his or her life, the defendant might be interested in finding some evidence that the person doesn't have a very long life expectancy. But that raises some very troubling questions, not the least of which is that this is essentially a fishing expedition. The victims may find out some things they don't want to know, things that have psychologic, employment, or insurance implications for them and perhaps for family members."

"Another way in which genetic testing will be important is in the diagnosis of the plaintiff's condition," Poulter said. If, for example, genetic testing showed that a person had the mutation for Huntington disease, any mental deterioration in the person would be more likely be due to the genes than to an environmental cause.

The most problematic application of genomic information, Poulter said, arises in attempts to sort out whether a disease should be blamed on the environment or on a person's genes. "There are two forms of this argument, which posits genetic factors and environmental causes as alternatives. In one, the plaintiff says, 'on the basis of family history, I don't have a genetic susceptibility to this cancer, birth defect, whatever. Therefore, it is more likely that this toxic exposure is the cause of my disease.' In the other, the defendant says that if the plaintiff has a genetic susceptibility, that susceptibility, rather than the toxic exposure, is the cause of the disease." Already, she said, there are a few cases in which defendants are seeking genetic testing of plaintiffs to see whether they have genetic susceptibilities to their diseases.

Those arguments ignore the possibility that the genetic susceptibility and the toxic exposure acted in combination, Poulter noted. If a person has a genetic

susceptibility to a disease, the toxic exposure might have triggered the disease, and a defendant can still be found liable. "In legal terms, we talk about the thin-skull case—if the defendant has caused an injury that is more severe than was expected, we say the defendant is liable. The defendant doesn't get to say, 'Oh, too bad, Joe had a thin skull. I am off the hook.' It is the other way around. They have to take plaintiffs as they find them." As research on identifying susceptibility and sensitivity genes progresses, some of these opposing arguments may be clarified.

In general, causation can also be understood in statistical terms, Poulter noted. One looks at how many cases of a disease there are in a population, how many of those were due to a particular environmental exposure, how many can be attributed to genetics, and how many were caused by a combination of the two. Then one can assume that the same odds apply to the case of the individual plaintiff. If more than 50% of all cases of the disease are attributed to an environmental toxicant, then the plaintiff's case is, too.

"Now, this is controversial," Poulter acknowledged. "Epidemiologists would have a concern about saying that group statistics have anything to do with what happened in an individual case. This is really a legal policy device to overcome what is otherwise a lack of any means of answering the question, even when you know that the substance is doing some harm." However, that type of analysis also illustrates the fallacy of the "alternative cause" model, which qualitatively and quantitatively ignores the possibility that environmental and genetic causes act in combination.

"Because many toxic-tort cases already invoke the alternative-cause model, the push in the future will almost certainly be toward giving genetic tests to plaintiffs to determine their susceptibility to the disease in question," Poulter said. But there is a downside in that many plaintiffs may not want their genetic tests in a court record, and, in the case of mutations that lead to serious disease, the results of genetic testing are particularly sensitive. "I would say that we need to exercise some caution," Poulter concluded. "We need to think through our models carefully and consider what information we truly need from genetic testing. Otherwise, we are going to be using this information or trying to use it when the meaning is unclear, in which case there will be a high probability of misuse."

In contrast with Poulter, whose concern was how the science of genomics could adversely affect the legal system, Larry Hourcle, a professor of environmental law at George Washington Law School in Washington, DC, spoke about how the legal system may impede the science. "The one legal issue that has the greatest chilling effect on the whole biotechnology movement is the liability issue." In particular, he suggested that efforts at environmental cleanup with genetically modified organisms could be substantially slowed by lawsuits or the fear of lawsuits.

In part, he said, the problem can be traced to the federal law that established the Superfund for cleaning up major hazardous-waste sites. According to the

law, Hourcle said, "if you cause or contribute to a site, you become potentially liable for the cost of cleaning up the whole site." That has implications for the cleanup process because in a few cases it has been claimed that a cleanup attempt made the situation worse. The group doing the cleanup could be sued to pay for much of or, potentially all the later work to clean the site. If the companies originally responsible for the hazardous-waste site have closed or gone bankrupt—something that is not uncommon in these cases—the cleanup company could be left holding the bag.

"So," Hourcle said, "there are some sites out there where, if you get involved with your biotechnology in trying to solve a problem and things go awry, you could be brought into an action with regard to paying for the increase in the cost or even the total cost of the cleanup."

"Partly because of that situation, work on developing genetically modified organisms to clean up the environment has been going much more slowly than it could have," said Gilbert Omenn, a public-health expert and executive vice president for medical affairs at the University of Michigan. "We still don't have a real field-scale bioremediation of a Superfund site," he said, even though in some cases the technology seems ready. Furthermore, more than a decade ago, researchers learned how to build modules of connected genes that would create a set of enzymes in a microorganism capable of breaking down vinyl chloride or other toxic chemicals in a series of steps into carbon dioxide, water, and a few other safe compounds. "It has been done in the laboratory over and over with many organisms, but it has still not been taken into the field on any significant scale. You have to ask why. Part of it is the fear of liability," he said. "Despite reassurances, that has not been settled." A second factor, perhaps bigger than the fear of liability, is the rhetoric of environmental cleanup. "That rhetoric is mostly about perfection, about 'negligible risk' so defined as to be indistinguishable from zero risk. The expectation of getting the last molecules eliminates some technologies, of which bioremediation is at the top of the list."

What can be done to smooth the interplay between science and the law in the case of the emerging genomics revolution? Forum speakers offered several suggestions.

"Jury-reform provisions would seem to be very simple and commonsensical," said Franklin Zweig, president and chief executive officer of the Einstein Institute for Science, Health and the Courts: "First, allowing jurors to take notes; many courts do not. Second, allowing juries to propound questions of the witnesses, particularly the expert witnesses; most courts do not. Third, pre-examining the exhibitory evidence, the documentary evidence, so that the quick flash of the slide on the screen can be related to the actual witness's testimony. Fourth, allowing the use of briefing books; sometimes, they are not allowed."

Probably the most important reform, Zweig said, would be to introduce the use of instructional witnesses for the jury—impartial experts appointed by the judge who could provide a backdrop for the contested scientific issues in the

Box 3
Ethical and Social Issues

The increased genomic knowledge that will be appearing over the next few years will raise or intensify a variety of ethical and social issues in addition to the legal ones, forum speakers said. And how society handles these issues could well affect the success of genomics itself.

Many of the ethical and social issues will be variants of issues that have already been raised by the ability to detect disease genes, such as the gene that causes Huntington disease. In the coming years, physicians and researchers will pinpoint an increasing number of sensitivity genes—genes that increase one's vulnerability to disease when one is exposed to various environmental toxicants but that do not guarantee that one will develop the disease—and this will change the complexion of the field, said Richard Sharp, of NIEHS. Tests for the sensitivity genes are different from tests for disease genes in two important ways, he said: many more people will turn out to have the sensitivity genes than have the disease genes, and the presence of the genes will be much less predictive of the person's future health. "The development of these tests," Sharp said, "is going to put new spins on familiar problems in bioethics: issues related to informed consent, protection against possible discrimination and stigmatization, and the presentation of research results. Will employers or insurance companies inappropriately single out people as being at risk on the basis of genetic sensitivities to environmental agents? I think there is much more opportunity for misuse and misapplication of these tests."

Notions of personal responsibility will feel the effect of the new genetic tests, Sharp said. "What obligations do employers have to protect their most vulnerable workers? Should we raise the bar as to what is an acceptable risk to an employer now that we know that some people in the workplace are going to be particularly susceptible to occupational hazards? How should regulatory agencies handle the availability of this information? And what should each of us as individuals do in response to known genetic sensitivities to environmental or occupational agents? Should we change jobs? Are we guilty of another form of victim-blaming in this context? Are we blaming people who get sick, shifting the focus of responsibility to their bad genes, as opposed to their harmful workplace?" Those are all questions that society will have to grapple with, given the capabilities that will be coming in the near future.

"The new genomic capabilities will also greatly increase the potential for genetic discrimination," said Paul Locke, of the Pew Environmental Health Commission. "There has been a great deal of discussion about genetic discrimination in health insurance and in the workplace, including legislation introduced in Congress to ban such discrimination; but such discrimination could also take place in a number of other spheres. Some people who are discussing whether this sort of genetic discrimination might take place in adoption," Locke said. "If you want to apply to adopt, we want to take a look at your genes to see whether you have the longevity gene or maybe a gene that affects your abilities. This is something that brings home the message that people on the street and people in the policy world are concerned about genetic discrimination."

"Privacy and confidentiality issues will also be important to iron out," Locke said. One of the most important goals for gathering genomics information is to use it to protect public health, but this laudatory goal must be balanced with serious

privacy and confidentiality issues. "And, finally, there is the issue of property rights. Who owns genetic information? If we assign ownership to genetic information, that has severe ramifications for how all this genomics could work."

More generally, Locke worries that such issues as privacy and property rights could affect scientists' ability to do research in genomics. "We will need a lot of information to figure out how to interpret this sort of technology. Then the question is raised: where is that information going to come from?" Researchers will need large quantities of genomic and medical data on many people if they are to learn to interpret genomic information, but current and future legislation on genetic privacy might make it much harder for scientists to accumulate that data.

"The privacy interests, which are very important and run deep through our society, are eventually going to bump up against the use of some of these techniques. When that happens, scientists have to focus on their information needs. Do they need this sort of data and what form do they need them in? For example, would scientists be happy with blinded information? When they get blinded information and use it, are there times when they are going to need to unblind it? And how difficult is that, and how difficult should it be?

"One of the challenges for scientists is to demonstrate social, societal, and public-health benefits of this type of information.

"Attorneys also have some challenges. They have to begin to think about how they are going to foster these emerging sciences because they do have great promise for improving public health and preventing disease.

"And we have to think about tailoring legislation very carefully, using a legal scalpel and not a legal scythe when we write definitions and legislation so that we do not put something on the books that impedes scientific progress."

case. "They would essentially be providing an operational glossary so that the jury could weigh the contested evidence presented by the expert witnesses."

"Judges need help as well," Zweig said, "because few of them have any background in science, particularly the complex sorts of science that are often crucial in court cases." The mission of the Einstein Institute is to provide judges and other court personnel with the tools they need to deal with evidence from genetic sciences, environmental science, and other fields of research. Levie, who is also affiliated with the Einstein Institute, described its work this way: "The organization has been working with a number of scientists throughout the country to try to educate judges, not so much on how to decide any particular issue, but to expose them to some of the basic terminology and to have them at least start thinking about the legal questions that are going to be coming down the pike."

No matter how well prepared judges are for a scientific case, they will still have to rely on the experts to provide objective and effective testimony, Levie noted. That is one way that individual scientists can make a difference. "Every time I get an opportunity to talk to a group of scientists, I stress the obligation of scientists to get involved in the legal process. Most say 'I will give you an opinion privately, Judge. I will advise you, and you can tell the parties I am

advising you; but don't ask me to testify, because I don't feel like being deposed and cross-examined in court. It is a very unpleasant experience.' And, yes, it certainly can be an unpleasant experience. But I ask you to ask yourselves this question: If the people you would consider good scientists are not willing to come into a courtroom to educate judges and juries, then who will do it? Are those the kinds of opinions you want presented to judges and juries? The decisions made will affect the legal system and the business and scientific community for years to come."

Finally, Zweig saw a role for the National Academies. The courts may appoint individual experts, panels of experts, or instructors, but the bottom line that has come out of our instruction to date is a big question from the courts as to who is objective on the issue of applied risk assessment in biotechnology, particularly in bioremediation disputes. That is a difficult question to answer. The National Academies, with its long history of vetting science, is, we believe, in the best position to provide a continuing resource to courts and legislatures. It has to be beyond attack or suspicion. It has to have a super-objective, super-nonbiased, super-nonconflicted character about it, even to the point where holdings must be divested, if it is to provide the kind of confidence that judges need that risk-assessment information is indeed objective."

In short, given the complexity and contentiousness of the issues, it will always be difficult for juries to know which experts to believe, and the nature of our legal system guarantees that there will always be competing expert opinions in a case. The best way to provide juries with scientific information that they can trust as objective is to find an objective set of experts to provide such a starting point. "We are going to have in the court system a big wave of litigation on the issue of risk versus benefits and disputes related to them," Zweig said. "Unless the National Academies applies its letterhead here in a truly objective fashion, courts and legislatures could be paralyzed on issues related to biotechnology applications by the end of this decade."

SUMMARY OF KEY POINTS

This report summarizes the proceedings of a forum that was convened by the National Academies to examine various emerging biotechnology-based approaches and associated legal issues related to evaluating potential human health and environmental effects caused by exposure to environmental contaminants and cleaning up contaminated areas. The forum brought together scientists from academe, government, and industry and members of the legal community, including lawyers and judges, to discuss these complex scientific and legal issues. The key points made at the forum and in this report are summarized below; they represent the viewpoints of the forum speakers and should not be taken as report conclusions.

• Technologies developed with emerging genomic information are being used to study how and why different versions of genes (polymorphisms) alter a person's response to the environment, making the person more or less susceptible to developing a particular disease. Such information might some day allow physicians to improve the diagnosis, treatment, and prevention of environmental diseases.

• The study of environmental diseases is proving to be complex. For example, such diseases might require the interaction of two or more genes as well an environmental contaminant.

• Biotechnology is being used to develop microorganisms and plants for use in bioremediation and phytoremediation, respectively. These genetically engineered organisms might eventually be used to remove some of the worst toxicants (such as organic compounds and heavy metals) from the environment, particularly at large-scale contamination sites.

• For several reasons, the widespread application of genomics will probably lead to litigation in the U.S. court system. For example, an employer's knowledge of a job applicant's genetic susceptibility to a particular environmental exposure might be used as a basis for not hiring that applicant. The applicant, in turn, might file a lawsuit against the employer citing discrimination in hiring.

• Legal cases involving complex scientific issues have been problematic largely because judges and juries often do not have the appropriate background in science. As cases involving emerging genomic information enter the legal system, this problem could worsen. Several organizations have been established to educate judges about genetics, environmental science, and other fields of research.

• The threat of litigation could impede progress in the application of new biotechnology-based approaches.

APPENDIXES

A

Forum Agenda

WELCOME

Margaret Strand, *Oppenheimer, Wolff Donnelly & Bayh, Washington, D.C.*

OPENING REMARKS

Gilbert Omenn, *University of Michigan*

OPENING PRESENTATIONS

Daniel Drell, *U.S. Department of Energy*
William Suk, *National Institute of Environmental Health Sciences*
Richard Levie, *ADR Associates, L.L.C., Washington, D.C.*

SESSION I: EVALUATING POTENTIAL HUMAN HEALTH EFFECTS FROM EXPOSURE TO ENVIRONMENTAL CONTAMINANTS

Richard Sharp, *National Institute of Environmental Health Sciences*
John Groopman, *Johns Hopkins School of Public Health*
William Thilly, *Massachusetts Institute of Technology*
Paul Locke, *Johns Hopkins School of Public Health and the Environmental Law Institute, Washington, D.C.*
Susan Poulter, *University of Utah College of Law*

SESSION II: REMEDIATING CONTAMINANTS IN THE ENVIRONMENT

Robert Burlage, *Oak Ridge National Laboratories*
Mitch Lasat (AAAS Fellow), *U.S. Environmental Protection Agency*
Franklin Zweig, *Einstein Institute for Science, Health, and the Courts, Chevy Chase, MD*
Phil Sayre, *U.S. Environmental Protection Agency*
LaReesa Wolfenbarger (AAAS Fellow), *U.S. Environmental Protection Agency*
Laurent Hourcle, *George Washington University*

SUMMARY OF FORUM

Gilbert Omenn, *University of Michigan*

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Speaker Biographies

Robert Burlage is a staff scientist at the Environmental Sciences Division of Oak Ridge National Laboratory. His research interests include the expression of genes that are involved in the bioremediation of hazardous waste, particularly in situ.

Daniel Drell is a biologist and program manager in the Human and Microbial Genome Program at the Office of Biological and Environmental Research of the Department of Energy. He also manages the Ethical, Legal, and Social Issues Program for the Human Genome Program and has written and spoken extensively on this topic.

John Groopman is professor and chairman of the Department of Environmental Health Sciences in the School of Hygiene and Public Health at Johns Hopkins University. His research interests include the development of molecular biomarkers reflective of exposure to and risk posed by environmental carcinogens.

Larry Hourcle is a professor of environmental law at George Washington Law School. He also codirects the George Washington University Environmental Law Program and serves as acting director of the university's Institute for the Environment. He is an expert on legal issues associated with hazardous-waste remediation.

Mitch Lasat is an American Association for the Advancement of Science (AAAS) fellow working on phytoremediation issues in the Environmental Protection Agency's Technology Innovation Office and National Center for Environmental Research. Before becoming a AAAS fellow, he was a research associate professor at Cornell University, where he investigated plant mechanisms that allow environmental phytoremediation.

Richard Levie is a principal with ADR Associates in Washington, DC. He is a retired associate judge of the Superior Court of the District of Columbia, where he served for more than 14 years. As a judge, he presided over cases involving medical and legal malpractice, tobacco injury and class action, asbestos personal injury, and property damage, leaded-paint personal injury, discrimination, benzene, and insurance coverage.

Paul Locke is the deputy director of the Pew Environmental Health Commission and a visiting scholar at the Johns Hopkins School of Public Health. He is also affiliated with the Environmental Law Institute in Washington, DC. His research interests include the study of biologic markers in risk modeling of environmental tobacco-smoke exposure and the application and use of public-health expert scientific testimony in the courtroom.

Gilbert Omenn is executive vice president for medical affairs at the University of Michigan. He is also chief executive officer of the University of Michigan Health System and a professor of internal medicine, human genetics, and public health. His research interests include genetic predispositions to environmental and occupational health hazards, chemoprevention of cancers, health promotion for older adults, science-based risk analysis, and health policy. He was elected a member of the Institute of Medicine in 1978.

Susan Poulter is a professor of law at the University of Utah College of Law. She has written and spoken extensively on science and the law in toxic-injury litigation and on risk assessment and environmental law.

Phil Sayre is the associate division director in the Environmental Protection Agency (EPA) Risk Assessment Division, which is part of the Office of Pollution Prevention and Toxics. He works on risk issues that pertain to industrial chemicals and biotechnology products that fall within the scope of the Toxic Substances Control Act. He also works with EPA's Remediation Technology Development Forum where he cochairs a working group with industry to develop plants for the remediation of soils contaminated with petroleum hydrocarbon.

Richard Sharp is a biomedical ethicist at the National Institute of Environmental Health Sciences. He holds a PhD in moral philosophy, and his professional

interests focus on the ethical, legal, and social implications of research on genetic susceptibilities to disease.

William Suk is director of the Office of Program Development and director of the Hazardous Substances Basic Research and Training Program at the National Institute of Environmental Health Sciences (NIEHS). He is also involved with the Environmental Genome Project at NIEHS. His research interests include linking exposures with disease and developing research and prevention strategies to reduce the risk of environmentally induced diseases and disorders.

William Thilly is a professor of toxicology and director of the Center for Environmental Health Sciences at Massachusetts Institute of Technology. His research interests include the causes and mechanisms of mutation in humans, cell kinetics, and genetic change and cancer.

LaReesa Wolfenbarger is an environmental-science fellow at the Environmental Protection Agency and is sponsored by the American Association for the Advancement of Science. Her research has focused on ecologic, evolutionary, and genetic processes that influence animal and plant populations.

Franklin Zweig is president and chief executive officer of the Einstein Institute for Science, Health, and the Courts. The mission of the institute is to provide judges, courts, and court-related personnel with knowledge tools related to criminal and civil proceedings involving evidence from the genetic sciences and from new discoveries and technologies in the environmental sciences and neurosciences.